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Adverse Events in Clinical Trials of Ibrutinib and Acalabrutinib for B-Cell Lymphoproliferative Disorders: A Systematic Review and Network Meta-Analysis

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Disclosures

• None





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Background

- BTK inhibitors are increasingly used in B-cell lymphoproliferative neoplasms, including CLL, MCL, and Waldenstrom's macroglobulinemia
- Ibrutinib, a first-generation BTK inhibitor, has been associated with increased risk of cardiovascular adverse events
- Acalabrutinib, a second-generation BTK inhibitor is characterized by less off-target effects, and is thought to be associated with a decreased risk of cardiovascular and other AEs
- Head to head comparison of ibrutinib and acalabrutinib has not been conducted





Aims and Methods

- Searched PubMed, Embase, Scopus, and Web of Science from database inception through November 15th 2019
- Inclusion criteria:
 - Prospective trials (single arm or randomized) with ibrutinib, ibrutinib plus anti-CD20 antibody, or acalabrutinib as investigational agents.
- Network meta-analysis of AEs from prospective clinical trials of ibrutinib and acalabrutinib in B-cell lymphoproliferative disorders to compare their safety profile
- Augmented Bayesian network meta-analysis and meta-regression





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Results

- 27 prospective clinical trials, 29 study arms, 3,207 patients were analyzed in 3 groups ibrutinib, ibrutinib plus anti-CD20 antibody, and acalabrutinib
- Most common any grade AEs
 - Ibrutinib: diarrhea (46%, 95% CI 36-55%), myalgias/arthralgias (37%, 95%CI 28-46%), fatigue (33%, 95% CI 24-42%)
 - Acalabrutinib: headache (37%, 95%Cl 26-48%), diarrhea (30%, 95% 20-41%), peripheral edema (21%, 95% 15-28%)
- Most common any grade cardiovascular AEs
 - Ibrutinib: bleeding/bruising (32%, 95% CI 23-41%), HTN (23%, 95% 15-32%), AF (9%, 95% 3-15%)
 - Acalabrutinib: bleeding/bruising (41%, 95% CI 30-52%), HTN (6%, 95% CI 1-11%)



Cardiovascular AEs and Infections

Side Effect	No.of Patients	Odds Ratios	Side Effect Rate	Side Effect Rates (%)	
		1	Acalabrutinib Ibrutinib	p value	
Hypertension					
All Grades	1757	- - -	5.5 23.2	<0.001	
Grade >= 3	2607 -	-	2.6 16.3	<0.001	
Atrial Fibrillation					
All Grades	2215	_ _	2.5 9.1	0.001	
Grade >= 3	3176	-	0.2 5.3	0.001	
Bleeding/Bruising					
All Grades	2345	_	40.6 32.2	0.020	
Grade >= 3	3063	_	1.5 3.7	0.021	
Infections					
All Grades	1550		56.5 35.3	0.035	
Grade >= 3	2840	_ _	12.6 18.8	0.003	
	0.0	0.5 1.0 1.5 2.0	 D		
<-Favors AcalabrutinibFavors Ibrutinib>					

Significant difference favoring acalabrutinib for:

- Any grade HTN (OR 0.26, 95% CI 0.17-0.40) p<0.0001
- Grade 3 HTN (OR 0.15, 95% 0.08-0.27) p<0.0001
- Any grade AF (OR 0.35, 95% 0.18-0.66), p=0.0012
- Grade 3 AF (OR 0.04, 95% 0.01-0.25) p=0.0009



The p-values are for the tests that the network meta-analysis Odds Ratios adjusted for age and follow-up duration are different than the null value of 1.0



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Limitations

- Asymmetry in number of trials (less prospective trials examining acalabrutinib)
- Shorter follow-up in acalabrutinib trials





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Conclusions

- Within the context of the available data, acalabrutinib appears to have an overall improved safety profile compared to ibrutinib.
- This is particularly true for cardiovascular AEs, including AF and HTN





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