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Research Article

Real-World Impact of Atrial Fibrillation on Cardiovascular Outcomes and Healthcare Resource Utilization in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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Abstract

Purpose: This study evaluated the impact of atrial fibrillation (AFib) on cardiovascular (CV) outcomes and healthcare resource utilization (HCRU) in patients with CLL/SLL overall, by age, and by Bruton tyrosine kinase inhibitor (BTKi) therapy. **Materials and Methods:** This retrospective study used the US Symphony database to identify newly diagnosed adults with CLL/SLL (2014-2024). Occurrence of AFib was assessed for 1 year after diagnosis. Subsequent CV outcomes and HCRU were compared, with subgroup analyses conducted in patients ≥65 years. Exploratory analyses compared outcomes among first-line BTKi (ibrutinib, acalabrutinib, or zanubrutinib). **Results:** Among 233,362 CLL/SLL patients, 13.1% had AFib within 1 year. Significantly higher proportions of patients with AFib had subsequent stroke (14.3% vs 8.9%), bleeding (27.9% vs 19.1%), and heart failure (54.5% vs 18.9%) versus without AFib (P<.0001), and had 128% higher odds to incur inpatient service (P<.0001). Results were consistent in elderly patients. Rates of AFib within 1 year of first-line BTKi treatment were 11% (zanubrutinib), 13% (acalabrutinib), and 16% (ibrutinib) (P<.0001). Compared with ibrutinib and acalabrutinib, a lower proportion of patients with AFib receiving zanubrutinib had subsequent stroke (12.2% vs 9.4% vs 4.8%, respectively), bleeding (27.4% vs 21.5% vs 17.4%), and heart failure (50.9% vs 45.6% vs 39.6%) (P<.002). Compared with zanubrutinib, the odds of inpatient HCRU within 1 year were 29% higher with acalabrutinib (P=.0005) and 69% higher with ibrutinib (P<.0001). **Conclusions:** Findings highlight significant real-world CV and HCRU burden incurred by CLL/SLL patients with AFib. Zanubrutinib appears to offer potentially lower rates of AFib-related CV and HCRU complications.

Keywords: Chronic Lymphocytic Leukemia, Atrial Fibrillation, Bruton Tyrosine Kinase Inhibitors, Cardiovascular Outcomes, Healthcare Resource Utilization, Real-World Evidence.

Introduction

Chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL/SLL) are clinically indistinguishable, indolent forms of B-cell malignancy that occur predominantly in older adults, a population at elevated risk of cardiovascular (CV) risk [1-3]. Atrial fibrillation (AFib) is a common cardiovascular comorbidity in patients with CLL/SLL [3-5], and is associated with downstream complications inclusive of stroke, bleeding, and heart failure, as well as increased healthcare resource utilization (HCRU) [6, 7].

Bruton tyrosine kinase inhibitors (BTKi) have transformed the management of CLL/SLL and are effective first-line therapies, but differ in their cardiac safety profiles [8]. Ibrutinib, a first-generation BTKi, has been associated with off target cardiac toxicities, including AFib [9], whereas second-generation BTKi such as zanubrutinib and acalabrutinib demonstrate improved selectivity and lower reported rates of AFib [10, 11]. Accordingly, current National Comprehensive Cancer Network (NCCN) guidelines favor second-generation BTKi over first-generation BTKi due to CV safety considerations [8].

While the association between AFib and CLL has been reported [4, 12-14], real-world evidence on its clinical and economic impact is limited. In addition, real-world, BTKi-specific comparisons of AFib-related clinical and economic burden remain sparse.

To address this evidence gap, the present study evaluated the real-world impact of AFib on CV outcomes and HCRU in a large, contemporary cohort of patients with CLL/SLL. Outcomes were assessed overall, in elderly patients (aged ≥65 years), and in an exploratory analysis comparing patients initiating first line BTKi therapy with zanubrutinib, acalabrutinib, or ibrutinib.

Materials and Methods

Study Design

This retrospective study utilized an open claims healthcare database (US Symphony Health, an ICON plc Company, PatientSource®) to identify newly diagnosed adults with CLL/SLL between January 1, 2014 and August 31, 2024, with follow-up through August 31, 2025.

The primary objective of this study was to evaluate the impact of AFib on clinical outcomes and healthcare resource utilization in patients with CLL/SLL. Patients were included if they had a first diagnosis of CLL/SLL (ICD-9-CM: 204.1x, 200.8x; ICD-10-CM: C91.1x, C83.0x) during the study period. In this primary analysis, the first diagnosis date was defined as the index date. Patients were included if they were aged ≥18 years at the index date with at least one medical or pharmacy activity within 30 days prior to the index date. A subgroup analysis of this cohort was performed for patients aged ≥65 years at the index date.

Additionally, an exploratory analysis assessed the impact of AFib on clinical outcomes in patients receiving first-line BTKi therapy. In this analysis, patients initiated first-line BTKi therapy (zanubrutinib, acalabrutinib, or ibrutinib) within the study period; the date of treatment start was defined as the index date for this exploratory analysis.

