

MINI-REVIEW

At the crossroad of cardiology and oncology

Bruton tyrosine kinase inhibitors and cardiovascular adverse events

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Abstract

Bruton tyrosine kinase inhibitors (BTKi) have transformed the management of chronic lymphocytic leukaemia and other B-cell malignancies, yet their therapeutic benefit is tempered by clinically relevant cardiovascular toxicities (predominantly atrial fibrillation, hypertension, bleeding and ventricular arrhythmias). Pharmacological differences in cardiotoxicity arise from binding mode and kinase selectivity profiles. First- and second-generation covalent BTKi (ibrutinib, acalabrutinib, zanubrutinib) irreversibly target Cys481, leading to off-target engagement of other kinases that regulate cardiac electrophysiology and also express homologous cysteine residues. In contrast, non-covalent BTKi, such as pirtobrutinib, achieve selective and persistent BTK occupancy through Cys481-independent interactions, substantially attenuating off-target kinase inhibition and associated cardiotoxicity. Mechanistic insights support proactive baseline cardiovascular risk assessment and structured longitudinal surveillance to enable early detection, risk-adapted management and sustained BTKi therapy. This mini-review describes how such concepts apply to the issue of BTKi-associated cardiovascular adverse events.

KEYWORDS

Bruton's tyrosine kinase, cardiovascular toxicity, chronic lymphocytic leukemia, inhibitors, management

1 | INTRODUCTION

Bruton tyrosine kinase inhibitors (BTKi) have profoundly reshaped the therapeutic management of B-cell malignancies, such as chronic lymphocytic leukaemia (CLL), Waldenström macroglobulinaemia,

mantle cell lymphoma and others. By targeting a key component of **B-cell receptor** (BCR) signalling (Minotti et al., 2025), these agents can provide excellent disease control; however, their use is accompanied by clinically relevant cardiovascular (CV) toxicity that manifests primarily as cardiac arrhythmias or hypertension. Platelet dysfunction

Abbreviations: BTK, Bruton tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukaemia; CVAEs, cardiovascular adverse events; MOA, mechanism of action. Massimiliano Camilli and Cristina Madaudo are co-principal authors.

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may occur as well, exposing patients to varying grades of bleeding (Quartermaine et al., 2023).

The current repertoire of BTKi includes **ibrutinib** (first generation covalent inhibitor), **acalabrutinib** and **zanubrutinib** (second generation covalent inhibitors), and **pirtobrutinib** (non-covalent inhibitor), with all of them being approved for continuous treatment until disease progression or unacceptable toxicity occur. Ibrutinib and acalabrutinib also are approved for fixed duration therapy in combination with the **Bcl-2** inhibitor, **venetoclax** (Eichhorst et al., 2026). Whereas covalent inhibitors (cBTKi) act by binding irreversibly to a cysteine residue of BTK (Cys481), pirtobrutinib does not engage with Cys481 but still achieves persistent occupation and inhibition of BTK. The mechanism of action (MOA) of pirtobrutinib builds on its remarkably longer plasma half-life compared with cBTKi (Mato et al., 2023) and its propensity towards establishing a network of hydrogen, water and π stacking bonds with amino acids lining the active site of BTK (Gomez et al., 2023). Pirtobrutinib may thus work in patients who develop resistance to cBTKi because of C481S mutation, the latter being an intuitive consequence of continuous exposure of Cys481 to a cBTKi (Minotti et al., 2025).

Here we briefly discuss the spectrum and possible mechanisms of CV adverse events (CVAEs) associated with the clinical use of BTKi, with an innovative insight into cardiac inflammation and focus on cardiac arrhythmias in the CLL patient (Graphical Abstract).

2 | THE SPECTRUM OF CARDIOVASCULAR TOXICITY

Much of what we know about CV toxicity of BTKi derives from trials and observational studies of patients treated with continuous BTKi therapy. Hypertension represents the most common CV side effect associated with BTKi, with an apparent incidence of 71% in previously normotensive patients and with worsening blood pressure occurring in 83% of those with pre-existing hypertension (Cohen et al., 2023). The development of ibrutinib-associated hypertension is associated with a greater than twofold increase in risk of other major cardiac events (e.g., atrial and ventricular arrhythmias, heart failure) (Caldeira et al., 2019), requiring early diagnosis and prompt management.

