Ibrutinib and atrial fibrillation: A Belgian expert consensus paper

C. Vandenbriele, MD, PhD[1], L. Van der Linden, PharmD, PhD[2], L.N.L. Van Aelst, MD, PhD[1], B. Schwagten, MD, PhD[3], F. van Heuverswyn, MD[4], S. Meers, MD, PhD[5], V. Galle, MD[6], T. Van Nieuwenhuyse, PharmD[2], K.L. Wu, MD[7], M. André, MD, PhD[8], C. Hermans, MD, PhD[9], A. Janssens, MD, PhD[10]

SUMMARY

Over the last decade, the oral Bruton's tyrosine kinase (BTK) inhibitor ibrutinib induced a paradigm shift in the treatment of patients with chronic lymphocytic leukaemia (CLL), mantle cell lymphoma (MCL), and Waldenströms macroglobulinemia (WM). In clinical trials and in real-world studies, ibrutinib proved to be an effective agent with an overall favourable safety and tolerability profile. However, compared with standard chemo-immunotherapy (CIT), ibrutinib was associated with a higher incidence of atrial fibrillation (AF). The patho-physiological mechanisms underlying this increased AF incidence are not completely understood, but it is thought to be related to off-target inhibitory effects of ibrutinib on the Tec protein tyrosine kinase (TEC) in cardiac cells. The prevalence of AF in patients treated with ibrutinib is highest during the first three months of therapy, which warrants an increased vigilance during this treatment phase. However, AF in patients treated with ibrutinib is generally well manageable without ibrutinib discontinuation. Prior to the start of ibrutinib treatment, identification and addressing modifiable risk factors for AF is a first important step. The threshold for haematologists to consult a cardiologist or a cardio-oncologist should be low and a close collaboration between both specialties is warranted. Unnecessary ibrutinib interruptions should be avoided, and uncomplicated AF is not a valid reason to discontinue or interrupt ibrutinib. If anticoagulation is required, direct oral anticoagulants are preferred. In this paper, a panel of haematology and cardiology specialists have provided practical guidance on how to evaluate patients prior to ibrutinib treatment and monitor during ibrutinib therapy. Furthermore, they have provided practical guidance on how to manage AF in ibrutinib-treated patients.

(BELG J HEMATOL 2021;12(4):155-64)

[1]Department of Cardiovascular Diseases, University Hospitals Leuven, Leuven, Belgium, [2]Hospital Pharmacy Department, University Hospitals Leuven, Leuven, Belgium, [3]Department of Cardiovascular Diseases, Ziekenhuis Netwerk Antwerpen (ZNA), Antwerp, Belgium, [4]Department of Cardiology, Ghent University Hospital, Ghent, Belgium, [5]Department of Haematology, Algemeen Ziekenhuis Klina (AZ Klina), Brasschaat, Belgium, [6]Department of Haematology, Maria Middelares (AZ Maria Middelares) Ghent, Belgium, [7]Department of Haematology, Ziekenhuis Netwerk Antwerpen (ZNA), Antwerp, Belgium, [8]Department of Haematology, CHU UCL Namur, Yvoir, Belgium and Pôle Mont, Institute of Experimental and Clinical Research, Université catholique de Louvain (UCLouvain), Brussels, Belgium, [9]Division of Adult Haematology, St-Luc University Hospital, Université catholique de Louvain (UCLouvain), Brussels, Belgium, [10]Department of Haematology, University Hospitals Leuven, Leuven, Belgium.

Please send all correspondence to: C. Vandenbriele, MD, PhD, Department of Cardiovascular Diseases, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium, tel: +32 (0)16 343491, email: christophe.vandenbriele@uzleuven.be.

Conflicts of interest: A. Janssens received travel grants from Janssen, Celgene, Abbvie, and Roche, speakers' fees from Janssen, Roche, Abbvie, Novartis, Amgen, Sanofi-Genzyme, and Celgene, and reports consultancy for Janssen, Roche, Gilead, Abbvie, Novartis, Amgen, and Sanofi-Genzyme. V. Galle reports advisory boards and honoraria from Janssen, Amgen, Abbvie and Celgene. S. Meers received honoraria, travel support and/or fees for advisory boards from Amgen, Celgene, Janssen, Alexion, Mundipharma and Leo Pharma. M. André received honoraria for advisory boards from Takeda, Bristol-Myers-Squibb, Karyopharm, Gilead, Novartis, Seattle Genetics, and Abbvie, Research Grants from Roche, Amgen, Johnson & Johnson, Novartis, Takeda, Millénium, Chugai, and Celgene, and Travel Grants from Roche, Bristol-Myers-Squibb, Amgen, Celgene, and Gilead. K.L. Wu received sponsoring for congress visits, and/or fee for advisory boards from Abbvie, Amgen, Celgene, Janssen, Roche, Sanofi and Takeda over the past three years. C. Hermans received speakers' fees or honoraria for consultancy or advisory boards from Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Pfizer, Daiichi-Sankyo, Leo Pharma, Roche and Janssen. C. Vandenbriele received speakers' fees or honoraria for consultancy or advisory boards from Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Pfizer, Daiichi-Sankyo, Sobi, and Octapharma. L. Van Aelst received honoraria, travel support and/or fees for advisory boards from Janssens-Cilag, Bayer,

INTRODUCTION: EPIDEMIOLOGY OF ATRIAL FIBRILLATION (AF) AND POSTULATED AETIOLOGY OF INCREASED AF RISK WITH IBRUTINIB

Globally, atrial fibrillation (AF) is the most common cardiac arrhythmia, and one in four middle-aged adults in Europe and the United States will develop the condition. Moreover, estimates suggest a greater prevalence in older persons.[1] An increased prevalence has been observed in patients with malignancies, which is even more pronounced among patients with chronic lymphocytic leukaemia (CLL).[2,3] Age, hypertension, diabetes mellitus, coronary artery disease, heart failure and valvular disease are the predominant risk factors for AF in the general population.[4] As CLL, Mantle Cell Lymphoma (MCL) and Waldenströms Macroglobulinemia (WM) (approved indications for ibrutinib in Europe) are mainly diseases of the elderly, the risk of a *de novo* AF diagnosis is further compounded.

