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Practical Management of Cardiovascular Adverse Events with BTKi Treatment in Patients with Chronic Lymphocytic Leukemia: A Consensus Report by Hematologists and Cardiologists

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Abstract

Background: Cardiovascular (CV) adverse events (AEs), especially atrial fibrillation (AF) and hypertension, have been reported in patients receiving treatments for chronic lymphocytic leukemia (CLL), including Bruton's tyrosine kinase inhibitors (BTKis). Although these AEs are managed effectively in most cases and AE management guidelines exist, practical management approaches are inconsistent across regions and practices. We aimed to address these inconsistencies by developing consensus recommendations. ***Summary:*** A European expert panel was assembled comprising eight hematologists and six cardiologists. Literature analysis, expert interviews, and the Delphi method were used to gain consensus on screening, monitoring, and treatment of AF and hypertension statements. ***Key Messages:*** Maintaining BTKi treatment is paramount to maximize time to next treatment; for patients at high risk of progression, this can be achieved by appropriately treating hypertension and AF and adjusting the BTKi dose. Patients

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should be risk-stratified as low, moderate, high, or very-high risk of cancer therapy-related CV toxicity and treated according to their disease status so that CLL treatment can be maintained. Patient education on symptom monitoring, home blood pressure monitoring, and electrocardiograms (baseline, every 3 months) are recommended to detect/monitor AF and hypertension. Close collaboration between hematologists and cardiologists is vital to achieve optimal patient outcomes.

Introduction

The treatment landscape of chronic lymphocytic leukemia (CLL) has evolved considerably, especially with the approval of targeted agents. Most patients with CLL are now receiving targeted therapies such as Bruton's tyrosine kinase inhibitors (BTKis), B-cell lymphoma-2 inhibitors (BCL-2is), anti-CD20 monoclonal antibodies (mAbs), and combinations of these agents as both continuous therapy and time-limited treatment regimens, which have consistently shown improved PFS versus chemoimmunotherapy (CIT). Per the current European Society for Medical Oncology (ESMO) guidelines, in patients with CLL without a *TP53* mutation or del17p, regardless of IGHV status, preference should be given to time-limited therapies due to the potential for reduced toxicity, reduced risk of polypharmacy, and the benefit of retreatment at relapse [1]. A recent real-world study showed that patients treated with targeted therapies in the first or subsequent lines of therapy had significantly longer overall survival (OS) (8.5 years [95% CI: 8.0–9.1]) versus those who never received them (3.5 years [95% CI: 3.5–3.9]) [2]. The majority of these patients were treated with the BTKi ibrutinib, which has been approved to treat CLL in Europe since October 2014 [2, 3]. A pooled analysis of 3 randomized trials in patients with CLL/small lymphocytic lymphoma showed that the first-line treatment with ibrutinib plus or minus anti-CD20 mAB was associated with OS rates similar to the age-matched general European and US populations [4, 5].

Adverse events (AEs) are observed with all therapies, and each treatment option has a unique safety profile. It is important for patients to be fully informed of all potential AEs when considering treatment options, especially the choice of time-limited treatment and its impact on potential polypharmacy and retreatment options [1]. Specifically, mAbs, such as rituximab and obinutuzumab, may cause infusion-related reactions, hypersensitivity, and immunosuppression; the BCL-2i, venetoclax, could lead to tumor lysis syndrome; BTKis may cause side effects such as atrial fibrillation (AF), arterial hypertension, bleeding, infections, and ventricular arrhythmias, also leading to sudden cardiac death although this is rare, occurring at <0.1% per year [6–18]. While not associated with the hematologic AEs commonly seen with CIT, an increase in certain cardiovascular (CV) AEs, such as new-onset hypertension and AF, became evident with covalent BTKis over time [19, 20]. Given the benefits of BTKis in the treatment of CLL, it is important to appropriately manage the treatment-emergent AEs.

The second-generation BTKis acalabrutinib (approved November 2020 [21]) and zanubrutinib (approved November 2021 [22]) were developed to be more target-specific with fewer off-target effects [8, 23]. The non-covalent BTKi pirtobrutinib is approved in the USA for patients with relapsed/refractory CLL who have received at least two prior lines of therapy, including a BTKi and a BCL-2i [24], and has recently received a positive opinion for European approval as monotherapy in patients with relapsed/refractory CLL after treatment with another BTKi [25]. While initial efficacy results showed parity with ibrutinib [8, 23], CV AEs have been reported in varying rates with all BTKis (online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000547426) [8, 16, 26–37].

The prevalence of BTKi-associated CV AEs differs from some of the other common AEs in CLL. Neutropenia rates of exceed 50% with FCR, BR, and venetoclax+obinutuzumab [16, 38, 39] and infection rates surpass 70% with pirtobrutinib and zanubrutinib [11, 16]. Hypertension rates exceed 15% with zanubrutinib, ibrutinib, and venetoclax+ibrutinib [8, 15, 40] while AF rates are approximately 10–15% for acalabrutinib and ibrutinib [8]. It is also important to consider that patients with CLL may also present with underlying CV disease; for example, approximately 6% of patients may be expected to have AF [41] and 47–66% have hypertension at the time of CLL diagnosis [42].

