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Hypertension as a Cardiovascular Toxicity of Bruton's Tyrosine Kinase Inhibitors for Chronic Lymphocytic Leukemia

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Introduction

In 2014, ibrutinib, a covalent Bruton's tyrosine kinase inhibitor (BTKi), became available as a treatment for chronic lymphocytic leukemia (CLL) in Canada. It was welcomed with enthusiasm given its oral administration, lower rate of neutropenia and infections, and efficacy in heavily pretreated and high-risk del17p subtypes, at a time when only chemotherapy and monoclonal antibodies were available.[1] Soon adverse events (AE) due to off-target effects emerged; particularly concerning were cardiac arrhythmias, bleeding, and hypertension (HTN). Second-generation BTKis were designed to target BTK more directly, and fortunately, clinical trials reported a lower rate of cardiac AEs. Less attention has been given to HTN despite it being an important modifiable risk factor for subsequent cardiac AEs. This is particularly relevant for CLL, given that the predominantly elderly patient population with CLL tend to survive as long as age-matched peers. This review focuses on HTN as an adverse effect of BTKis, and recommending a management approach.

Many contemporary CLL studies with BTKi define HTN as an AE using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0[2], and typically consider severe HTN to be grade 3-5 **(Table 1)**. HTN is generally defined as a disorder characterized by a pathological increase in blood pressure (BP), which is defined as a repeated elevation in the BP exceeding 140 over 90 mm Hg. It is clinically relevant even at a grade 2 level from a global perspective for most patients.

Ibrutinib

The RESONATE trial was the original Phase 3 trial on which Health Canada's approval for ibrutinib was based **(Table 2)**. In this study, patients with relapsed or refractory (R/R) CLL/small lymphocytic leukemia (SLL) were randomized to receive ibrutinib or ofatumumab.[1] HTN was not reported as an AE, perhaps because

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Prehypertension (systolic BP 120-139 mmHg or diastolic BP 80-89 mmHg)	Stage 1 hypertension (systolic BP 140-159 mmHg or diastolic BP 90-99 mmHg); medical intervention indicated; recurrent or persistent (≥24 hours); symptomatic increase by >20 mmHg (diastolic) or to >140/90 mmHg if previously WNL; monotherapy indicated	Stage 2 hypertension (systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Death

Table 1. Adverse Effect Grading of Hypertension; *courtesy of Anthea Peters, MD and Sheri Koshman, MD, BScPharm, PharmD, ACPR, FCSHP*

Abbreviations: BP: blood pressure; **WNL**: within normal limits.

there was a low suspicion for HTN as an AE and the median follow-up was relatively short at 9.4 months, which may not have been enough time to pick up these signals. With longer follow-up, HTN and other cardiovascular AEs like atrial fibrillation (AF) and bleeding became known AEs of clinical interest. High-grade (≥3) HTN and AF occurred at 9% and 6%, respectively when median follow up extended to 41 months.[3] Very long follow up (74 months median) revealed that treatment-emergent HTN occurred at a median 13.8 months.[4] Whereas the incidence of AF and all other AEs declined over time, HTN and bruising remained constant.[4] Most patients who developed HTN had a history or had relevant risk factors (68%), and most (63%) were treated with concomitant HTN medications.

After the RESONATE trial, the focus turned to ibrutinib in the treatment-naïve setting, and a trial compared ibrutinib to chlorambucil in patients older than 65 years **(Table 2)**. The initial report with a median follow-up of 18 months reported high-grade HTN in 4% of patients in the ibrutinib arm, which subsequently rose to 9% and then 12%, with all-grade HTN being reported at 23-25% (at a median follow-up of 57 and 89 months, respectively).[5,6] Over half of patients were on concomitant anti-hypertensive treatment (73% in ibrutinib and 61% in chlorambucil arms). The Alliance A041202 trial, which also randomized elderly patients with treatment-naïve CLL (median 71 years) to ibrutinib with or without rituximab (I+R and I, respectively) vs. bendamustine and rituximab (BR) as the control arm, reported a very high incidence of high-grade HTN in both ibrutinib arms of 29% (I) and 34% (I+R), compared to 15% in the BR arm.[7] Long-term analysis found that the incidence of AF and HTN continued to rise over time, but the incidence rate decreased for both.[8]