Atrial fibrillation (AF) has been documented in approximately 5–7% of patients treated with ibrutinib in phase III clinical trials (Borioni et al., 2023), although systematic cardiac monitoring suggests that the true incidence may be substantially higher for real-life patients. AF typically develops within the first year of treatment and is more frequent in older patients, those with prior arrhythmias, pre-existing cardiovascular disease, left atrial enlargement or treatment-emergent hypertension (Quartermaine et al., 2023). Compared with ibrutinib, second-generation BTKi appeared to be associated with a lower incidence of AF, and possibly a longer time-to-event (Minotti, 2024).

Ventricular arrhythmias (VA) and sudden cardiac death are less frequent complications of BTKi therapy. Current evidence suggests that VA may represent a class effect, developing with both first- and second-generation BTKi. The overall incidence is low, but

observational studies and pharmacovigilance analyses indicate a higher-than-expected risk, typically occurring after several months of continuous therapy (Borioni et al., 2023).

Bleeding also represents a common side effect of BTKi, although the majority of cases are mild and clinically manageable. Any-grade bleeding has been observed in approximately 30–50% of patients treated with ibrutinib, whereas major haemorrhagic events may occur in only 3–5% (Quartermaine et al., 2023). The risk is increased in older patients, in those with a prior history of bleeding, as well as in subjects receiving concomitant antiplatelet or anticoagulant therapy. Despite a more favourable profile, second-generation BTKi remain associated with a non-negligible risk of bleeding (Quartermaine et al., 2023).

3 | CARDIOVASCULAR ADVERSE EVENTS OF BTKi ARE CLASS EFFECTS

Data from clinical trials show that acalabrutinib and zanubrutinib induce lower rates of CVAEs compared with ibrutinib (Tam & Thompson, 2024), which may well be consistent with efforts to improve the selectivity of second generation BTKi and avoid inhibition of kinases other than BTK (Podoll et al., 2023; Shadman et al., 2023) (Table 1). This acknowledged, the risk of CVAEs is far from abated (Quartermaine et al., 2023). Moreover, and as said earlier, the available evidence shows that ibrutinib, acalabrutinib and zanubrutinib may differ in terms of time-to-event, with second generation cBTKi taking more time than ibrutinib to induce, for example, AF/flutter (Minotti, 2024) (see also Table 1). These facts highlight that CV toxicity is a dynamic process, which makes long-term safety data and therefore surveillance crucial for establishing whether a given BTKi is indeed better tolerated from a CV perspective than others. On a different note, the available evidence shows that pirtobrutinib induces lower rates of CVAEs compared with cBTKi. Taking into account that long-term safety data for pirtobrutinib are rather limited at this point in time, these facts still seem to be consistent with the improved selectivity of pirtobrutinib compared with cBTKi (Gomez et al., 2023).

The aforesaid notions, and considerations around homologies between BTK and other kinases (Minotti et al., 2025), call for attention to cause-and-effect relations between targeting/not targeting Cys481 and the degree of selectivity with which drugs inhibit BTK and other kinases. BTK relays signals from the B-cell receptor (BCR) to downstream effectors of B-cell proliferation, migration and homing in lymph nodes, such as NF- κ B and **PI3K-Akt** pathways (Wiestner, 2013). By binding irreversibly to Cys481, cBTKi can thus achieve the intended therapeutic goal of suppressing key players of B-cell malignancies; however, much of the unintended occurrence of CVAEs probably builds on the very same MOA. Cysteine residues homologous to Cys481 can in fact be found in nine other kinases, including **ERBB2** and **ERBB4** receptors that have long been considered as key factors of cardiac contractility (Cools et al., 2025) and rhythmogenesis (Meng et al., 2021). The avidity of cBTKi for cysteine residues, and the dissemination of such residues to both homologous and different positions of other members of the **TEC kinase** family to

TABLE 1 Comparative pharmacological and cardiovascular profile Bruton tyrosine kinase inhibitors.