In most of the real-world studies, the frequency of ibrutinib-associated CV AEs was consistent with clinical trial findings, including AF (3–25%) and hypertension (3–17%) [17, 43–53] (online suppl. Table 1), with no newly identified safety signals. Interestingly, in real-world studies in Europe, rates of hypertension and AF were comparable or lower than those reported in clinical trials [43–45]. This may be due to more regular screening for AF in clinical trials, resulting in higher incidence than

that seen in the real world. However, the proportion of patients discontinuing ibrutinib due to toxicities in these real-world studies ranged from 6 to 22% [43–45, 54]. There are limited real-world data with other BTKis, although initial studies suggest a higher rate of CV events and discontinuations due to AEs in clinical practice versus clinical trials [17, 52, 53] (online suppl. Table 1). Further longer term follow-up from randomized trials and real-world evidence are needed to fully assess the CV AE profiles for these newer BTKis.

As demonstrated in clinical trials and real-world studies, hypertension, AF/atrial flutter, and ventricular arrhythmias have now been confirmed as a class effect common to all BTKis, with appropriate warnings and precautions included in all BTKi product labels and supported by suitable monitoring and management in the cardio-oncology treatment guidelines [18, 19, 55–59]. For example, the European Society of Cardiology (ESC) guidelines include the mention of an increased incidence of AF and arterial hypertension with specific cancer treatments like ibrutinib [60]. Even though the CV AEs observed with BTKi treatments are mostly low grade, they are different from the classical AEs seen by hematologists. Guidelines lack practical information on the management of certain CV AEs and drug-drug interactions, especially for managing patients seen in daily clinical practice who may be older, have comorbidities, and/or are taking concomitant drugs. To address this issue, a panel was formed of expert hematologists and cardiologists from different regions across Europe who are involved in the care of patients receiving CLL treatment; individual interviews were held, followed by a joint consensus meeting. The objective was to gain key practical recommendations on the management of CV AEs in patients receiving BTKi treatment for CLL.

Methods

Literature Review

A literature search for publications from the past 5 years was conducted using the PubMed database on the incidence and management of CV AEs associated with treatment for CLL (focusing on European guidelines). The objective of the literature search was to identify gaps and inconsistencies in management strategies for CV AEs of interest (AF and hypertension) to enable further discussion with experts through individual interviews and develop a practical management consensus through a joint meeting.

Interviews with Experts from Central European and Baltic Countries

Eight hematologists and six cardiologists from Bulgaria, Croatia, Czechia, Hungary, Lithuania, Slovakia, Slovenia, and the United Kingdom were identified, forming the steering committee. A series of discussion topics on CV AEs, informed by literature search, was developed with input from the steering committee chairs, Dr Talha Munir, a hematologist from Leeds, UK, and Professor Nikola Bulj, a cardiologist from Zagreb, Croatia. Interviews were then conducted with the other steering committee members to obtain their perspectives on the management of CV AEs in patients treated for CLL. All feedback received from the interviews was collated and summarized.

Development of Consensus Statements

Consensus statements relating to the management of CV AEs in patients receiving treatment for CLL were developed by the steering committee chairs. The developed statements were largely in line with the 2022 ESC cardio-oncology guidelines [60]; however, some practical recommendations were made to align them with the scenarios seen in everyday clinical practice, considering the heterogeneity of the patient population in the real world, along with local country/regional practices.

Consensus Meeting

The regional experts, comprising the team of authors, gathered in a virtual consensus meeting for review of the consensus statements. The Delphi technique was used to reach a consensus on all statements [61]. The panel members voted anonymously on each statement. Voting options were "Agree" and "Do not agree." A consensus was considered to be reached when ≥75% of panelists voted "Agree" for a particular statement. Where consensus was not reached, a discussion was held to further explore the statement. This was followed by further general discussion around the topics presented. Key practical recommendations were developed using expert guidance gathered from the literature analysis, expert interviews, and the joint consensus meeting.

CV AEs with BTKis

CV AEs have been reported with all BTKis and other CLL treatments in clinical trials. Patients treated in RCTs are not representative of patients in the real world, who may have more comorbidities and be frailer. In

particular, there are limitations when assessing AF or hypertension risk from RCTs as they are neither aimed nor powered to assess these outcomes; thus, caution should be exercised before making conclusions about the comparative safety of BTKis based on RCT evidence alone [56]. Long-term clinical data and real-world evidence are therefore important for assessing BTKi AE profiles. In the pooled analysis of four studies (PCYC-1122e, RESONATE-2, iLLUMINATE, and ECOG-ACRIN E1912), ibrutinib therapy with up to 6 years of follow-up showed that the incidence of hypertension, AF, infection, and bleeding generally declined over time [62].

Regional Disparities in the Management of CV AEs

During the interviews with the panelists, it became clear that, even though ESC onco-cardiology guidelines are widely accepted and followed, these guidelines lack recommendations for specific areas. It was also evident that local factors like availability of drugs, reimbursement requirements, general patient health, and the differences in geographical size and transport options for patients play a role in how patients with CLL are managed across various countries within Europe. Online supplementary Table 2 depicts the level of agreement on the topics presented to the panelists during the individual interviews. There was general agreement on the use of guidelines, screening of high-risk patients, monitoring of blood pressure (BP) by patients at home, AF being treated by a cardiologist, patient education on possible CV AEs, and the need for more information on drug-drug interactions between CLL treatments and concomitant CV treatments. Patients should also be involved in all decisions relating to their CLL treatment.

While all the panelists agreed that the collaboration between a hematologist and cardiologist is vital for patient care, there was great variation on the level of collaboration from region to region. There was general disagreement in terms of referrals, as these often vary from region to region. Some hematologists are internal medicine specialists and therefore can treat most of the CV AEs themselves, whereas others refer patients to cardiologists. Of the patients who are referred to cardiologists, some are referred within the same treatment center, while others may need to seek cardiology care elsewhere. Few centers have specialist onco-cardiologists available for consultation. There is also significant variation between regions on available medications and healthcare structure.