The rates of HTN were not as high in two trials focused on younger, fit patients. A progression-free survival (PFS) and overall survival (OS) advantage was seen with I+R over fludarabine, cyclophosphamide, and rituximab (FCR) in the E1912 Phase 3 trial that enrolled younger (median 57 years), fit patients with CLL.[9] The I+R arm had a significantly higher rate of high-grade HTN (18.8% vs. 8.2%, p=0.002) and AF (7.4% vs. 3.2%) and longer follow-up revealed that high-grade HTN remained higher in the I+R arm than in the FCR arm (11.4% vs. 1.9%, p<0.001), as did AF (4.5% vs. 0.0%, p=0.004).[10] FLAIR, a British trial with the same treatment arms and similar enrolment criteria, but with planned treatment cessation after minimal residual disease achievement, found a lower incidence of HTN than in the E1912 study, with 2% high-grade HTN in the I+R arm.[11] Of note, only 13% of patients in the I+R arm reported baseline HTN compared to >50% in the RESONATE, RESONATE-2, and A041202 trials.

A novel fixed-duration combination of ibrutinib and venetoclax was tested in the GLOW trial, which randomized treatment-naïve elderly patients to standard chemoimmunotherapy (chlorambucil + obinutuzumab [CO]) or ibrutinib + venetoclax (IV).[12] Despite a very high prevalence of HTN at baseline (71% IV vs. 63% CO), the rate of high-grade HTN was only 7.5% in the IV arm, perhaps due to the limited exposure to ibrutinib.

A systematic review that pooled safety data from eight randomized clinical trials found that ibrutinib had a risk ratio (RR) for HTN of 2.82 (p<0.001) and a RR for AF of 4.69 (p<0.001).[13] Another study pooling trial data on 300 CLL patients found that most (69%) patients had HTN at baseline, and 47% were on HTN medications.[14] The majority treated with ibrutinib had new or worsening HTN (62%), whereas high grade HTN occurred in almost one-fifth. Risk factors for new, worsening, and very severe HTN were male gender, tobacco, and chronic kidney disease, and older age was a risk factor for very severe HTN. HTN was reversible upon discontinuing ibrutinib, except for 11% of patients.

The rate of HTN observed was >10-fold higher than rates predicted in the Framingham Heart Study, leaving little doubt that HTN is an effect of ibrutinib.[15] Roeker *et al*. reported that 49.5% of patients with preexistig HTN developed high grade HTN and 20.6% had to change their CV medication regimen in the first year after starting ibrutinib.

Acalabrutinib

The second-generation BTKi's were designed to bind more specifically to their kinase target and acalabrutinib was the first in this class to be approved. The first published phase 3 trial randomized patients with R/R CLL to receive acalabrutinib vs. investigator's choice of idelalisib (idela) + rituximab vs. bendamustine + rituximab (BR) (ASCEND).[16] In the initial results, HTN rates were low at 3% all-grade and 2% grade 3-4 in the patients treated with acalabrutinib with a median exposure of 16 months. Even after an extended duration of acalabrutinib exposure (median

