BTK Inhibitors Are Associated with Significantly Lower Hospitalization and Reduced Cardiovascular Morbidity Compared to Venetoclax-Based Regimens in CLL/SLL: A Propensity Score-Matched Real-World Analysis

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INTRODUCTION

Covalent BTK inhibitors and venetoclax-based regimens are the dominant treatment paradigms for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). They differ fundamentally in structure: BTK inhibitors are continuous oral monotherapy, whereas venetoclax and anti-CD20 antibody regimens are fixed-duration, infusion-dependent, and require ramp-up with tumor lysis syndrome monitoring. These differences plausibly translate into divergent healthcare utilization. BTK inhibitors additionally carry a recognized atrial arrhythmia signal, while comparative data on other cardiovascular endpoints remain sparse. No randomized trial has compared these strategies across hospitalization and cardiovascular morbidity.

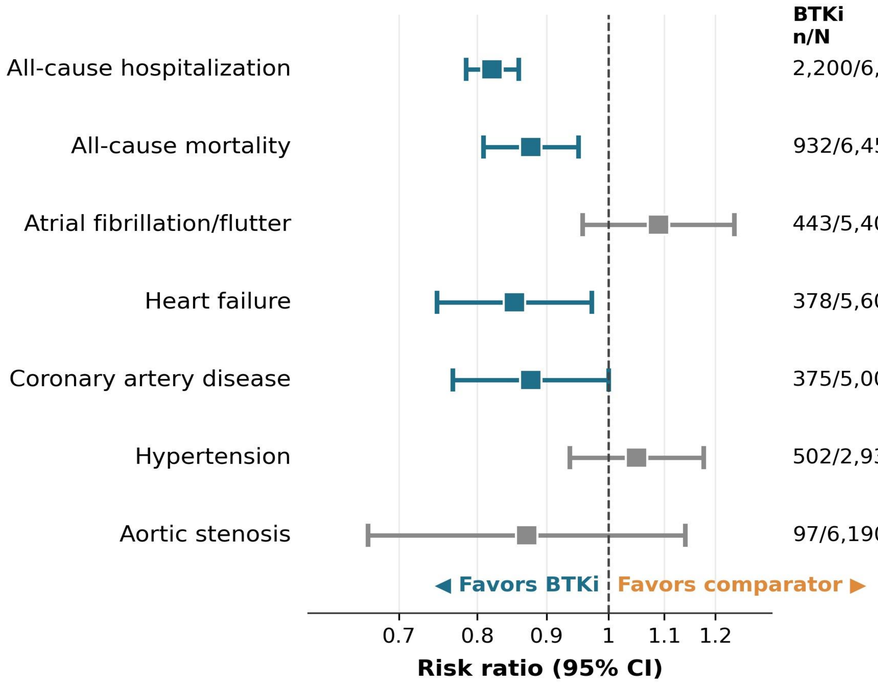
AIM

To compare all-cause hospitalization, mortality, and incident cardiovascular morbidity between BTK inhibitor monotherapy and venetoclax/anti-CD20-containing regimens in CLL/SLL, using a large federated real-world network with propensity score matching.

METHOD

- **Data:** TriNetX Research Network (111 HCOs). Adults with CLL/SLL diagnosed 2016–2023.
- **Cohorts:** BTKi — ibrutinib, acalabrutinib, or zanubrutinib (n=8,661) vs. venetoclax, rituximab, or obinutuzumab (n=9,823); mutually exclusive.
- **Matching:** 1:1 propensity score matching on demographics, cardiovascular comorbidities, medications, and labs → 6,456 pairs.
- **Endpoints:** all-cause hospitalization and mortality; incident AF, heart failure, CAD, hypertension, and aortic stenosis over 730 days.
- **Analysis:** risk ratios with 95% CIs; Kaplan-Meier with log-rank testing.

RESULTS



	BTKi n/N	Ven/CD20 n/N	Risk ratio (95% CI)	p
All-cause hospitalization	2,200/6,456	2,682/6,456	0.820 (0.785–0.858)	<0.001
All-cause mortality	932/6,456	1,064/6,456	0.876 (0.808–0.950)	0.001
Atrial fibrillation/flutter	443/5,409	406/5,399	1.089 (0.957–1.239)	0.195
Heart failure	378/5,609	446/5,638	0.852 (0.747–0.972)	0.017
Coronary artery disease	375/5,008	432/5,051	0.876 (0.767–1.000)	0.049
Hypertension	502/2,933	486/2,979	1.049 (0.936–1.176)	0.409
Aortic stenosis	97/6,190	111/6,166	0.870 (0.664–1.140)	0.314

CONCLUSIONS

- BTK inhibitor monotherapy was associated with substantially lower all-cause hospitalization (34.1% vs. 41.5%; RR 0.82), the largest effect observed.
- Mortality, heart failure, and CAD were also lower; the CAD interval reached 1.000 and is hypothesis-generating.
- Atrial fibrillation was numerically higher with BTKi but not significant, consistent with the known class effect.
- **Limitations:** the comparator includes chemoimmunotherapy, not venetoclax alone; infusion regimens carry inherent encounter burden; residual hemoglobin imbalance and absent molecular risk data limit causal inference.

ACKNOWLEDGEMENTS

This study used data from the TriNetX Research Network. TriNetX had no role in study design, analysis, or interpretation.

No funding was received for this work.

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