Assessing Baseline CV Risk

In general, all cardio-oncology patients should be stratified as being low, intermediate, high or very high risk of cancer-related CV toxicity [55, 63]. While baseline CV risk assessment may influence the initial choice of therapy, it should not affect the ongoing monitoring strategy for patients treated with a BTKi. As there are no specific tools for baseline CV risk assessment in patients taking BTKis, ESC guidelines recommend using the appropriate Heart Failure Association-International Cardio-Oncology Society (HFA-ICOS) risk proforma (Class IIa) designed for vascular endothelial growth factor TKIs. Briefly, general guidance for risk-stratifying all patients receiving any TKI may include baseline BP and QTc measurements [55, 63]. Patients are identified as either low, moderate, high, or very high risk of cancer therapy-related CV toxicity. For high-risk patients (e.g., males, patients aged ≥65 years, patients with a previous history of hypertension, diabetes, QTc ≥480 ms, AF, heart failure, cardiomyopathy, or severe coronary artery disease or valvular heart disease), a baseline echocardiogram, transthoracic echocardiogram, and measurement of natriuretic peptides are recommended before starting therapy with a TKI. Those identified as low or medium risk are suitable for routine or close oncology follow-up, whereas patients at high or very high risk are recommended for cardiology follow-up. Local guidelines may also suggest geriatric assessments to determine if patients are fit for treatment [64].

Hypertension: Screening, Monitoring, and Referral

Patients initiating BTKi treatment should monitor their BP at home weekly for the first 3 months, then monthly thereafter to monitor for new or worsening hypertension. BP measurements at every clinic visit are recommended [55, 65] and are sometimes a regional requirement for reimbursement. The panelists agreed that it is important to actively take follow-up BP measurements, particularly in patients with uncontrolled hypertension. Referral to a cardiologist should be made if the patient has suspected secondary or resistant hypertension or does not reach the target BP with three antihypertensive medications (difficult-to-control hypertension) [66]. The panelists voted unanimously for the statement: "Referral to cardiology should be initiated for difficult-to-treat hypertension." Thus, the expert panel reached a consensus on all three statements pertaining to screening, monitoring, and referral for the

management of hypertension. These statements are listed in online supplementary Table 3. Importantly, the availability of cardiologists in some European countries may be limited. As a result, in some countries, hematologists and general practitioners can manage lower grade CV AEs, if required. The guidelines outlined here recommend consulting cardiology colleagues in the first instance. If no assistance is available, then hematologists can follow the recommendations below.

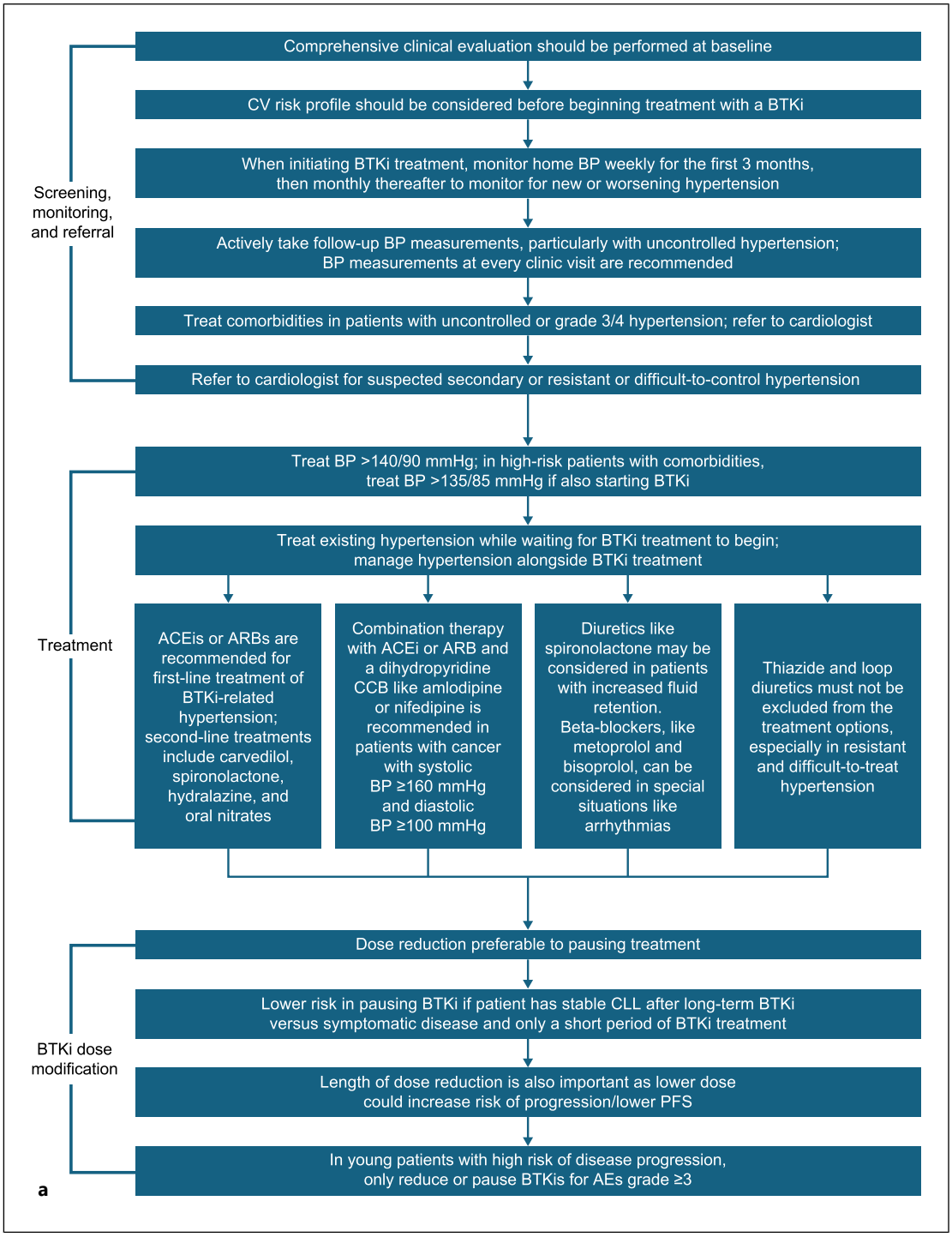
Hypertension: Treatment and BTKi Dose Modification