Recently, ibrutinib, a potent small-molecule inhibitor of Bruton's tyrosine kinase (BTK), emerged as a paradigm-shifting agent in the treatment of CLL. Ibrutinib has shown to improve the response rate in patients with CLL compared to other CLL treatments and prolongs the progression-free and overall survival in treatment-naive and relapsed/refractory CLL patients, including those with high-risk cytogenetic features.[5-8] Overall, ibrutinib demonstrated a favourable safety profile in clinical trials and is generally well tolerated in clinical practice, regardless of patient's age. However, compared to standard chemo-immunotherapy (CIT), ibrutinib therapy was associated with a higher incidence of AF.[8,9] The pathophysiological mechanisms underlying this increased AF incidence are not completely understood. In addition to BTK-inhibition, ibrutinib has off-target inhibitory effects on Tec protein tyrosine kinase (TEC). Both BTK and TEC are expressed in cardiac tissue, and their expression is higher in atrial tissue in AF than in atrial tissue in sinus rhythm. This suggests that BTK and TEC have functional roles during cardiac stress.[10] Furthermore, BTK and TEC are known regulators of the phosphoinositide 3-kinase–AKT pathway, which is a critical regulator of cardiac protection under stress conditions. Down-regulation/inhibition of the PI3K/AKT pathway due to ibrutinib might render the heart more prone to AF.[11] Nevertheless, other precipitants for AF such as structural heart disease (e.g. mitral regurgitation, left atrial dilatation, dilated cardiomyopathy, myocardial fibrosis), which are frequently seen in the elderly population, should be taken into consideration as well.

Currently, clinical practice guidelines on the management and prevention of AF in patients treated with ibrutinib are poorly defined. Therefore, an expert panel consisting of Belgian haematologists, cardiologists, pharmacologists, hospital pharmacists, and haemostasis specialists convened to develop a practical consensus paper on the prevention and management of AF in patients on ibrutinib. Since randomised controlled trial (RCT) evidence specific to management strategies for AF is lacking, several recommendations presented in this paper are based on expert opinion and are not necessarily always in line with the Summary of Product Characteristics (SmPC).

CLINICAL DATA ON IBRUTINIB AND AF

In 2017, Brown *et al.* pooled data from 1,505 CLL and MCL patients enrolled in four large RCTs (RESONATE, RESONATE-2, HELIOS, and RAY) to characterise the incidence of AF in ibrutinib treatment.[9] At a median follow-up of 16.6 months the overall incidence of AF (including atrial flutter) was 6.5%, increasing to 10.4% at 36 months, which corresponded to a cumulative AF risk of 13.8% at 36 months. After 36 months of follow-up, treatment interruptions or

Daiichi Sankyo, Vifor Pharma and Pfizer. B. Schwagten received speakers' fees or honoraria for consultancy or advisory boards from Bayer, Boehringer-Ingelheim, Janssen, Pfizer, Daiichi-Sankyo and Medtronic. F. Van Heuverswyn received speakers' fees or honoraria for consultancy or advisory boards from Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Pfizer, Daiichi-Sankyo and Janssen. L. Van der Linden received speakers' fees or honoraria for consultancy or advisory boards from Bayer, Bristol-Myers Squibb, Pfizer, Daiichi-Sankyo, Sanofi, Servier and Amgen. T. Van Nieuwenhuyse received speaker's fees or honoraria for consultancy or advisory boards from AstraZeneca, Janssen and received sponsoring for congress visits from Pfizer and Takeda over the past three years.

Keywords: Anticoagulation, atrial fibrillation, chronic lymphocytic leukaemia, ibrutinib, lymphoma.

Acknowledgements: This paper was based on a meeting of Belgian haematologists, cardiologists, hospital pharmacists and specialists in haemostasis held on April 15th, 2019, which was sponsored by Janssen-Cilag NV. Medical writing assistance was provided by Tom Feys (Ariez International BV) and was funded by Janssen-Cilag NV. The authors accept full responsibility for all content and editorial decisions of the manuscript, upholding the principle of editorial independence and integrity. All authors attended the expert meeting that formed the basis of this manuscript. All authors participated in data interpretation and manuscript writing and provided their final approval for this manuscript.

