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REVIEW ARTICLE

Cardiovascular Safety of Bruton Tyrosine Kinase Inhibitors: From Ibrutinib to Next-Generation Agents

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Abstract

Bruton tyrosine kinase (BTK) plays a pivotal role in B-cell receptor signaling, making it a key therapeutic target in hematologic malignancies. Bruton tyrosine kinase inhibitors (BTKIs) have revolutionized the treatment landscape, improving survival outcomes in conditions such as chronic lymphocytic leukemia and mantle cell lymphoma. However, despite their clinical efficacy, BTKIs—particularly first-generation agents such as ibrutinib—are associated with significant cardiovascular toxicity, including atrial fibrillation, hypertension, bleeding, and, in rare cases, ventricular arrhythmias and heart failure. This narrative review explores the evolving landscape of BTKI-related cardiovascular toxicity, from first-generation drugs to next-generation agents that have improved safety profiles. We summarize current evidence on the incidence, mechanisms, and risk factors of BTKI-induced cardiovascular events and highlight potential predictive tools and mitigation strategies. Given the increasing use of these agents, a comprehensive understanding of their cardiovascular impact is essential for optimizing treatment selection and patient outcomes. Future research should focus on refining risk stratification models and developing cardioprotective strategies to ensure the long-term safety of BTKI therapy.

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Key Points

Bruton tyrosine kinase inhibitors (BTKIs) have revolutionized the treatment of hematologic malignancies but are associated with significant cardiovascular toxicities, including atrial fibrillation, hypertension, and bleeding.

The risk of cardiovascular complications varies between BTKIs, with first-generation agents such as ibrutinib having greater toxicity than second- and third-generation inhibitors.

Close cardiovascular monitoring and individualized treatment strategies can help mitigate risks and improve the long-term safety of BTKI therapy.

1 Introduction

Bruton tyrosine kinase (BTK) is a cytoplasmic non-receptor tyrosine kinase that belongs to the TEC family of non-receptor tyrosine kinases [1, 2]. It is also a membrane-binding protein expressed in all hematopoietic cells, except for T cells and natural killer cells [1, 2]. BTK is primarily expressed in B cells and plays a crucial role in the first steps of antigen receptor signaling by transmitting and amplifying signals [3]. BTK is activated by antigen receptors, mostly by B-cell receptors, growth factors, cytokine receptors, and other signaling factors. Active BTK initiates a cascade of downstream molecular signals resulting in B-cell proliferation and differentiation. Moreover, BTK is overexpressed in B-cell tumors, supporting the survival and proliferation of these cells [4, 5]. BTK underexpression leads to altered B-cell development, defects in functional responses, and less effective immunologic (especially infective) responses [6]. On the other hand, BTK overexpression is involved in autoimmune diseases such as systemic lupus erythematosus and antinuclear autoantibody production [6, 7]. Having a pivotal role in the activation, maturation, and migration of B cells as well as B-cell neoplasms such as chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), Waldenström's macroglobulinemia (WM), marginal zone lymphoma, and autoimmune disorders, BTK has become the target of many drugs; BTK inhibitors (BTKIs) are some of the most important. There are three generations of BTKIs—first and second generations irreversibly inhibit BTK by interfering with the B-cell antigen receptor pathway, whereas the third generation inhibits BTK reversibly, leading to B-cell death [8]. Importantly, due to both on-target and off-target kinase inhibition, BTKIs are associated with a broad range of adverse events, including the risk of bleeding, diarrhea, infections, arthralgia, cardiovascular toxicity (atrial and ventricular arrythmias [VAs], hypertension) [9]. These side effects have been frequently observed in patients receiving first-generation BTKIs (i.e., ibrutinib-based therapy), whereas second- and third-generation BTKIs have shown a reduced risk of major cardiovascular side effects [10]. Moreover, some data suggest that the similar incidence rates of hypertension and bleeding in patients treated with both first- and second-class BTKIs might be a class effect of these drugs [5]. Due to the risk of cardiovascular consequences of such therapies, all patients undergoing BTKI therapy should have a cardiovascular examination, including comprehensive anamnesis, electrocardiography (ECG), and blood pressure (BP) measurement to identify the main risk factors, especially for the development of atrial fibrillation (AF). Patients aged <70 years without major cardiovascular risk factors can be treated with either ibrutinib or second-generation BTKIs, whereas patients with known risk factors should be treated with second-generation BTKIs. Patients with ongoing AF can also undergo BTKI therapy with second-generation drugs. Chronic heart failure with reduced ejection fraction (left ventricular ejection fraction <40%) is considered a relative contraindication to BTKI therapy by expert consensus, because of the uncertain but potentially increased risk of VAs and sudden cardiac death [11]. However, patients with well-controlled chronic heart failure can still be treated with BTKIs under continuous medical supervision. Notably, BTKI therapy-associated hypertension is often observed, especially with first-generation drugs—although incidence data may slightly vary—with its frequency increasing over time [12–14].