According to international consensus, the CV risk profile of all patients with hypertension should be considered before beginning treatment with a BTKi [66]. In general, pharmacologic therapy should be initiated when BP is ≥140/90 with a target of ≤120/80 [58, 67, 68], although local guidelines may offer variations for specific age groups or based on ambulatory BP monitoring [65]. Angiotensin-converting enzyme inhibitors (ACEis) or angiotensin II receptor blockers are recommended for first-line treatment of BTKi-related hypertension. Combination therapy with ACEi or angiotensin II receptor blocker and a dihydropyridine (DHP) calcium channel blocker (CCB) like amlodipine or nifedipine is recommended in patients with cancer with systolic BP ≥160 mm Hg and diastolic BP ≥100 mm Hg; single-pill combinations are recommended for those receiving combination therapy. Thiazide and thiazide-like diuretics may be considered in patients with increased fluid retention and as a part of combination therapy. Use of mineralocorticoid receptor antagonists should be considered in resistant hypertension. Beta-blockers, like metoprolol and bisoprolol, can be considered in special situations like arrhythmias, tachycardia AF prevention, and heart failure with reduced/mid-range/preserved ejection fraction; in case of BTKi-related AF, treatment with β-blockers alone or in combination are recommended [55, 68, 69]. As per the British Society of Haematology guidelines for BTKi-related AE management, second-line treatments include carvedilol, spironolactone, hydralazine, and oral nitrates [65].

The panelists were asked if treatment with antihypertensives should begin before or alongside CLL treatment. The panelists agreed that hypertension can be managed alongside BTKi treatment, and there is no need to wait for the hypertension to be resolved before starting BTKis. Some guidelines recommend starting treatment with antihypertensives for BP above 150/90 mm Hg. However, 130/85 mm Hg is a reasonable threshold for starting treatment in high-risk CLL patients if they are also starting BTKi treatment (Fig. 1a); high and very-high risk CLL being defined as those with a CLL-International Prognostic Index (CLL-IPI) score of ≥4 [70, 71]). The panelists also agreed that treatment of hypertension should be aggressive in patients with uncontrolled hypertension.

The panelists unanimously agreed that hypertension should be treated per ESC guidelines (with different BP thresholds for patients with coronary artery disease, chronic kidney disease, and those who are older, etc.), and that patients should be educated on lifestyle improvements (online suppl. Table 4). Patients who develop uncontrolled or grade 3/4 hypertension should be referred to a cardiologist or hypertension specialist. Thiazide and loop diuretics must not be excluded from the treatment options, especially in resistant and difficult-to-treat hypertension. It is important to look for comorbidities (e.g., sleep apnea, hyperthyroidism, obesity, secondary hypertension, etc.) in these patients. Dose reductions and/or interruptions of BTKi treatment while finding the most effective antihypertensive may be required. The decision to pause BTKi treatment also depends on CLL status; if the patient does not have progressive disease after long-term BTKi treatment, there is less risk in pausing BTKis than if the patient has symptomatic disease and has only been on BTKi treatment for a shorter time (Fig. 1a). Any decision to reduce the dose of a BTKi or interrupt treatment should be based on currently available guidelines and summary of product characteristics or prescribing information for each BTKi [3, 21, 22].

Dose modification of BTKi should be avoided where possible, especially in patients at high and very-high risk of progression (patients with CLL-IPI score of ≥4), but it is important to balance this with aggressive management of hypertension to prevent further complications such as AF and heart failure [78, 79]. BTKi dose can be reduced when optimal BP control is not achieved despite maximum antihypertensive therapy [65]. If grade 3 or 4 toxicity occurs, BTKi treatment should be interrupted, and the dose reduced according to the summary of product characteristics or prescribing information [66]. In cases of repeated toxicity, the BTKi treatment should be discontinued, according to the summary of product characteristics or prescribing information, and alternative CLL therapy should be considered [3, 21, 22]. Online supplementary Table 4 lists the consensus statements presented to the panelists on BTKi dose modifications due to hypertension. All panelists agreed that CLL treatment should be maintained, if possible, with dose



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adjustments as necessary. Dose adjustments should be considered with caution in patients whose CLL is at high risk of progression, whereas in all other patients, dose adjustments can be made if needed. Overall, maintaining BTKi treatment was considered the priority, particularly in younger patients.

