# Cardiovascular Safety of Next-Generation BTK Inhibitors Versus Ibrutinib in Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: A Systematic Review and Meta-analysis of Randomized Phase 3 Trials

*Priya Kumar[1], Allah Dad[2], Aiman Aziz[3], Muhammad Arham[4], Ayesha Javed[5], Abdul Haseeb Hasan[2], Haseeb Tareen[6], Radhika Garimella[7], Usman Mazhar[8], Muhammad Shahmir Nawaz[9], Hamza Zaheer[9], Haris Bin Tahir[9]*

**1,832**
PATIENTS ANALYZED
(3 PHASE 3 TRIALS)

**59% Lower**
LOWER RISK OF ANY-GRADE
ATRIAL FIBRILLATION/FLUTTER

**87% Lower**
LOWER RISK OF
CARDIAC-RELATED DISCONTINUATION

**46% Lower**
LOWER RISK OF ANY-GRADE
HYPERTENSION

## OBJECTIVE

- To compare cardiovascular safety outcomes between next-generation BTK inhibitors and ibrutinib in adults with CLL/SLL
- To specifically evaluate rates of atrial fibrillation/flutter, hypertension, and cardiac-related treatment discontinuation across both drug groups
- To help physicians choose the safer BTK inhibitor for patients with heart-related risks

### STUDY SNAPSHOT

**Data Sources:** PubMed, ClinicalTrials.gov, Cochrane CENTRAL

**Trials Included:** ALPINE, ELEVATE-RR, BRUIN CLL-314

**Population:** Adults with CLL/SLL from phase 3 RCTs

**Pooling Method:** Fixed- or random-effects models, selected based on heterogeneity ($I^2$)

**Comparator:** Ibrutinib (first-generation BTK inhibitor)

**Primary Outcomes:** Atrial fibrillation/flutter, hypertension, cardiac-related discontinuation

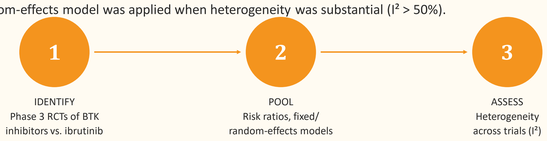
## METHODOLOGY

### ❑ Study Design and Search Strategy

- This was a systematic review of phase 3 randomized controlled trials comparing next-generation BTK inhibitors with ibrutinib.
- Eligible trials were identified through PubMed, ClinicalTrials.gov, and Cochrane CENTRAL.
- Eligible trials enrolled adults with CLL/SLL and reported cardiovascular adverse events.
- Trials were screened against predefined eligibility criteria, specifically phase 3 RCTs directly comparing a next-generation BTK inhibitor with ibrutinib in patients with CLL/SLL.

### ❑ Statistical Analysis

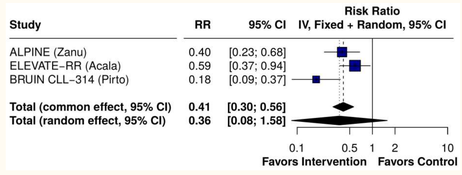
- Outcomes were expressed as risk ratios (RR) with 95% confidence intervals.
- Effect estimates were pooled using fixed- or random-effects models, selected based on between-study heterogeneity.
- Heterogeneity across pooled outcomes was assessed using the $I^2$ statistic.
- Extracted data were standardized and converted into dichotomous outcome format for pooling.
- Meta-analyses were performed using RevMan and R statistical software.
- A random-effects model was applied when heterogeneity was substantial ($I^2 > 50\%$).



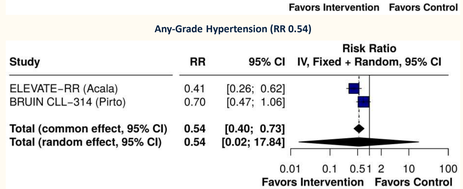

## RESULTS

- Three phase 3 randomized trials, including 1,832 patients, were analyzed.
- Any-grade atrial fibrillation/flutter occurred significantly less often with next-generation BTK inhibitors (RR, 0.41; 95% CI, 0.30-0.56; P<0.001).
- Cardiac-related treatment discontinuation was significantly lower with next-generation BTK inhibitors (RR, 0.13; 95% CI, 0.04-0.43; P<0.001).
- Any-grade hypertension was significantly less frequent with next-generation BTK inhibitors (RR, 0.54; 95% CI, 0.40-0.73; P<0.001).
- Rates of grade ≥3 atrial fibrillation/flutter and grade ≥3 hypertension did not differ significantly between groups.
- Moderate heterogeneity was observed across several cardiovascular outcomes.

**Any-Grade Atrial Fibrillation/Flutter (RR 0.41)**




**Cardiac-Related Discontinuation (RR 0.13)**




**Any-Grade Hypertension (RR 0.54)**




## BACKGROUND

- BTK inhibitors have transformed the treatment of chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).
- Ibrutinib, the first approved BTK inhibitor, is associated with cardiovascular adverse events, including atrial fibrillation and hypertension.
- These cardiovascular effects can lead to dose reduction or early treatment discontinuation, limiting the drug's long-term benefit.
- Next-generation BTK inhibitors, including acalabrutinib, zanubrutinib, and pirtobrutinib, were developed with greater kinase selectivity to reduce this off-target cardiovascular toxicity.
- Direct, head-to-head cardiovascular safety data comparing these newer agents with ibrutinib remained limited before this analysis.

**ALPINE: Zanubrutinib vs. Ibrutinib**

**ELEVATE-RR: Acalabrutinib vs. Ibrutinib**

**BRUIN CLL-314: Pirtobrutinib vs. Ibrutinib**

## CONCLUSION

Among randomized phase 3 trials in CLL/SLL, next-generation BTK inhibitors were associated with improved cardiovascular tolerability compared with ibrutinib, driven primarily by reductions in any-grade atrial fibrillation/flutter, hypertension, and cardiac-related treatment discontinuation. These findings support a cardiovascular risk-informed approach to BTK inhibitor selection in clinical practice.

### KEY TAKEAWAYS

**59% Lower Risk of AFib/Flutter**

**87% Lower Risk of Cardiac Discontinuation**

**46% Lower Risk of Hypertension**

**Risk-Informed BTKi Selection**

*1University of Cincinnati, Cincinnati, OH; 2Sentara Northern Virginia Medical Center, Woodbridge, VA; 3Karachi Institute of Medical Sciences, Karachi, Pakistan; 4Sheikh Zayed Medical College, Rahim Yar Khan, Pakistan; 5King Edward Medical University, Lahore, Pakistan; 6Henry Ford Health, Jackson, MI; 7McLaren Health Care/Oakland/MSU Program, Pontiac, MI; 8Rawalpindi Medical University, Rawalpindi, Pakistan; 9Lahore General Hospital, Lahore, Pakistan*

*BTKi = Bruton tyrosine kinase inhibitor*