Real-World Impact of Atrial Fibrillation on Cardiovascular Outcomes and Healthcare Resource Utilization in Patients With Chronic Lymphocytic Leukemia

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CONCLUSIONS

- Findings highlight significant real-world CV and HCRU burden incurred by patients with CLL/SLL and AFib
- Exploratory analyses suggest 1L zanubrutinib offers potentially favorable outcomes over other BTKis in lessening AFib and related clinical and HCRU complications

INTRODUCTION

- While the association between atrial fibrillation (AFib) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) has been reported,[1-3] real-world evidence on its clinical and economic impact is limited
- Bruton tyrosine kinase inhibitors (BTKis) are effective therapies for treatment-naive CLL/SLL; however, they differ in their cardiac safety profiles[4]
- The primary objective of this study was to evaluate the real-world impact of AFib on cardiovascular (CV) outcomes and healthcare resource utilization (HCRU) in patients within 1 year of CLL/SLL diagnosis
  - Additionally, the impact of AFib was examined among patients within 1 year of initiating first-line (1L) BTKi therapy, inclusive of zanubrutinib, acalabrutinib, and ibrutinib

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 was to evaluate the impact of AFib on CV outcomes and HCRU in patients with CLL/SLL, as well as the following:
  - First diagnosis of CLL/SLL (ICD-9-CM: 204.1x, 200.8x; ICD-10-CM: C91.1x, C83.0x) recorded during the study period, with the date of first diagnosis defined as index date
  - At least one documented medical or pharmacy encounter within <30 days prior to index date
  - Aged 18 years or older at the time of the index date
- An exploratory analysis was conducted to assess impact of AFib on clinical outcomes and HCRU in adult patients initiating 1L BTKi therapy, including zanubrutinib, acalabrutinib, or ibrutinib, within the study period
  - In this exploratory analysis, the date of treatment initiation was defined as index date

Study Outcomes

- Baseline demographics and clinical characteristics included age, sex, race/ethnicity, and CV comorbidities (stroke, bleeding, heart failure) within 365 days prior to index date
- Patients were followed for 1 year after CLL/SLL diagnosis to assess occurrence of AFib, after which patients were categorized into "With AFib" and "Without AFib" groups
- Development of CV outcomes (stroke, bleeding, heart failure) was assessed
  - For patients with AFib, CV outcomes were captured after the first AFib onset date through the end of study period
  - For patients without AFib, CV outcomes were captured after the index date through the end of study period
- HCRU (inpatient, outpatient, and other medical/hospital services) was assessed up to 1 year after the index date
- A subgroup analysis of the primary objective was performed for elderly patients aged ≥65 years at index date

Statistical Analysis

- Descriptive statistics summarized the proportion of patients experiencing cardiac outcomes and HCRU
- Comparisons between groups were performed using chi-square tests, with $P<.05$ considered statistically significant
- Multiple logistic regression model was used to assess the association between AFib and inpatient visits within 1 year after CLL/SLL diagnosis, adjusting for age, sex, race/ethnicity, region and CV outcomes

RESULTS

Impact of AFib in Patients With CLL/SLL

- Among 233,362 newly diagnosed patients with CLL/SLL, 13.1% (30,518) had AFib within 1 year of CLL/SLL diagnosis (**Table 1**)

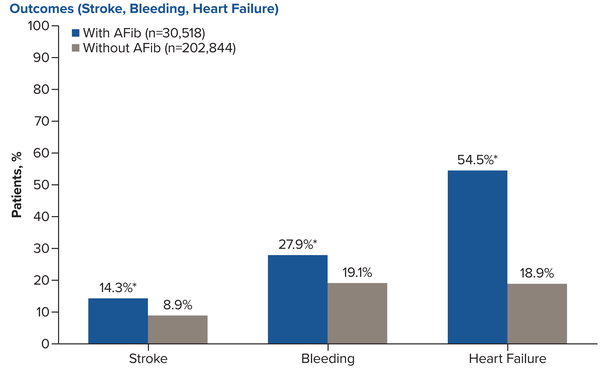
Table 1. Baseline Characteristics for CLL/SLL Patients With or Without AFib