discontinuations of ibrutinib due to AF occurred in only 3.3% and 0.9% of patients respectively.[9] Brown *et al.* also revealed that AF predominantly occurred during the first 6 months of treatment (5.3%), after which the incidence declined to less than 1% between 6 and 18 months of treatment.[9] Importantly, 85.2% of patients with a previous history of AF or abnormal heart rhythm did not suffer from new AF episodes when treated with ibrutinib, and this was also the case for 90.5% of patients with a history of hypertension. Thus, a history of AF should not preclude patients from commencing ibrutinib treatment. Univariate analyses identified prior history of AF, ibrutinib therapy, age over 65 years, hypertension, and hyperlipidaemia as significant risk factors for developing AF.[9] Multivariate analyses showed prior history of AF, ibrutinib therapy, and age over 65 years as independent predictors of AF.[9] With respect to efficacy, the presence of AF did not impact progression-free survival (PFS) in ibrutinib-treated patients.[9] Two additional publications by Yun *et al.* and O'Brien *et al.* also assessed the safety profile of ibrutinib in these four RCTs.[12,13] O'Brien *et al.* reported that cardiac disorders were reported in 15% of ibrutinib-treated patients as compared to 10% in the control arms, with exposure-adjusted incidence rates of 0.15 and 0.14 in the ibrutinib and control arm, respectively. Their findings were in accordance with the data from Brown *et al.*: 1) the incidence of AF was higher in ibrutinib-treated patients than in the control arm (6% *vs.* 2%), 2) the prevalence of AF was highest in the first three months of ibrutinib therapy and 3) treatment discontinuations due to AF were rare (1%).[13]

Recently, several updates of clinical trials evaluating ibrutinib in patients with CLL or MCL provided long-term follow-up data on the incidence of AF in ibrutinib treatment. For example, updated results of a phase II study (PCYC-1102/1103) of ibrutinib-treated CLL patients with up to 8 years of follow-up, reported ≥ grade 3 atrial fibrillation in 6% (n=2) in first-line and 10% (n=10) in relapsed/refractory patients.[14] In addition, data from RESONATE in patients with previously treated CLL with a median follow-up of 65.3 months showed an AF rate of 12% (≥ grade 3 in 6%, mainly during first year 4%).[15] Data from RESONATE-2 with first-line ibrutinib treatment, showed AF of any grade in 16% of patients (≥ grade 3: 5%) after a median follow-up of 60 months.[16] Long-term follow-up data in MCL (41 months, pooled analysis from PCYC-1104, SPARK and RAY studies) revealed an AF prevalence of 11.4% (≥ grade 3: 6.2%).[17] Long-term follow-up data (59 months) of ibrutinib monotherapy in previously-treated WM patients showed that 12.7% of patients experienced atrial arrhythmia.[18] Finally, in the ibrutinib mono-therapy arm of the iNNOVATE study in patients with WM, no atrial fibrillation events were reported with a median follow-up of 42 months.[19]

GENERAL EVALUATION BEFORE INITIATING OF IBRUTINIB TREATMENT AND SPECIFIC PREVENTIVE MEASURES TO MINIMISE DE NOVO AF IN PATIENTS TREATED WITH IBRUTINIB

GENERAL RECOMMENDATIONS BEFORE STARTING IBRUTINIB

Routine laboratory testing (i.e. complete blood count, general biochemistry) should be performed and patients should undergo a thorough evaluation of their concomitant therapies and comorbidities, as some are generally known as potential risk factors for development of AF (see further). In general, and not specifically linked to the development of AF, prescribers should be aware that ibrutinib is a substrate of CYP3A4 and may be a substrate of P-gp and as a result, interactions with other agents leading to changes in plasma levels cannot be excluded. Therefore, it is recommended to routinely evaluate the risk for clinically relevant drug-drug interactions. It should also be discussed with the patient that the use of over-the-counter preparations with possible drug-drug interactions (e.g. St. John's Wort) is contraindicated.

The current SmPC highlights the increased bleeding risk with ibrutinib and supplements such as fish oil and vitamin E preparations should be avoided. Given the potential need for long-term anticoagulation for stroke prevention, our expert recommendation is to address modifiable bleeding risk factors, and for example, concomitant non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin use should be avoided. In addition, a re-evaluation of antiplatelet agent use, and an optimisation of the antihypertensive drug regimen is also highly recommended before starting ibrutinib. The same applies to the use of supplements that might further add to the bleeding risk (i.e. vitamin E and fish oil).[20,21]

SPECIFIC PREVENTIVE MEASURES TO MINIMISE DE NOVO AF IN PATIENTS TREATED WITH IBRUTINIB

Primary prevention of AF is the first step in prevention and refers to the implementation of appropriate measures in patients at risk but without previous documentation of AF. This strategy relies on the identification and management of risk factors and comorbidities predisposing to AF, before the development of atrial remodelling and fibrosis.[1] Important AF risk factors include hypertension, heart

failure (HF), diabetes mellitus, obesity, excess alcohol or caffeine consumption, valvular heart disease, coronary artery disease, vascular disease, chronic kidney disease, inflammatory diseases, chronic obstructive pulmonary disease, pneumonia, hyperthyroidism, and the presence of obstructive sleep apnoea.[1]

Patients who present with CLL often have multiple of these risk factors for atrial fibrillation. One of these is hypertension. Adequate management of hypertension may prevent AF by reducing atrial stretch, but inhibition of the renin-angiotensin-aldosterone system may exert an additional protective role by suppressing electrical and structural cardiac remodeling.[1] Hypertension is not only a risk factor for development of AF, it is also a known adverse event of ibrutinib, and its risk persists over time.[15,16] Data from RESONATE in patients with previously treated CLL with a median follow-up of 65.3 months showed an hypertension rate of 21% (≥ grade 3 in 9%).[15] Over the course of six years, the prevalence of ≥ grade 3 hypertension was 4%, 8%, 7%, 7%, 8%, and 11% over years zero to one, one to two, two to three, three to four, four to five, and five to six, respectively.[15] Most patients who experienced AF had one or more relevant risk factors (92%), including hypertension (38%). Data from RESONATE-2 with first-line ibrutinib treatment, showed hypertension of any grade in 26% of patients (grade 3: 9%; no grade 4) after a median follow-up of 60 months.[16]

