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Addressing cardiovascular toxicities of Bruton tyrosine kinase inhibitors in chronic lymphocytic leukaemia: practical recommendations for haematologists in central and eastern Europe

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Abstract

Advances in understanding the biology of chronic lymphocytic leukaemia **(**CLL) translated into revolutionary treatments with improved survival outcomes. Consequently, the traditional chemoimmunotherapy courses shifted to targeted therapies, including inhibitors of the Bruton tyrosine kinase (BTKis). BTKis correlate with an increased risk over time of toxicities of the cardiovascular (CV) system, which require proper management. An expert meeting involving 14 haematology and cardiology opinion leaders from 5 Central Eastern European countries was held, aiming to find pragmatic approaches for haematologists to identify the CLL patients at CV risk before starting the BTKis therapy, and further recognize, manage and monitor *de novo* cardiotoxicities occurring under treatment. Geographical variations have been described, including availability of reimbursed BTKis, national registries, and presence of cardio-oncology units. The experts discussed controversies, unmet needs and potential solutions by exemplifying local challenges and best practices. Each patient requires a personalized strategy based on multiple factors, hence practical pathways to follow during the continuity of care in CLL patients requiring BTKis have been proposed. Rigorous evaluation of the CV risk, periodic assessments of cardiotoxicity during BTKis treatment and work in multidisciplinary teams are vital for managing CV complications without unnecessary interruptions of the CLL treatment.

Keywords CLL, BTK inhibitors, Cardiovascular toxicity, Cardio-oncology

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Background

The most common adult leukaemia in Europe and North America, chronic lymphocytic leukaemia (CLL) is a malignancy affecting usually the elderly population, with a median age at diagnosis of 70–72 years [1–3]. Advancements in understanding the CLL biology translated into revolutionary treatments that improved survival outcomes and inherently changed the management of the disease [1–5]. The standard of care has shifted from traditional chemoimmunotherapy approaches to targeted therapies with inhibitors of the Bruton tyrosine kinase (BTK) and BCL2 inhibitors, which are now dominant in multiple geographies [1, 6–10].

Identified in 1993, BTK is part of the B-cell receptor (BCR) signalling pathway that is one of the pathogenic mechanisms of CLL [2, 3, 11, 12]. The first generation (1G) BTK inhibitor (BTKi) ibrutinib brought remarkable survival benefits, while its extensive use showed an increased risk over time of toxicities on platelets (bleeding) and cardiovascular (CV) system (mainly hypertension, atrial fibrillation, ventricular arrhythmias and heart failure [HF]) [3, 13–15]. The mechanisms of cardiotoxicity are not fully known, but arrythmias may be partly explained by the interactions with pathways involving the phosphoinositide 3-kinase (PI3K) in cardiomyocytes and other proteins from the TEC kinase family from the heart tissue, leading to disruptions of the normal ion current, prolongation of the action potential, and amplified or abnormal automaticity [16–19]. Suppression of PI3K caused by the off-target inhibition of other kinases is also believed to be one of the mechanisms leading to HF [19]. Consequently, second generation (2G) of BTK inhibitors (BTKis) with more selective effects were developed. The molecules in clinical use are acalabrutinib and zanubrutinib, with increased specificity for BTK and improved tolerability due to a lesser off-target kinase inhibition [11, 13]. In clinical trials, and real-world studies, the 2G BTKis have been associated with a lower incidence of cardiotoxicity [20–24]. However, the true incidence of *de novo* CV toxicities under 1G and 2G BTKis remains unknown, especially that pre-existing CV diseases (CVD) and other comorbidities and treatments that increase the risk for CVD are highly prevalent in the typical elderly CLL population [18, 25, 26].

Clinical predictors of cardiotoxicity under BTKi treatment would prove valuable tools for practitioners, yet only one model was proposed for incident atrial fibrillation, which incorporates prior history of hypertension, atrial fibrillation, valvular heart disease, older age and male sex [27]. In general, treatment decisions are tailored based on the safety and efficacy of available treatments, along with patient and health care system factors [1, 28, 29], which in the old aged CLL patient population have to also include the concomitant diseases influencing life expectancy [28]. In this context, it becomes crucial to recognize, minimize and treat the cardiotoxicities of a cancer treatment without discontinuing the antineoplastic drugs, under the umbrella of a new concept named *permissive cardiotoxicity* that involves a multidisciplinary approach between haemato-oncologists and cardiologists [30]. Cardio-oncology, a new discipline in the field of cardiology focusing on cancer patients is now increasingly implemented in routine practice [18, 26, 31].

A key landmark in the CV management of patients with haemato-oncological diseases and survivors of such malignancies was reached in 2022, when the professional societies of cardiology and haematology have released the first European cardio-oncology guideline [26, 32]. Definitions, diagnosis, treatment and prevention of CV toxicities related to the cancer therapy and CVD management are covered by the guideline. The BTKi class is covered to some degree, with recommendations for baseline CV risk assessment and on-treatment monitoring provided [26]. CV toxicities of cancer therapy are more detailed in a paper issued by the International Cardio-Oncology Society (IC-OS) [31]. More specific papers on the CV risk assessment and CVD management in patients with CLL receiving BTKis have been lately developped by other groups and published as consensus statement [33, 34] or best practices [35–37]. Currently, no guideline is dedicated specifically to the CV risk and CVD assessment, and management of emerging CV toxicities in CLL patients receiving BTKi treatment.