Drug	Binding mode and selectivity	Half-life ($t_{1/2}$) and dosing schedule ^a	Main cardiovascular adverse events and prevalence	Time-to-event pattern	Long-term CV safety evidence
Ibrutinib	First-generation covalent BTKi; low-kinase selectivity and high off-target inhibition	$t_{1/2} \sim 4\text{--}6$ h; 420 mg once daily	AF in 5–7% of patients (higher incidence with systematic surveillance); HTN in 71% of previously normotensive patients and worsening in 83% of those with pre-existing hypertension; VA uncommon but documented; bleeding 30–50% (any grade)	AF typically occurs within the first year (median 5–8 months); HTN may accumulate over time	Extensive long-term and real-world evidence
Acalabrutinib	Second-generation covalent BTKi; improved selectivity, lower off target inhibition	$t_{1/2} \sim 0.6\text{--}2.8$ h; 100 mg twice daily	AF in 3–9% of patients; HTN in 3–9% of patients; lower VA signal than ibrutinib but may increase with follow-up; bleeding risk persists	Delayed AF onset compared with ibrutinib	Supported by phase III studies and growing real-world data
Zanubrutinib	Second-generation covalent BTKi; improved selectivity, lower off-target inhibition	$t_{1/2} \sim 2\text{--}4$ h; 160 mg twice daily or 320 mg once daily	AF in 2–2.5% of patients; HTN in $\sim 11\text{--}13\%$ of patients; VA uncommon; bleeding is frequent but mostly low grade	Lower AF incidence than ibrutinib; time to event likely delayed compared to ibrutinib and acalabrutinib	Supported by phase III studies and growing real-world data
Pirtobrutinib	Next-generation, highly selective non-covalent BTKi; C481-independent binding	$t_{1/2} \sim 19$ h; 200 mg once daily	AF < 5% in available studies; HTN, HF and VA not yet fully characterised; bleeding risk appears lower but remains under investigation	Insufficient data to define reliable time to event patterns	Only phase III studies; long-term cardiovascular safety data to mature

^aFor key pharmacokinetic properties refer to 1. Tam, C.S., Ou, Y.C., Trotman, J., and Opat, S. (2021). Clinical pharmacology and PK/PD translation of the second-generation Bruton tyrosine kinase inhibitor, zanubrutinib. *Expert Rev Clin Pharmacol* 14: 1329–1344; 2. Mato, A.R., Woyach, J.A., Brown, J.R., Ghia, P., Patel, K., Eyre, T.A., et al. (2023). Pirtobrutinib after a covalent BTK inhibitor in chronic lymphocytic leukaemia. *N Engl J Med* 389: 33–44.

which BTK belongs (Ortutay et al., 2008), also anticipate interactions of these drugs with other regulators of cardiac electrophysiology, for example, **c-Src kinase** (Xiao et al., 2020). This scenario accommodates the concept that CVAEs are class effects of cBTKi and may explain how non-covalent binding makes pirtobrutinib seemingly safer than either ibrutinib, acalabrutinib or zanubrutinib (Gomez et al., 2023). Accordingly, studies of patients who discontinued cBTKi because of cardiac symptoms show that they did not experience recurrence of the same cardiac adverse event when switched to pirtobrutinib (Shah et al., 2025). More knowledge in this setting may be offered by **rocbrutinib**, a fourth-generation BTKi inhibitor that, depending on the mutational status of Cys481, can switch from covalent to non-covalent binding modes (Sharma et al., 2026). With that said, the definition of ‘selectivity’ remains uncertain at this point in time. Pirtobrutinib selectivity changes if one uses biochemical or cellular assays (Gomez et al., 2023), which denotes the importance of how much drug eventually reaches BTK. Selectivity of second generation cBTKi versus ibrutinib, and of acalabrutinib versus zanubrutinib, also depends on which particular assay is used (Minotti, 2024). Finally, much work is needed to understand how cBTKi, pirtobrutinib or next-generation mixed inhibitors, such as rocbrutinib, compare with respect to resynthesis of BTK or innocent kinases and how this reflects site-specific BTKi concentrations during the course of clinical treatment.