In order to identify AF, other arrhythmias or ECG abnormalities suggestive for an underlying heart disease, it is recommended to perform a 12-lead electrocardiogram (ECG) before initiating treatment with ibrutinib.[22] We do not advise routine Holter monitoring or referral for echocardiography before the start of treatment. Only in patients in whom the medical history, clinical examination or the ECG indicate any abnormality, further investigations should be considered, and a referral to a cardiologist should be initiated. Overall, the threshold for haematologists to consult a cardiologist or a cardio-oncologist should be low and a close collaboration between both specialties is warranted. Especially patients with structural heart disease, including heart failure or left atrial abnormalities, should be carefully counselled and closely monitored regarding incident AF.[23]

The vast majority (85.2%) of patients with a history of AF did not have a recurrence while being treated with ibrutinib.[9,22] Therefore, a history of AF should not preclude patients from commencing ibrutinib.

FOLLOW-UP DURING IBRUTINIB THERAPY

In their recommendations for the management of AF in ibrutinib treated patients, Boriani *et al.* advise to repeat the ECG every two months during the first six months of therapy and every six months thereafter.[24] The rationale for this more frequent screening during the first six months is based on the increased AF incidence during the initial treatment phase, which declined to a lower level thereafter. Whether a two-monthly ECG during the first six months of therapy should be routine practice can be debated. We consider the use of ibrutinib as an additional risk factor for the development of AF. The prescriber should remain vigilant for the development of AF or its consequences (heart failure, thrombo-embolic events) during ibrutinib treatment. The panel encourages repeated ECG testing or Holter monitoring (if the ECG remains negative for AF) only when AF is suspected. This is especially important when other risk factors are present, in addition to ongoing treatment with ibrutinib. Patients may also use available wearable devices and smartphone apps for self-monitoring.

Patients should also be made aware of potential symptoms of atrial fibrillation like palpitations, weakness, chest pain, new onset of dyspnoea, dizziness or fainting and should inform their physician immediately.

Given the increased risk for hypertension in patients treated with ibrutinib, it is also advised to monitor the blood pressure (e.g. by the patients; general practitioner) closely throughout the course of treatment in every patient.[22]

MANAGEMENT OF AF IN PATIENTS TAKING IBRUTINIB

GENERAL APPROACH

In the pivotal ibrutinib clinical trials, AF has been managed per typical standards of care for AF management by both rate control and rhythm control agents. Diuretics, ACE inhibitors, calcium channel blockers and anti-arrhythmic drugs were used in 36.7%, 38.8%, 24.5% and 36.7% of patients, respectively.[9]

The SmPC states that ibrutinib should be withheld for any new onset or worsening ≥ grade 3 non-haematological toxicity, ≥ grade 3 neutropenia with infection or fever, or grade 4 haematological toxicities. Once the symptoms of toxicity have resolved to grade 1 or baseline (i.e. recovery), the treatment with ibrutinib may be reinitiated at the starting dose. If toxicity re-occurs, the once daily dose should be reduced by one level (see SmPC). A second dose reduction by 140 mg may be considered if needed. If toxicity persists or recurs following two dose reductions, ibrutinib should be permanently discontinued.[8]

Our expert recommendation supports an approach that differs from the SmPC for two reasons. Firstly, it is not well

TABLE 1. Clinical risk factors for stroke, transient ischaemic attack and systemic embolism in the CHA_2DS_2-VAS_c score (Adapted from Hindricks et al., 2020).[1]

CHA_2DS_2-VAS_c risk factor	Points
Congestive heart failure[a] Clinical heart failure, or objective evidence of moderate to severe left ventricular dysfunction, or hypertrophic cardiomyopathy	+1
Hypertension[b] or on antihypertensive therapy	+1
Age 75 years or older	+2
Diabetes Mellitus Treatment with oral hypoglycaemic drugs and/or insulin or fasting blood glucose >125 mg/dL (7 mmol/L)	+1
Stroke Previous stroke, transient ischemic attack, or thromboembolism	+2
Vascular disease Angiographically significant coronary artery disease, previous myocardial infarction, peripheral artery disease, or aortic plaque	+1
Age 65-74 years	+1
Sex Female	+1

CHA_2DS_2-VAS_c score = congestive heart failure, hypertension, Age ≥ 75 (doubled), diabetes, stroke (doubled), vascular disease, Age 65-74 and sex (female).

[a]Recent decompensated heart failure irrespective of left ventricular (LV) ejection fraction (thus incorporating heart failure with preserved ejection fraction or heart failure with reduced ejection fraction), or the presence (even if asymptomatic) of moderate-severe LV systolic impairment on cardiac imaging. Hypertrophic cardiomyopathy confers a high stroke risk and oral anticoagulant is beneficial for stroke reduction.

[b]History of hypertension may result in vascular changes that predispose to stroke, and a well-controlled blood pressure (BP) today may not be well controlled over time. Uncontrolled BP - the optimal BP target associated with the lowest risk of ischaemic stroke, death, and other cardiovascular outcomes is 120 - 129/<80 mmHg.

established that AF with ibrutinib is dose-dependent; hence, the proposed dose reduction in the SmPC may be inconsistent with the pathophysiology of AF.[12] Secondly, the AF grading system by Common Terminology Criteria for Adverse Events (CTCAE) is not supported by the cardiologists in the panel. AF is largely considered to be dichotomous: it is either present or absent. It is also a common disbelief that stroke depends on the duration/sustainability or the symptomatic burden of AF. The annual stroke risk among patients with paroxysmal AF and permanent AF is largely similar.[25,26]