Clinical Trial	N	Treatment Arm (median age)	Study Population	Median Follow-up (mo.)	Median Duration of Treatment (mo.)	Afib/aflutter (%)		HTN (%)	
						All grade	Grade 3-4	All grade	Grade 3-4
Ibrutinib									
RESONATE[1]	195	Ibrutinib (67)	R/R CLL	9.4	8.6	10 (5)	6 (3)	NR	NR
	191	Ofatumumab (67)			5.3	1 (0)	0 (0)	NR	NR
RESONATE[3]	195	Ibrutinib (67)	R/R CLL	41.0	41	24 (12)	12 (6)	41 (21)	18 (9)
RESONATE[4]	195	Ibrutinib (67)	R/R CLL	74	71	24 (12)	12 (6)	41 (21)	18 (9)
RESONATE-2[40]	135	Ibrutinib (73)	TN CLL/SLL; ≥65 yrs	18.4	17.4	8 (6)	2 (1)	19 (14)	6 (4)
	132	Chlorambucil (72)			7.1	1 (1)	0 (0)	NR	0 (0)
RESONATE-2[6]	135	Ibrutinib (73)	TN CLL/SLL; ≥65 yrs	57.0	57.1	22 (16)	7 (5)	35 (26)	12 (9)
RESONATE-2[5]	135	Ibrutinib (73)	TN CLL/SLL; ≥65 yrs	88.5	74	NR	8 (6)	NR	17 (12)
E1912[9]	352	Ibrutinib + rituximab (57)	TN CLL/SLL; <=70 yrs	33.6	33.0	26 (7.4)	11 (3.2)	NR	66 (19)
	158	Fludarabine + cyclophosphamide + rituximab (57)			5 cycles	5 (3.2)	2 (1.2)	NR	13 (8)
E1912[10]	352	Ibrutinib + rituximab (57)	TN CLL/SLL; <=70 yrs	70	58.9	NR	(4.5)	NR	(11.4)
Alliance[7]	180	Ibrutinib (71)	TN CLL; ≥65 yrs	38.0	NR	31 (17)	17 (9)	NR	53 (29)
	181	Ibrutinib + Rituximab (71)				25 (14)	10 (6)	NR	61 (34)
	176	Bendamustine + rituximab (70)				5 (3)	5 (3)	NR	25 (15)
Alliance[8]	180	Ibrutinib (71)	TN CLL; ≥65 yrs	55	NR	66 (18)	NR	198 (55)	103 (29)
	176	Bendamustine + rituximab (70)				6 (3)	NR	47 (27)	21 (12)
ILLUMINATE[41]	113	Ibrutinib + obinutuzumab (70)	TN CLL; ≥65 yrs or unfit	31.3	29.3	8 (7)	6 (5)	15 (13)	4 (4)
	115	Chlorambucil + obinutuzumab (72)			5.1	0	0	5 (4)	4 (3)

Clinical Trial	N	Treatment Arm (median age)	Study Population	Median Follow-up (mo.)	Median Duration of Treatment (mo.)	Afib/aflutter (%)		HTN (%)	
						All grade	Grade 3-4	All grade	Grade 3-4
FLAIR[11]	386	Ibrutinib + rituximab (63)	TN CLL ≤75 yrs and fit	53	NR	18 (5)	2 (1)	17 (5)	6 (2)
	385	Fludarabine + cyclophosphamide + rituximab (62)				NR	1 (<1)	2 (1)	1 (<1)
GLOW[12]	106	Ibrutinib + Venetoclax (71)	TN CLL; ≥65 yrs	27.7	15	15 (14.2)	7 (6.6)	14 (13.2)	8 (7.5)
	105	Chlorambucil + Obinutuzumab (71)			6	2 (1.9)	0	5 (4.8)	2 (1.9)
Acalabrutinib									
ASCEND[16]	310	Acalabrutinib (68)	R/R CLL	16.1	15.7	8 (5)	2 (1)	5 (3)	3 (2)
		Idelalisib + rituximab (67)			11.5	4 (3)	2 (1)	5 (4)	1 (1)
		Bendamustine + rituximab (67)			5.6	1 (3)	1 (3)	0	0
ASCEND[17]	310	Acalabrutinib (68)	R/R CLL	46	44.2	12 (8)	2 (1)	12 (8)	7 (5)
		Idelalisib + rituximab (67)			11.5	4 (3)	1 (1)	7 (6)	1 (1)
		Bendamustine + rituximab (67)			5.6	1 (3)	1 (3)	0	0
ELEVATE-RR[22]	265	Ibrutinib (65)	R/R CLL with del17p or del11q	40.9	35.5	42 (16)	9 (3)	61 (23.2)	24 (9.1)
	268	Acalabrutinib (66)			38.3	25 (9)	12 (4)	25 (9.4)	11 (4.1)
ELEVATE-TN[18]	178	Acalabrutinib + obinutuzumab (70)	TN CLL/SLL, ≥65 yrs or unfit	28.3	27.7	6 (3)	1 (1)	13 (7)	5 (3)
	179	Acalabrutinib (70)			27.7	7 (4)	0 (0)	8 (4)	4 (2)
	177	Chlorambucil + obinutuzumab (71)			5.6	1 (1)	0 (0)	6 (4)	5 (3)
ELEVATE-TN[19]	178	Acalabrutinib + obinutuzumab (70)	TN CLL/SLL, ≥65 yrs or unfit	46.9	46.6	7 (3.9)	1 (0.6)	14 (7.9)	6 (3.4)
	179	Acalabrutinib (70)			45.7	11 (6.1)	2 (1.1)	13 (7.3)	5 (2.8)
	177	Chlorambucil + obinutuzumab (71)			5.6	1 (0.6)	0	7 (4.1)	6 (3.6)
AMPLIFY[20]	291	Acalabrutinib + Venetoclax (61)			12.9	2 (0.7)	1 (0.3)	12 (4.1)	8 (2.7)
	284	Acalabrutinib + Venetoclax + Obinutuzumab (61)			12.9	6 (2.1)	2 (0.7)	11 (3.9)	6 (2.1)