Molecular mechanisms of cardiotoxicity are in all likelihood pleiotropic, and looking at selectivity does not fully establish the biologic

complexity of BTKi-associated AF/flutter and other CVAEs. Lack of knowledge also limits our understanding of BTKi-associated ventricular tachyarrhythmias and sudden cardiac death. Once believed to associate only with ibrutinib use, ventricular tachyarrhythmias were subsequently associated with acalabrutinib and zanubrutinib, although with seemingly lower incidence rates (Brown et al., 2023; Quartermaine et al., 2023). In the case of ibrutinib-related polymorphic ventricular tachycardia, the QTc interval was normal and no short–long–short pattern at arrhythmia initiation was observed (Beyer et al., 2017; Tomcsányi et al., 2016). These findings might be taken to involve perturbances of the phosphorylation of **ryanodine receptor 2** and consequent changes in cardiac sarcoplasmic reticulum Ca^{2+} handling (Salem et al., 2019), but how precisely this occurs remains unknown, and which particular kinase or kinases are inhibited by cBTKi calls for firm affirmation. On a cautionary note, we acknowledge that the vast majority of data was obtained for ibrutinib, with generalisations to other BTKi, thus introducing biases typical of assumptions.

4 | INTERPLAY OF BTKi WITH PATIENT AND DISEASE CHARACTERISTICS

Patients eligible for BTKi usually present for treatment with characteristics such as age of ≥ 65 years and one or more pre-existing comorbidities that predispose them to the same CVAEs as those attributed to BTKi. For example, in age-matched subjects of the general

Practical Cardiovascular Management Algorithm for Patients Receiving Bruton Tyrosine Kinase Inhibitors (BTKi)