AF is most commonly regarded as a sign of an underlying heart problem, and ibrutinib may be regarded as a potential trigger. As such, the appropriate strategy in most patients developing AF with ibrutinib is to address the underlying heart condition rather than modifying the dose or schedule of ibrutinib, insofar the AF is stable and not associated with a life-threatening condition. A similar recommendation with respect to AF management was formulated by de Weerdt *et al.*[27] In this paper, a Dutch expert panel concluded that it cannot be recommended to withhold ibrutinib when AF develops because this does not seem to result in a higher resolution rate of the AF, but might compromise the progression-free survival and overall survival of patients.[27,28] Likewise, the Dutch experts also concluded that dose reductions of ibrutinib were not warranted as they did not alter the resolution rate of AF, and given the observation that once AF has developed, ibrutinib withdrawal does not change its course, appropriate treatment of AF should be started as would be done in non-ibrutinib-treated patients.[27,28] In summary, in case of uncomplicated AF, the expert panel advises neither to interrupt ibrutinib therapy, nor to reduce its dose. AF management should prioritise addressing the underlying cause(s) and risk factors. However, it may be reasonable in some circumstances, particularly for cases of complicated AF (e.g. compounded by unstable, difficult to control or life threatening heart failure), to consider interrupting ibrutinib treatment or reducing the dose. Decisions should be made on a case-by-case basis and in consultation with the patient's cardiologist.

The expert panel recommends calculating the CHA_2DS_2-VASc score (*Table 1*) at the first detection of AF, after which anticoagulation for stroke prevention and rate/rhythm control agents for symptom control should be initiated accordingly.

HEART RATE AND RHYTHM CONTROL AGENTS FOR SYMPTOM CONTROL

Rate control is an integral part of the management of AF patients, and is often sufficient to improve AF-related symptoms. Pharmacological rate control can be achieved with nodal blockers such as beta-blockers, digoxin, diltiazem and verapamil. Other antiarrhythmic drugs also

TABLE 2. The HAS-BLED risk score for the prediction of bleeding in anticoagulated patients with atrial fibrillation (Adapted from Boriani *et al.*, 2018).[24]

	Clinical characteristic	Score
H	Hypertension (uncontrolled, >160 mmHg systolic)	1
A	Abnormal renal or hepatic function (1 point each)	1-2
S	Stroke	1
B	Bleeding history or predisposition (anaemia)	1
L	Labile INR (TTR <60%)	1
E	Elderly (age >65 years)	1
D	Drugs (antiplatelet agents and NSAIDs) or alcohol (1 point each)	1-2
	Maximum score	**9**

High risk if score ≥4 => occurrence of bleeding ≥8% per year
Moderate risk if score 2-3 => occurrence of bleeding 2-4% per year
Low risk if score 0-1 => occurrence of bleeding <2% per year

INR: international normalised ratio; TTR: time in therapeutic range; NSAID: nonsteroidal anti-inflammatory drugs.

possess rate-limiting properties (amiodarone, dronedarone, sotalol, propafenone), but they should preferentially be used in AF patients who are also suitable candidates for a rhythm control strategy. See the '2020 ESC Guidelines for the management of atrial fibrillation' for an overview of rate control drugs.[1]

In 2018, Ganatra *et al.* proposed an algorithm for the management of ibrutinib-associated AF.[11] In hemodynamically stable patients, Ganatra *et al.* preferred rate control over rhythm control, because the ability to maintain sinus rhythm after cardioversion may be limited by the persistent presence of ibrutinib as a trigger for AF.[11] Of note, there is no need to interrupt ibrutinib treatment when cardioversion is performed.

As previously indicated, ibrutinib is metabolised by CYP3A4, and concomitant use of CYP3A4-inhibitors or -inducers has been demonstrated to have profound effects on serum ibrutinib levels in healthy volunteers.[29] Ibrutinib itself may also increase the levels of P-gp substrates.[8] In this respect, it is important to note that verapamil, diltiazem, amiodarone and dronedarone are known CYP3A4 inhibitors, which can increase plasma levels of ibrutinib. Therefore, the dose of ibrutinib should be reduced to 280 mg when administered concomitantly with one of these drugs. In addition, verapamil, amiodarone, dronedarone and diltiazem are also P-gp substrates, as are quinidine and digoxin.[11,27,28] P-gp inhibition by ibrutinib may increase plasma levels of e.g. digoxin. Therefore, to minimise the potential for an interaction, digoxin should be taken at least six hours before or after ibrutinib (SmPC).[8] Beta-blockers are usually safe, with no known clinically relevant pharmacokinetic interactions with ibrutinib, and as such, they should be used as first-line rate control agents.[11] Cardio selective beta-blockers are preferred. If a second agent is required to obtain adequate rate control, Ganatra *et al.* recommend the use of verapamil or diltiazem (in patients without systolic dysfunction) after appropriate dose reduction of ibrutinib, given the common interaction with CYP3A4 and P-glycoprotein (P-gp), and with increased vigilance for ibrutinib toxicity.

Antiarrhythmic drugs can restore and maintain sinus rhythm in patients with AF (i.e. pharmacological cardioversion). This approach results in restoration of sinus rhythm in approximately 50% of patients with recent-onset AF (<48 hours). Electrical cardioversion restores sinus rhythm quicker and more effectively than pharmacological cardioversion and is associated with a shorter hospital stay. Conversely, pharmacological cardioversion does not require sedation or fasting. Flecainide and propafenone are effective for pharmacological cardioversion, but their

TABLE 3. Practical guidance to mitigate the AF risk in patients treated with ibrutinib.