2 First-Generation BTKIs

The first generation of BTKIs, ibrutinib, entered clinical trials in the early 2010s, initially focusing on patients with relapsed or refractory B-cell malignancies [15]. Key phase I and II trials showed remarkable efficacy and that it was well tolerated despite some adverse events [16, 17]. The clinical success revolutionized the treatment of B-cell malignancies and paved the way for the development of new BTKIs with higher selectivity and reduced toxicity (Table 1).

2.1 Ibrutinib

Ibrutinib, the first approved BTKI, is a pillar in the therapy of B-cell neoplasms because of its effectiveness and wide spectrum of use [18]. It is an oral, once-daily therapy that has been shown to improve overall and progression-free survival in many B-cell malignancies [19]. As the first-in-class BTKI, a wealth of data and clinical trials demonstrate the

Table 1 Summary of generation, binding type, selectivity, indications, cardiovascular risk, and key trials of Bruton tyrosine kinase inhibitors (BTKIs)

BTKI	Generation	Binding type	Selectivity	Primary indications	CV risk	**Key trials**
Ibrutinib	First	Irreversible (covalent)	Low (off-target EGFR, ITK, TEC)	CLL, MCL, WM, MZL, SLL	High (AF 16–44%, hypertension ~30%, bleeding)	RESONATE, RESONATE-2, ELEVATE-RR
Acalabrutinib	Second	Irreversible (covalent)	Higher than ibrutinib	CLL, MCL	Moderate (lower AF incidence than ibrutinib)	ASCEND, ELEVATE-TN
Zanubrutinib	Second	Irreversible (covalent)	Higher than ibrutinib	CLL, MCL, WM	Lower CV risk than ibrutinib	ASPEN, ALPINE
Tirabrutinib	Second	Irreversible (covalent)	High selectivity	Primary CNS lymphoma, WM	Limited data, potentially lower AF risk	Japanese trials
Orelabrutinib	Second	Irreversible (covalent)	High selectivity	CLL, MCL	Limited data, fewer major CV events reported	Chinese trials
Pirtobrutinib	Third	Reversible (noncovalent)	Very high	CLL, MCL, SLL	Lower CV risk than first-generation BTKIs	BRUIN trial
Vecabrutinib	Third	Reversible (noncovalent)	Very high	Under investigation (CLL)	No data available	Preclinical studies

AF, atrial fibrillation; CLL, chronic lymphocytic leukemia; CNS, central nervous system; CV, cardiovascular; EGFR, epidermal growth factor receptor; ITK, interleukin-2-inducible T-cell kinase; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma; WM, Waldenström's macroglobulinemia

effectiveness of ibrutinib in B-cell tumors and its adverse effects [16]. Ibrutinib is an irreversible BTKI; however, because of its non-selectiveness for BTK, it can bind to other kinases (such as epidermal growth factor receptor [EGFR], interleukin-2-inducible T-cell kinase [ITK], and TEC family kinases) [20, 21], leading to adverse, off-target effects. Although it has a wide spectrum of use and numerous clinical benefits, it is limited by its cardiovascular adverse effects, such as atrial arrythmias, especially AF, hypertension, and bleeding. Heart failure and ventricular tachycardia (VT) are less commonly observed effects. Non-cardiovascular side effects include diarrhea, infections, fatigue, arthralgia, myalgia, cytopenia, headache, and dermatologic manifestations such as cutaneous rushes. Adverse effects have been observed, especially with long-term use [4, 5, 20, 22]. Unlike second-generation BTKIs, ibrutinib has an atrial-specific pro-arrhythmic effect, proven in both in vitro and real-world studies [22]. The cumulative ibrutinib-related AF incidence rate over a 12-month follow-up period is between 16 and 44%; it is more likely to occur in the first 3 months of therapy, although a late onset (up to 18 months post-medication) has been described [22, 23]. The mechanism by which ibrutinib increases the incidence of AF is still not fully understood; it is suggested that BTK (which is expressed in the atria) inhibition might be involved in atrial fibrosis and structural remodeling, eventually leading to AF [24]. Ibrutinib inhibits many kinases, so more pathways, such as cardiac phosphatidylinositol 3-kinase/protein kinase B (PI3K-Akt) signaling, could be involved in the pathogenesis of ibrutinib-associated AF [25]. Recent findings suggest that atrial *AKAP1* expression might be reduced in patients who develop ibrutinib-induced AF [24, 26]. Recently, the ACEF (Age, Creatinine, Ejection Fraction) score has been proposed to predict the risk of developing paroxysmal AF in patients diagnosed with CLL and set to start ibrutinib therapy [27].

3 Second-Generation BTKIs

Second-generation BTKIs, which show a higher selectivity for BTK, were developed to reduce the adverse effects related to off-target kinase inhibition observed with ibrutinib use. Drugs such as acalabrutinib and zanubrutinib show fewer cardiovascular adverse effects, particularly AF, as demonstrated by the ELEVATE-RR, ASPEN, and ALPINE trials. Despite the increased selectivity of both generations of BTKIs, bleeding (especially major episodes) has been observed, and hypertension can also develop or worsen [8, 10].

