Exploring Side Effect Profile of Bruton Tyrosine Kinase Inhibitors on the Cardiovascular System

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Introduction

- Bruton tyrosine kinase (BTK) inhibitors are a class of drugs that target the BTK enzyme, which plays a crucial role in survival and proliferation signaling pathways of B cells.
- These inhibitors are primarily used to treat lymphoma and leukemias such as Chronic lymphocytic leukemia (CLL), Small lymphocytic lymphoma (SLL), Mantle cell lymphoma (MCL), and Marginal zone lymphoma (MZL).
- While they have transformed the landscape for B-cell malignancies, concerns regarding their cardiovascular (CV) safety persist, undermining the need to understand such CV adverse effects (AE) to guide appropriate clinical decision-making.

Objectives

- To evaluate the incidence and spectrum of CVAEs for BTKis through a meta-analysis of randomized clinical trial data.

Methods

•A systematic review identified 25 monotherapy trials from 2015-2024 that evaluated five BTK inhibitors:

BTK Inhibitor	Total # of Patients	Total # of Trials	# of Phase I Trials	# of Phase II Trials	# of Phase I/II Trials	# of Phase III Trials
Ibrutinib	442	5	0	3	1	1
Pirtobrutinib	323	1	0	0	1	0
Zanubrutinib	938	8	2	3	1	2
Nemtabrutinib	242	2	0	1	1	0
Acalabrutinib	1,001	9	1	2	3	3
Total	**2,956**	**25**	**3**	**9**	**7**	**6**

- A meta-analysis using the R meta package applied a random-effects model to calculate pooled proportions with 95% confidence intervals. Heterogeneity was assessed via the I^2 statistic.
- The primary outcome was pooled incidence of CVAEs, including atrial fibrillation, hypertension, hemorrhage, angina, bleeding, and cardiovascular insufficiency.

Results

- Notable cardiovascular adverse events resulted for Ibrutinib, Acalabrutinib, and Zanubrutinib on an individual drug basis.
- Findings for Nemtabrutinib and Pirtobrutinib were non-significant on an individual drug basis.

Table 1. Notable Cardiovascular Adverse Events of Ibrutinib

Ibrutinib				
Cardiovascular Adverse Event	**Occurance Rate**	**95% Confidence Interval**	**P-Value**	**I^2-Value**
Hypertension	20%	13–29%	0.001	75.60%
Atrial Fibrillation	8.90%	6.0-13.2%	0.4692	0%
Angina	2%	0-6%	0.496	0%
CV insufficiency	2%	0-6%	0.496	0%

Table 2. Notable Cardiovascular Adverse Events of Acalabrutinib

Acalabrutinib				
Cardiovascular Adverse Event	**Occurance Rate**	**95% Confidence Interval**	**P-Value**	**I^2-Value**
Hypertension	11%	7-17%	<0.0001	80.30%
Atrial Bibrillation	5.90%	4.2-8.1%	0.3132	15%
Hemorrhage	14%	0-96%	<0.0001	98%
Bleeding	14%	1-75%	0.0036	88%

Table 3. Notable Cardiovascular Adverse Events of Acalabrutinib

Zanubrutinib				
Cardiovascular Adverse Event	**Occurance Rate**	**95% Confidence Interval**	**P-Value**	**I^2-Value**
Hypertension	10%	6-17%	<0.0001	84.90%
Atrial Fibrillation	3.00%	1-12%	0.0251	80%
Hemorrhage	34%	16-59%	<0.0001	94%

Table 4. Notable Cardiovascular Adverse Events of included BTK inhibitors

Pooled Data				
Cardiovascular Adverse Event	**Occurance Rate**	**95% Confidence Interval**	**P-Value**	**I^2-Value**
Hypertension	14%	11-17%	<0.0001	83.50%
Atrial Fibrillation	6%	5-8%	0.0203	46.8%%
Hemorrhage	28%	15-47%	<0.0001	96%

Discussion

- BTKis are associated with a clinically meaningful incidence of CVAEs - particularly hypertension, atrial fibrillation, and hemorrhage.
- Although rates are lower than those historically seen with ibrutinib, baseline cardiovascular risk assessment and close monitoring remain important with second-generation BTKis.
- Limitations of the study include:
  - Substantial heterogeneity across studies, possibly due to non-standardized reporting of VCAEs.
  - Limited trial data for agents like pirtobrutinib and nemtabrutinib restricts the generalizability of findings for these newer BTK inhibitors.
- Future direction:
  - Analysis of real-world data to view CVAE in more broader and more diverse patient populations

References