Parameter, n (%)	With AFib (N=30,518)	Without AFib (N=202,844)
Median age at index (IQR)	72 (69-75)	69 (62-73)
Sex		
Female	10,422 (34.2)	89,100 (43.9)
Male	20,096 (65.9)	113,737 (56.1)
Age groups		
18-55 years	578 (1.9)	22,255 (11.0)
56-64 years	2272 (7.4)	40,932 (20.2)
>65 years	27,668 (90.7)	139,657 (68.9)
Race/ethnicity		
Native American/Alaskan Inuit Non-Hispanic	59 (0.2)	414 (0.2)
Asian Non-Hispanic	196 (0.6)	1905 (0.9)
Black Non-Hispanic	1640 (5.4)	13,285 (6.6)
Hispanic	937 (3.0)	8458 (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	7032 (23.0)	48,902 (24.1)
Cardiovascular outcomes at baseline (365 days prior to index date)		
AFib	19,682 (64.5)	4774 (2.4)
Stroke	2126 (7.0)	5903 (2.9)
Bleeding	3315 (10.9)	10,835 (5.3)
Heart failure	8507 (27.9)	10,417 (5.1)

Index date was defined as the first CLL/SLL diagnosis date.
Abbreviations: AFib, atrial fibrillation; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; IQR, interquartile range.

- Significantly higher proportions of CLL/SLL 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%) than those without AFib ($P<.0001$; **Figure 1**)

Figure 1. Proportion of Patients With CLL/SLL With or Without AFib Experiencing CV Outcomes (Stroke, Bleeding, Heart Failure)



For patients with AFib, CV outcomes were captured after the first AFib onset date; for those without AFib, CV outcomes were captured after the index date (first CLL/SLL diagnosis date).
Abbreviations: AFib, atrial fibrillation; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CV, cardiovascular. *$P<0.0001$

- A significantly greater proportion of patients with CLL/SLL and AFib utilized outpatient, inpatient, and other medical/hospital services within 1 year of CLL/SLL diagnosis than those without AFib ($P<.0001$; **Table 2**)
  - Patients with AFib also had a higher likelihood of incurring inpatient service versus those without (odds ratio [OR]: 2.28, 95% CI [2.21, 2.35], $P<.0001$)
- In the subgroup analysis of elderly patients aged ≥65 years, CV outcomes and HCRU were similar to the overall analysis
  - 16.5% developed AFib within 1 year of CLL/SLL diagnosis
  - A significantly higher proportion of patients with AFib experienced stroke (14.6% vs 10.3%), bleeding (28.0% vs 19.4%), and heart failure (55.8% vs 22.9%) compared to those without AFib ($P<.0001$)
  - HCRU use was significantly higher in elderly patients with AFib versus those without AFib, with similar rates to the overall analysis (all services, $P<0.001$; **Table 2**)

Table 2. Healthcare Resource Utilization Within 1 Year of CLL/SLL Index Date

	All Patients			Patients Aged ≥65 Years		
	With AFib (N=30,518)	Without AFib (N=202,844)	*P*-Value	With AFib (N=27,668)	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 the first CLL/SLL diagnosis date.
Abbreviations: AFib, atrial fibrillation; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; IQR, interquartile range; SD, standard deviation.

