Cardiovascular Adverse Events associated with Second Generation Bruton Tyrosine Kinase Inhibitor Therapy in patients with chronic lymphocytic leukemia: A Systematic Review and Meta-Analysis.

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Introduction

- Acalabrutinib and Zanubrutinib, second-generation (Bruton Tyrosine Kinase Inhibitor) BTK inhibitors that are more selective and potent than the first-generation.
- Cardiovascular Adverse Events (CVAE) in second-generation BTKIs used for chronic lymphocytic leukemia (CLL) in any clinical setting has yet to be studied.
- Hence, the need to better define association is warranted to improve BTKi therapy maintenance with minimal disruption.

Design

- Systematic searches of PubMed, PubMed Central, Cochrane, Scopus, and Embase were conducted from inception until January 14, 2023.
- All randomized clinical trials (RCT) phase II/III in which patients received Acalabrutinib or Zanubrutinib for CLL in any clinical setting were included.
- The outcomes of this meta-analysis were CVAE that had any bleeding, major hemorrhage, acute coronary syndrome, AV block, hypotension, atrial fibrillation, and cardiac arrest. Additionally, cardiovascular events leading to death, all-cause mortality and subgroup analysis when compared with ibrutinib were assessed.
- Heterogeneity was measured by the I^2 test.

Results

Total of 1774 studies that were identified from the initial database search

Total of 5 trials were included in this meta-analysis

- 3 relapsed and refractory (RR)
- 2 treatment naive

Data from 2588 patients was pooled:
- 1484 with RR
- 1104 with naïve disease

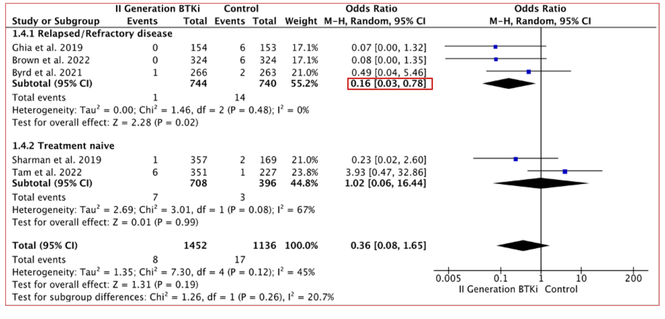


Figure 1. Forest plot using random effect model for the **cardiovascular events leading to death** stratified based on the disease status among studies including CLL population

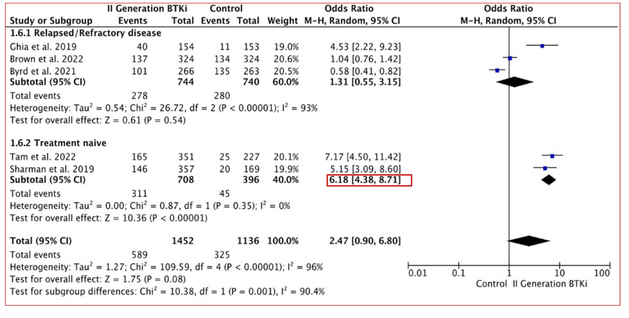


Figure 2. Forest plot using random effect model for **any bleeding events** stratified based on the disease status among studies including CLL population

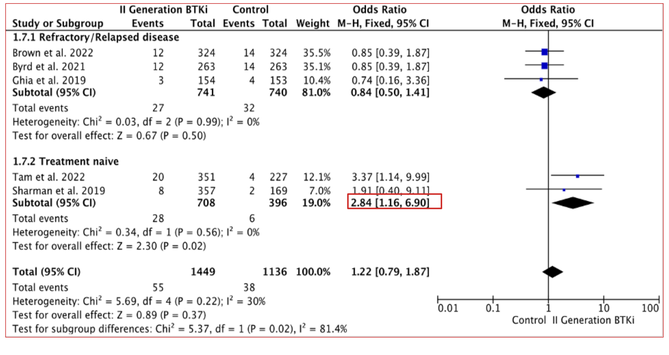


Figure 3. Forest plot using fixed effect model for **major bleeding events** stratified based on the disease status among studies including CLL population

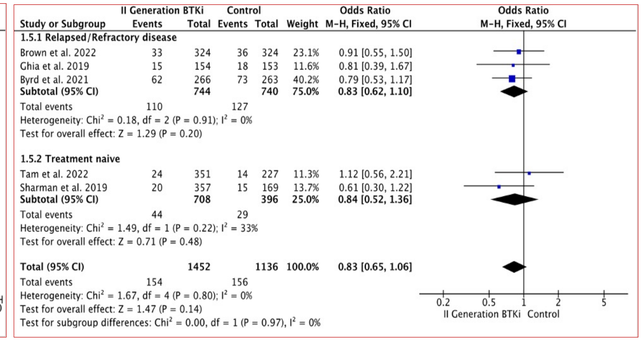


Figure 4. Forest plot using fixed effect model for **all cause mortality** stratified based on the disease status among studies including CLL population

Discussion

No significant differences were observed between two groups for observed **adverse events viz. all- cause mortality, and cardiovascular mortality.**

Further **stratifications based on disease status** pooling of the data from three studies of **RR CLL** showed **significant reduction in cardiovascular mortality.** (**OR 0.16**, 95% CI 0.03 to 0.78; n = 1484; I^2 = 0%).

For **treatment naïve C**LL there is **significant higher risk of any bleeding** (**OR 6.18**, 95% CI 4.38 to 8.71; n= 1104, I^2=0%) **and major bleeding** (**OR 2.84**, 95% CI 1.16 to 6.90; n = 1104; I^2 = 0%).

However, for all-cause mortality, cardiovascular mortality, hypertension, and stroke there was no significant difference across two groups.

Available evidence did not show significant differences among two groups for overall CLL population, however among relapsed cases BTKis showed reduced cardiovascular mortality and for naïve group there were higher bleeding risk. Further large-scale controlled trials are required to support that new-generation BTKis for its safety and tolerability.

References

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