Published data in a standardized manner on the current status of BTKis use in the Central and Eastern European (CEE) countries, including information on the healthcare system applicable for the CLL care, lack. Insights based on personal and institutional experience have been gathered from the experts involved in this project to provide a better understanding of the local context of CLL management (Table 1). In light of these geographical variations, the aim of this paper is to map out practical recommendations for haematologists across CEE to identify CLL patients at CV risk before starting BTKi treatment, and recognize, manage and monitor *de novo* cardiotoxicities during treatment with BTKis.

Methods

A panel of 14 opinion leaders in fields of haematology and cardiology from 5 countries in CEE was organized and included several virtual meetings logistically supported by AstraZeneca. Three meetings were held on June 05, 06 and 20, 2024. From each country, 1 expert in cardiology and either 1 or 2 experts in haematology (1 haematologist from Montenegro and 2 haematologists from Bulgaria, Croatia, Serbia, and Slovenia) working in academic hospitals participated in the panel meetings.

Table 1 The local context of the CLL management in 5 countries from CEE [38–42]

	Bulgaria	Croatia	Montenegro	Serbia	Slovenia
CLL epidemiology					
Incidence	250/year	230/year (cca. 4.5–6.5/100000)	35–40/year (cca. 5.4–6.2/100000)	*Data not available*	7.2/100,000
Healthcare system and treatment access					
BTKis available	Ibrutinib, acalabrutinib, zanubrutinib	Ibrutinib, acalabrutinib, zanubrutinib	Ibrutinib, acalabrutinib (via donation from AstraZeneca)	Ibrutinib, acalabrutinib (via donation from AstraZeneca)	Ibrutinib, acalabrutinib, zanubrutinib
Reimbursement BTKis (Y/N and which)	Y – ibrutinib, acalabrutinib, zanubrutinib	Y – ibrutinib, acalabrutinib, zanubrutinib	Y – ibrutinib, N- acalabrutinib, N- zanubrutinib	Y – ibrutinib N – acalabrutinib	Y - ibrutinib, acalabrutinib, zanubrutinib
CLL excellence centers (Y/N)	Y[†]	Y[†]	N	N	N
CLL disease/BTKis treatment registries (Y/N)	Y - National Cancer Registry	Y	N	N	N
Cardio-oncology specialists (Y/N)	Y	Y	N	Y	Y
MDT including haematology, cardiology & other specialists (Y/N)	N	N	N	N	N
Guidelines					
Local CLL guidelines/protocols (Y/N)	Y	Y	N	Y	N
Local guidelines/protocols for monitoring CV complications during cancer therapies (Y/N)	N	N	N	N	N

[†]University Hospitals are considered excellence centers, not specifically for CLL

Abbreviations BTKi(s) Bruton-tyrosine kinase inhibitor(s), *CLL* chronic lymphocytic leukaemia, *CV* cardiovascular, *MDT* multidisciplinary team, *N* No, *Y* Yes

A pre-meeting survey of 56 questions was developed for this project (Additional File 1). Questions were organized in four main topics: pre-treatment CV risk assessment, management protocols for CV events, long-term CV care and coordination and special considerations (e.g., country specifics and/or call for actions). All experts responded in anonymized manner to the preliminary survey. The average time to fill the survey was around 45 min. Data from the survey were retrieved in an excel sheet and responses grouped under the main topics. No formal statistical analysis was used, but the responses and their distribution were used as support for the discussions.

The experts established the structure of the manuscript, with focus on (i) pre-BTKi CV risk assessment and stratification, (ii) identification and assessment of CV toxicities under BTKi therapy and (iii) management and monitoring of the CV toxicities emerging during the BTKi therapy. The experts discussed guidelines, and relevant published data (without a formal literature review) to describe the general or local context or practice and shared their independent opinion and experience. For each topic of interest, besides the specificities of the subject covered, the experts agreed on a pragmatic approach and consistent structure, including checklists, elaborating to a greater extent on controversies, and unmet needs. Disparities among countries in the access to CV risk assessment and management of CVD as cardiotoxicities during BTKi treatment of CLL patients submerged, and local circumstances and solutions with potential applicability in the medical communities in the larger CEE region were exemplified.

Results and discussion

Pre-BTKi CV risk assessment and stratification

The principle that guides prevention strategies is that the CVD risk is a continuous variable, therefore it should be assessed since the diagnosis of the CLL, and before starting any treatment, but without delays in initiating the optimal CLL therapy [26, 43]. The risk assessment includes a comprehensive patient history, information on CV factors, clinical exam (with focus on CV signs and/or presence of symptoms), 12-lead electrocardiogram (ECG), and blood pressure (BP) measurement. A checklist was further developed based on the experts discussion and published literature (see Table 2) [26, 31, 33, 35].