Exploratory Analysis: Comparison of 1L BTKi

- In the exploratory analysis, 22,636 patients with CLL/SLL who initiated 1L BTKi therapy were identified (zanubrutinib [n=1864], acalabrutinib [n=5447], or ibrutinib [n=15,325]; **Table 3**)

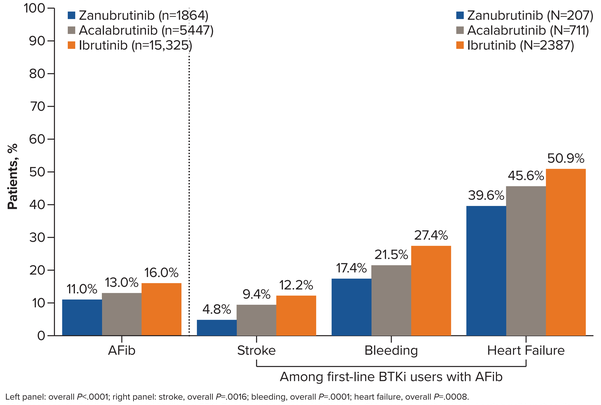
Table 3. Baseline Characteristics for Patients Receiving 1L BTKi Therapy

Parameter, n (%)	Zanubrutinib (N=1864)	Acalabrutinib (N=5447)	Ibrutinib (N=15,325)
Median age at index (IQR)	73 (66-78)	72 (64-76)	70 (64-73)
Sex			
Female	731 (39.2)	2051 (37.7)	5745 (37.5)
Male	1133 (60.8)	3396 (62.4)	9580 (62.5)
Age groups			
18-55 years	102 (5.5)	403 (7.4)	1271 (8.3)
56-64 years	298 (16.0)	1092 (20.1)	2958 (19.3)
>65 years	1464 (78.5)	3952 (72.6)	11,096 (72.4)
Race/ethnicity			
White, Non-Hispanic	1224 (65.7)	3525 (64.7)	9795 (63.9)
Black, Non-Hispanic	130 (7.0)	401 (7.4)	1296 (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)	1239 (22.8)	3499 (22.8)
Cardiovascular outcomes at baseline (365 days prior to index date)			
AFib	158 (8.5)	460 (8.4)	922 (6.0)
Stroke	37 (2.0)	98 (1.8)	353 (2.3)
Bleeding	76 (4.1)	265 (4.9)	630 (4.1)
Heart failure	108 (5.8)	364 (6.7)	735 (4.8)

Index date was defined as 1L BTKi treatment start date.
Abbreviations: 1L, first-line; AFib, atrial fibrillation; BTKi, Bruton tyrosine kinase inhibitor; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; IQR, interquartile range.

- In patients initiating 1L BTKi, the rate of AFib within 1 year of treatment for 1L zanubrutinib versus acalabrutinib versus ibrutinib was 11% versus 13% versus 16%, respectively (overall $P<.0001$; **Figure 2**, left panel)
- Compared to 1L ibrutinib and 1L acalabrutinib, a lower proportion of patients with CLL/SLL and AFib treated with 1L 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%) ($P<.002$ across values; **Figure 2**, right panel)

Figure 2. Proportion of Patients With CLL/SLL and CV Outcomes, Stratified by 1L BTKi Therapy



Left panel: overall $P<.0001$; right panel: stroke, overall $P=.0016$; bleeding, overall $P=.0001$; heart failure, overall $P=.0008$.
Abbreviations: 1L, first line; AFib, atrial fibrillation; BTKi, Bruton tyrosine kinase inhibitor; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CV, cardiovascular.

- A smaller proportion of patients with AFib treated with 1L zanubrutinib (46.4%) incurred inpatient services than 1L ibrutinib (60.4%) and 1L acalabrutinib (51.5%) within 1 year of treatment (overall, $P<.0001$)
- In multivariate regression, patients receiving 1L acalabrutinib had 29% higher odds to require inpatient services within 1 year of treatment compared with 1L zanubrutinib (OR: 1.29, 95% CI [1.12, 1.50], $P=.0005$)
  - Similarly, patients receiving 1L ibrutinib had 69% higher odds than patients receiving 1L zanubrutinib (OR: 1.69, 95% CI [1.48, 1.93], $P<.0001$) to require inpatient service within 1 year of treatment

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DISCLOSURES

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