Study Outcomes

Baseline demographics and clinical characteristics were assessed, including age, sex, race/ethnicity, geographic region, and pre-existing cardiovascular events of interest (AFib, stroke, bleeding, heart failure) within 365 days prior to the index date for each analysis. Patients were followed for 1 year after the index date to assess occurrence of AFib, after which patients were categorized into "With AFib" and "Without AFib" groups. Identification of AFib utilized ICD-9 and ICD-10 codes for "atrial fibrillation" and "atrial flutter" (ICD-9: 427.31, 427.32; ICD-10: I48).

Development of CV outcomes (stroke, bleeding, and heart failure) was assessed (see Supplementary Table 1 for ICD-9 and ICD-10 codes). For patients with AFib, CV outcomes were captured after the first AFib onset date through the end of the study. For patients without AFib, CV outcomes were captured after the index date through end of the study. Additionally, HCRU up to 1 year after the index date was assessed, including inpatient services, outpatient visits, and other medical/hospital services.

Statistical Analysis

Descriptive statistics summarized baseline characteristics and the proportion of patients experiencing CV outcomes. Comparisons between groups were performed using Chi-Square test for categorical variables and Kruskal-Wallis test for continuous variables with P-values <.05 considered statistically significant. A Cox regression model with AFib as a time-dependent covariate was used to assess the associations between AFib and CV outcomes. Multiple logistic regression was used to assess the association between AFib and inpatient visits within 1 year after CLL diagnosis, adjusting for age, sex, race/ethnicity, region and CV outcomes. Odds ratios (ORs) and 95% confidence intervals (CI) were estimated. Sensitivity analyses were conducted that excluded patients with baseline or pre-exposure cardiac events (stroke, bleeding, and heart failure) with or without baseline or pre-exposure AFib (see footnote of Supplemental Table 2).

Results

Primary Analysis: Impact of AFib on Cardiovascular Outcomes and Healthcare Resource Utilization in Patients with CLL/SLL.

In the primary analysis, a total of 233,362 patients newly diagnosed with CLL/SLL were identified. Of these patients, 13.1% (n=30,518) experienced ≥1 AFib diagnosis within one year of CLL/SLL diagnosis (Table 1).

Parameter, n (%)	Patients With AFib (N = 30,518)	Patients Without AFib (N = 202,844)	P-value
Median age at index (IQR)	72 (69–75)	69 (62–73)	<.0001
Sex			<.0001
Female	10,422 (34.2)	89,100 (43.9)	
Male	20,096 (65.9)	113,737 (56.1)	
Age groups			<.0001
18-55 years	578 (1.9)	22,255 (11.0)	
56-64 years	2,272 (7.4)	40,932 (20.2)	
>65 years	27,668 (90.7)	139,657 (68.9)	
Race/Ethnicity			<.0001
American Indian/Alaska Native Non-Hispanic	59 (0.2)	414 (0.2)	
Asian Non-Hispanic	196 (0.6)	1,905 (0.9)	
Black Non-Hispanic	1,640 (5.4)	13,285 (6.6)	
Hispanic	937 (3.0)	8,458 (4.2)	
Other	8 (0.03)	69 (0.03)	
Native Hawaiian/Pacific Islander Non-Hispanic	2 (0.01)	24 (0.01)	
White Non-Hispanic	20,644 (67.7)	129,787 (64.0)	
Unknown/Missing	7,032 (23.0)	48,902 (24.1)	
Cardiovascular outcomes of interest at baseline (365 days prior to index date)			
AFib	19,682 (64.5)	4,774 (2.4)	<.0001
Stroke	2,126 (7.0)	5,903 (2.9)	<.0001
Bleeding	3,315 (10.9)	10,835 (5.3)	<.0001
Heart failure	8,507 (27.9)	10,417 (5.1)	<.0001

AFib: atrial fibrillation; **CLL/SLL:** chronic lymphocytic leukemia/small lymphocytic lymphoma; **IQR:** interquartile range.

Table 1: Baseline Characteristics for Patients With CLL/SLL in Primary Analysis.

Through end of study, significantly higher proportions of patients with CLL/SLL and AFib had subsequent stroke (14.3% vs 8.9%), bleeding (27.9% vs 19.1%), and heart failure (54.5% vs 18.9%) than those without AFib, respectively (P<.0001; Figure 1). Median follow-up time (interquartile range) was 34.9 (16.0, 62.1) months for patients with AFib and 55.0 (29.5, 87.8) months for patients without AFib. Sensitivity analyses were consistent with these findings (Supplemental Table 2).