To note, documented CVD, diabetes mellitus, chronic kidney disease or a highly elevated single risk factor are automatically classifying patients at high or very high-risk [26]. In patients at high-risk, the screening should be conducted in depth and include full lipid profile, cardiac biomarkers, echocardiography.

Controversies and unmet needs

Currently, there is no CV risk stratification tool tailored for patients with CLL and BTKi therapy, and, in general, commonly used risk charts do not include patients with cancers [44]. At the same time, for haemato-oncological treatments such as BCR-ABL kinase inhibitors used in chronic myeloid leukaemia or proteosome inhibitors and

Table 2 Checklist of pre-BTKi treatment CV risk assessment

Initial CV risk assessment
☐ Patient history
☐ Concomitant conditions
☐ CVD: arrythmia, heart failure, hypertension, ischemic heart disease, valvular heart disease, left ventricular dysfunction, hypertension
☐ Non-CVD: diabetes, obesity, dyslipidemia, chronic kidney disease
☐ Genetic predisposition*
☐ Cancer history and cancer treatment history (previous cardiotoxic medications)
☐ Other concomitant treatments (previous cardiotoxic medications, CYP3A4 inhibitors, anticoagulants)
☐ CV risk factors (age, smoking, diabetes, obesity, dyslipidemia, chronic kidney disease, sedentary behaviour and alcohol consumption)
☐ Clinical exam
☐ Height and weight measurement (BMI calculation)
☐ Heart rate and BP measurement
☐ Auscultation (tachycardia, audible S3, loud P2, rales)
☐ CV signs (guided by CV symptoms presence): peripheral oedema, hepatomegaly, ascites, jugular venous distension, hepatojugular reflux, cold proximal extremities, oliguria
☐ ECG
☐ Standard baseline laboratory tests (as per routine practice)
Next steps
☐ Risk stratification
☐ High/very high risk if documented CVD, diabetes mellitus, chronic kidney disease or a highly elevated single risk factor
☐ *ESC CVD Risk app*
☐ Refer high-risk patients to cardiologist
☐ Further work-up: full lipid profile, cardiac biomarkers (NT-proBNP), echocardiography

* Not standardized or widely used for CV risk stratification

Abbreiations BMI body mass index, *BP* blood pressure, *CV(D)* cardiovascular (disease), *ECG* electrocardiogram, *ESC* European Society of Cardiology, *NTpro-BNP* N-terminal prohormone of brain natriuretic peptide

Table 3. Definitions used for CVD as cardiotoxicity [31]

Hypertension as cardiotoxicity
- An increase in systolic and/or diastolic BP (thresholds >130/80 mm Hg) after the initiation of cancer treatment without any other contributing changes; it is distinct from chronic hypertension.

Atrial fibrillation (AF)/flutter and ventricular tachycardia as cardiotoxicities:
- Similar definitions to those used in standard practice.

Heart failure as cardiotoxicity:
- The cardiac dysfunction could be asymptomatic or symptomatic (HF)
- Cardiac dysfunction as cardiotoxicity includes:
- (i) reduction of left ventricular ejection fraction (LVEF),
- (ii) symptoms of congestive HF,
- (iii) signs of HF (S3 gallop, tachycardia, or both), and
- (iv) reduction in LVEF from baseline by ≥5% to < 55% with HF signs or symptoms or by ≥10% to < 55% with no HF signs or symptoms

Abbreviations AF atrial fibrillation, *BP* blood pressure, *HF* heart failure, *LVEF* left ventricle ejection fraction

immunomodulatory drugs used in multiple myeloma, such tools (European Society of Cardiology [ESC] Heart Failure Association [HFA]-ICOS proformas) have been developed [26]. ESC guidelines for cardio-oncology recommend risk calculation for patients with cancer aged >40 years, based on the updated Systemic Coronary Risk Estimation (SCORE2) and SCORE2-Older Persons (OP), that estimate the 5- and 10-year fatal and non-fatal CVD events [26, 45]. Of note, in older individuals, the relationship between CVD risk and traditional risk factors (lipids and BP) reduces with increasing age, whereas ageing adds a competing risk of non-CVD mortality [45]. Lastly, based on CVD mortality rates, each country is classified in a cluster – thus, Slovenia is included in the moderate-risk cluster, Croatia in the high-risk cluster, and Bulgaria, Montenegro and Serbia in very-high risk cluster, which should be accounted for when estimating the 10-year risk for total CVD events (for that, the ESC CVD Risk app is available) [45].

