Cardiovascular and Treatment Discontinuation Outcomes With Next-Generation BTK Inhibitors in Chronic Lymphocytic Leukemia: A Systematic Review and Meta-Analysis of Randomized Trials

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INTRODUCTION

- Bruton tyrosine kinase inhibitors (BTKi) are a cornerstone of therapy for chronic lymphocytic leukemia (CLL), providing durable disease control in both frontline and relapsed settings.
- Although effective, first-generation BTKi, particularly ibrutinib, are associated with cardiovascular toxicities, including atrial fibrillation and hypertension, which may contribute to treatment interruption or discontinuation.
- Second-generation covalent BTKi (acalabrutinib and zanubrutinib) and the non-covalent BTKi pirtobrutinib were developed to improve selectivity and tolerability while maintaining clinical efficacy.
- We performed a systematic review and meta-analysis of randomized clinical trials to compare cardiovascular safety and treatment discontinuation outcomes associated with next-generation BTKi in patients with CLL.

AIM

To evaluate cardiovascular safety and treatment discontinuation outcomes associated with next-generation Bruton tyrosine kinase inhibitors in patients with chronic lymphocytic leukemia by performing a systematic review and meta-analysis of randomized clinical trials.

METHOD

- Systematic literature search of PubMed/MEDLINE, Embase, Cochrane CENTRAL, and major hematology conference proceedings (ASH, EHA, and SOHO) was performed to identify eligible studies.
- Randomized phase II and III clinical trials evaluating acalabrutinib, zanubrutinib, or pirtobrutinib in patients with CLL/SLL were included. Reviews, editorials, duplicate publications, subgroup analyses, and non-randomized studies were excluded.
- Primary outcomes included atrial fibrillation/flutter, hypertension, grade ≥3 adverse events, and treatment discontinuation due to adverse events.
- Pooled risk ratios (RRs) with 95% confidence intervals (CIs) were calculated using random-effects meta-analysis. Statistical heterogeneity was assessed using the I^2 statistic. Analyses were performed in R using the meta and metafor packages.

CONCLUSIONS

- Next-generation BTK inhibitors were associated with significantly lower rates of atrial fibrillation/flutter and treatment discontinuation compared with comparator regimens in randomized CLL trials.
- A trend toward fewer grade ≥3 adverse events was observed; however, substantial heterogeneity was present across studies.
- No significant overall reduction in hypertension was identified, suggesting that cardiovascular benefits may vary according to comparator regimen and study population.
- These findings support the improved tolerability of next-generation BTK inhibitors and may help guide treatment selection for patients requiring long-term BTK inhibitor therapy.

RESULTS

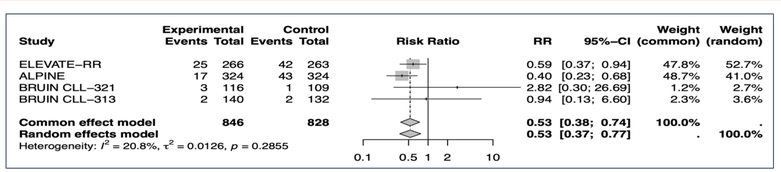


Figure 1. Comparison of atrial fibrillation/flutter between next-generation BTK inhibitors and comparator regimens, demonstrating a significantly lower risk with next-generation BTK inhibitors.

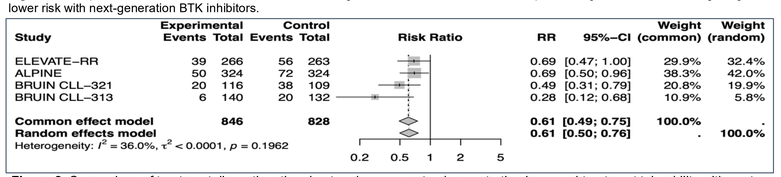


Figure 2. Comparison of treatment discontinuation due to adverse events, demonstrating improved treatment tolerability with next-generation BTK inhibitors.

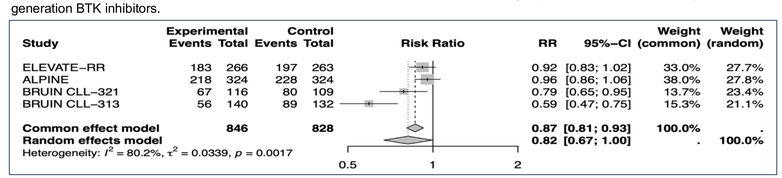


Figure 3. Comparison of grade ≥3 adverse events, demonstrating a trend toward fewer severe adverse events with next-generation BTK inhibitors.