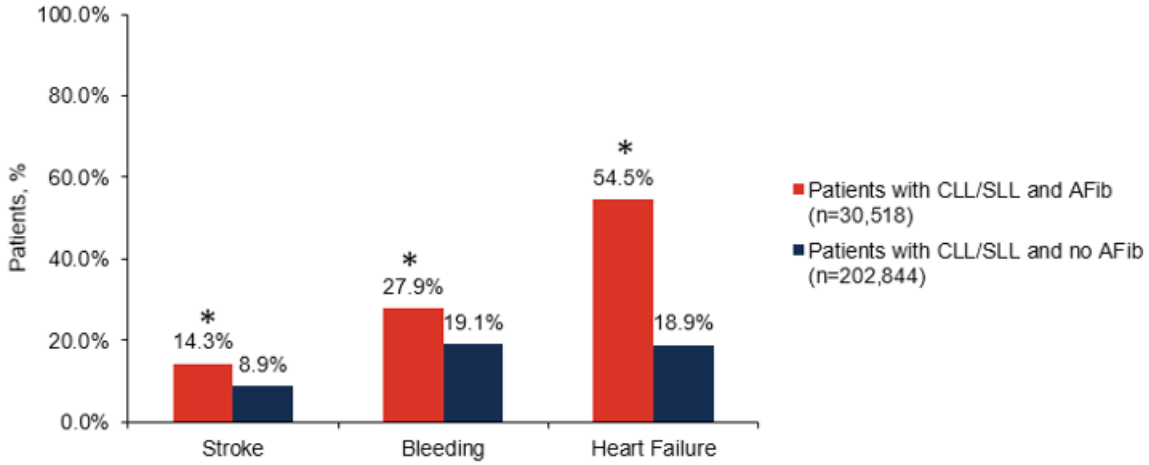

Figure 1: Proportion of patients with CLL/SLL with or without AFib experiencing cardiovascular events of interest (stroke, bleeding, heart failure).

For patients with AFib, outcomes were captured after the first AFib onset date through end of study. For patients without AFib, outcomes were captured after the index date (first diagnosis of CLL/SLL) through end of study. AFib, atrial fibrillation; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma. *P<.0001

In the Cox regression analyses with AFib as a time-dependent covariate, AFib was associated with all CV outcomes evaluated. Compared with patients without AFib, those with AFib had 47% higher hazard of stroke (HR 1.47; 95% CI 1.42–1.53; P<.0001), 67% higher hazard of bleeding (HR 1.67; 95% CI 1.63–1.71; P<.0001), and 182% higher hazard of heart failure (HR 2.82; 95% CI 2.76–2.88; P<.0001). Older age (≥65 years) was also a consistent risk factor across CV outcomes, with nearly 2-fold higher hazard of stroke (HR 1.89; 95% CI 1.82–1.94; P<.0001), modestly higher hazard of bleeding (HR 1.10; 95% CI 1.08–1.12; P<.0001), and more than 2-fold higher hazard of heart failure (HR 2.60; 95% CI 2.54–2.67; P<.0001) compared with younger patients. All outcome associations are reported in Supplemental Table 3.

Additionally, AFib was associated with higher HCRU in patients with CLL/SLL (Table 2). A significantly greater proportion of patients with CLL/SLL and AFib had ≥1 patient visit within 1 year of CLL/SLL diagnosis than those without AFib (54.9% vs 23.2%, P<.0001), as well as 128% higher odds to incur inpatient service (OR: 2.28, 95% CI [2.21, 2.35], P<.0001).

	All Patients			**Patients Aged ≥65 Years**		
	Patients With AFib (N=30,518)	**Patients Without AFib (N=202,844)**	***P*-Value**	**Patients With AFib (N=27,668)**	**Patients Without AFib (N=139,657)**	***P*-Value**
Outpatient visits						
Mean (SD)	16.2 (15.2)	11.2 (12.8)		15.9 (14.8)	10.9 (12.1)	
Median (IQR)	12.0 (5.0, 22.0)	7.0 (3.0, 15.0)	<.0001	12.0 (5.0, 22.0)	7.0 (3.0, 15.0)	<.0001
≥1 visit, n (%)	29,051 (95.2)	185,485 (91.4)	<.0001	26,280 (95.0)	127,395 (91.2)	<.0001
Inpatient services						
Mean (SD)	1.8 (3.1)	0.6 (1.9)		1.8 (2.9)	0.6 (1.7)	
Median (IQR)	1.0 (0.0, 2.0)	0.0 (0.0, 0.0)	<.0001	1.0 (0.0, 2.0)	0.0 (0.0, 0.0)	<.0001
≥1 visit, n (%)	16,752 (54.9)	47,136 (23.2)	<.0001	15,185 (54.9)	33,542 (24.0)	<.0001

Other medical/hospital services						
Mean (SD)	9.6 (14.7)	5.8 (11.2)		9.4 (14.3)	5.8 (11.1)	
Median (IQR)	4.0 (1.0, 12.0)	2.0 (0.0, 6.0)	<.0001	4.0 (1.0, 12.0)	2.0 (0.0, 6.0)	<.0001
≥1 visit, n (%)	24,991 (81.9)	142,097 (70.1)	<.0001	22,608 (81.7)	97,866 (70.1)	<.0001
Index date was defined as date of CLL/SLL diagnosis. **AFib:** atrial fibrillation; **CLL/SLL:** chronic lymphocytic leukemia/small lymphocytic lymphoma; **IQR:** interquartile range; **SD:** standard deviation.						