After launching the HFA ICOS proformas, the ESC Council for Cardiology Practice focusing on the tyrosine kinase inhibitors became more specific in 2023, recommending to use the proforma proposed for vascular endothelial growth factors (VEGF) TKIs before starting a BTKi therapy [46]. Risk factor classes include prior CVD, increased cardiac biomarkers (pre-treatment, if measured), demographic and CV risk factors, previous cardiotoxic cancer treatment, and lifestyle CV risk factors, based on which the risk level could be further calculated and used as guidance in referring the patients to cardiologists before starting the BTKi treatment [43]. The need of assessing the lipid profile in all patients, as part of the general CV risk assessment or only in high-risk patients is to some extent guided by local practice. Nevertheless, hyperlipidemia with non-high-density lipoprotein cholesterol level >145 mg/dL (3.76 mmol/L) is considered a medium risk factor on the above mentioned proforma [43]. Although clinically relevant and very pragmatic, proformas have not been yet validated and do not have a widespread use in routine practice [47].

Lastly, the genetic testing as part of the CV risk stratification is in its very early stages, far for implementation in routine practice, despite admitting that cardiotoxicity is the combined effect of the cancer therapy, the cancer itself and patient characteristics, including the genetic susceptibility to CV complications [48, 49].

Identification and assessment of CV toxicities under BTKi therapy

In practices where the treatment journey of the CLL patient includes monthly visits for treatment prescription, routine exams could identify early signs and/or symptoms of emerging CV toxicities. Once cardio-oncology emerged as discipline, the definitions used for CVD as cardiotoxicities have been uniformized for a common understanding (Table 3.) [31]. The cardiotoxicity profile of BTKis covered in this paper includes hypertension, atrial fibrillation, ventricular arrhythmia (VA), and HF

[50–52]. Overall, the spectrum of CV events reported for 2G BTKis is lower as compared to 1G BTKis [24, 37, 50].

The general framework agreed by experts was that any new or worsening CV signs or symptoms, increases of BP and heart rate should prompt further work-up for diagnosis and specific intervention. Immediate referral to cardiology specialist should occur in case of any new cardiac symptoms, significant changes in ECG and echocardiography, uncontrolled hypertension, or sudden onset of arrythmia (Table 4) [26, 31, 48, 51–53].

Table 4 Checklist of specific CV assessment during treatment with BTKi

General framework (at every clinical visit) – check for:
- ☐ Signs and symptoms (new/worsening)
- ☐ BP and heart rate (at home & at clinic)
- ☐ ECG (frequency as per routine practice)
- ☐ Concomitant medications

And, as the case:
- ☐ Refer to cardiologist
- ☐ Immediate referral in case of any new cardiac symptoms, significant changes in ECG and echocardiography, uncontrolled hypertension, sudden onset of arrythmia

De novo hypertension
- ☐ Condition predominantly asymptomatic
- ☐ For diagnosis: confirm ambulatory/home BP measurements
- ☐ Treatment threshold for patients with malignancies to receive medications potentially cardiotoxic > 130/80 mmHg
- ☐ Treatment – it may be initiated by the haematologist

De novo AF
- ☐ Asymptomatic/symptomatic
- ☐ AF symptoms: palpitations, fatigue, dizziness, dyspnea, chest pain and anxiety
- ☐ For diagnosis: ECG, echocardiography and +/- 24-hr Holter monitoring
- ☐ For treatment: risk score before anticoagulation
- ☐ Treatment – cardio-oncology team/cardiologist*, with immediate referral for treatment initiation (Note: if symptoms are not serious, treatment with beta-blockers and/or diuretics could be initiated by the haematologist, with immediate referral to cardio-oncology team/cardiologist*)

De novo VA
- ☐ Asymptomatic (incidental finding)/symptomatic
- ☐ History red flags: arrhythmic syncope, family history of premature or sudden cardiac death, proarrhythmic conditions
- ☐ Symptoms: syncope
- ☐ For diagnosis: ECG, and 24-hr Holter monitoring
- ☐ Ventricular tachycardia: emergency requiring hospitalization (immediate referral to cardiologist/emergency department for treatment initiation)
- ☐ Treatment – cardio-oncology team/cardiologist*

De novo HF
- ☐ Asymptomatic/symptomatic
- ☐ Congestion symptoms: dyspnea, orthopnea, paroxysmal nocturnal dyspnea, peripheral (ankle) edema, nocturnal cough, bendopnea, abdominal bloating, early satiety
- ☐ Inadequate perfusion symptoms: intolerance at exertion, fatigue, difficulty concentrating/confusion
- ☐ For diagnosis: 12-lead ECG, NT-proBNP, echocardiography
- ☐ Treatment – cardio-oncology team/cardiologist*, with immediate referral for treatment initiation

*Cardiology specialist in countries where no cardio-oncology team exists

*Abbreviations**AF* atrial fibrillation, *BP* blood pressure, *ECG* electrocardiogram, *hr* hour, *NTpro-BNP* N-terminal prohormone of brain natriuretic peptide

Other practical aspects important for the haematologists treating patients with CLL receiving BTKis were that hypertension usually combines with other CV metabolic factors, with a multiplicative effect on the CV risk [51], and, compared to office BP, home monitoring of BP values are usually lower [51]. Also, incidental non-sustained ventricular tachycardia may be a common finding during routine cardiological evaluations before starting cancer therapy, and in such cases, further assessments are necessary [53].