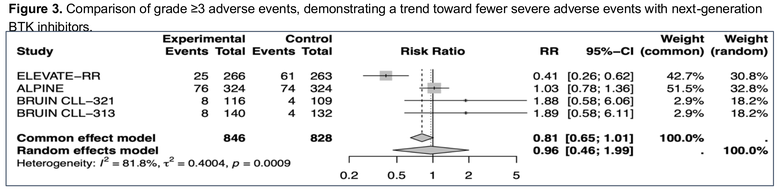


Figure 4. Comparison of hypertension between treatment groups, showing no significant overall difference across randomized trials.

Trial	Setting	Experimental Arm	Comparator	N
ELEVATE-RR	Relapsed/Refractory	Acalabrutinib	Ibrutinib	529
ALPINE	Relapsed/Refractory	Zanubrutinib	Ibrutinib	648
BRUIN CLL-321	Post-cBTKi	Pirtobrutinib	Idelalisib/Rituximab or Bendamustine/Rituximab	238
BRUIN CLL-313	Frontline	Pirtobrutinib	Bendamustine/Rituximab	272

Table 1. Characteristics of Randomized Clinical Trials Included in the Meta-Analysis

KEY FINDINGS

✓ **1,674 patients** from **4 randomized clinical trials** were included.

✓ **Next-generation BTK inhibitors significantly reduced:**

- Atrial fibrillation/flutter (RR **0.53**, 95% CI **0.37–0.77**)
- Treatment discontinuation due to adverse events (RR **0.61**, 95% CI **0.50–0.76**)

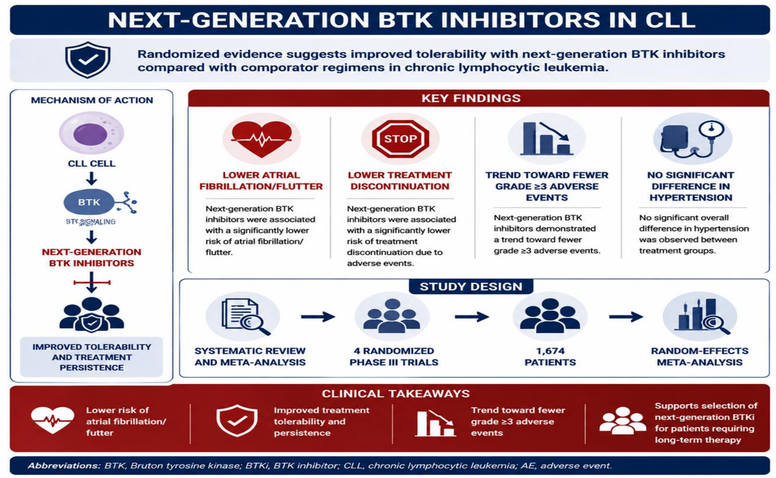
✓ **No significant overall difference was observed for:**

- Hypertension (RR **0.96**, 95% CI **0.46–1.99**)

✓ **Grade ≥3 adverse events demonstrated a trend toward reduction**

- RR **0.82**, 95% CI **0.67–1.00**
- Significant heterogeneity was observed across studies.

✓ **Lower heterogeneity was observed for atrial fibrillation and treatment discontinuation**, supporting the consistency of these findings.



REFERENCES

Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: Results of the ELEVATE-RR trial. *J Clin Oncol.* 2021;39:3441-3452.
Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med.* 2023;388:319-332.
Sharman JP, Munir T, Grosicki S, et al. Phase III trial of pirtobrutinib versus idelalisib/rituximab or bendamustine/rituximab in covalent Bruton tyrosine kinase inhibitor–pretreated chronic lymphocytic leukemia/small lymphocytic lymphoma (BRUIN CLL-321). *J Clin Oncol.* 2025;43:2538-2549.
Woyach JA, Brown JR, Mato AR, et al. Pirtobrutinib versus bendamustine plus rituximab as first-line treatment for chronic lymphocytic leukemia/small lymphocytic lymphoma (BRUIN CLL-313). *[Use the final publication citation exactly as published or the conference abstract if the full manuscript is not yet available.]*
Wierda WG, Brown JR, Abramson JS, et al. NCCN Clinical Practice Guidelines in Oncology: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. *J Natl Compr Canc Netw.* 2022;20:622-634.
Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood.* 2018;131:2745-2760.
Schwarzer G. meta: An R package for meta-analysis. *R package version 8.0-2.*
Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw.* 2010;36(3):1-48.