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Real-world impact of atrial fibrillation (AFib) on cardiovascular (CV) outcomes in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)

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Background: AFib is a common comorbidity in patients with CLL/SLL and may contribute to increased risk of CV complications and healthcare resource utilization (HCRU). However, real-world evidence characterizing the impact of AFib on stroke, bleeding, heart failure, and HCRU in this population remains limited. In addition, Bruton tyrosine kinase inhibitors (BTKis) differ in their CV safety profiles, and comparative data on AFib burden across BTKi therapies are lacking. This study evaluated the association of AFib with CV outcomes and HCRU in a large real-world CLL/SLL cohort and in a subgroup of patients receiving first-line (1L) BTKi therapy.

Methods: This retrospective study used data from the TriNetX Dataworks-USA database. Adult patients were included if they had ≥2 CLL/SLL diagnoses ≥14 days apart and ≥1 activities in the year before first diagnosis. Patients were categorized by the presence or absence of AFib within 24 months after CLL/SLL diagnosis. CV outcomes (stroke, bleeding, and heart failure) were assessed through end of follow-up. Cox regression models with AFib as a time-dependent covariate evaluated associations between AFib and CV outcomes and were adjusted for age, sex, race, ethnicity, and geographic region. Logistic regression evaluated the association between AFib and having ≥1 inpatient or emergency visit within 2 years of CLL/SLL diagnosis and was adjusted for age, sex, race, ethnicity, geographic region, stroke, bleeding, and heart failure. Subgroup analyses were conducted in patients aged ≥65 years and among patients receiving 1L BTKi therapy (zanubrutinib [zanu], acalabrutinib [acala], or ibrutinib [ibru]).

Results: A total of 66,092 patients with CLL/SLL were identified from 2014 to 2026. Among these patients, 9899 (15.0%) developed AFib within 24 months of diagnosis. Compared with patients without AFib, those with AFib were older (median age, 77 vs 70 years), more often male (66.1% vs 55.9%), and had higher baseline rates of stroke (6.1% vs 2.3%), bleeding (9.3% vs 4.4%), and heart failure (23.0% vs 3.9%; all P<.0001). Patients with AFib had higher rates of stroke (12.6% vs 6.7%), bleeding (24.9% vs 15.0%), and heart failure (46.9% vs 13.1%) within 2 years of CLL/SLL diagnosis than those without AFib (all P<.0001). Additionally, AFib was associated with increased risk of stroke (HR, 1.99; 95% CI, 1.85-2.15), bleeding (HR, 2.32; 95% CI, 2.21-2.44), and heart failure (HR, 3.65; 95% CI, 3.49-3.82; all P<.0001). Patients with AFib had greater HCRU than those without AFib, with higher rates of having ≥1 inpatient visit (51.4% vs 23.4%) or emergency visit (39.0% vs 20.2%) within 2 years of CLL/SLL diagnosis (both P<.0001). AFib was associated with 148% higher odds of an inpatient or emergency visit within

2 years of CLL/SLL diagnosis (OR, 2.48; 95% CI, 2.37-2.61; *P*<.0001). Similar patterns were observed in patients aged ≥65 years.
Among 4584 patients initiating 1L BTKi therapy from 2021 to 2025 (1L zanu, n=1228; 1L acala, n=2089; 1L ibru, n=1267), baseline comorbidity burden was generally comparable across treatment cohorts, including mean CCI (3.5, 3.4, and 3.6, respectively) and baseline AFib prior to index date (11.2%, 10.7%, and 8.8%, respectively). Within 24 months of BTKi initiation, AFib occurred in 14.7% (zanu), 17.0% (acala), and 18.6% (ibru) of patients. Odds of AFib were higher with acala (OR, 1.42; 95% CI, 1.10-1.84; *P*=.0075) and ibru (OR, 2.00; 95% CI, 1.51-2.63; *P*<.0001) than zanu after adjusting for age, sex, race, ethnicity, region, and baseline AFib status. Among patients with AFib, heart failure was less frequent with zanu than with acala or ibru (27.2% vs 43.4% and 43.2%, respectively; *P*=.0006), while rates of stroke and bleeding were not significantly different across BTKi cohorts. Compared with zanu, ibru was associated with 39% higher odds of an inpatient or emergency visit within 2 years of BTKi initiation (OR, 1.39; 95% CI, 1.17-1.64; *P*=.0002); no significant difference was observed vs acala.

Conclusions: In this real-world analysis, AFib within 24 months of CLL/SLL diagnosis was associated with increased risk of stroke, bleeding, heart failure, and HCRU, including among patients aged ≥65 years. In patients treated with 1L BTKi, zanu appears to be associated with a lower adjusted risk of AFib than acala and ibru. These findings underscore the substantial clinical and economic burden of AFib in CLL/SLL and reinforce the importance of CV risk considerations in BTKi selection.