Controversies and unmet needs

Early detection of CVD in patients with CLL treated with BTKis represents an unmet clinical need and is crucial for implementing timely measures [54]. Advancing age influences both rates and risks of CVD and is an important contributor in the assessment of the cardiotoxicity, with multiple reports indicating that CLL patients with CVD are mostly elderly [36, 51, 54, 55]. True incidence of emerging CVD under BTKi therapy is unknown and it is challenging to distinguish if truly drug-related or not. Emergent CVD could be a consequence of other comorbidities or autonomic cardiac dysfunction due to the cancer treatment [54], and all malignancies are known to be associated with an increased risk of AF and HF [47]. A population-based study performed in Sweden before the introduction of BTKi therapies (2007–2010) showed that one-third (32%) of patients with CLL had baseline CVD at the time of diagnosis, with hypertension and AF being most prevalent (22%, and respectively, 9% at CLL diagnosis) [56]. The study showed that, as compared to age-matched general population, patients with CLL had an overall higher risk for CVD, irrespective of age, pre-existing CVD or CLL treatment, findings applicable before starting to administer BTKis [56]. In a retrospective review conducted in patients receiving BTKis between 2013 and 2022, less than one-third (27%) of patients had prior CVD and one in ten (12%) experienced CV adverse events during BTKi therapy, with odds of developing cardiotoxicity being higher in patients with history of CVD and those treated with 1G BTKis [57]. Additional real-world research showed that patients with CLL have a higher probability to develop AF than general adult population, whereas the risk for developing HF and atrial flutter is similar [58]. In patients with CLL and pre-existing CVD, the odds of developing *de novo* AF or hypertension following treatment with 1G BTKi therapy are higher [59, 60]. Lastly, in patients under BTKi treatment, the risk of developing CV complications increases over time and often hypertension and other forms of CVD persist [61]. All these results stress the need for regular assessments of cardiotoxicity during BTKi treatment

in order to ensure early identification of signs and symptoms of any diseases in the CV spectrum, and their adequate management [62].

Among unmet needs are the limited evidence and validation for applying specifically for patients with CLL receiving BTKis the scores AF-related score risk CHA2-DS2-VASC for predicting stroke and HAS-BLED for bleeding risk [36]. Since risk is dynamic and influenced by increasing age and comorbidities, it should be re-assessed at every contact with the patient with AF [36].

Management and monitoring of CV toxicities during BTKi therapy

The multidisciplinary approach is essential to ensure the adequate management of the emerging BTKi-related cardiotoxicities while balancing the risk-benefit of the continued CLL treatment and specific pharmacological interventions for the CV complications [33, 36]. The dual objective of treating cardiotoxicities is to mitigate the CV complications and avoid unneeded interruptions of the cancer treatment [31, 32, 36]. Complex cases and patients with uncontrolled CVD should be always referred to the cardio-oncology/cardiology services, as available in each country.

Patient education and self-care are crucial components of the effective management of multiple chronic CVD [48, 51, 52]. Enough time should be allocated for discussions with patients and their families to understand the importance of recognizing and reporting new or change in symptoms and signs and how and when to contact the treating physician (haematologist and/or cardiologist) or to immediately visit the emergency department [48, 63]. Information should be provided in various formats, with reiteration of messages at regular intervals [48]. More specifically for hypertensive patients, telemonitoring and mobile applications may prove useful as reminders and registering BP data [51].

Based on ESC guidelines recommendations, experts discussed and proposed a simple framework to guide haematologists in the monitoring and management of CLL patients presenting the most frequently cardiotoxicities encountered in routine practice (Table 5) [48, 51–53].

In case of pre-existing CVD or *de novo* cardiotoxicities, the BTKi treatment approach (continue, reduce dose or discontinue) is to be tailored based on specific recommendations included in the label (Table 6) [64–66]. The collaboration between haematologists and cardiologists is a pre-requisite in all cases to optimize patient's outcomes and should be continuous, starting from the diagnosis of the CLL and sustained throughout the patients' care (Fig. 1).

The frequency of specific CV monitoring strategies usually follows the local practice, which is heterogeneous, and highly depends on the CV burden of the patient. While ECG could be performed in some practices at every visit, in others it is routinely performed more rarely. Experts agreed that, in general, more frequent (i.e., every 3 or 6 months) targeted CV assessments including cardiological examination, 12-lead ECG, echocardiography, and cardiac troponins should occur in selected cases, otherwise, these would be performed annually or only when clinically indicated.

