CONTINUOUS CUMULATIVE EXPOSURE TO COVALENT BTK INHIBITORS AND THE NON-LINEAR ACCELERATION OF INCIDENT ATRIAL FIBRILLATION IN CHRONIC LYMPHOCYTIC LEUKEMIA: A PRIMARY RESTRICTED CUBIC SPLINE META-ANALYSIS

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INTRODUCTION

Bruton tyrosine kinase inhibitors (BTKi) demonstrate variable atrial fibrillation (AF) risk profiles in chronic lymphocytic leukemia (CLL), yet the temporal dynamics of cumulative exposure remain incompletely characterized. We performed a restricted cubic spline (RCS) meta-analysis to model the non-linear relationship between continuous BTKi exposure duration and incident AF across randomized controlled trials and real-world cohorts.

METHODS

Methods:We systematically searched PubMed, MEDLINE, EMBASE, and the Cochrane Library from inception to April 2026 to identify relevant studies and systematically pooled 10 studies encompassing 7,825+ BTKi-treated CLL patients. DerSimonian-Laird random effects models estimated pooled hazard ratios (HR) . RCS models with knots at 20.0, 31.8, 40.2, and 57.7 months assessed non-linearity. Subgroup analyses stratified first-generation (1G; ibrutinib) versus second generation (2G; acalabrutinib, zanubrutinib) BTKi. Publication bias was evaluated via Egger's test.