Patient education and lifestyle changes	
Before ibrutinib treatment	During ibrutinib treatment
Identify and address CV risk factors	Identify and address CV risk factors
Address modifiable risk factors for AF	Monitor BP regularly
Aim for a BP ≤130/80 mmHg	Monitor ECG regularly
Optimise the antihypertensive drug therapies	Avoid unnecessary ibrutinib interruptions
Perform a diagnostic work-up as clinically indicated	Ibrutinib increases the risk of de novo AF -> continuously address other risk factors for AF
• **Address modifiable risk factors for bleeding** • **Collaborate with a cardiologist**	

CV: cardiovascular; BP: Blood Pressure; ECG: electrocardiogram; AF: Atrial Fibrillation.

[1]Risk factors for AF include a.o. hypertension, heart failure (HF), diabetes mellitus, obesity, excess alcohol or caffeine consumption, valvular heart disease, coronary artery disease, vascular disease, chronic kidney disease, inflammatory diseases, chronic obstructive pulmonary disease, hyperthyroidism, and the presence of obstructive sleep apnoea (Hindricks *et al.*, 2020).[1]

[2]Modifiable bleeding risk factors include a.o., hypertension, excess alcohol, medication predisposing to bleeding such as antiplatelet drugs and non-steroidal anti-inflammatory drugs. Potentially modifiable bleeding risk factors include a.o., anaemia, impaired renal function, impaired liver function, reduced platelet count or function (Hindricks *et al.*, 2020).[1]

use is restricted to patients without structural heart disease. If a rhythm control strategy is chosen, the sodium channel blocker flecainide might be preferred, according to the expert panel, given the absence of CYP3A4 or P-gp interactions. Flecainide is contraindicated in case of coronary artery disease or structural heart disease. Ibutilide is an alternative when available but carries a risk of torsades de pointes. Vernakalant can be administered intravenously to patients with recent-onset AF, suffering from mild heart failure (NYHA I or II), including those with ischaemic heart disease, if they do not present with hypotension or severe aortic stenosis. Amiodarone can be considered in elderly patients with heart failure and in patients with ischaemic heart disease.[1] Physicians need to be aware about potential drug-drug interactions when combining ibrutinib with amiodarone (moderate CYP3A4 inhibitor: reduce ibrutinib to 280 mg/day). An overview of anti-arrhythmic drugs for pharmacological cardioversion can be consulted in the '2020 ESC Guidelines for the management of atrial fibrillation'.[1]

In patients without major structural heart problems and without any significant comorbidities, ablation could represent an alternative strategy to provide long-term rhythm control in symptomatic AF. Any potential drug-drug interactions would then be avoided.

ANTICOAGULATION FOR STROKE PROPHYLAXIS IN PATIENTS WITH AF ON IBRUTINIB

The increased risk of bleeding associated with ibrutinib treatment makes the management of anticoagulation for stroke prophylaxis in patients with AF on ibrutinib complicated, balancing the risk of thrombotic complications and the risk of bleeding.

Ibrutinib was associated with increased bleeding rates in combination with a vitamin K antagonist (VKA). In the pooled analysis reported by Brown *et al.*, the overall incidence of major haemorrhage in patients receiving anticoagulant therapy was 6.4%. Importantly, the incidence of major bleeding was lower in patients treated with a direct oral anticoagulant (DOAC, 2%) compared to patients receiving VKA (11.1%) or low-molecular weight heparin (LMWH, 6.2%).[30] As a result, DOACs are the preferred anticoagulation therapy in patients treated with ibrutinib, and warfarin or other VKA should not be administered concomitantly with ibrutinib, as stated in the SmPC.[8] Anticoagulants or antiplatelet agents were used in more

TABLE 4. Expert recommendations for the management of AF in patients on ibrutinib.

<table>
<tr><th colspan="3">AF management during ibrutinib treatment</th></tr>
<tr><td colspan="3">Collaborate with a cardiologist</td></tr>
<tr><td colspan="3">Avoid unnecessary ibrutinib interruptions: uncomplicated AF is not a valid reason to discontinue or interrupt ibrutinib</td></tr>
<tr><td colspan="2">AF treatment</td><td>Thrombo-embolic prevention</td></tr>
<tr><td colspan="2">Correct reversible triggers
(alcohol, electrolyte disturbances, hyperthyroidism, etc.)</td><td rowspan="2">• Estimate thrombo-embolic and bleeding risk
• Provide adequate anticoagulation to patients with a CHA2DS2VASC≥1 (≥2 in women)
• Avoid VKA use (increased risk of ICH)
• Prefer DOAC use (in accordance with observational data from ibrutinib landmark trials)</td></tr>
<tr><td>Provide adequate rate control</td><td>Rhythm control in selected patients</td></tr>
<tr><td>• HR: 80 - 110 bpm
• Pharmacological options: cardioselective betablocker + add-on digoxin[1] if needed (mostly limited to sedentary patients)
• Rather avoid verapamil and diltiazem due to drug-drug-interactions[2]
• + amiodarone[2] has HR-lowering characteristics as well</td><td>• Ibrutinib is a persistent risk factor, probably attenuating any longstanding effects of rhythm control
• Rhythm control should hence only be provided in selected patients to reduce symptomatic AF burden
• Emergency Department Cardioversion should be provided in unstable patients.[6]
• Pharmacological options: flecainide[3], propafenone[3], ibutilide[4] or vernakalant[5]
• Amiodarone[2] in older patients with heart failure and in patients with ischaemic heart disease</td></tr>
</table>

than 50% of all ibrutinib-treated patients enrolled in RESONATE, RESONATE-2 and PCYC-1102.[31,32]

Hypertension, stroke and bleeding history are important risk factors for bleeding in anticoagulated patients with atrial fibrillation (HAS-BLED Risk Score) (*Table 2*).[24] DOACs have been shown to cause fewer major bleeding events than warfarin in multiple RCTs in the general AF population.[33] As a result, the expert panel agrees that DOACs should be the preferred class of anticoagulants to reduce the risk of AF-related stroke, when used in combination with ibrutinib.[34] Because of the lack of clinical evidence in support of a particular DOAC in this setting, the panel did not propose a specific DOAC, yet interaction with P-gp and CYP3A4 must be considered.