Clinical Trial	N	Treatment Arm (median age)	Study Population	Median Follow-up (mo.)	Median Duration of Treatment (mo.)	Afib/aflutter (%)		HTN (%)	
						All grade	Grade 3-4	All grade	Grade 3-4
Zanubrutinib									
	259	Fludarabine + cyclophosphamide + rituximab/ bendamustine + rituximab (61)			5.6	2 (0.8)	2 (0.8)	7 (2.7)	2 (0.8)
ALPINE[25]	325	Ibrutinib (68)	R/R CLL/SLL	29.6	24.3	43 (13.3)	13 (4.0)	74 (22.8)	44 (13.6)
	327	Zanubrutinib (67)			28.4	17 (5.2)	8 (2.5)	76 (23.5)	49 (15.1)
ALPINE[42]	325	Ibrutinib (68)	R/R CLL/SLL	42.5	NR	(7.1)	(5.2)	(25.3)	(16.0)
	327	Zanubrutinib (67)				(17.0)	(3.4)	(27.2)	(17.0)
SEQUOIA[43]	241	Zanubrutinib (70)	TN CLL/SLL ≥65 yrs or unfit	26.2	26.1	8 (3.3)	1 (0.4)	29 (12)	15 (6)
	238	Bendamustine + rituximab (70)			5.5	6 (2.6)	3 (1.3)	20 (9)	11 (5)
	111	Zanubrutinib (with del17p) (70)			30	5 (4.5)	4 (3.6)	10 (10)	5 (5)
SEQUOIA[26]	241	Zanubrutinib (70)	TN CLL/SLL ≥65 yrs or unfit	61.2	60.5	(7.1)	(1.4)	47 (19.6)	29 (12.1)
	238	Bendamustine + rituximab (70)			5.5	(3.5)	(2.2)	28 (12.3)	14 (6.2)

Table 2. Rates of Atrial Fibrillation/flutter and Hypertension; *courtesy of Anthea Peters, MD and Sheri Koshman, MD, BScPharm, PharmD, ACPR, FCSHP*

Abbreviations: CLL: chronic lymphocytic leukemia; **I: ibrutinib; I + R:** ibrutinib + rituximab; **Mo:** months; **NR:** not reported; **R/R:** relapsed/refractory; **SLL:** small lymphocytic lymphoma; **TN:** treatment-naïve; **yrs:** years.