Table 5 Checklist of management and monitoring of CV toxicities during BTKi therapy [48, 51–53]

HTN
☐ Monitoring: mandatory regular BP measurements
☐ 1 L treatment of choice: ACE-inhibitors/ARB
☐ Grade 3 toxicity:
☐ Anti-HTN medication adjustment/new treatment (avoid CYP34a inhibitors*)
☐ In case of uncontrolled hypertension (on multiple anti-HTN treatment): refer to cardiologist
AF
☐ Monitoring: ECG, echocardiography, 24-hr Holter monitoring
☐ Uncontrolled heart rate: interrupt BTKi
☐ Treatment – cardio-oncology team/cardiologist**
☐ Guiding principle (pathway):
☐ A – Anticoagulation/avoid stroke
☐ B – Better symptom management
☐ C – Cardiovascular and Comorbidity optimization
☐ Preferred choice for anticoagulation is apixaban
VA
☐ Monitoring: ECG, echocardiography, 24-hr Holter monitoring
☐ Uncontrolled heart rate: interrupt BTKi
☐ Treatment – cardio-oncology team/cardiologist**
HF
☐ Monitoring: periodic echocardiogram or if clinically indicated (cardiologist's decision); cardiac biomarkers (cardiologist's decision)
☐ Treatment – cardio-oncology team/cardiologist**

*Strong CYP3A4 inhibitors include ketoconazole, itraconazole, posaconazole, voriconazole, indinavir, nelfinavir, lopinavir, ritonavir, saquinavir, clarithromycin, telithromycin, nefazodone, and cobicistat. Moderate CYP3A4 inhibitors include fluconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fosamprenavir, imatinib, verapamil, amiodarone, dronedarone, grapefruit and Seville oranges. Mild CYP3A4 inhibitors include azithromycin and fluvoxamine[50–52].; **Cardiology specialist in countries where no cardio-oncology team exists.

Abbreviations ACE = angiotensin-conversion enzyme; BTKi(s) = Bruton-tyrosine kinase inhibitor(s); ECG = electrocardiogram; HF = heart failure; VA = ventricular arrhythmia.

Controversies and unmet needs

An important unmet need affecting all chronic diseases is sustained adherence to treatments. In patients with CLL and concomitant CVD, polytherapy is common, which brings additional challenges to the optimal management of both conditions. Multiple factors influence adherence, among which dosing is significantly associated with adherence (patients are more adherent to less frequent dosing) [67]. Once recent meta-analysis assessed the impact of the polypills on treatment adherence and clinical outcomes in patients with or high-risk for CVD, finding that patients receiving polypills (fixed-dose

Table 6 BTKi treatment approach for emerging cardiotoxicities according to each label (1G/2G BTKis in use) [64–66]

	Adverse event occurrence	Dose modification		
		Interrupt	Reduce dose	Discontinue
1G BTKi ibrutinib (recommended total daily dose: 420 mg)				
Grade 2 HF	1st	√	√ *(once toxicity has resolved to grade 1 or baseline, resume at 280 mg/day)*	-
	2nd	√	√ *(once toxicity has resolved to grade 1 or baseline, resume at 140 mg/day)*	-
	3rd	-	-	√
Grade 3 arrhythmias	1st	√	√ *(once toxicity has resolved to grade 1 or baseline, resume at 280 mg/day*)*	
	2nd	-	-	√
Grade 3 or 4 HF Grade 4 arrhythmias	1st	-	-	√
2G BTKis				
Acalabrutinib *(recommended total daily dose: 200 mg)*				
Grade 3 or greater non-haematological toxicities	1 st and 2nd	√ *(once toxicity has resolved to G1 or baseline, resume at 100 mg every 12 h)*	-	-
	3rd	√	√ *(once toxicity has resolved to grade 1 or baseline, resume at 100 mg/day)*	
	4th	-	-	√
Zanubrutinib *(recommended total daily dose: 320 mg)*				
Grade 3 or greater non-haematological toxicities	1st	√ *(once toxicity has resolved to G1 or baseline, resume at 320 mg once daily or 160 mg twice per day)*	-	-
	2nd	√	√ *(once toxicity has resolved to grade 1 or baseline, resume at 160 mg once daily or 80 mg twice per day)*	-
	3rd	√	√ *(once toxicity has resolved to grade 1 or baseline, resume at 80 mg once per day)*	-
	4th	-	-	√

Note: Risk-benefit assessment is recommended before resuming treatment

Abbreviations: *1G* first generation, *2G* second generation, *BTKis* Bruton tyrosine kinase inhibitors, *HF* heart failure

combinations) are more adherent to their regimen, and have a lower risk of CV events [68]. Similarly, another meta-analysis in patients with established CVD and at high-risk showed that polypills improved adherence, without an increase in adverse events [69]. However, availability of polypills in each country is impacted by healthcare policies, and polypills may not be preferred by clinicians because they do not allow an easy monitoring of patients, and titration is difficult [69].

