Risk of Hypertension in Patients Newly Diagnosed with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) and Treated with Covalent Bruton Tyrosine Kinase Inhibitors (cBTKi): A Real-World Study

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CONCLUSIONS

- This real-world study shows that patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) treated with first-line (1L) covalent Bruton tyrosine kinase inhibitors have a high comorbidity burden, with more than half having pre-existing hypertension
- Patients newly diagnosed with CLL/SLL and treated with 1L zanubrutinib or acalabrutinib have lower rates of both new-onset hypertension and worsening hypertension compared to those treated with 1L ibrutinib
- These findings suggest that risk of developing hypertension is an important consideration in the long-term management of patients with CLL/SLL

BACKGROUND

- Covalent Bruton tyrosine kinase inhibitors (cBTKis), including ibrutinib (1st generation), acalabrutinib (2nd generation), and zanubrutinib (2nd generation), are a mainstay of 1L therapy in CLL/SLL[1]
- However, there are concerns about a potential association between cBTKis and cardiovascular adverse events including hypertension[2]
- Generally, hypertension has been associated with increased major cardiovascular adverse events, including arrhythmia, myocardial infarction, stroke, heart failure, and cardiovascular death[3]

OBJECTIVES

- This real-world study aimed to describe and compare new-onset or worsening hypertension events among CLL/SLL patients treated with 1L zanubrutinib or 1L acalabrutinib compared to those treated with 1L ibrutinib

METHODS

- **Data source**: This retrospective cohort study used the Symphony Integrated Database (IDV®), which contains de-identified and tokenized information that allows linkage of patient-level data from various sources, such as hospital claims, physician offices, and prescription data, with record date as recent as one month prior
- **Design**: Patients who were newly diagnosed with CLL/SLL and started 1L treatment with zanubrutinib, acalabrutinib, or ibrutinib between Jan 2019 – July 2023, were included
- **Index date**: The index date was that of 1L therapy initiation during the study period
- **Main outcome measures**: The primary outcomes for the 3 cBTKi cohorts were new-onset or worsening hypertension within 1-year after the index date
  - New-onset hypertension was defined as the presence of dispensed new prescriptions of antihypertensive medications during follow-up in patients without baseline hypertension
  - Worsening hypertension in patients with preexisting hypertension was defined by either a ≥2-fold augmentation of antihypertensive dose relative to baseline dose or addition of an antihypertensive medication
  - Baseline hypertension was defined as with either a medical encounter related to hypertension or use of antihypertensive medication within 1 year prior to index date
- **Statistical analysis**:
  - Proportions and event rates of new-onset hypertension, worsening hypertension, and new-onset or worsening hypertension were evaluated during a 1-year follow-up period
  - Cox proportional hazards model was used to calculate the hazard ratios (HRs) of new-onset or worsening hypertension between zanubrutinib vs ibrutinib and between acalabrutinib vs ibrutinib
  - Inverse probability of treatment weighting (IPTW) was used to balance baseline confounders (eg, age, sex, cardiovascular risk factors, race/ethnicity, region, and comorbidities) between cohorts, and IPTW-weighted HRs were calculated

RESULTS

Disposition and Baseline Characteristics

- **Baseline characteristics**:
  - A total of 837 patients received 1L zanubrutinib; 5071 received 1L acalabrutinib; and 9409 received 1L ibrutinib
  - The baseline demographics — including age, sex, and race/ethnicity — were similar across the three patient cohorts. For example, the mean age was 70 years for 1L zanubrutinib-treated patients, 70 years for acalabrutinib, and 69 years for ibrutinib (**Table 1**). Baseline comorbidities and cardiovascular risk factors also showed minimal differences between study cohorts
  - At baseline, the prevalence of preexisting hypertension was 51.7% (zanubrutinib), 51.2% (acalabrutinib), and 50.2% (ibrutinib) (**Table 1**)
- **New or worsening hypertension**:
  - During the 1-year follow-up, the proportions of patients with new-onset hypertension were 13.9% (zanubrutinib), 12.4% (acalabrutinib), and 18.0% (ibrutinib) (**Table 2**). Compared to ibrutinib, zanubrutinib and acalabrutinib were associated with a lower risk of developing new-onset hypertension (zanubrutinib, IPTW-weighted HR=0.76, 95%CI: 0.57-1.01; acalabrutinib, IPTW-weighted HR=0.70, 95%CI: 0.61-0.80) (**Figure 1A**)
  - For worsening hypertension, the proportions of patients were 14.1% (zanubrutinib), 10.2% (acalabrutinib), and 18.2% (ibrutinib) (**Table 2**). Compared to ibrutinib, zanubrutinib and acalabrutinib were also associated with a lower risk of developing worsening hypertension as well (zanubrutinib, IPTW-weighted HR=0.72, 95%CI: 0.55-0.94; acalabrutinib, IPTW-weighted HR=0.55, 95%CI: 0.48-0.63) (**Figure 1B**)
  - Similar trends were observed across study cohorts for the overall new-onset or worsening hypertension (**Table 2**; **Figure 1C**)