44 months), the HTN rate remained low at 8% all-grade and 5% high grade.[17]

In the treatment-naive setting, the ELEVATE-TN trial randomized older (≥65 years) or unfit patients to receive indefinite acalabrutinib, acalabrutinib + obinutuzumab (AO), or CO.[18] HTN and AF rates were similar to the standard CIT arm in this study and out to 4 years[19], which aligns with the greater on-target effect of available BTKi. The AMPLIFY trial randomized fit and young (median age 61 years) patients to fixed duration novel agent combinations, including acalabrutinib, and at interim analysis all grade HTN was only 3-4% in all arms **(Table 2)**.[20]

A retrospective analysis of 762 patients treated with acalabrutinib monotherapy in four clinical trials, including the ASCEND trial and the ELEVATE-TN trial, specifically analyzed CV AEs.[21] HTN occurred in 67 patients (9% all grade, 5% grade ≥3) at a median of 6.5 months. Most of these patients (64%) had preexisting HTN. No patients discontinued due to HTN and only 19% of those who developed HTN started a concomitant medication.

The ELEVATE-RR trial is particularly important because it randomized patients to ibrutinib vs. acalabrutinib for R/R CLL with del17p or del11q for a more definitive efficacy and safety comparison. The trial showed that acalabrutinib had a non-

inferior PFS compared to ibrutinib and an improved safety profile.[22] Any grade AF or flutter and any grade (and grade ≥3) HTN were significantly less frequent with acalabrutinib (16% vs. 9%; 22.8% vs. 8.6%) **(Table 2)**. Seymour *et al*. further analyzed AEs in the ELEVATE-RR trial using a novel statistical method that combines the duration of AEs, recurrence, and grade weighting.[23] While the incidence of AF, HTN, and bleeding were all significantly higher in patients taking ibrutinib, the incidence rates of these AEs adjusted for drug exposure were 2.0, 2.8, and 1.6-fold higher, respectively. The median time to onset of HTN was similar between the two drugs (7.0 months vs. 8.1 months). HTN did not lead to treatment discontinuation or dose reduction in any patient in this study. Subgroups of age, number of prior lines of therapy, and previous history of HTN all had a higher incidence of HTN with ibrutinib treatment. In those with and without a prior history, HTN rates were lower with acalabrutinib, with a relative rate reduction of 54%.

A RWE analysis of 280 patients starting treatment with acalabrutinib for B-cell cancer (89% with CLL) with a primary endpoint of new or worsened HTN, defined as a systolic BP of >130 mmHg compared to Framingham heart-predicted and ibrutinib-related rates.[24] Almost 60% of patients had developed new or worsened HTN over a median follow-up of 41 months, with 3.5% of those with new HTN having more than grade 3 HTN. Compared to the Framingham risk predicted rate, they found an observed-to-expected ratio of 8.5 (p<0.001). Acalabrutinib does, therefore, cause HTN, albeit in fewer cases than ibrutinib.

Zanubrutinib

Zanubrutinib is another second-generation covalent BTKi (cBTKi). Randomization of patients with R/R CLL to zanubrutinib vs. ibrutinib in the ALPINE trial similarly found superior PFS for zanubrutinib.[25] While zanubrutinib had a lower overall rate of cardiac AEs (21.3% vs. 29.6%), HTN was not significantly different between treatment arms, with 23.5% vs. 22.8% having any grade and 15.1% vs. 13.6% having grade ≥3 HTN (zanubrutinib vs. ibrutinib), respectively **(Table 2)**. The SEQUOIA trial, which randomized treatment-naive patients to zanubrutinib vs. BR (median age 70 years) reported grade ≥3 HTN at a rate of 12% with 5-year follow-up, but the exposure-adjusted incidence rate (EAIR) of HTN was higher with zanubrutinib than the standard BR arm (0.50 vs. 0.38).[26]