While the topic of atherosclerotic disease/acute coronary syndromes is not covered by this paper, an important topic of discussion in the medical community is whether the combination of BTKis with antiplatelets, and particularly, the dual-antiplatelet therapy (DAPT), increases the bleeding risk [70]. BTKis inhibit platelet aggregation through multiple mechanisms, among the most known is the inhibition of glycoprotein VI collagen pathway [70, 71]. Randomized controlled and real-world evidence studies including patients receiving both BTKis and DAPT lack, hence the effects of their combined interaction on the platelets are not fully known [70]. Some papers suggest delaying the start of BTKi in patients with recent coronary artery stent receiving DAPT, until DAPT is not further required [11] or, more conservatively, to consider alternative treatment options than BTKis [72]. Nevertheless, the collaborative discussions between

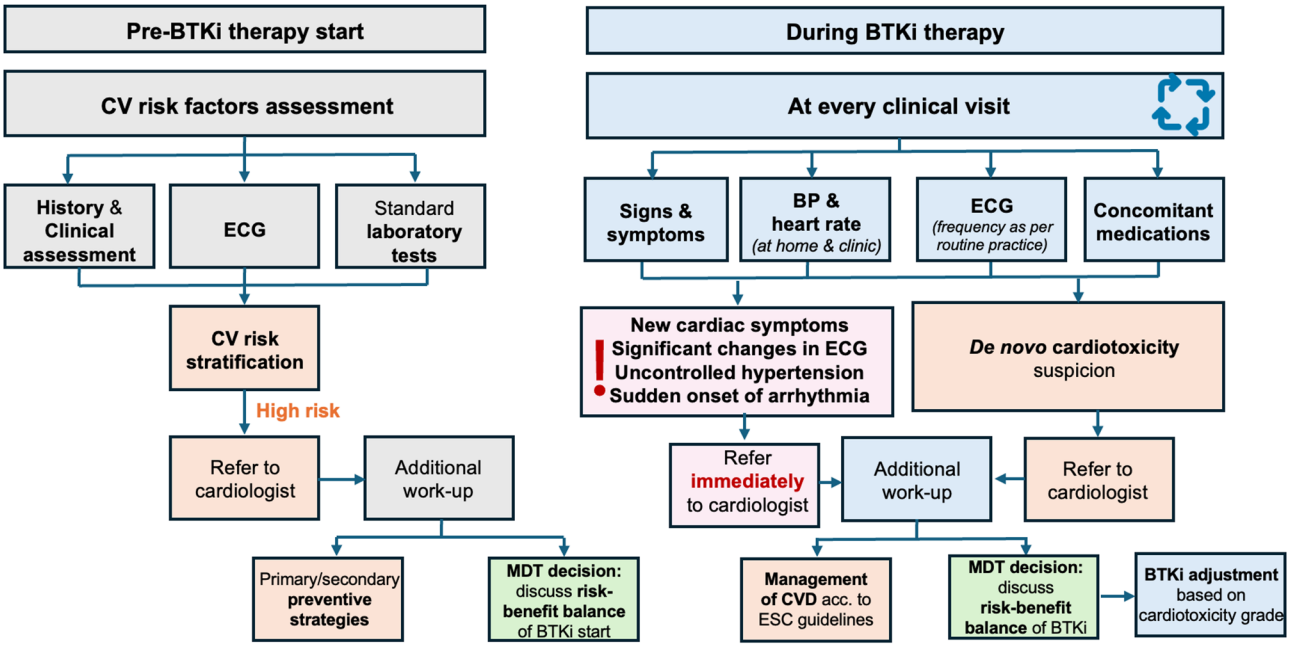

Fig. 1 Summarized clinical pathway for CV risk assessment, and monitoring in CLL patients with BTKi therapy. Abbreviations BP = blood pressure; BTKi = Bruton tyrosine kinase inhibitor; CVD = cardiovascular diseases; ECG = electrocardiogram; MDT = multidisciplinary team

haematologists and intervention cardiologists are the centerpiece of the optimal management of CLL patients treated with BTKis and requiring DAPT [70]. On the other hand, there is an interest on the BTKi antiplatelet properties on the atherosclerotic plaque, with a potential role on prevention of the stent thrombosis [73] and further benefits in patients with acute myocardial infarction using DAPT [71].

Disparities in access to cardio-oncology units in CEE and recommendations

Pre-BTKi CV risk assessment and stratification

Clinical pathway

An established clinical path for CLL patients requiring further cardiology work-up is in place in big clinical centers, but it may be lacking in small community centers. Some areas may be under-staffed and under-resourced and performing echocardiography in time in centers not having cardio-oncology services is delayed, which may impact further CLL treatment decisions. In such cases, identifying and mapping existing resources and developing and/or further adapting the referral network to the healthcare system are recommended.

Local insights

A real-world study on 1G BTKIs performed in Croatia showed no benefit of having pre-treatment cardiologic consultations [74]. In Slovenia, a formal cardio-oncology unit is still in development and there are only a few cardiologists that have additional insight into oncology.

Identification and assessment of CV toxicities under BTKi therapy

Epidemiology

Data on incidence of pre-existing CVD in CLL is scarce in countries across CEE. In a recent small-sized analysis performed in Bulgaria in CLL patients requiring frontline treatment, more than half of patients (59%) had at least one CVD before starting treatment [75].