The experts discussed BTKi dose adjustments and the impact on efficacy. Real-world evidence and meta-

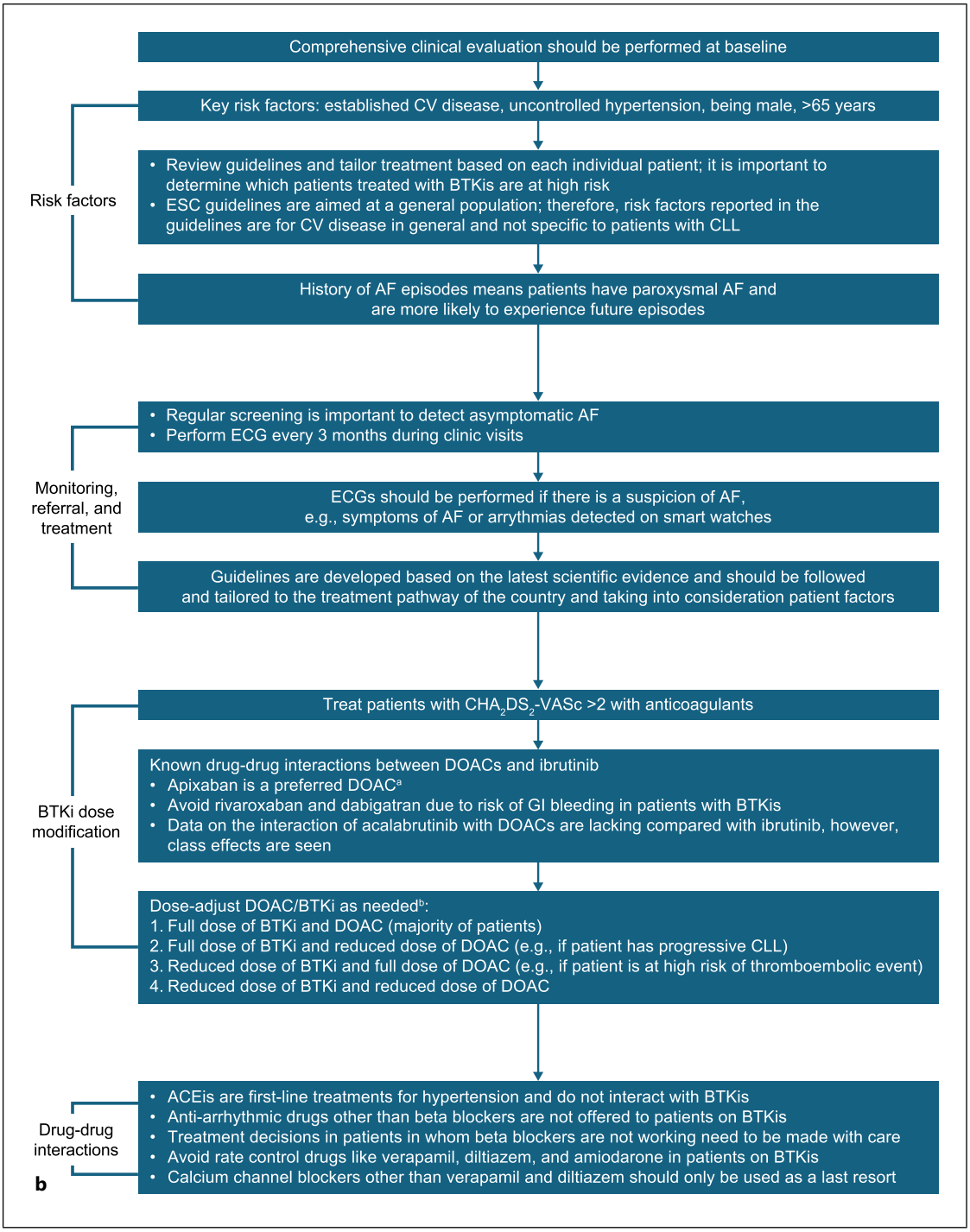

Fig. 1. Expert recommendations on the management of hypertension (**a**) and AF (**b**). GI, gastrointestinal; DOAC, direct-acting oral anticoagulants. [a]Recommendation on the use of apixaban is based on clinical experience only. [b]DOAC dose can be informed by clinical trial data on deep vein thrombosis [72–77].

analysis data indicate that dose reductions do not impact clinical outcomes [43–46], but clinician experience with BTKis showed a lower dose can have an increased risk of disease progression and potentially lower PFS, especially in patients at high risk of progression. Although not a general recommendation, some clinicians suggest

reducing the BTKi dose to reduce the severity of AEs in older patients, as reported in real-world studies [80, 81], but in younger patients with a high risk of disease progression, it is preferable to only reduce or stop BTKis for grade ≥3 AEs [80, 81]. It is also important to consider for how long it is necessary to reduce or interrupt the dose. In patients with comorbidities who are at high risk of CV AEs, initiating treatment with a lower dose of BTKi or switching to an alternative BTKi may be considered. This approach may enable patients to continue treatment for a longer time without interruption, although it should be noted that this is not supported by the official summary of product characteristics or prescribing information for BTKis [3, 21, 22]. Of note, an interventional study evaluating the efficacy and safety of ibrutinib monotherapy or ibrutinib+venetoclax combination with proactive/reactive dose modifications in patients with untreated CLL is ongoing (TAILOR study, NCT05963074) [82]. Close collaboration between the hematologists and cardiologists is vital to find the balance between efficacy and toxicity (Fig. 1a).

AF: Baseline Assessment, Screening, Monitoring, and Referral

A comprehensive clinical evaluation should be performed at baseline, considering the patient's history, comorbidities, risk factors, and concomitant medications [56, 83, 84]. For high-risk patients or those with a prior history of cardiac disease, all CV risk factors should be optimized and predisposing factors should be identified and treated where possible [84]. Baseline and serial (every 3–6 months) electrocardiograms (ECGs) should be performed during the first 12 months of BTKi therapy [65]. Baseline echocardiography is recommended in high-risk patients scheduled to receive BTKis, and transthoracic echocardiography is recommended in all patients who develop AF during BTKi therapy. Opportunistic screening for AF by pulse-taking or ECG rhythm strip is recommended at every clinic visit during BTKi therapy [55]. If the patient's CHA_2DS_2-VASc score is ≥2, 24-h Holter monitoring may be performed to help identify asymptomatic AF [85]. Patients should self-monitor for palpitations, dyspnea, and fatigue during BTKi treatment and be advised to seek assistance if these should occur [18]. Patients should be encouraged to use smart watches or smartphone applications that detect AF if available and appropriate for the patient, as these technologies might play a role in early diagnosis [86].