Table 2: Healthcare Resource Utilization Within 1 Year of CLL/SLL Index Date in Primary Analysis.

In the sub-analysis of elderly patients aged ≥65, CV outcomes and HCRU were similar to the overall analysis. Within 1 year of CLL/SLL diagnosis, 16.5% of elderly patients developed AFib. Through end of study, a significantly higher proportion of elderly patients with CLL/SLL and AFib experienced stroke (14.6% vs 10.3%), bleeding (28.0% vs 19.4%), and heart failure (55.8% vs 22.9%) compared with those without AFib, respectively (P<.0001). Additionally, a significantly higher proportion of elderly patients with CLL/SLL and AFib used ≥1 inpatient service within 1 year of CLL/SLL diagnosis than those without AFib (54.9% vs 24.0%; P<.0001; Table 2).

Exploratory Analysis: Impact of AFib on Clinical Outcomes in Patients Receiving First-line BTKi Therapy

In the exploratory analysis, 22,636 patients with CLL/SLL were identified who initiated first-line BTKi therapy (zanubrutinib [n=1,864], acalabrutinib [n=5,447], or ibrutinib [n=15,325]; Table 3).

Parameter, n (%)	**Zanubrutinib (N=1,864)**	**Acalabrutinib (N=5,447)**	**Ibrutinib (N=15,325)**	***P*-value**
Median age at index (IQR)	73 (66–78)	72 (64–76)	70 (64–73)	<.0001
Sex				.347
Female	731 (39.2)	2,051 (37.7)	5,745 (37.5)	.
Male	1,133 (60.8)	3,396 (62.4)	9,580 (62.5)	.
Age groups				<.0001
18-55 years	102 (5.5)	403 (7.4)	1,271 (8.3)	.
56-64 years	298 (16.0)	1,092 (20.1)	2,958 (19.3)	.
≥65 years	1,464 (78.5)	3,952 (72.6)	11,096 (72.4)	.
Race/Ethnicity				.0399
White, Non-Hispanic	1,224 (65.7)	3,525 (64.7)	9,795 (63.9)	.
Black, Non-Hispanic	130 (7.0)	401 (7.4)	1,296 (8.5)	.
Hispanic	70 (3.8)	206 (3.8)	569 (3.7)	.
Asian, Non-Hispanic	25 (1.3)	64 (1.17)	123 (0.8)	.
Unknown/Missing	408 (21.9)	1,239 (22.8)	3,499 (22.8)	.
Cardiovascular outcomes of interest at baseline (365 days prior to index date)				
Afib	158 (8.5)	460 (8.4)	922 (6.0)	<.0001
Stroke	37 (2.0)	98 (1.8)	353 (2.3)	.4316
Bleeding	76 (4.1)	265 (4.9)	630 (4.1)	.693

Heart failure	108 (5.8)	364 (6.7)	735 (4.8)	<.0001

Index date was defined as first-line BTK inhibitor treatment start date. **AFib:** atrial fibrillation; **BTK:** Bruton tyrosine kinase; **CLL/SLL:** chronic lymphocytic leukemia/small lymphocytic lymphoma; **IQR:** interquartile range.

Table 3: Baseline Characteristics for Patients With CLL/SLL Receiving First-Line BTK Inhibitor Therapy in Exploratory Analysis.

Within 1 year of initiating first-line therapy, the proportion of patients with CLL/SLL receiving zanubrutinib who developed AFib was significantly less (11.1%) than those receiving acalabrutinib (13.1%) or ibrutinib (15.6%; P<.0001; Figure 2, left panel). Among patients with CLL/SLL and AFib, a significantly smaller proportion of patients treated with zanubrutinib experienced stroke, bleeding, and heart failure than those receiving acalabrutinib or ibrutinib, respectively (overall P<.01; Figure 2, right panel). Sensitivity analyses were consistent with these findings (Supplemental Table 4).