AF screening

While the ESC cardio-oncology guideline recommends opportunistic screening for AF by means of pulse-taking or ECG rhythm strip at each clinical visit performed by patient during treatment with BTKis, and transthoracic echocardiography in all patients developing AF *de novo* during BTKi therapy [26], the latter may not be easily conducted across many CEE clinical center. The local cardiology teams will decide on the best approach in each case, based on resources available. Early identification of AF, by any means, remains crucial in initiating the adequate antiarrhythmic strategy. A study evaluating the burden of AF in patients with CLL receiving BTKi therapy found that initiation of an antiarrhythmic intervention (pharmacologic treatment or procedure) after the development of the cardiotoxicity was associated with reduction in subsequent overall arrhythmic burden [76].

Management and monitoring of CV toxicities during BTKi therapy

Treatment start

In some countries from CEE (i.e., Bulgaria, Slovenia, Croatia), the antihypertensive treatment could be initiated by the haematologist given the double specialty (internal medicine and haematology).

Multidisciplinary meetings

A common finding was that, although a multidisciplinary care model is in place and discussions between cardiologists and haematologists take place in all participating countries, no formal, regular cardio-haematology multidisciplinary meetings are held in routine practice as in the oncological services (i.e., tumor boards). However, in complex situations, ad-hoc meetings are organized and decisions documented. Presumably, with cardio-oncology services being implemented at a larger extent, best practices will be developed and used as model to transfer into the routine care of CLL patients under BTKi therapy.

Continuity of care documents

An unmet clinical need at country and regional level is the continuity of care as services and documentation. Whereas organizing all medical records issued in separated services accessed by patients during the management of their CLL and associated comorbidities is challenging and dependent of multiple healthcare system related factors, the informational continuity and collaborative care could enhance communication between providers in cross-disciplinary teams, save time during patient's visits and potentially reduce risks of medical errors [77, 78]. In addition, standardized data would facilitate relevant real-world analyses on multiple areas of interest concerning CLL patients, including cardiac toxicities.

Best practices – Slovenia

Anticoagulation clinics are known in medicine as facilities with competence in the management of patients using anticoagulant treatment, which are either independent or in-house services present in big clinical centers [79]. The anticoagulation clinic in Slovenia is affiliated to the academic clinical centers and general hospitals, where specialists (angiology physicians) are available daily for consultation. Patients could be referred also to outpatient practices, where individualized anticoagulation treatment could be initiated. All patients receiving anticoagulation treatment are usually managed in a regional anticoagulation clinic. Patients with CLL presenting bleeding during BTKi treatment are referred to haematologists, with angiology physicians providing opinion on complex situations with concomitant BTKis and direct oral anticoagulants or BTKis and DAPT.

Best practices – Serbia

The largest national haematology centre is found in University Clinical Centre in Belgrade and has established a collaboration with the cardio-oncology outpatient unit of another hospital in Belgrade. Every patient on BTKis with *de novo* CV toxicity or worsening of a preexisting CV condition is referred to this cardio-oncology department for cardiac assessment and treatment of the CV complication, and also opinion on further BTKi treatment administration. A new cardio-oncology unit, that will also be in the University Clinical Centre from Belgrade is about to be formed as part of cardiology clinic, but in the same facility as the haematology clinic, with the common aim of further improving the management of BTKi-related CV adverse events.

Conclusion

Experts from 5 countries in CEE discussed about the assessment of the CV risk and identification, management and monitoring of the CV complications in patients with CLL treated with BTKis from the clinical perspective of haematologists and cardiologists, and differences between countries have been noticed. Each case requires a personalized approach based on multiple patient and disease characteristics, hence practical pathways to follow during the continuity of care in CLL patients requiring BTKi therapy have been proposed. Rigorous evaluation of the CV risk of the CLL patients, regular assessments of cardiotoxicity during BTKi treatment and work in multidisciplinary teams are key to manage CV complications without unnecessary interruptions of the CLL treatment.

Abbreviations

1G	First generation
2G	Second generation
N	No
Y	Yes
ACE	Angiotensin-conversion enzyme
AF	Atrial fibrillation
BCL	B-cell receptor
BMI	Body mass index
BP	Blood pressure
BTK	Bruton tyrosine kinase
BTKi(s)	BTK inhibitor(s)
CEE	Central and eastern Europea
CLL	Chronic lymphocytic leukaemia
CV	Cardiovascular
CVD	CV diseases
DAPT	Dual-antiplatelet therapy
ECG	Electrocardiogram
ESC	European Soiety of Cardiology
HF	Heart failure
HFA	Heart Failure Association
HTN	Hypertension
IC-OS	International Cardio-Oncology Society
LVEF	Left ventricular ejection fraction
MDT	Multidisciplinary team
NTpro-BNP	N-terminal prohormone of brain natriuretic peptide
PI3K	Phosphoinositide 3-kinase
SCORE2	Systemic coronary risk estimation

SCORE2-OP	Systemic coronary risk estimation-older persons
VA	Ventricular arrhythmia
VEGF	Vascular endothelial growth factors

Supplementary Information

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Supplementary Material 1

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This paper is an expert opinion/review. The responses to the preliminary survey completed by participating experts are available on request from the corresponding author.

Declarations

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This paper is an expert opinion/review. The ethic approval was not applicable (no human research involved).

Consent for publication
Not applicable.

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