In patients with preexisting AF, bleeding risk (HAS-BLED) should be assessed and all modifiable risk factors for bleeding should be controlled [85]. Anticoagulant treatment should be chosen based on patient profile. Direct-acting oral anticoagulants (DOACs) are preferred to vitamin K antagonists (VKAs) like warfarin due to their improved safety profile (e.g., reduced bleeding) and noninferiority with efficacy [56, 65, 85]. Dose reduction of DOACs can be considered during the period of full-dose BTKi treatment for patients with high bleeding risk. In patients with a high risk of stroke who are unable to use an oral anticoagulant, low molecular weight heparin (LMWH) can be considered [87].

Management of BTKi-induced AF is complex and requires a multidisciplinary approach with close collaboration between the hematologist and cardiologist, specialist onco-cardiologist, or multidisciplinary team [88]. Patients who develop new AF during BTKi treatment should be promptly referred to a cardiologist for joint decision-making regarding the need for anticoagulation, pharmacological/nonpharmacological treatment of symptoms, and rate/rhythm control [65, 89]. Decisions about the choice of alternative rate treatment, antiarrhythmic treatment, or cardioversion depend on concomitant cardiac disease and should be performed in agreement with a consulting cardiologist [85].

Most (93%) of the cardiologists agreed that genetics, advanced age, high BP, underlying heart disease, alcohol use, diabetes/obesity, and family history are the most important risk factors for AF. The strongest predictors of AF are previous attacks of AF. All panelists agreed that every attempt to optimize patients' CV health should be made before CLL treatment but should not stop patients from starting CLL treatment if clinically indicated. The panelists unanimously agreed that if asymptomatic AF is detected, the patient should be referred to the cardiologist (online suppl. Table 5).

The panelists agreed that among the classical risk factors for AF, established CV disease, in particular heart failure or uncontrolled hypertension, pose the highest risks. Being male and >85 years of age are also key risk factors. Previous episodes of AF (paroxysmal AF) are a strong predictor of future AF episodes; in these cases, future AF episodes should not be considered as new onset. Therefore, defining disease and conditions are important discussions when determining a patient's risk factors. It is also important to determine which BTKi-treated patients are at high risk for AF. Guidelines should be reviewed, and the risk score must be calculated for each patient based on the individual risk factors. It should be noted that risk factors reported in ESC

guidelines are aimed at CV disease in the general population and are not specific to patients with CLL; therefore, collaboration between cardiology and hematology is essential to manage these patients optimally (Fig. 1a).

The panelists discussed the frequency of ECGs while screening and monitoring for AF in patients undergoing BTKi treatment. They agreed that AF screening should be performed in patients who are at high risk. They also agreed that a baseline ECG should be performed on every patient before starting CLL treatment. As BTKis can increase the risk of AF, patients receiving these agents can be considered at risk and should be screened regularly, especially to detect asymptomatic AF. Indeed, clinical trials in which patients required regular ECGs reported higher rates of AF than those in which ECGs were only conducted with standard-of-care frequency, illustrating that asymptomatic AF may be more prevalent in general practice [90]. The panelists agreed that as ECGs provide information for only a brief snapshot of time, they should be performed every 3 months in patients receiving BTKis to improve the chances of detecting asymptomatic disease. An ECG should also be performed if there is a suspicion of AF from clinical examination or from patient reports, e.g., symptoms of AF or arrhythmias detected on smart watches (Fig. 1a).

AF: Treatment and BTKi Dose Modification

Although a multidisciplinary approach is important in managing BTKi-induced AF, in some countries, hematologists may manage lower grade CV AEs. A rate control strategy for AF should be used first in most patients presenting with AF. Beta-blocker treatments approved for heart failure, such as bisoprolol, carvedilol, and metoprolol, are recommended [55, 65, 91, 92]. Digoxin can be considered in these patients, but verapamil and diltiazem, due to CYP3A4 interactions, are relative contraindications [84]. Although non-DHP CCBs like diltiazem and verapamil should be avoided where possible, they can be considered along with BTKi dose reductions and close monitoring if the target pulse rate (below 110 bpm or even lower in symptomatic patients) is not achieved. CCBs should only be used in patients with preserved ejection fraction and without β-blockers. Low-dose digoxin can be considered 6 h before or after the BTKi dose with close monitoring of plasma levels and toxicity [87]. Electrical cardioversion should only be undertaken after a transesophageal echocardiogram is performed to rule out potential thrombi and is only appropriate for select patients; it may not be suitable for all patients on BTKi therapy [57, 93].

As per the ESC guidelines for AF, treatments for rhythm control include cardioversion, antiarrhythmic drugs, percutaneous catheter ablation, endoscopic and hybrid ablation, and open surgical approaches [92]. Hemodynamically unstable patients with new-onset AF should undergo urgent electrical cardioversion. Rhythm control and thus electrical cardioversion may be considered in symptomatic patients in whom antiarrhythmic drugs are contraindicated. After repeated episodes of AF in highly symptomatic patients, antiarrhythmic medication or catheter ablation may be considered [85]. Catheter ablation may be an attractive early treatment option for patients receiving BTKis who develop AF and are at risk of recurrence because of long-term treatment with BTKis [57]. All antiarrhythmic agents except amiodarone are associated with arrhythmia risk, so caution should be exercised when considering them; amiodarone is also not the most suitable treatment as it has drug-drug interactions with BTKi [56, 94].