3.1 Acalabrutinib

Acalabrutinib is a second-generation irreversible BTKI that shows higher selectivity for BTK (and, at clinically relevant concentrations, only inhibits BMX and ERBB4, with no interactions with EGFR, ITK, or TEC family kinases) [4, 21, 28] compared with ibrutinib, thereby reducing side effects [22]. The ASCEND trial showed a lower overall incidence

of AF (and atrial flutter), hypertension, and hemorrhages in relapsed/refractory CLL treated with an acalabrutinib-based regimen than in those receiving an ibrutinib-based regimen [29]. Overall, acalabrutinib is better tolerated than and has shown efficacy similar to that of ibrutinib in patients with CLL [30, 31]. Acalabrutinib has a lower association with AF, probably because of its higher molecular specificity [7, 22, 29, 31, 32]. In the MCL treatment setting, acalabrutinib has been associated with better tolerance and a lower incidence of adverse effects – no cases of AF were reported in a clinical trial [33] – and the incidence of bleeding does not differ from that with other treatments [34].

3.2 Zanubrutinib

Zanubrutinib is another second-generation, highly selective, irreversible BTKI and is more effective than ibrutinib with fewer off-target effects [35]. It has a broad range of uses, including in WM, MCL, and CLL [36–38]. Furthermore, it is more effective than ibrutinib in terms of progression-free survival in CLL and small lymphocytic lymphoma (SLL) [39]. Zanubrutinib has a lower incidence of AF than ibrutinib in patients with WM, and fewer cases of bleeding have been observed [4, 22, 35, 40, 41]. The overall incidence of AF, VAs, and hypertension is lower with zanubrutinib than with ibrutinib [40–45]. Additionally, zanubrutinib has a lower incidence of hypertension [37].

3.3 Tirabrutinib

Tirabrutinib is a highly selective, oral, second-generation BTKI developed in Japan. It has not yet been approved for use in Europe or the USA. Its clinical use is currently limited to Korea, Japan, and Taiwan [46]. It is used to treat various neoplasms such as recurrent or refractory primary central nervous system lymphoma, WM, and lymphoplasmacytic lymphoma [47, 48]. Tirabrutinib irreversibly inhibits BTK with greater selectivity than ibrutinib [4]. A 3-year follow-up reported the absence of new-onset AF in patients treated with tirabrutinib [46].

3.4 Orelabrutinib

Orelabrutinib is an effective oral, irreversible BTKI approved by Chinese drug authorities for the treatment of MCL and CLL/SLL [4, 49]. It has also been used in other conditions, such as refractory and relapsed autoimmune hemolytic anemia [50] and idiopathic multicentric Castleman disease [51]. Orelabrutinib provides long-lasting and selective inhibition of BTK, with few adverse reactions [52]. Although data are limited, it appears to be associated with fewer major adverse cardiovascular events, arrythmias, and instances of hypertension and bleeding [52].

4 Third-Generation BTKIs

The third generation of BTKIs represents an advanced class of drugs and has been developed to further improve the selectivity and safety profile of earlier generations. They offer reversible, non-covalent, BTK inhibition and enhanced specificity, which in turn increases their utility and specificity, providing a potentially lower risk of off-target effects, including reduced cardiovascular side effects. Moreover, their longer half-life gives sustained effect, reducing dosing frequency [53–55].

4.1 Vecabrutinib

Vecabrutinib is a highly specific third-generation reversible BTKI that is currently being studied in vitro for the treatment of CLL. No data are available regarding its cardiovascular effects because it has not yet been deployed for human use [56–58].

4.2 Pirtobrutinib

Pirtobrutinib (Loxo-305) is a novel selective, non-covalent BTKI that has shown positive responses in relapsing/remitting MCL, CLL, and SLL [59–63]. The drug does not rely on covalent binding to the p.C481 site. Consequently, there is no resistance after the appearance of BTK p.C481S point mutations, and it continues to be an effective therapy. Moreover, pirtobrutinib is associated with fewer adverse cardiovascular effects than is ibrutinib, particularly lower grade effects such as bleeding, hypertension, and atrial arrythmias [60, 64, 65].

4.3 Nemtabrutinib

Another non-covalent BTKI under investigation is nemtabrutinib (formerly MK-1026 and ARQ-531), which maintains B-cell receptor pathway inhibition in both wild-type and C481-mutated BTK by forming hydrogen bonds with E475 and Y476 residues [66]. Unlike pirtobrutinib, nemtabrutinib is a less selective kinase inhibitor that also targets SRC, AKT, ERK, Lyn, and Syk and has shown preclinical activity in various hematologic malignancies. Preliminary results from the Bellwave-001 phase I/II trial demonstrated encouraging efficacy in relapsed/refractory CLL, including in patients with prior BTK inhibition and B-cell lymphoma 2 (*BCL-2*) inhibitor exposure [66]. However, although common adverse events included hypertension (10%), the cardiovascular safety profile of nemtabrutinib remains

insufficiently characterized, and further studies are needed to assess its arrhythmic and hemodynamic effects [66, 67].