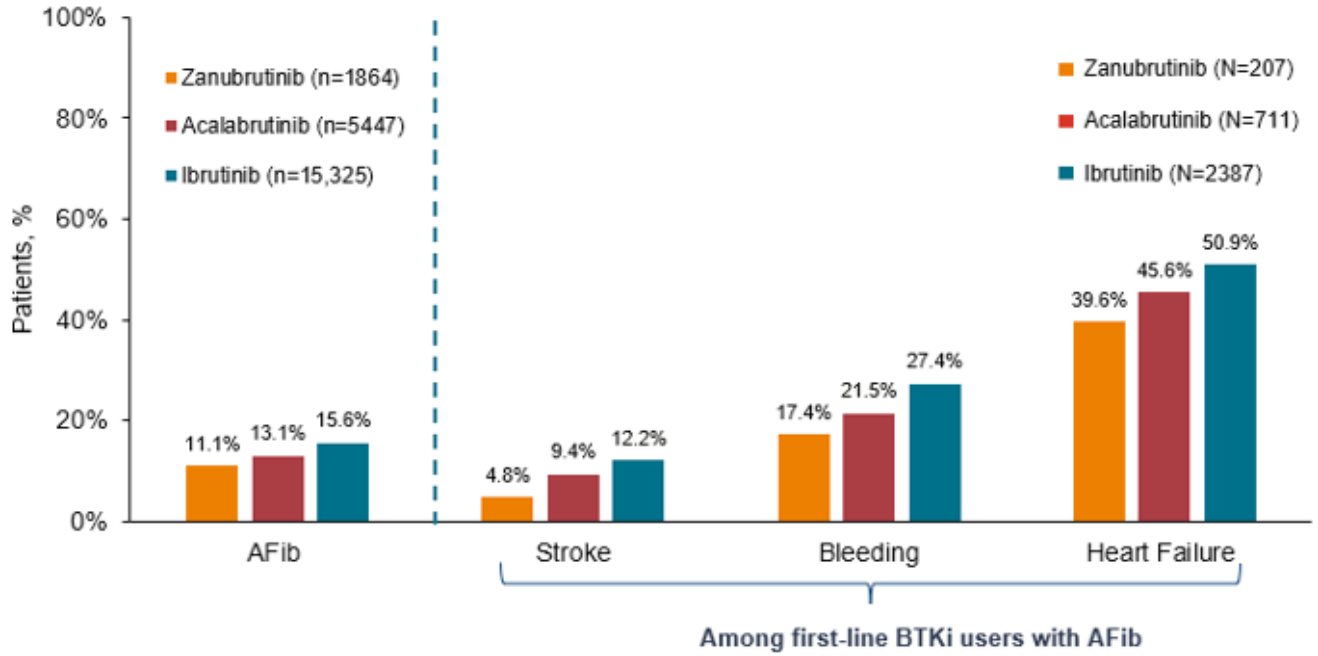

Figure 2: Proportion of patients with CLL/SLL experiencing cardiac outcomes of interest by first-line BTK inhibitor therapy.

For patients with AFib, stroke, bleeding, and heart failure were captured after the first AFib onset date through end of study. AFib, atrial fibrillation; BTK, Bruton tyrosine kinase. Overall P value among BTKi for AFib (left panel), P<.0001; overall P value among BTKi for all CV outcomes (right panel), P<.01.

As observed in the primary analysis, patients with AFib consistently had higher HCRU compared with patients without AFib across all BTKi (Table 4). Among BTKi, ibrutinib was associated with the highest inpatient service utilization, whereas zanubrutinib was associated with the lowest. Patients receiving first-line acalabrutinib had 29% higher odds of requiring inpatient services within 1 year of treatment compared with patients receiving first-line zanubrutinib (OR: 1.29, 95% CI [1.12, 1.50], P=.0005). Similarly, patients receiving first-line ibrutinib had 69% higher odds than patients receiving first-line zanubrutinib (OR: 1.69, 95% CI [1.48, 1.93], P<.0001) to require inpatient service within 1 year of treatment. All associations with inpatient services are reported in Supplemental Table 5.

	Patients With AFib				**Patients Without AFib**			
	Zanubrutinib (N = 207)	**Acalabrutinib (N = 711)**	**Ibrutinib (N = 2387)**	***P* Value (overall)**	**Zanubrutinib (N = 1657)**	**Acalabrutinib (N = 4736)**	**Ibrutinib (N = 12,938)**	***P* Value (overall)**
Outpatient Visits								
Mean (SD)	14.8 (14.9)	14.8 (14.0)	15.7 (14.0)		9.0 (11.7)	10.0 (11.9)	10.3 (11.9)	
Median (IQR)	10.0 (4.0, 22.0)	11.0 (4.0, 22.0)	12.0 (5.0, 22.0)	.0169	5.0 (1.0, 12.0)	6.0 (2.0, 14.0)	6.0 (2.0, 15.0)	<.0001
≥1 visit, n (%)	195 (94.2)	667 (93.8)	2317 (97.1)	.0001	1370 (82.7)	4088 (86.3)	11226 (86.8)	<.0001
Inpatient Services								
Mean (SD)	1.2 (2.0)	1.5 (2.4)	1.9 (3.1)		0.4 (1.4)	0.5 (1.6)	0.6 (1.5)	
Median (IQR)	0.0 (0.0, 2.0)	1.0 (0.0, 2.0)	1.0 (0.0, 3.0)	<.0001	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	<.0001
≥1 visit, n (%)	96 (46.4)	366 (51.5)	1442 (60.4)	<.0001	254 (15.3)	920 (19.4)	3034 (23.5)	<.0001
Other Medical/ Hospital Services								
Mean (SD)	9.8 (13.5)	9.6 (11.7)	8.4 (10.7)		5.8 (9.8)	6.7 (10.9)	5.9 (10.5)	
Median (IQR)	5.0 (1.0, 15.0)	5.0 (1.0, 14.0)	4.0 (1.0, 12.0)	.0156	2.0 (0.0, 8.0)	2.0 (0.0, 10.0)	2.0 (0.0, 8.0)	<.0001
≥1 visit, n (%)	167 (80.7)	601 (84.5)	1942 (81.4)	.1358	1077 (65.0)	3200 (67.6)	8393 (64.9)	.0033

Index date was defined as first-line BTK inhibitor treatment start date. **AFib:** atrial fibrillation; **BTK:** Bruton tyrosine kinase; **IQR:** interquartile range; **SD:** standard deviation.