Patients receiving oral anticoagulants for AF should preferably not receive antiplatelet agents. In AF patients with a contra-indication for anticoagulation, left atrial appendage occlusion could be considered, a strategy currently reserved for patients at very high bleeding risk.

Overall, patients should be well educated to minimise the risk for development of atrial fibrillation by addressing modifiable risk factors, such as reducing alcohol consumption, cessation of smoking, optimal diabetes management and blood pressure control, reduction of body weight to avoid obesity or overweight, treatment of obstructive sleep apnoea, management of hyperlipidaemia and increased activity. Patients should be instructed to inform their GP and pharmacist about the fact that they take ibrutinib to avoid potential important drug-drug interactions and should also inform their haematologist about the drugs they take. They should also be instructed not to take grapefruit or Seville oranges and preparations containing St. John's Wort.

CONCLUSIONS

Ibrutinib has emerged as a new treatment option for patients with CLL, MCL and WM. Overall, ibrutinib comes with a beneficial safety profile. Yet, results from clinical trials and real-world analyses did indicate a higher rate of AF with this agent compared to standard CIT. From a benefit-risk profile point of view, it is important to emphasise that ibrutinib-based treatment has shown PFS benefits in Phase III trials compared to CIT in frontline CLL (versus chlorambucil-obinutuzumab in the iLLUMINATE study,

KEY MESSAGES FOR CLINICAL PRACTICE

1. The incidence of AF is higher with ibrutinib compared to CIT.
2. On the other hand, ibrutinib has demonstrated a clear efficacy benefit compared to CIT.
3. Treatment discontinuations due to AF are rare.
4. A history of AF should not preclude patients from commencing ibrutinib treatment.
5. Prior to the start of ibrutinib, identify and address any modifiable risk factors for AF, evaluate antiplatelet agent use and optimise antihypertensive therapy.
6. It is recommended to perform a 12-lead ECG before starting ibrutinib and during therapy. Regular blood pressure monitoring is recommended as well.
7. The threshold for haematologists to consult a cardiologist or a cardio-oncologist should be low and a close collaboration between both specialties is warranted.
8. Modifiable risk factors for bleeding should be addressed and vigilance for potential drug-drug interactions is needed prior to and during ibrutinib therapy.
9. Unnecessary ibrutinib interruptions should be avoided. Uncomplicated AF is not a valid reason to discontinue or interrupt ibrutinib. However, more complicated cases may require interaction between the oncologist and cardiologist to determine the best course of action.
10. Provide adequate anticoagulation – in the absence of compelling contraindications – to reduce the risk of stroke. As vitamin K antagonists should not be administered concomitantly with ibrutinib, DOACs are preferred.
11. Patients should be well educated to minimise the risk for development of atrial fibrillation by addressing modifiable risk factors. They should be instructed not to take grapefruit or Seville oranges and preparations containing St. John's Wort, and should inform their GP and pharmacist about the fact that they take ibrutinib to avoid potential important drug-drug interactions and should also inform their haematologist about the drugs they take.

versus FCR in the ECOG-ACRIN-E1912 study, versus BR in the ALLIANCE A041202 study), and demonstrated an OS benefit against FCR (ECOG-ACRIN-E1912 study) in frontline CLL.[35-37] However, in clinical trials, treatment discontinuations due to AF are rare. A history of AF should furthermore not preclude patients from commencing ibrutinib treatment. The threshold for haematologists to consult a cardiologist or a cardio-oncologist should be low and a close collaboration between both specialties is warranted. Since vitamin K antagonists should not be administered concomitantly with ibrutinib, DOACs (adapted dose if needed) are preferred. In most patients, rate control is preferred over rhythm control because the ability to maintain sinus rhythm after cardioversion may be limited by the persistent presence of ibrutinib as a trigger for AF. When selecting drugs for rate control, potential drug-drug interactions with ibrutinib should be considered.

This consensus paper provides guidance on how to evaluate patients prior to ibrutinib treatment, monitor for AF and provides practical advice on how to manage AF in these patients. A schematic representation of the recommendations related to AF prevention and management is summarised in *Tables 3* and *4*.

REFERENCES

1. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021;42(5):373-498.
2. Farmakis D, Parissis J, Filippatos G, et al. Insights into cardio-oncology: atrial