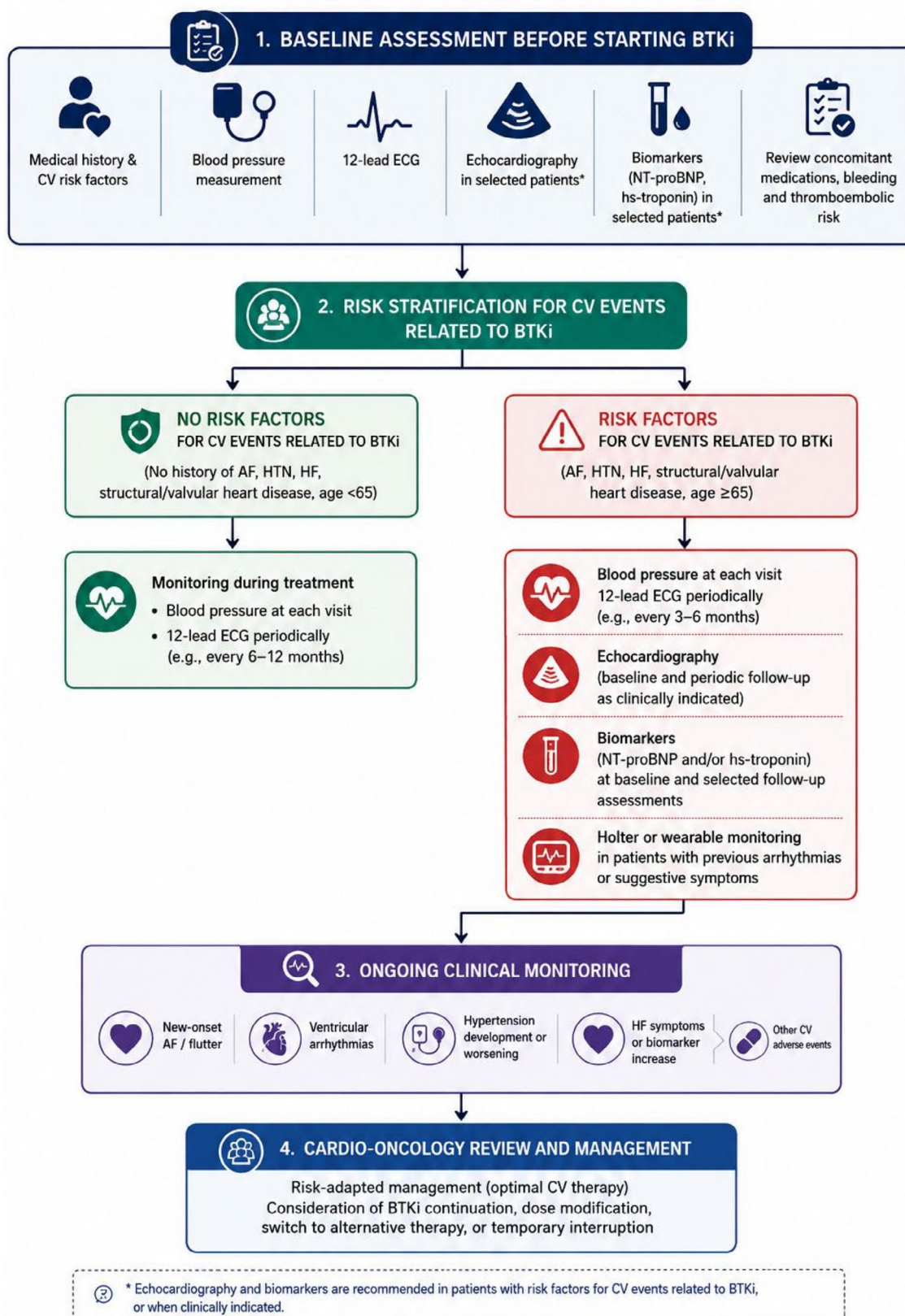


FIGURE 1 Legend on next page.

FIGURE 1 Practical cardiovascular surveillance and management algorithm for patients receiving Bruton tyrosine kinase inhibitors. Proposed practical algorithm for cardiovascular risk assessment, surveillance and management in patients receiving Bruton tyrosine kinase inhibitors (BTKi). Before treatment initiation, all patients should undergo a structured cardiovascular evaluation, including medical history, assessment of cardiovascular risk factors, blood pressure measurement, 12-lead electrocardiography, review of concomitant medications, and evaluation of thromboembolic and bleeding risk. Echocardiography and cardiac biomarkers may be considered in selected patients with pre-existing cardiovascular disease or other high-risk features. Patients are subsequently stratified according to the presence or absence of risk factors for BTKi-associated cardiovascular adverse events (in particular AF), including prior arrhythmias, hypertension, heart failure, structural or valvular heart disease, and age ≥ 65 years. During therapy, all patients should undergo regular blood pressure monitoring and periodic ECG surveillance, whereas higher-risk individuals may benefit from more intensive follow-up, including rhythm monitoring through Holter recordings or other wearable devices. Ongoing surveillance should focus on the early identification of new-onset AF/flutter, ventricular arrhythmias, hypertension or heart failure manifestations. Detection of a CVAE should prompt multidisciplinary cardio-oncology evaluation and implementation of individualised management strategies. AF, atrial fibrillation; HTN, hypertension; HF, heart failure.

population, the overall incidence rate of AF was 3.3 per 1000 person-years, with higher incidence in men compared to women (Vermond et al., 2015). Likewise, sudden cardiac death and out-of-hospital cardiac arrest increase disproportionately for subjects aged >65 years (Empana et al., 2022). These facts make it difficult to understand whether BTKi act as causative agents of CVAEs or as triggers of pathophysiologically expected clinical events (Esposito et al., 2025).