Table 4: Healthcare Resource Utilization Within One Year After Index Date in Exploratory Analysis.

Discussion

In this large, real-world analysis, AFib occurred in 13% of patients within the first year of CLL/SLL diagnosis and was associated with significantly higher rates of stroke, bleeding, heart failure, and HCRU. These associations were consistent in a sub-analysis of elderly patients, highlighting the heightened clinical and economic burden of AFib in a population vulnerable to CV complications. Our findings support those of previous real-world studies that highlight the substantial clinical burden of AFib and its association with patient-related factors in CLL/SLL, including older age and comorbidities [12, 15]. This study further extends existing literature by quantifying downstream HCRU associated with AFib in a large, contemporary claims-based cohort. The substantially higher rates of inpatient utilization and other medical encounters observed in CLL/SLL patients with AFib are consistent with increased downstream interventions following diagnosis of AFib. In the context of BTKi therapy, the increased HCRU observed here may also reflect additional clinical complexities in patients receiving first-line BTKi, including treatment modification and multidisciplinary care. Further, our

findings underscore the importance of proactive risk assessment of comorbidities when selecting CLL/SLL therapies, including BTKi [16].

Exploratory analyses suggested clinically meaningful differences in AFib-related outcomes across first-line BTKi therapies. Patients treated with zanubrutinib experienced lower rates of AFib, fewer subsequent CV events, and reduced inpatient HCRU compared with those receiving acalabrutinib or ibrutinib. These findings align with the pharmacologic design of zanubrutinib, which achieves sustained BTK inhibition while minimizing off-target kinase activity that may contribute to CV toxicity [10, 17, 18]. Consistent with this, the six-year follow-up from the phase 3 SEQUOIA study reported low rates of AFib and no new safety concerns with zanubrutinib [19].

Our exploratory findings also complement head-to-head clinical trial data and pooled analyses demonstrating the favorable profile of zanubrutinib vs ibrutinib in patients with CLL/SLL [17, 20]. A recent real-world practice change report similarly described a low incidence of cardiac events following transition from ibrutinib to zanubrutinib [21]. Indirect comparison and real-world data also suggest that zanubrutinib may also provide superior efficacy and durability compared with acalabrutinib. In a matching-adjusted indirect comparison (MAIC) using ALPINE individual patient data and ASCEND aggregate data, zanubrutinib significantly reduced the risk of progression or death in relapsed/refractory CLL (HR 0.68; 95% CI 0.46–0.99, P=.0448) and achieved nearly three-fold higher complete response rates (OR 2.90; 95% CI 1.13–7.43; P=.0270) compared with acalabrutinib [22]. These findings are supported by a real-world multicenter study (N = 505) reporting longer time to discontinuation with zanubrutinib versus acalabrutinib (median 30.1 vs 14.0 months; HR 0.41; 95% CI 0.34–0.51), with 12-month treatment persistence of 74% vs 55%, respectively [23]. Taken together with the current study, zanubrutinib may offer potentially favorable outcomes over other BTKi in lessening AFib and related clinical and HCRU complications, but future analyses with longer follow-up are warranted to confirm these findings.

This study has limitations inherent to retrospective claims analyses, including potential misclassification of diagnoses and lack of clinical details such as disease severity, laboratory parameters, and treatment adherence. The absence of certain clinical variables from this claims database (eg, body mass index) may also contribute to unmeasured confounding. Additionally, our findings reflect patterns in insured populations and may not generalize to all care settings, and uneven BTKi subgroup sizes may affect treatment-specific comparisons. Lastly, our findings should be interpreted in the context of the multifactorial etiology of AFib in CLL, which reflects a combination of patient age, comorbidities, and treatment effects. Despite these limitations, our findings provide robust real-world evidence highlighting clinical and economic burdens associated with AFib in CLL/SLL, with exploratory analyses suggesting that selection of BTKi therapy may influence AFib-related outcomes.

Conclusions

Taken together, these findings highlight the real-world burden of AFib on CV outcomes and HCRU in CLL/SLL and suggest that zanubrutinib may offer tangible early advantages over other commonly-used BTKi therapies. Future studies with longer follow-up are warranted to confirm these findings.

Conflict of Interest

The authors declare the following conflicts of interest:

DE: Honoraria: BeOne Medicines, Ltd; Consulting or advisory role: BeOne Medicines, ADC Therapeutics; Speaker's bureau: Incyte, AstraZeneca; DA: None to disclose; KY, MX, QF, DY, AKA, DvB, GRW: Current employment: BeOne Medicines, Ltd. MF: Honoraria: Zoll; Consulting: AstraZeneca, Abbvie, Janssen, Pfizer; Research funding: Medtronic, AstraZeneca.