Online supplementary Table 6 lists the statements pertaining to the treatment of AF and BTKi dose modification/discontinuation in patients with AF. The panelists agreed that patients should be advised of the possible risk of AEs and should be involved in treatment decisions. They also agreed that the CHA_2D_2-VASC and HAS-BLED scores should be utilized in all patients. The panelists voted unanimously on the statement: "Treatment for AF should be initiated per local guidelines under mutual collaboration between the hematologist and the cardiologist." They added that the ESC guidelines for AF (general population) should be followed. When considering antiarrhythmic drugs for the treatment of AF, a cardiology consultation should be obtained. The panelists also emphasized that CLL treatment should be managed by appropriately treating AF and adjusting the dose of BTKis as needed. Again, BTKi dose adjustments should be approached with caution in patients receiving it as first-line therapy or those at high risk of progression; however, it can be done in patients on long-term maintenance treatment.

There was general disagreement among the panelists for the statement, "Each treatment center should devise their own guidelines" (online suppl. Table 6). They discussed that guidelines are developed based on the latest scientific evidence and should be followed, and each patient's score should be individualized, based on

their risk factors. Therefore, each center should follow the internationally accepted guidelines but should devise their own treatment pathways for implementing the guidelines and incorporating local factors that should be considered. The panelists agreed that the statement should be modified to, "Each treatment center should devise their own treatment pathways for implementing the internationally accepted guidelines."

With regard to anticoagulation use, direct factor Xa inhibitors may be preferred in older patients with multiple comorbidities [95, 96] or in patients with CLL who develop AF with appropriate BTKi dose reductions and close monitoring [97]. DOACs are the preferred anticoagulant therapies over VKA or LMWH [98], but dabigatran should be avoided in patients receiving BTKis, given dabigatran is a direct thrombin inhibitor [57]. Similarly, rivaroxaban undergoes CYP3A4-mediated metabolism and there is a theoretical risk that levels of rivaroxaban may be increased in the circulation with concomitant use of ibrutinib [57]. Apixaban can be considered the preferred DOAC in these patients based on clinical experience, registry data showing fewer bleeding episodes, and findings from the phase 3 CARAVAGGIO trial in cancer patients with deep vein thrombosis [57, 72, 88, 89]. Routine use of aspirin should be discontinued or minimized, and patients should be monitored for signs of bruising/bleeding. Dual antiplatelet therapy should be avoided, and patients should be advised to stop vitamin E, fish oil, other online supplements, and nonsteroidal anti-inflammatory drugs before beginning BTKi therapy [85, 88, 89, 99]. If short-term dual antiplatelet therapy is indicated, BTKi should be avoided, and a cardiology consultation should be obtained [89]. Alternatively, if it is decided to start or continue BTKi therapy, VKA needs to be replaced with a DOAC, and single antiplatelet therapy in combination with a DOAC, instead of triple therapy, should be considered [85].

Temporary dose reduction of BTKi may alleviate AF that is not optimally controlled with a β-blocker [65]. No interruption of the BTKi dose is required for grade <3 (asymptomatic or nonurgent medical intervention indicated) AF. For grade ≥3 AF, BTKi treatment should be interrupted but restarted as soon as possible once AF is under control [85, 89]. It is reasonable to lower the dose of BTKis in patients with bleeding manifestations while on anticoagulation [96]. If CHA_2DS_2-VASc score >1, DOAC can be used, and BTKi treatment can be withheld if the rate is uncontrolled; once the rate is controlled, BTKis can be resumed at a reduced dose, or therapy can be changed [18].

It is not recommended to discontinue BTKi treatment, as it may lead to disease progression, and the probability of conversion of AF to sinus rhythm after discontinuation is low [85, 96]. BTKis should be discontinued if unprovoked (without a clear cause), initial AF or significant ventricular tachycardia occurs during the first 3 months of treatment or if they recur during treatment [100, 101] and in patients with clinically relevant nonmajor bleeding on concomitant anticoagulant [97]. Patients with a CHA_2DS_2-VASc score of >2 should be considered for temporary BTKi hold until AF control or discontinuation of BTKi and initiating an alternative therapy for CLL, along with the use of anticoagulation therapy [83, 98, 100, 101]. While the CHA_2DS_2-VASc score is used to predict the stroke risk in patients receiving BTKi who develop new AF, the validity of this score is not well established in patients with cancer [102]; additional studies focusing on the optimal CHA_2DS_2-VASc thresholds in patients receiving BTKis are needed [18]. The decision to hold or change to another BTKi should be individualized and involve the treating hematologist or hemato-oncologist, cardiologist, and the patient [57]. Based on current data, the current German Onkopedia guidelines state that patients already receiving the first-line ibrutinib therapy without relevant side effects should not be switched to acalabrutinib or zanubrutinib, as the study data show no benefits in overall survival to recommend switching [103]. Treatment should be according to the summary of product characteristics or prescribing information for each drug [3, 21, 22].