On a different note, cardiac magnetic resonance imaging shows that patients treated with ibrutinib and evaluated for suspected cardiotoxicity frequently display diffuse myocardial inflammation and interstitial fibrosis, which independently predict the risk of subsequent major adverse cardiac events (Buck et al., 2023). These findings strongly suggest that cBTKi-related cardiotoxicity extends beyond functional electrophysiological disturbances and may reflect tissue injury orchestrated by inflammation. Mounting experimental and translational data implicate the NLRP3 inflammasome as a central cytokine-activating platform in atrial cardiomyocytes and fibroblasts. Activation of NLRP3 promotes the maturation and secretion of interleukin-1 beta (IL-1 β) and IL-18, known to drive atrial electrical instability, extracellular-matrix deposition and pro-fibrotic remodelling (Poppenborg et al., 2025; Toldo & Abbate, 2024). Although direct demonstration that ibrutinib activates the atrial NLRP3 inflammasome in humans is not yet available, the myocardial phenotype observed by clinical imaging is highly consistent with the pattern of the NLRP3-mediated inflammatory response, cytokine release and subsequent structural remodelling (Toldo & Abbate, 2024).

Whilst waiting for a direct demonstration of these mechanisms, it is worth noting that inflammation is inherently associated with the oncological disease for which BTKi are recommended. For example, in the settings of CLL, there is both an expansion of memory T cells and a significant skewing between different T helper cells, which eventually cause an imbalance between pro- and anti-inflammatory interleukins (Puzzolo et al., 2021). Moreover, T effector cells are dysfunctional, because they fail to release perforin and granzyme (which are needed to kill CLL cells) but keep releasing interleukins (which still can cause AF/flutter) (Kabanova et al., 2016). Although ibrutinib was shown to induce rapid down-regulation of inflammatory markers in CLL patients (Palma et al., 2018), one cannot escape that BTKi therapy begins when the patient is exposed to risks related to both advanced age and disease-induced systemic inflammation.

5 | PREVENTION AND MANAGEMENT OF CARDIOVASCULAR SIDE EFFECTS

The mechanistic insights discussed earlier provide a framework for translating biological facts into practical strategies for prevention, early detection and management of CV toxicity associated with BTKi therapy.

The practical surveillance strategy proposed in Figure 1 integrates available recommendations with emerging evidence on BTKi-associated toxicity (Lyon et al., 2022; Quartermaine et al., 2023), although the optimal timing of echocardiographic surveillance, biomarker assessment and rhythm monitoring remains uncertain and based only on consensus of experts.

5.1 | Baseline cardiovascular risk assessment

Before initiating BTKi therapy, a structured CV evaluation is recommended to identify patients at increased susceptibility to treatment-emergent toxicity (Lyon et al., 2022). Advanced age (≥ 65 years), pre-existing atrial arrhythmias, hypertension, a QTc interval ≥ 480 ms, structural heart disease and a prior bleeding represent key clinical risk modifiers. Baseline electrocardiography and blood pressure assessment should be routinely performed. Echocardiography may help identifying myocardial function impairment, severe valvular heart disease and atrial dilatation, and should be advised for patients with the aforementioned risk factors. Biomarkers such as high-sensitivity cardiac troponin and natriuretic peptides are not routinely recommended at baseline; in contrast, assessment of metabolic risk factors, including dyslipidaemia and diabetes mellitus, are highly recommended and formally included in the guidelines (Lyon et al., 2022).

Risk stratification tools, such as CHA₂DS₂-VASc and HAS-BLED, may assist in evaluating thromboembolic and haemorrhagic risk in patients with AF (Lyon et al., 2022; Van Gelder et al., 2024). A graded CV risk assessment is increasingly reflected in contemporary treatment algorithms, which tend to favour second-generation BTKi over ibrutinib in patients with elevated baseline CV risk. From a mechanistic perspective, pre-existing atrial remodelling or subclinical myocardial disease should be considered to herald a lower threshold to arrhythmogenesis. An ECG-Holter monitor also may be considered at

baseline for identification of asymptomatic supraventricular and ventricular arrhythmias, in order to establish pre-treatment burden and start appropriate management.