5 Prediction Tools for Cardiovascular Adverse Effects in BTKI Therapy

The prediction of cardiovascular adverse events in patients undergoing BTKI therapy has garnered increasing attention because of the growing use of these agents in hematologic malignancies and their recognized cardiovascular toxicities [68]. Such complications can substantially affect treatment tolerability and adherence, highlighting the urgent need for effective risk stratification and monitoring strategies (Table 2) [69–72]. Furthermore drug–drug interactions between BTKIs and cardiovascular medications, particularly agents affecting BP, heart rate, and coagulation pathways, are clinically relevant and require individualized therapeutic adjustments (Table 3) [73].

5.1 Clinical and Laboratory Predictors

Baseline cardiovascular risk assessment is a cornerstone of prediction, integrating clinical history, physical examination, and known risk factors. History of AF and age ≥65 years are consistently identified as predictors of BTKI-associated AF [74]. A meta-analysis of ibrutinib-treated patients confirmed that older age and prior AF significantly increased the likelihood of ibrutinib-induced AF [75]. Baseline electrocardiographic evidence of left atrial enlargement has been associated with an increased risk of developing AF during ibrutinib therapy [74]. Retrospective studies highlight the significant role of comorbidities such as HF and hypertension in the development of AF among patients treated with ibrutinib [11]. In a cohort of 298 individuals with CLL, 17% developed AF, and prior AF (hazard ratio 3.5) and HF (hazard ratio 3.4) were identified as major risk factors. Additionally, male sex, hypertension, and valvular heart disease have been linked to an increased likelihood of AF [10, 11]. Predictive models incorporating these variables have categorized patients into different risk groups, with AF incidence rates ranging from 4% to 33% over a decade [76–78]. Hypertension is a common complication of BTKI therapy [79]. Factors such as diabetes, elevated baseline systolic BP, and cytochrome P450 (CYP)-3A4 inhibitor use predict new-onset hypertension in patients without prior hypertension [71]. For those with pre-existing hypertension, significant predictors of worsening hypertension are advanced age, higher body mass index, and concurrent CYP3A4 inhibitor use [74, 79]. Although the incidence of hypertension appears to be lower with acalabrutinib than with ibrutinib, it remains a key concern [71, 80]. A risk of heart failure, particularly among patients with pre-existing AF or coronary artery disease, has been reported in patients receiving ibrutinib and acalabrutinib. Laboratory biomarkers such as N-terminal pro-B-type natriuretic peptide (NT-proBNP) and troponin T have shown promising results in the early detection of cardiotoxicity: elevated levels of these markers correlate with reduced myocardial strain and adverse cardiovascular events [81, 82]. Ciuculete et al. [81] studied the cardiotoxic effects of ibrutinib in 31 patients after 3 months of treatment. They observed a significant increase in troponin T and NT-proBNP levels ($p = 0.019$ and $p = 0.03$, respectively) compared with the control group. Likewise, ibrutinib showed a time-dependent impact on serum cardiac biomarkers in CLL. In a study by Mulder et al. [82] of the 86 biomarkers that changed during treatment, 12 remained elevated, six of which were linked to AF or other cardiovascular diseases.

Table 2 Management of cardiovascular Bruton tyrosine kinase inhibitor (BTKI)-related toxicities

CV toxicity	Frequency	Management	Discontinue BTKI?
Hypertension	High (up to 80%)	HTN therapy	Consider, if severe or refractory
Bleeding	Common (minor)	Not needed	No
	Infrequent (severe)	Not needed	No
	Rare (major, requiring transfusion or hospitalization)	Discontinue BTKI, consider platelet transfusion	Yes
AF	Common	Rate control (beta-blockers); consider anticoagulation	No
VAs	Rare	Positive anamnesis: switch to second-generation BTKIs or *BCL2* inhibitors	Yes
		New onset: consider beta-blockers	Yes

AF, atrial fibrillation; *BCL2*, B-cell lymphoma 2; CV, cardiovascular; HTN, hypertension; VA, ventricular arrhythmia

Table 3 Summary of clinically relevant drug–drug interactions with Bruton tyrosine kinase inhibitors (BTKIs)

