CARDIOVASCULAR TOXICITY, BLEEDING, AND SECOND PRIMARY MALIGNANCY RISK WITH COVALENT VS NONCOVALENT BTK INHIBITORS IN CLL: A SYSTEMATIC REVIEW AND META-ANALYSIS

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BACKGROUND

Covalent BTK inhibitors (cBTKi; **ibrutinib, acalabrutinib, zanubrutinib**) are associated with cardiovascular toxicities, including atrial fibrillation, hypertension, and bleeding. **Pirtobrutinib**, a highly selective noncovalent BTKi, may offer a more favorable safety profile. Additionally, patients with CLL on BTKi remain at elevated risk for second primary malignancies (SPM). We conducted a systematic review and meta-analysis comparing cardiovascular toxicity, bleeding, and SPM risk across covalent and noncovalent BTKi in CLL.

OBJECTIVE

- Identify randomized head-to-head BTKi evidence reporting atrial fibrillation/flutter, hypertension, and major bleeding.
- Quantify risk ratios for compatible outcomes and examine heterogeneity.
- Keep nonrandomized pirtobrutinib and SPM evidence separate from causal class comparisons.

METHODS

Eligibility: Phase 3 head-to-head BTKi trials in CLL/SLL with extractable cardiovascular and bleeding outcomes. Pirtobrutinib phase 1/2, regulatory, and SPM studies were included as supportive evidence.

Analysis: Risk ratios were pooled using **random-effects meta-analysis**; heterogeneity was assessed with I^2. SPM outcomes were summarized descriptively because of differences in study design, comparators, and follow-up.

INTERPRETATION

Atrial fibrillation: More-selective BTKi significantly reduced AF/flutter compared with ibrutinib, although the magnitude of benefit varied across trials.

Other toxicities: Hypertension reduction was inconsistent across agents, and major bleeding was not significantly reduced.

Clinical interpretation: BRUIN CLL-314 provides the only direct randomized noncovalent vs covalent comparison and supports a favorable cardiovascular profile for pirtobrutinib. Current SPM data are insufficient to establish a causal safety ranking among BTKi classes.

RESULTS

Randomized comparative evidence

3 phase 3 head-to-head trials; **N=1,847**.

- AF/flutter significantly favored more-selective BTKi (**RR 0.38; 95% CI 0.21–0.68; I^2=72%**).
- Hypertension was not significantly reduced (**RR 0.69; 95% CI 0.39–1.21; I^2=87%**).
- Major bleeding was similar (**RR 0.96; 95% CI 0.56–1.64; I^2=0%**).

SPM context

- FLAIR: fewer other cancers with **ibrutinib–venetoclax vs FCR** (**HR 0.46; 95% CI 0.28–0.76**); MDS/AML **1 vs 11**.
- Retrospective BTKi cohort: **SPM observed/expected ratio 2.2 (1.7–2.9)**, without causal attribution.

Study / comparison	Evidence layer	N	AF/flutter; hypertension	Bleeding / SPM
ELEVATE-RR acalabrutinib vs ibrutinib	cBTKi vs cBTKi	529 safety	9.4% vs 16.0%; 9.4% vs 23.2%	Any bleed 38.0% vs 51.3%; major 4.5% vs 5.3%
ALPINE zanubrutinib vs ibrutinib	cBTKi vs cBTKi	648 safety	7.1% vs 17.0%; 27.2% vs 25.3%	Major hemorrhage 4.0% vs 3.7%
BRUIN CLL-314 pirtobrutinib vs ibrutinib	ncBTKi vs cBTKi	662 ITT	2.4% vs 13.5%; 10.6% vs 15.1%	Comparative major-bleed rate not in primary safety summary
POOLED AF/FLUTTER	**Random effects; 3 RCTs**	**1,832 safety**	**RR 0.38 (0.21–0.68); I^2 72%**	**—**
POOLED HYPERTENSION	**Random effects; 3 RCTs**	**1,832 safety**	**RR 0.69 (0.39–1.21); I^2 87%**	**—**
POOLED MAJOR BLEED	**Random effects; 2 RCTs**	**1,177**	**—**	**RR 0.96 (0.56–1.64); I^2 0%**
FLAIR SPM context	I+V vs FCR; not class-pure	786	—	Other cancers HR 0.46 (0.28–0.76); MDS/AML 1 vs 11

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