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Ethical Guidelines: No institutional review board/independent ethics committee review was required for this secondary analysis of deidentified existing data.

Supplemental Tables

Condition	ICD-9 Codes	ICD-10 Codes
Atrial Fibrillation	427.31 (Atrial Fibrillation); 427.32 (Atrial Flutter)	I48.0 (Paroxysmal atrial fibrillation); I48.1 (Persistent atrial fibrillation); I48.2 (Chronic atrial fibrillation); I48.9 (Unspecified atrial fibrillation and atrial flutter); I48.3 (Typical atrial flutter); I48.4 (Atypical atrial flutter)
Stroke	433.X, 434.X, 436, 433.x1, 434.x1 (Ischemic stroke); 435.X (TIA)	I63.0–I63.9 (Cerebral infarction); G45.9 (TIA)

Bleeding	GI Bleeding: 456.0, 456.20, 530.21, 530.7, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.x; Intracranial hemorrhage: 430, 431, 432.x, 852.x, 853.x; Other: 423.0, 459.0, 596.7, 599.71, 719.1x, 784.8, 786.3	Intracranial hemorrhage: I60, I61, I62, S06.36, S06.4, S06.5, S06.6; GI bleed: K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K66.1, K62.5, K28.2, K28.4, K28.6, K92.0, K92.1, K92.2, K22.11, K29.41, K29.51, K29.61, K29.21, K29.91, K29.81, K31.82, K57.01, K57.91, K57.33, K55.21, K63.81, K31.811, K29.01, I85.01, I85.11; Eye bleed: H05.23, H43.1; Menorrhagia: N92, N93, N95.0; Respiratory: R04; Joint: M25.0
Heart Failure	428 (Congestive heart failure), 428.1 (Left heart failure), 428.2X (Systolic), 428.3X (Diastolic), 428.4X (Combined), 428.9 (Heart failure)	I50.X (Heart failure), I50.1 (Left ventricular failure), I50.2x, I50.3X (CHF), I50.4X (Combined), I50.9 (Heart failure)

Supplemental Table 1: ICD-9 and ICD-10 codes for cardiac complications of interest.

Sensitivity Analysis 1[b]			
	Patients With AFib (N=15,964)	**Patients Without AFib (N=178,336)**	***P*-Value**
Stroke, n (%)			<.0001
Yes	1600 (10.02)	12968 (7.27)	.
No	14364 (89.98)	165368 (92.73)	.
Bleeding, n (%)			<.0001
Yes	3730 (23.37)	30551 (17.13)	.
No	12234 (76.63)	147785 (82.87)	.
Heart Failure, n (%)			<.0001
Yes	5930 (37.15)	27433 (15.38)	.
No	10034 (62.85)	150903 (84.62)	.
Sensitivity Analysis 2[c]			
	Patients With AFib (N = 6279)	**Patients Without AFib (N = 175,333)**	***P*-Value**
Stroke, n (%)			<.0001
Yes	578 (9.21)	12679 (7.23)	.
No	5701 (90.79)	162654 (92.77)	.
Bleeding, n (%)			<.0001
Yes	1377 (21.93)	29914 (17.06)	.
No	4902 (78.07)	145419 (82.94)	.
Heart Failure, n (%)			<.0001
Yes	2193 (34.93)	26591 (15.17)	.
No	4086 (65.07)	148742 (84.83)	.

[a]For patients with AFib, stroke, bleeding, and heart failure were identified after the first AFib onset date; for patients without AFib, these events were identified after the index date (first CLL/SLL diagnosis). [b]Secondary Analysis 1 excluded patients with a history of stroke, bleeding, or heart failure at baseline (within 365 days prior to index date) and those who developed these events between CLL/SLL diagnosis and first AFib. [c]Secondary Analysis 2 excluded patients with a history of AFib, stroke, bleeding, or heart failure at baseline (within 365 days prior to index date) and those who developed any of these events between CLL diagnosis and first AFib. AFib, atrial fibrillation; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma.

Supplemental Table 2: Sensitivity Analyses Excluding Patients With Baseline or Intercurrent Events Prior to AFib or Index Date[a].