Cardiac drug class	Interaction with BTKI	Mechanism	Management recommendations
Sacubitril/valsartan (ARNI)	↑ Hypotension; ↑ Hyperkalemia risk	Valsartan (ARB): RAAS blockade → ↑ hypotension/hyperkalemia Sacubitril: Neprilysin inhibition → ↑ vasodilation/diuresis Additive effects with BTKI (hypotension, dehydration)	Monitor BP, potassium, and renal function Avoid concurrent ACEI/ARBs unless guideline-directed Ensure hydration to reduce hypotension risk Adjust doses if symptomatic
Beta-blockers	↑ Risk of bradycardia	Additive effects on heart rate reduction	Monitor heart rate; consider dose reduction of beta-blockers if symptomatic bradycardia occurs
Calcium channel blockers (non-DHP: diltiazem, verapamil)	↑ BTKI plasma levels (CYP3A4 inhibition)	Non-DHP CCBs inhibit CYP3A4, reducing BTKI metabolism.	Avoid or use with caution; consider dose reduction of BTKI. Monitor for toxicity (e.g., arrhythmia, bleeding)
Amiodarone	↑ BTKI plasma levels; ↑ QT prolongation risk	CYP3A4 inhibition by amiodarone; additive QT effects (rare with BTKI)	Avoid if possible; monitor ECG for QT prolongation. Consider alternative antiarrhythmics
Digoxin	↑ Digoxin toxicity risk	BTKI (e.g., ibrutinib) inhibits P-gp, increasing digoxin absorption	Monitor digoxin levels; adjust dose as needed
Statins (CYP3A4 substrates: simvastatin, atorvastatin)	↑ Risk of myopathy/rhabdomyolysis	Additive myopathy risk (pharmacodynamic); CYP3A4 competition if combined with inhibitors	Use lower statin doses or switch to non-CYP3A4 statins (e.g., pravastatin, rosuvastatin). Monitor CK levels
Ezetimibe	No significant interaction	No CYP450 or P-gp involvement	No dose adjustment needed
ACEIs	↑ Hyperkalemia risk; ↑ hypotension (if dehydration)	Additive hyperkalemia (ACEI) + BTKI (rare); dehydration from diarrhea (BTKI)	Monitor potassium and renal function; ensure hydration. Adjust ACEI dose if BP drops excessively
Sartans (ARBs)	Similar to ACE inhibitors	Additive hyperkalemia and hypotension risk	Same as ACEIs
SGLT2i	↑ Risk of volume depletion/AKI	Osmotic diuresis (SGLT2i) + diarrhea (BTKI) → dehydration	Monitor hydration status, BP, and renal function. Avoid in hypovolemia
Semaglutide	↑ GI side effects (nausea, diarrhea); ↓ BTKI absorption (theoretical)	Additive GI effects; delayed gastric emptying may alter BTKI absorption	Monitor GI tolerance; separate administration times if GI distress occurs

ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BP, blood pressure; CCB, calcium channel blocker; CK, creatine kinase; CYP, cytochrome P450; DHP, dihydropyridine; ECG, electrocardiograph; GI, gastrointestinal; P-gp, P-glycoprotein; RAAS, renin-angiotensin-aldosterone system; SGLT2i, sodium-glucose co-transporter-2 inhibitors

Genetic determinants are emerging as another predictive avenue. Specific polymorphisms in BTK signaling pathways, such as GATA4 rs804280 and KCNQ1 rs163182, have been linked to elevated risks of cardiovascular toxicity, with patients carrying multiple risk alleles facing a significantly increased likelihood of adverse events [68, 83].

5.2 Instrumental Predictors: Electrocardiography, Echocardiography, and Cardiovascular Magnetic Resonance

Instrumental tools, including ECG, echocardiography, and cardiovascular magnetic resonance (CMR), play crucial roles in risk stratification. From an ECG perspective, the effects of BTKIs on the QTc interval remain unclear [9]. Some authors have described QTc prolongation with these agents, particularly in broader cardio-oncology contexts, but dedicated studies of ibrutinib have shown either no significant QTc prolongation or even a mild QTc shortening [84, 85]. For instance, in a controlled QT study in healthy volunteers, ibrutinib did not prolong the QTc interval at either therapeutic or supratherapeutic doses [85]. Similarly, a retrospective clinical series found significant QTc shortening after ibrutinib exposure [84]. However, QT dispersion appeared to increase, raising the hypothesis of repolarization heterogeneity as a potential pro-arrhythmic mechanism [84]. Overall, given the conflicting evidence and lack of clear prognostic significance, routine QTc monitoring is not universally recommended, but clinical judgment should prevail, particularly in high-risk individuals [9]. Extended rhythm monitoring has further demonstrated its ability to identify arrhythmias and predict major adverse cardiac events, and a high AF burden (≥10%) is significantly associated with increased mortality [86]. Artificial intelligence-enabled ECG algorithms offer a novel predictive approach. In a cohort of 754 patients newly diagnosed with CLL, an artificial intelligence-ECG score ≥0.1 was strongly predictive of AF, even after adjusting for other clinical risk factors [87]. Pre-treatment echocardiographic markers, such as left atrial (LA) size and volume, strongly predict new-onset AF [74]. LA diameters ≥32 mm and area ≥18 cm^2 correlate with increased AF risk, whereas advanced parameters such as elevated E/e' (early diastolic mitral inflow velocity to early diastolic mitral annular velocity) and impaired LA mechanics (e.g., peak atrial longitudinal strain and peak atrial contraction strain) have shown additional predictive value [88]. CMR provides unique insights into myocardial structure, such as late gadolinium enhancement and elevated T1/T2 signals, which have been associated with major adverse cardiac events in BTKI-treated patients. In a cohort of 49 patients receiving ibrutinib, CMR identified myocardial injury markers predictive of future events, underscoring its utility in selected high-risk cases [89].