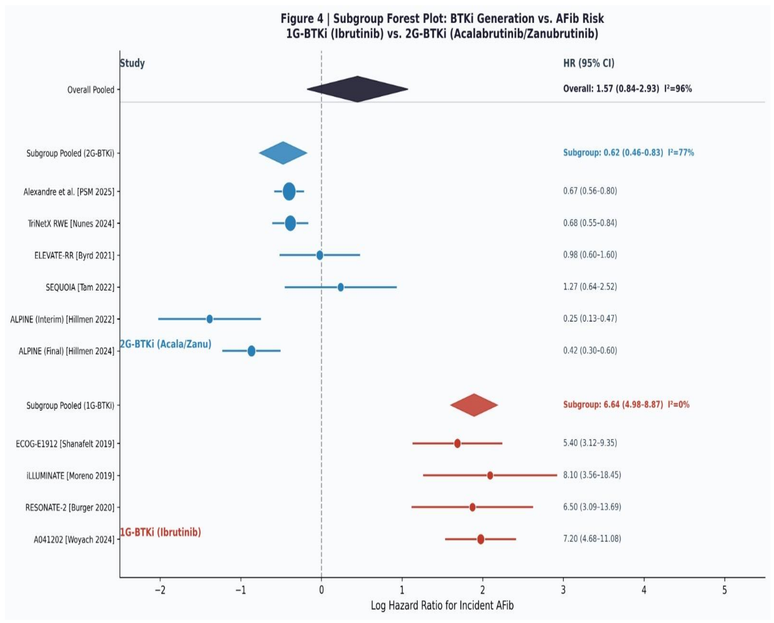
RESULTS

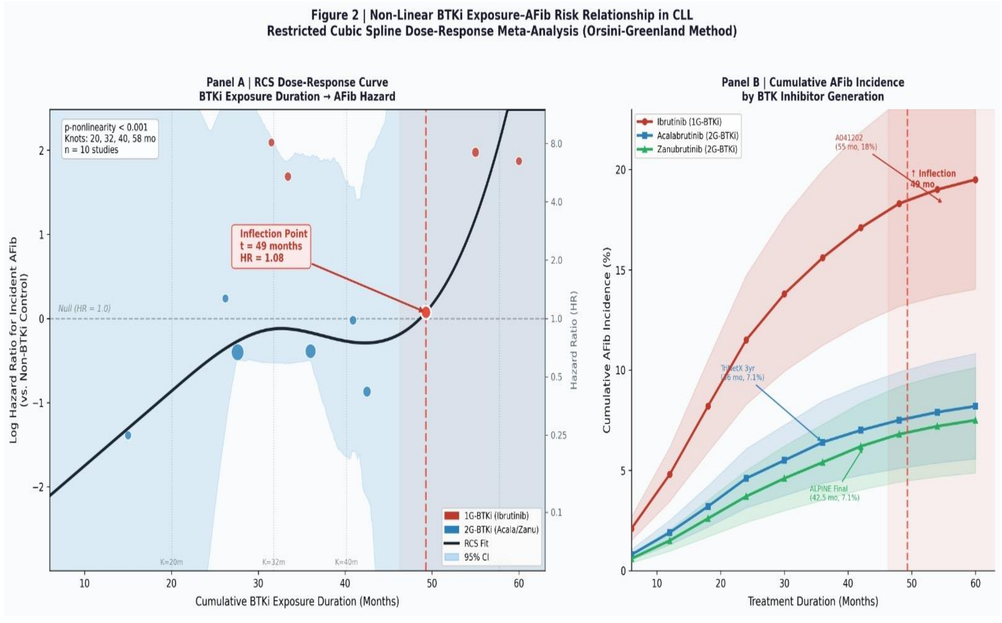
The pooled HR was 1.565 (95% CI 0.836–2.930, p=0.1612) with substantial heterogeneity (I^2=96.2%, τ^2=0.9468, Q=237.01, p<0.0001). RCS modeling revealed significant non-linearity (p<0.001) with an inflection point at 53.4 months (HR=2.17), indicating accelerated AF risk beyond 4.5 years of continuous exposure. Subgroup analysis demonstrated divergent risk profiles: 1G-BTKi HR=6.64 (95% CI 4.98–8.87, I^2=0%), 2G-BTKi HR=0.62 (95% CI 0.47–0.83, I^2=77%). Cumulative 60-month AF incidence was 19.5% for ibrutinib, 8.2% for acalabrutinib, and 7.5% for zanubrutinib. Key trials included ALPINE final (zanubrutinib 7.1% vs. ibrutinib 17.0% at 42.5 months), A041202 (ibrutinib 18% at 55 months), and TriNetX (acalabrutinib HR=0.68 vs. ibrutinib at 36 months). Egger's test showed no significant publication bias (p=0.101).

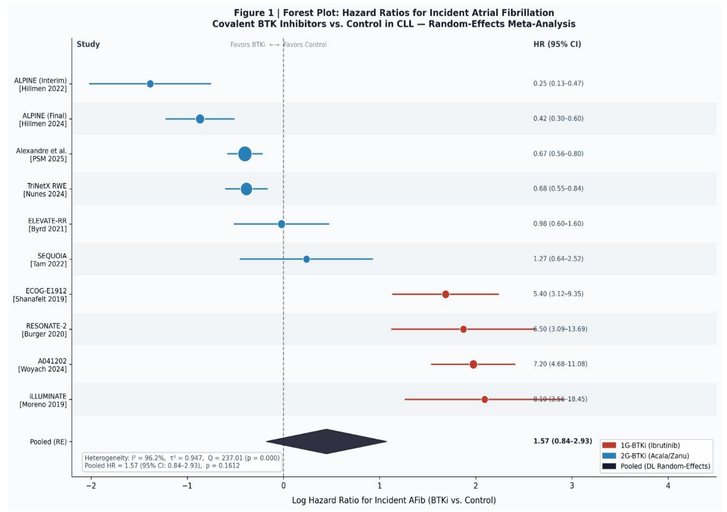
CONCLUSIONS

Continuous BTKi exposure exhibits non-linear AF acceleration with a critical inflection at approximately 4.5 years, predominantly driven by first-generation agents. Second-generation BTKi demonstrate 38% lower AF risk with superior cardio-oncologic safety profiles, supporting preferential use in CLL patients requiring prolonged therapy; however, heterogeneity within this class suggests acalabrutinib and Zanubrutinib warrant independent evaluation.

RESULTS







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