Table 1. Demographic and Baseline Characteristics at Treatment Initiation

	Zanubrutinib (n=837)	Acalabrutinib (n=5071)	Ibrutinib (n=9409)
Mean age (SD)	70 (8.4)	70 (8.3)	69 (8.1)
Sex, n (%)			
Female	318 (38.0)	1952 (38.5)	3611 (38.4)
Male	519 (62.0)	3119 (61.5)	5798 (61.6)
Race/Ethnicity, n (%)			
White Non-Hispanic	564 (86.6)	3399 (84.8)	6026 (81.9)
Black Non-Hispanic	43 (6.6)	378 (9.4)	833 (11.3)
Asian Non-Hispanic	12 (1.8)	63 (1.6)	81 (1.1)
Hispanic	30 (4.6)	156 (3.9)	399 (5.4)
Charlson Comorbidity Index grouping, n (%)			
0	353 (42.2)	2266 (44.7)	4096 (43.5)
1	134 (16.0)	886 (17.5)	1685 (17.9)
2	148 (17.7)	755 (14.9)	1377 (14.6)
3	74 (8.8)	430 (8.5)	821 (8.7)
4+	128 (15.3)	734 (14.5)	1430 (15.2)
CV risk factors, n (%)			
Hyperlipidemia	277 (33.1)	1704 (33.6)	3062 (32.5)
PVD-related conditions	29 (3.5)	191 (3.8)	334 (3.5)
Sleep apnea	84 (10.0)	576 (11.4)	986 (10.5)
Type 2 diabetes	157 (18.8)	832 (16.4)	1699 (18.1)
Any of the CV risk factors above	380 (45.4)	2333 (46.0)	4242 (45.1)
Baseline hypertension,[a] n (%)	433 (51.7)	2596 (51.2)	4724 (50.2)

[a]Baseline hypertension was defined as with either a medical encounter related to hypertension or use of antihypertensive medication within 1 year prior to index date.
CV, cardiovascular; PVD, peripheral vascular disease; SD, standard deviation.

Table 2. Event Rate of New-Onset or Worsening Hypertension in 1L cBTKi Cohorts

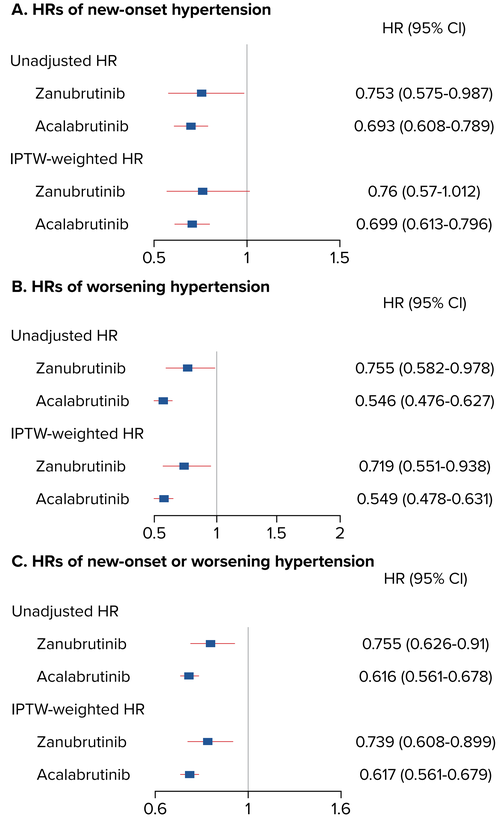
	Zanubrutinib (n=404)	Acalabrutinib (n=2475)	Ibrutinib (n=4685)
1-year new hypertension			
Developing new hypertension, n (%)	56 (13.9)	306 (12.4)	844 (18.0)
Median time to new hypertension, months (min, max)	3.5 (0.1,11.9)	3.4 (0,12)	4.2 (0,12)
Event rate (per 100 pts-mons) (95% CI)	1.44 (1.09-1.87)	1.32 (1.18-1.48)	1.92 (1.79-2.05)

	Zanubrutinib (n=433)	Acalabrutinib (n=2596)	Ibrutinib (n=4724)
1-year worsening hypertension			
Developing worsening hypertension, n (%)	61 (14.1)	265 (10.2)	862 (18.2)
Median time to worsening hypertension, months (min, max)	4.9 (0.1,11.6)	3.3 (0,11.9)	4.4 (0,12)
Event rate (per 100 pts-mons) (95% CI)	1.52 (1.17-1.96)	1.1 (0.97-1.24)	2.02 (1.89-2.16)

	Zanubrutinib (n=837)	Acalabrutinib (n=5071)	Ibrutinib (n=9409)
1-year new/worsening hypertension			
Developing new/worsening hypertension, n (%)	117 (14)	571 (11.3)	1706 (18.1)
Median time to new/worsening hypertension, months (min, max)	4 (0.1,11.9)	3.3 (0,12)	4.3 (0,12)
Event rate (per 100 pts-mons) (95% CI)	1.48 (1.23-1.78)	1.21 (1.11-1.31)	1.97 (1.88-2.07)

1L, first-line; cBTKI, covalent Bruton tyrosine kinase inhibitor; CI, confidence interval; pts-mons, patient-months.

Figure 1. HRs of New-Onset and Worsening Hypertension in 1L cBTKi



1L, first-line; cBTKI, covalent Bruton tyrosine kinase inhibitor; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting.

LIMITATIONS

- This study utilizes the Symphony Integrated Database (IDV®), an open claims database that may have observational gaps and potential under-representation of healthcare encounters. Additionally, new-onset or worsening hypertension was identified based on prescription records rather than actual blood pressure measurements, which may lead to misclassification of hypertension cases
- While this study used a large real-world database, there are limitations that are inherent to the observational nature of the study design and the secondary use of administrative claims databases. These include the likelihood of unmeasured confounding and biases stemming from the definitions of cohorts and endpoints of interest, eg, selection and measurement biases

DISCLOSURES

AKA: Employment and equity holder in BeOne. **LZ:** Employment and equity holder in BeOne. **WA:** Employment and equity holder in BeOne. **QF:** Employment and equity holder in BeOne. **NL:** Consulting or advising roles for AbbVie, AstraZeneca, BeOne, Lilly, Genentech, Janssen, and Pharmacyclics; and research funding from AbbVie, AstraZeneca, BeOne, Lilly, Genentech, Octapharma, Oncternal, MingSight, and TG Therapeutics.

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