In the settings of first-line CLL treatment, there may be cases when the CV risk of a patient is too high to consider therapy with BTKi. In such defined conditions, regimens such as venetoclax in combination with the anti-CD20 antibody, **obinutuzumab**, can be considered (Eichhorst et al., 2026).

5.2 | Cardiovascular monitoring during therapy

Cardiovascular surveillance is the cornerstone of clinical management of patients treated with BTKi. Serial rhythm assessment with opportunistic ECG, ECG-Holter or wearable devices may be useful in selected patients with prior arrhythmias or suggestive symptoms to facilitate early detection of AF and other rhythm disturbances. Blood pressure monitoring throughout treatment also is advised (Lyon et al., 2022), in particular over the first 3 months of treatment. Reliance on symptom-driven detection alone would in fact underestimate the burden of blood pressure increase or atrial arrhythmias, particularly in older patients or those with limited symptom awareness. Periodic re-assessment and optimisation of CV risk factors, including diabetes mellitus and dyslipidaemia, are essential as well. Efforts to devise long-term surveillance are recommended for patients treated with acalabrutinib or zanubrutinib, who may develop AF at longer follow-up.

During monitoring, cardiac biomarkers, such as troponin or natriuretic peptides, may provide additional information. Elevations of such biomarkers have been observed during BTKi therapy and may reflect early myocardial stress or subclinical injury, supporting a potential role for biomarker-guided surveillance in selected high-risk patients (Ganatra et al., 2025), although their routine use in this setting remains limited at this point in time.

Enhanced surveillance is recommended in the setting of drug-drug interactions that may result in increased plasma exposure to BTKi, reflecting reduced BTKi elimination or metabolic clearance by concomitant drugs that engage with **P-glycoprotein** (PgP) or inhibit **CYP3A4**, respectively (Van Gelder et al., 2024). Drugs, such as **amiodarone** or **diltiazem**, should be used with great caution, whereas potent CYP3A4 inhibitors, such as triazole antifungals, should be contraindicated. Here, there is a potential note of distinction for pirtobrutinib vis-à-vis cBTKi. The available data do in fact suggest that triazole antifungals and other potential perpetrators of drug-drug interactions do not increase plasma exposure to pirtobrutinib as extensively as they do for cBTKi, although the precise mechanism for such a difference remains to be established (Tian et al., 2025).

5.3 | Management of cardiovascular side effects

AF/flutter remains the most clinically impactful CV complication associated with BTKi therapy (Boriani et al., 2023). Management strategies

should prioritise rate control through use of beta-adrenoceptor blockers, with careful selection of agents to minimise pharmacokinetic interactions. In those patients who achieve heart rate control, BTKi treatment can often be continued under close cardio-oncology surveillance. For recurrent or clinically significant events under ibrutinib (e.g., AF with haemodynamic instability), temporary treatment interruption, dose reduction or switching to a more selective second-generation BTKi or to a non-covalent agent, such as pirtobrutinib, may reduce the likelihood of recurrent CV toxicity whilst preserving disease control.

Anticoagulation requires individualised balancing of thromboembolic complications of AF and concomitant risk of bleeding from platelet dysfunction (Steffel et al., 2021; Van Gelder et al., 2024). Direct oral anticoagulants (DOACs) have long been preferred over vitamin K antagonists, but there is some controversy as to which particular DOAC would be more appropriate for the patient treated with BTKi. **Apixaban** and **edoxaban** have emerged as the two most popular options in this setting. Apixaban, in particular, has accumulated the largest real-world experience in patients with haematologic malignancies and concomitant AF, showing acceptable safety even in the context of BTKi-related platelet dysfunction, provided that careful dose selection and clinical surveillance are applied (Agrawal et al., 2026). Apixaban is both a PgP and CYP3A4 substrate, with these facts calling for further monitoring of drug-drug interactions. Edoxaban also is a PgP substrate but, when compared to apixaban, it shows the unquestionable advantage of not competing for CYP3A4. Edoxaban may thus represent a more valid option to avoid dose adjustments, especially in patients receiving multiple interacting therapies (Boriani et al., 2018).