6 Practical Management of Cardiovascular Toxicities in Patients Receiving BTKI Therapy

6.1 Hypertension Management

Hypertension is a frequently observed cardiovascular adverse effect of BTKI therapy, especially with ibrutinib, and its prevalence appears to rise progressively over time during its use [13, 71, 90]. Studies have indicated that nearly 80% of patients experience either new-onset or worsening hypertension during treatment [71]. In a recent paper, researchers explored the pharmacokinetics of ibrutinib in patients with B-cell lymphoproliferative disorders, highlighting a significant correlation between drug exposure and the incidence of hypertension [91]. The results suggested that elevated levels of dihydrodiol-ibrutinib, a metabolite of ibrutinib**,** contribute to this adverse effect [91]. Furthermore, results from another recent study suggested that patients with pre-existing hypertension benefited most from combination therapy with beta-blockers and hydrochlorothiazide, whereas those who developed hypertension after starting BTKI therapy responded better to angiotensin-converting enzyme inhibitors or angiotensin receptor blockers combined with hydrochlorothiazide [92]. Some BTKIs such as acalabrutinib appear to have a weaker association with hypertension and might therefore be considered as a therapeutic option in selected patients [93]. Effective hypertension management should start with a comprehensive cardiovascular risk assessment before initiating treatment, ensuring optimal baseline BP control through appropriate antihypertensive therapy when necessary [94]. During therapy, BP should be monitored regularly, ideally at every clinical visit, or more frequently if the patient has pre-existing hypertension [20]. For newly developed or worsening hypertension, there is currently no established first-line agent for BTKI-associated hypertension. Antihypertensive choices should be individualized, but dihydropyridine calcium channel blockers (e.g., amlodipine) are often preferred because of their favorable safety profile and lack of CYP3A4 interaction [11]. Renin-angiotensin-aldosterone system inhibitors are also commonly used [11, 79]. For patients with co-existing AF, vasodilating beta-blockers (e.g., labetalol, carvedilol, or nebivolol) are often preferred as they can manage both conditions effectively [94]. Lifestyle interventions, including sodium reduction, weight management, and regular physical activity, should complement pharmacologic treatment [94]. In severe or refractory hypertension, temporary dose reduction, interruption of BTKI, or renal denervation may be necessary, ideally under a multidisciplinary approach involving cardiologists and oncologists [95].

6.2 Bleeding Risk Mitigation

Bleeding is a common adverse effect of BTKIs, though it is typically limited to minor subcutaneous or mucosal manifestations, such as petechiae and ecchymoses [96]. Major bleeding events, defined as those requiring transfusion or hospitalization, have been reported in up to 10% of patients in early phase III trials with ibrutinib, whereas fatal hemorrhages remain rare, affecting less than 1% of cases [11, 15, 20, 97]. Before initiating BTKI therapy, a comprehensive bleeding history should be obtained, and any necessary procedures should be carefully scheduled in advance to reduce the risk of treatment interruptions [15]. Risk factors for bleeding during BTKI therapy include bleeding history, advanced age, and concomitant use of antiplatelet or anticoagulant agents. Laboratory findings such as prolonged collagen/epinephrine membrane closure time have also been associated with increased bleeding risk [11]. Management of minor bleeding typically does not require stopping BTKI therapy, as the bleeding resolves within 2–3 days after temporary cessation [20]. For major bleeding, immediate interruption of BTKI therapy is recommended, alongside platelet transfusion if clinically indicated, even when the platelet count appears normal [20]. Evidence indicates that platelet function typically normalizes within 5–7 days after discontinuing ibrutinib [98]. Anticoagulant and antiplatelet therapies should be administered with great caution, as warfarin is contraindicated because of its strong interaction with BTKI metabolism [99]. Ibrutinib is metabolized via CYP3A4, as are rivaroxaban and apixaban, whereas dabigatran and edoxaban are not [100]. Therefore, coadministration of ibrutinib and a direct oral anticoagulant might increase bleeding by elevating the plasma concentration of both drugs [97, 101]. The use of apixaban may be considered at reduced doses (e.g., 2.5 mg twice daily for apixaban) to balance the risk of bleeding and thromboembolism [20, 102]. In cases of periprocedural bleeding risk, it is recommended to hold BTKIs for 3 days for minor surgeries and 7 days for major interventions [20, 79]. In a recent paper, researchers analyzed bleeding adverse events associated with BTKI using data from the US Food and Drug Administration Adverse Event Reporting System [103]. Results indicated that the incidence of reported bleeding cases was higher with ibrutinib than with zanubrutinib and acalabrutinib, highlighting the need for careful risk assessment and monitoring in clinical practice [103]. Bleeding risk scores, such as HAS-BLED, have not been validated in patients with cancer, which lowers their utility. However, they might still be considered when assessing anticoagulation [5, 10, 22]. A retrospective multicenter study by Krečak et al. [104] investigated whether baseline absolute lymphocyte count (ALC) could help predict bleeding events in patients with CLL treated with BTKIs. The analysis showed that patients with an ALC $> 77.4 \times 10^9$/L had a significantly higher risk of bleeding, independent of other clinical variables, including comorbidity burden and use of antithrombotic agents [104]. These findings highlight the potential value of integrating tumor-related biomarkers, such as ALC, into future bleeding risk stratification models in patients receiving BTKI therapy.

6.3 AF Management

AF is a frequent and potentially therapy-limiting side effect of BTKI therapy, particularly with ibrutinib, with a reported incidence of 6–16% depending on patient age and comorbidities [105]. It often occurs within the first 3 months of therapy, though late-onset AF has also been observed [106].