The panelists agreed that patients with a CHA_2D_2-VASC score ≥2 should be treated with anticoagulants, with considerations made at the individual patient level, and that BTKi treatment increases HAS-BLED risk. The panelists discussed the possible scenarios for concomitant treatment of CLL and AF with dose adjustments as necessary. The four scenarios were: 1) full dose of BTKi and DOAC, which is the case for most patients; 2) full dose of BTKi and reduced dose of DOAC (for instance, in patients with progressive CLL); 3) reduced dose of BTKi and full dose of DOAC (for instance, in patients at high risk of a thromboembolic event); and 4) reduced dose of BTKi and reduced dose of DOAC. There is a paucity of data on DOAC dose reduction; this means that any dose reduction is classified as off-label use, and therefore, more information is needed to make any specific recommendations. In some cases, however, the decision to start a lower dose DOAC with a 10- to 14-day introduction period may be applied before continuing with the full

dose. The experts highlighted the importance of collaboration between the hematologist and cardiologist to evaluate the risk of CLL and thromboembolic events and determine the optimal treatment scenario for each patient (Fig. 1b).

Drug-Drug Interactions

Drug-drug interactions have important clinical implications when starting new treatments in a patient, especially in older and comorbid patients, due to polypharmacy [104]. Anticoagulant treatment often does not require stopping BTKi treatment, but it is crucial to keep potential interactions between BTKis and anticoagulation for AF treatment in mind [66, 83]. Cardiologists should be made aware of the potential for drug-drug interactions with CLL medications if they decide to use agents that interact with CYP3A4, such as amiodarone [89].

The panelists were asked about drug-drug interactions of CLL treatments with other concomitant CV drugs. For the statement, "These drug-drug interactions should not lead to treatment discontinuation in patients whose hypertension and AF have been treated appropriately," there was 100% consensus from the panelists (online suppl. Table 6).

During the general discussion for drug-drug interactions, the panelists discussed how the drugs used to treat AF and hypertension can be managed appropriately so that any drug-drug interactions would not lead to discontinuation of CLL treatment. The general consensus was that ACEis are the preferred first-line treatment for hypertension, as they do not interact with BTKis. The panelists recommended that amiodarone and the non-DHP CCB drugs (verapamil and diltiazem, which are also moderate CYP3A4 inhibitors) be avoided in patients receiving BTKis, although DHP CCBs (nifedipine, amlodipine, etc.) can be used. Rate control drugs other than β-blockers are not offered to patients on BTKis, and treatment decisions in patients who have failed β-blockers need to be made with care. The panelists also agreed that CCBs should only be used as a last resort in patients taking BTKis due to the potential interactions (Fig. 1b).

There are known drug-drug interactions between some of the DOACs and ibrutinib that lead to increased levels of both drugs. The expert panel recommended that the DOACs rivaroxaban, and dabigatran should be avoided due to the risk of gastrointestinal bleeding in patients taking BTKis. Apixaban can be considered a preferred DOAC due to the low rate of gastrointestinal bleeding with apixaban compared with other DOACs [105]; treatment decisions in patients with CLL can be informed by the phase 3 CARAVAGGIO trial data for patients with cancer-associated deep vein thrombosis [72]. The experts agreed that if patients are treated individually, then CLL treatment can usually be maintained, which should be the main treatment goal. A BTKi dose reduction, according to prescribing guidelines, is preferable to stopping the treatment altogether or immediately switching to an alternate treatment.

There is lack of drug-drug interaction data between acalabrutinib/other BTKis and DOACs around dose modifications, although a class effect can be considered likely, and interactions similar to those seen with ibrutinib may be assumed. Information on dose reductions for acalabrutinib and zanubrutinib in the guidelines focus on non-hematological toxicities, and there is no specific guidance for CV events, yet the advice given for ibrutinib is likely to be relatable to all BTKis. This might be a limitation for new patients starting on second-generation BTKis.

Conclusion

Patients with CLL who have a previous history of CV disease are at increased risk of experiencing CV AEs during CLL treatment, demonstrating the importance of screening and monitoring for CV AEs, especially hypertension and AF. Although the summary of product characteristics or prescribing information and treatment guidelines provide extensive recommendations for the management of CV AEs associated with BTKis, they sometimes lack specific practical management recommendations and actionable guidance. The panel of hematology and cardiology experts reached a consensus on most statements pertaining to screening, monitoring, referral, and treatment of hypertension and AF, BTKi dose modifications, and drug-drug interactions. One of the key recommendations was to establish greater collaboration between hematologists and cardiologists. The main aim should be to allow patients to stay on the CLL treatment by actively and aggressively managing any CV AEs.

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Conflict of Interest Statement

T.M. is an advisor and/or receives honoraria from Janssen, AbbVie, AstraZeneca, Morphosys, Alexion, Apellis, Gilead, Novartis, Sobi, Eli Lilly, and BeiGene. O.J. is a speaker for and/or in the advisory board of Johnson & Johnson, AstraZeneca, Eli Lilly, AbbVie, and Roche. L.L. receives speaker honoraria from Johnson & Johnson, AstraZeneca, Servier, AOP Pharma, Chiesi, Berlin-Chemie AG, Pfizer, and Swixx Biopharma. R.P. provides conference support for AbbVie. MSk is an advisor and/or receives honoraria from AbbVie, Johnson & Johnson, AstraZeneca, BeiGene, and Roche. E.C., V.G., M.G., I.M., A.P., L.P., Z.P., M.S.l., and N.B. have nothing to disclose.

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Author Contributions

T.M. and N.B. contributed to the development of the consensus statements. E.Č., V.G., M.G., O.J., L.L., I.M., A.P., L.P., R.P., Z.P., M.S., and M.Š. contributed to the discussion during the consensus meeting, and to the preparation, review, and approval of the manuscript.

Data Availability Statement

The data that support the findings of this study are openly available in PubMed at https://www.ncbi.nlm.nih.gov/.

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