Variable	Estimate	*P*-value	Hazard Ratio	Lower CL	Upper CL
Stroke (All Time)					
AFib [with vs without]	0.388	<.0001	1.474	1.421	1.53
Age at Index [65+ vs <65]	0.635	<.0001	1.887	1.823	1.954
Sex [male vs female]	-0.022	.095	0.978	0.952	1.004
Race/ethnicity [non-White vs White]	0.238	<.0001	1.269	1.22	1.32
Race/ethnicity [Unknown vs White]	0	.988	1	0.968	1.032
Region [Midwest vs Northeast]	0.044	.032	1.045	1.004	1.088
Region [South vs Northeast]	0.043	.02	1.044	1.007	1.083
Region [West vs Northeast]	-0.087	<.0001	0.917	0.877	0.958
Bleeding (All Time)					
AFib [with vs without]	0.513	<.0001	1.671	1.629	1.714
Age at Index [65+ vs <65]	0.093	<.0001	1.098	1.075	1.121
Sex [male vs female]	-0.092	<.0001	0.912	0.895	0.928
Race/ethnicity [non-White vs White]	0.204	<.0001	1.226	1.193	1.26
Race/ethnicity [Unknown vs White]	-0.006	.62	0.994	0.973	1.017
Region [Midwest vs Northeast]	-0.027	.05	0.973	0.947	1
Region [South vs Northeast]	-0.062	<.0001	0.94	0.917	0.964
Region [West vs Northeast]	-0.072	<.0001	0.931	0.904	0.959
Heart Failure (All Time)					
AFib [with vs without]	1.036	<.0001	2.819	2.757	2.882
Age at Index [65+ vs <65]	0.956	<.0001	2.6	2.538	2.665
Sex [male vs female]	0.127	<.0001	1.136	1.117	1.155
Race/ethnicity [non-White vs White]	0.206	<.0001	1.229	1.197	1.261
Race/ethnicity [Unknown vs White]	0.081	<.0001	1.084	1.062	1.106
Region [Midwest vs Northeast]	0.109	<.0001	1.116	1.088	1.144
Region [South vs Northeast]	0.038	.001	1.039	1.015	1.064
Region [West vs Northeast]	-0.11	<.0001	0.896	0.871	0.922

AFib: atrial fibrillation; **CL:** confidence limit.

Supplemental Table 3: Time-Dependent Cox Regression Analysis of Primary Analysis

Sensitivity Analysis 1[b]				
	Zanubrutinib	**Acalabrutinib**	**Ibrutinib**	***P*-value across BTKi**
	N=1587	**N=4607**	**N=13,127**	
Patients with AFib, n (%)	108 (6.8)	422 (9.2)	1540 (11.7)	<.0001
Sensitivity Analysis 2[c]				
	Zanubrutinib	**Acalabrutinib**	**Ibrutinib**	***P*-value across BTKi**
	N=1485	**N=4300**	**N=12,474**	
Patients with AFib, n (%)	41 (3.0)	206 (5.0)	1073 (9.0)	<.0001

[a]For patients with AFib, events were identified after the first AFib onset date. [b]Sensitivity Analysis 1 excludes patients with a history of stroke, bleeding, or heart failure at baseline (within 365 days prior to BTK inhibitor initiation) and those who developed these events between BTK inhibitor initiation and first AFib. [c]Sensitivity Analysis 2 excludes patients with a history of AFib, stroke, bleeding, or heart failure at baseline (within 365 days prior to BTK inhibitor initiation) and those who developed any of these events between BTK inhibitor initiation and first AFib. AFib, atrial fibrillation; BTK, Bruton tyrosine kinase.

Supplemental Table 4: Sensitivity Analyses of Patients With AFib by First-Line BTK Inhibitor Treatment[a].

Variable	**Estimate**	***P*-value**	**Odds Ratio**	**Lower CL**	**Upper CL**
AFib [with vs without]	1.0481	<.0001	2.852	2.612	3.114
1L BTKi [acalabrutinib vs zanubrutinib]	0.2572	.0005	1.293	1.119	1.495
1L BTKi [ibrutinib vs zanubrutinib]	0.5245	<.0001	1.69	1.479	1.93
Age at Index [65+ vs <65]	0.142	.0044	1.153	1.045	1.271
Sex [male vs female]	0.096	.0056	1.101	1.028	1.178
Race/ethnicity [non-White vs White]	0.2398	<.0001	1.271	1.153	1.4
Race/ethnicity [Unknown vs White]	0.0366	.3783	1.037	0.956	1.125
Region [Midwest vs Northeast]	0.0437	.4191	1.045	0.94	1.162
Region [South vs Northeast]	0.0837	.0922	1.087	0.986	1.199
Region [West vs Northeast]	-0.0321	.5664	0.968	0.868	1.081
Payment Type [Medicaid vs Commercial]	0.3235	.0001	1.382	1.174	1.627
Payment Type [Medicare vs Commercial]	0.1986	<.0001	1.22	1.116	1.333
Payment Type [Other/Unknown vs Commercial]	0.1129	.1578	1.12	0.957	1.309
Stroke [with vs without]	1.2444	<.0001	3.471	2.903	4.15
Bleeding [with vs without]	1.3956	<.0001	4.038	3.614	4.51
Heart Failure [with vs without]	1.4399	<.0001	4.22	3.831	4.65

1L, first-line; AFib, atrial fibrillation; BTKi, Bruton tyrosine kinase inhibitor; CL, confidence limit.

Supplemental Table 5: Multivariate Regression of Exploratory Analysis for Inpatient Visits Within 1 Year of 1L Treatment Start Date.

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