In line with the ABC (Atrial Fibrillation Better Care) pathway, management should aim to ensure "A—Anticoagulation/Avoid stroke, B—Better symptom control, and C—Cardiovascular and comorbidity optimization" [107]. Although cancer is a prothrombotic condition, patients with malignancy are frequently underrepresented in AF trials, complicating the application of standard anticoagulation strategies in this high-risk population [108]. These patients face an increased risk of thromboembolic events, further complicating treatment decisions in this high-risk group [23, 108]. Although commonly used thromboembolic (e.g., CHA_2DS_2-VASc) and bleeding (e.g., HAS-BLED) scores do not account for malignancy and have not been formally validated in this setting, they can still provide practical guidance [5–7, 10, 15, 23, 109]. In a recent large nationwide study, the CHA_2DS_2-VASc score showed a linear association with the risk of acute cerebrovascular events in hospitalized patients with AF and cancer, with even higher odds ratios per score increment than patients without cancer [110]. These findings underscore the utility of CHA_2DS_2-VASc in supporting anticoagulation decisions, although clinical judgment remains essential in tailoring therapy to individual patients with cancer [110]. A recent study introduced an updated PRECISE-DAPT cancer score by incorporating malignancy as a binary variable, demonstrating improved discrimination in identifying patients at high bleeding risk after myocardial infarction [111]. The modified score classified 94% of patients with cancer as at high bleeding risk, compared with 65.5% under the original model, and maintained its predictive value even in non-cancer populations [111]. Anticoagulation strategies depend on stroke risk: low-dose apixaban (2.5 mg twice daily) or enoxaparin have been proposed, whereas vitamin K antagonists such as warfarin should be avoided [20, 79, 102]. In hemodynamically stable AF, a rate control strategy is usually preferred [23]. Beta-blockers are preferred because of their safety profile and minimal drug interactions [79]. Calcium channel blockers such as verapamil and diltiazem, as well as P-glycoprotein substrates such as amiodarone, are generally avoided because of CYP3A4-mediated interactions

that may increase BTKI plasma levels and toxicity. However, in cases of life-threatening VAs (e.g., sustained VT or ventricular fibrillation [VF]), amiodarone remains an essential therapeutic option [100, 112]. However, managing ventricular rate can be challenging, often necessitating the addition of a second agent. In such cases, calcium channel blockers may be considered following an appropriate dose reduction of ibrutinib, with careful monitoring for potential ibrutinib-related toxicity [23]. Ibrutinib also increases plasma levels of digoxin via P-glycoprotein, potentially enhancing digoxin toxicity [23]. Therefore, if needed, smaller doses of digoxin, taken either 6 h before or after taking ibrutinib, should be considered, with more frequent monitoring of digoxin levels [23]. Catheter ablation may be considered for patients with refractory or recurrent AF, although evidence in this population is limited [113].

It is not recommended to discontinue ibrutinib if only atrial arrythmias are detected: in particular, AF is not dose-related to ibrutinib, and discontinuing the drug, on the other hand, would let the B-cell malignancy grow [114]. In patients with recurrent or difficult-to-manage AF, dose reductions of ibrutinib may be considered, as up to one-half of patients with BTKI-associated AF benefit from lower dosing without compromising hematologic efficacy [9]. Alternatively, switching to second-generation BTKIs with improved selectivity (e.g., acalabrutinib or zanubrutinib) or to non-BTKI regimens such as venetoclax may be appropriate in selected cases, particularly when arrhythmias remain refractory despite optimal cardiovascular management [10]. Cardio-oncology consultation should be considered early in the treatment course, particularly in patients with pre-existing cardiovascular disease, uncontrolled AF, or those requiring complex pharmacologic or rhythm interventions [79].

In a recent paper published in *Europace*, Shi et al. [115] explored the role of gut microbiota in ibrutinib-associated AF, revealing that *Lactobacillus gasseri* and its metabolite, butyrate, may mitigate atrial remodeling and reduce arrhythmic susceptibility, highlighting a novel avenue for cardioprotective strategies in patients receiving BTKIs [115].