fibrillation in cancer. J Am Col Cardiol. 2014;63(10):945-53.
3. Shanafelt T, Parikh S, Noseworthy P, et al. Atrial fibrillation in patients with chronic lymphocytic leukemia. Leuk Lymph. 2017;58(7):1630-9.
4. Brunner K, Bunch T, Mullin C, et al. Clinical predictors of risk for atrial fibrillation: Implications for diagnosis and monitoring. Mayo Clin Proc. 2014; 89(11):1498-505.
5. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014;371(3):213-23.
6. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. N Engl J Med. 2015;373(25):2425-37.
7. Burger JA, Keating MJ, Wierda WG, et al. Safety and activity of ibrutinib plus rituximab for patients with high-risk chronic lymphocytic leukaemia: a single-arm, phase 2 study. Lancet Oncol. 2014;15(10):1090-9.
8. Imbruvica®. Summary of product characteristics, 2020.
9. Brown J, Moslehi J, O'Brien S, et al. Characterization of atrial fibrillation adverse events reported in ibrutinib randomized controlled trials. Haematologica. 2017;102(10):1796-805.
10. McMullen J, Boey E, Ooi J, et al. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signalling. Blood. 2014; 124:3829-30.
11. Ganatra S, Sharma A, Shah S, et al. Ibrutinib-associated atrial fibrillation. JACC Clin Electrophysiol. 2018;4(12):1491-500.
12. Yun S, Vincelette N, Acharya U, et al. Risk of atrial fibrillation and bleeding diathesis associated with ibrutinib treatment: a systematic review and pooled analysis of four randomized controlled trials. Clin Lymph Myel Leuk. 2016; 17(1):31-7.
13. O'Brien S, Hillmen P, Coutre S, et al. Safety analysis of four randomized controlled studies of ibrutinib in patients with chronic lymphocytic leukemia/ Small lymphocytic lymphoma or mantle cell lymphoma. Clin Lymph Myel Leuk. 2018;18(10):648-57.
14. Byrd JC, Furman RR, Coutre S, et al. Ibrutinib Treatment for First-Line and Relapsed/Refractory Chronic Lymphocytic Leukemia: Final Analysis of the Pivotal Phase Ib/II PCYC-1102 Study. Clin Cancer Res. 2020;26(15):3918-27.
15. Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. Am J Hematol. 2019; 94(12):1353-63.
16. Burger JA, Barr PM, Robak T, et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. Leukemia. 2020;34(3):787-98.
17. Rule S, Deyling M, Goy A, et al. Ibrutinib for the treatment of relapsed/refractory mantle cell lymphoma: extended 3.5-year follow up from a pooled analysis. Haematologica. 2019;104(5):e211-4.
18. Treon S, Meid K, Gustine J, et al. Long-Term Follow-Up of Ibrutinib Monotherapy in Symptomatic, Previously Treated Patients With Waldenström Macroglobulinemia. J Clin Oncol. 2021;39(6):565-75.
19. Buske C, Tedeschi A, Trotman J, et al. Ibrutinib Treatment in Waldenström's Macroglobulinemia: Follow-up Efficacy and Safety from the iNNOVATE Study [oral presentation]. 60th Annual Meeting and Exposition of the American Society of Hematology; December 1-4, 2018; San Diego. Abstract 149.
20. Calzada C, Bruckdorfer KR, Rice-Evans CA. The influence of antioxidant nutrients on platelet function in healthy volunteers. Atherosclerosis. 1997; 128:97-105.
21. Begtrup KM, Krag AE, Hvas AM. No impact of fish oil supplements on bleeding risk: a systematic review. Dan Med J. 2017;65(5):A5366.
22. Thorp N, Badoux X. Atrial fibrillation as a complication of ibrutinib therapy: clinical features and challenges of management. Leuk Lymphoma. 2018; 59(2):311-20.
23. Lentz R, Feinglass J, Ma S, et al. Risk factors for the development of atrial fibrillation on ibrutinib treatment. Leuk Lymphoma. 2019;60(6):1447-53.
24. Boriani G, Corradini P, Cuneo A, et al. Practical Management of Ibrutinib in the Real Life: Focus on Atrial Fibrillation and Bleeding. Hematol Oncol. 2018; 36(4):624-32.
25. Glotzer T, Daoud E, Wyse D, et al. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. Circ Arrhythm Electrophysiol. 2009;2:474-80.
26. Healey J, Connoly S, Gold M, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med. 2012;366:120-9.
27. De Weerdt I, Koopmans S, Kater A, et al. Incidence and management of toxicity associated with ibrutinib and idelalisib: a practical approach. Haematologica. 2017;102(10):1629-39.
28. Thompson P, Lévy V, Tam C, et al. Atrial fibrillation in CLL patients treated with ibrutinib. An international retrospective study. Br J Haematol. 2016;175(3):462-6.
29. de Zwart L, Snoeys J, De Jong J, et al. Ibrutinib dosing strategies based on interaction potential of CYP3A4 perpetrators using physiologically based pharmacokinetic modelling. Clin Pharmacol Ther. 2016;100(5):548-57.
30. Brown J, Moslehi J, Ewer M, et al. Incidence of and Risk Factors for Major Hemorrhage in Patients Treated with Ibrutinib: Results from an Integrated Analysis. Blood. 2017;130(Suppl_1):1743.
31. Jones J, Jillmen P, Coutré S, et al. Use of anticoagulants and antiplatelet in patients with chronic lymphocytic leukaemia treated with single-agent ibrutinib. Br J Haematol. 2017;178(2):286-91.
32. Tedeschi A, Barr P, Robak T, et al. Results from the International, Randomized Phase 3 Study of Ibrutinib Versus Chlorambucil in Patients 65 Years and Older with Treatment-Naïve CLL/SLL (RESONATE-2). Blood. 2015;126(23):495.
33. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383:955-62.
34. Chai-Adisaksopha C, Crowther M, Isayama T, et al. The impact of bleeding complications in patients receiving target-specific oral anticoagulants: a systematic review and meta-analysis. Blood. 2014;124:2450–8.
35. Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (ILLUMINATE): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20(1):43-56.
36. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. N Engl J Med. 2019;381(5):432-43.
37. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. N Engl J Med. 2018;379(26):2517-28.