As far as hypertension is concerned, **angiotensin-converting enzyme** (ACE) inhibitors, **angiotensin receptor** blockers (ARBs) and **dihydropyridine calcium-channel** ($\text{Ca}_v1.2$) blockers should be considered first-line antihypertensive agents, with due attention paid to drug-drug interactions (Cohen et al., 2023; Lyon et al., 2022).

As for bleeding, most events are minor and do not require treatment discontinuation. Major haemorrhage warrants temporary interruption of BTKi therapy and supportive management, including platelet transfusion, when appropriate. In patients at very high bleeding risk or requiring long-term anticoagulant or antiplatelet therapy, alternative therapies might be considered. BTKi should generally be withheld before major invasive procedures (Boriani et al., 2018).

6 | CONCLUSION AND FUTURE PERSPECTIVES

BTKi can easily be said to be revolutionary drugs in terms of efficacy, although their clinical use is equally challenging on safety grounds. We briefly reviewed how BTKi-related CV events, and arrhythmias in particular, originate not only from off-target effects but also from complex interactions between BTKi and biologically vulnerable CV substrates. There is therefore no surprise that new-generation BTKi, although undoubtedly more selective than ibrutinib, may attenuate but not completely abrogate CV side effects. Despite significant

advances in our mechanistic understanding, important evidence gaps remain. Long-term CV safety data for newer agents, particularly non-covalent BTKi and other next-generation compounds, are still limited. Moreover, the true incidence of CV toxicity may be underestimated owing to under-detection of asymptomatic arrhythmias, which are not systematically captured in most clinical trials. Direct head-to-head comparisons specifically focussed on CV safety also are lacking in several clinical settings, making it difficult to accurately quantify the relative contribution of drug-specific effects versus patient-related factors. Importantly, advanced age, pre-existing CV comorbidities, as well as the inflammatory and immune dysregulation associated with CLL itself may act as major confounders when interpreting CV safety signals across studies. A mechanistically informed perspective supports proactive CV risk assessment, structured monitoring and individualised therapeutic strategies, particularly in patients with pre-existing arrhythmogenic vulnerability.

Integrating cardio-oncology principles into routine practice will be essential to optimise the balance between oncologic efficacy and CV safety. Offering the best available therapy remains a must and represents the North Star of contemporary cardio-oncology. All efforts should be made to continuing BTKi therapy as long as possible, before discontinuing it and switching to less effective therapies. In this regard, lessons from ibrutinib show that managing CVAEs by dose reduction is a valuable option to mitigate toxicity without compromising oncologic efficacy, offering superior clinical outcome and longer time to next treatment compared to ibrutinib discontinuation (Shadman et al., 2025). On a different note, there is now an opportunity to replace continuous BTKi therapy with BTKi-venetoclax fixed-duration regimens. Whilst providing intuitive advantages, such as limited exposure to BTKi toxicity and mitigation of risk of Cys481 mutation, fixed duration regimens offer deeper disease control that is evidenced by significant rates of undetectable measurable residual disease (Tedeschi et al., 2025). Given that disease eradication heralds normalisation of immune dysregulation and systemic inflammation, fixed duration regimens hold promise for removing an important component of BTKi-associated CVAEs. Forthcoming studies in that direction will tell us more about these new scenarios.

6.1 | Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <https://www.guidetopharmacology.org> and are permanently archived in the Concise Guide to PHARMACOLOGY 2025/26 (Alexander et al., 2025).

AUTHOR CONTRIBUTIONS

Massimiliano Camilli: Conceptualization; writing—original draft. **Cristina Madaudo:** Writing—original draft; conceptualization. **Emanuela Salvatorelli:** Writing—original draft; conceptualization. **Giorgio Minotti:** Conceptualization; writing—original draft; writing—review and editing. **Pierantonio Menna:** Conceptualization; writing—original draft.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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