6.4 VA Management

VAs, including VT and VF, are rare but life-threatening complications of BTKI therapy, particularly ibrutinib [74]. Two large clinical analyses published in 2017 and 2018 reported an incidence of VAs and/or sudden cardiac death of 6.0–7.9 events per 1000 person-years among patients with hematologic malignancies receiving ibrutinib [11, 96]. Given the limited data on the safety of BTKIs in patients with a history of VAs, expert consensus suggests that alternative therapies (e.g., venetoclax) should be strongly considered in individuals with prior symptomatic VAs, reduced ejection fraction (<40%), or a history of sudden cardiac death [11]. In such high-risk patients, multidisciplinary evaluation and close cardiac surveillance are warranted if BTKI therapy is pursued [7, 8]. For acute management of VT or VF, amiodarone—the most commonly used rhythm control agent for Vas—inhibits CYP3A4 and may increase the serum level of ibrutinib and zanubrutinib, potentially increasing the risk of side effects [116]. The efficacy of antiarrhythmic agents such as sotalol and flecainide in preventing or managing BTKI-induced arrhythmias remains unproven [117]. For long-term management, beta-blockers such as metoprolol or carvedilol may be beneficial, particularly in patients with a history of myocardial infarction or reduced ejection fraction [74, 79]. Some tyrosine kinase inhibitor-related VAs may resolve upon therapy discontinuation; however, the incomplete understanding of their underlying mechanisms and the potential for irreversible myocardial damage justify consideration of secondary prevention with implantable cardioverter-defibrillators, especially in cases of recurrent arrhythmias or when alternative treatment options are unavailable [118]. Therapy decisions should be individualized according to patient and disease characteristics [116]. Finally, although QTc prolongation has been inconsistently reported with BTKIs, it does not appear to represent a consistent class effect, particularly with agents such as ibrutinib. Therefore, routine QT interval monitoring is generally not required. However, in patients with baseline repolarization abnormalities, concomitant use of QT-prolonging drugs, or a history of VAs, ECG monitoring should be considered on a case-by-case basis [22]. In a recent paper, Li et al. [119] demonstrated that metformin mitigates ibrutinib-induced VA and cardiac dysfunction by enhancing 5′ adenosine monophosphate-activated protein kinase and PI3K-Akt pathway activity, offering a potential cardioprotective strategy to improve the cardiovascular safety of patients undergoing BTKI therapy [119].

7 Proposed Monitoring Plan for BTKI-Associated Cardiovascular Toxicity

A structured cardiovascular monitoring plan is crucial for patients receiving BTKI therapy to ensure early detection and management of cardiovascular complications. A comprehensive baseline assessment should include BP measurement, ECG, and, when indicated, echocardiography and biomarkers such as NT-proBNP and troponin. Given that hypertension and arrhythmias frequently develop within the first few weeks of therapy, a 1-month follow-up is essential for early intervention. At 3 months, monitoring should be risk-adapted, with repeated ECGs and echocardiography reserved for high-risk patients. Six-month and annual evaluations should be prioritized for those with pre-existing

	Baseline	1 month	3 months	6 months	Yearly
Blood pressure	✓	✓	✓	✓	✓
Electrocardiogram	✓	✓	✓ If heart failure risk	✓ If high risk	✓
Echocardiography	✓ If heart failure risk	—	—	✓ If heart failure risk	✓ If heart failure risk
NT-proBNP/troponin	✓ If heart failure risk	—	—	✓ If heart failure risk	✓ If heart failure risk

Fig. 1 Proposed cardiovascular monitoring plan for patients receiving Bruton tyrosine kinase inhibitor therapy. NT-proBNP, N-terminal pro-B-type natriuretic peptide

cardiovascular conditions or ongoing concerns related to BTKI therapy. This structured approach facilitates timely risk stratification, minimizes treatment interruptions, and enhances long-term cardiovascular outcomes (Fig. 1). Whenever baseline abnormalities are present, or new cardiovascular symptoms or arrhythmias emerge during follow-up, early cardiology referral—preferably to cardio-oncology services—should be strongly considered to optimize multidisciplinary care [79].

8 Conclusions

BTKIs have become a key therapeutic option for B-cell malignancies. Since the introduction of ibrutinib 2 decades ago, the development of second- and third-generation BTKIs has led to improved selectivity and potentially fewer side effects. Despite the strong clinical efficacy of ibrutinib, its cardiovascular toxicity—particularly AF, hypertension, and bleeding—remains a significant challenge. Acalabrutinib and zanubrutinib have demonstrated more favorable safety profiles, with lower incidences of cardiovascular complications. More recently, orelabrutinib and tirabrutinib have been approved in China and Japan, though their cardiovascular safety data are still limited. Third-generation inhibitors, such as vecabrutinib and pirtobrutinib, exhibit distinct pharmacological characteristics, and preliminary evidence suggests a lower cardiovascular risk, though further research is needed. As the use of BTKIs continues to expand, mitigating their cardiovascular toxicity is essential to ensure long-term treatment adherence and optimized patient outcomes.

Declarations

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Conflicts of interest GBZ has consulted for Aleph, Amarin, Balmed, Cardionovum, Crannmedical, Endocore Lab, Eukon, Guidotti, Innovheart, Meditrial, Menarini, Microport, Opsens Medical, Terumo, and Translumina, outside the present work. PS has received consulting fees from Axis-TV, AstraZeneca, BMS, Les Laboratoires Servier, Novartis, Menarini, and Sanofi, outside the submitted work. LS, FR, EBO, GP, MG, SC, GS, BS, ER, AL, FV, IC, VV, SS, and MB have no conflicts of interest.

Author contributions LS conceived the manuscript, drafted the initial version, and coordinated the responses to reviewers. FR and EB-O contributed to the manuscript drafting and literature review, alongside GP and MG. SC, PS, GS, BS, ER, AL, FV, GBZ, IC, VV, and SS provided critical internal review and supervision throughout the writing process. MB oversaw the project and provided final supervision and critical appraisal. All authors reviewed and approved the final version of the manuscript.

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