Several post hoc studies comparing the safety of zanubrutinib to ibrutinib have drawn similar conclusions regarding CV safety. In one study, AEs led to fewer discontinuations with zanubrutinib than ibrutinib (14.1% vs. 22.0%), and zanubrutinib was not discontinued due to HTN.[27] The EAIR of AF was significantly reduced with zanubrutinib (p<0.0001), whereas the reduction in HTN was not significant (p=0.06). The incidence of HTN in the ASPEN (Waldenstrom macroglobulinemia) and ALPINE trials after 32.6 months of median exposure was not significantly different with zanubrutinib (21.9% vs. 23.5% with ibrutinib).[28] The EAIR of HTN with zanubrutinib was not significantly different from ibrutinib in the ALPINE study, but was significantly lower in the ASPEN trial (p=0.0211), although HTN was lower at enrolment in patients treated with zanubrutinib. HTN incidence increased over time in the zanubrutinib arm with 8.8 % any grade and 4.2% grade ≥3 in the first year, to 18.0% any grade and 7.7% grade ≥3 in the fourth year, but remained constant in the BR arm (4.0% grade ≥3 in the first year to 4.0% grade ≥3 in the fourth year).

An indirect comparison of clinical trial treatment-naive patients who received acalabrutinib (monotherapy and in combination with obinutuzumab [AO]) and zanubrutinib using matched-adjusted indirect comparison (MAIC) attempts to compare the second-generation cBTKi's in the absence of a randomized trial.[29] The efficacy analysis favoured AO, but the BTKi monotherapies were not significantly different. Regarding safety, the odds of developing any grade HTN were significantly lower with acalabrutinib monotherapy vs. zanubrutinib (odds ratio [OR]: 0.44), but there were no significant differences in the odds of AF between the treatment groups. One must keep in mind the limitations of this type of methodology and indirect comparison. A meta-analysis compared 20 trials using the second-generation BTKi's zanubrutinib, acalabrutinib, and tirabrutinib. Safety analysis identified a significantly higher rate of grade ≥3 HTN with BTKi monotherapy vs. BTKi combinations (i.e. AO and AO + venetoclax), while grade ≥3 HTN or AF were not significantly different between acalabrutinib and zanubrutinib monotherapy (4 vs. 6% and 1 vs. 1%, respectively).[30]

Overall, there is an advantage to acalabrutinib and zanubrutinib over ibrutinib in terms of efficacy and cardiac AEs, but zanubrutinib may not offer an

advantage over ibrutinib regarding HTN. Clinicians should be aware of the need to monitor for HTN continuously.

Management of HTN in the Setting of BTKi

The 2022 European Society of Cardiology (ESC) Cardio-Oncology guidelines provide some recommendations for baseline risk assessment and monitoring during BTKi therapy, but do not offer recommendations for individual agents in this class.[31] BP monitoring is recommended at every visit (Class I, Level B evidence), as well as weekly home monitoring of BP during the first 3 months and every month thereafter (Class IIa, Level C). The guidelines also offer some guidance around a threshold for BP management depending on the level of elevation at home and the prognosis of the patients. In the case of incurable cancer with a prognosis >3 years, they recommend that treatment should be considered for systolic BPs of 135-139 mm Hg (class IIa) and systolic BPs higher than 140 mm Hg should be treated (Class I).

The 2020 Canadian Hypertension Guidelines are similar to these recommendations.[32] Notably, they prioritize out-of-office BP measurements, with home BP monitoring acceptable using proper technique. The diagnosis of HTN can be made with a BP of >135/85 mm Hg, measured twice daily for 7 days. If home measurement is not possible or feasible, office measurement can be used for diagnosis. Any single measurement >180/110 mm Hg can diagnose HTN. Serial office visits can also be used to make a diagnosis **(Table 3)**.

Thresholds for treatment initiation and related targets are based on the underlying CV risk of the patient, with those at higher risk being treated more aggressively with lower targets **(Table 4)**. These same principles can be applied to patients

Office Visit Number	Average BP Over Visits (mmHg)
1	180/110
2	140/90 + high-risk features including macrovascular target organ damage, diabetes mellitus, or chronic kidney disease (glomerular filtration rate) [GFR] <60 mL/min/1.73 m^2;
3	160/90
4+5	140/90

Table 3. Canadian HTN Guideline Recommendations for in-office BP diagnosis; *courtesy of Anthea Peters, MD and Sheri Koshman, MD, BScPharm, PharmD, ACPR, FCSHP*

Patient Population	Definition	Threshold for Treatment Initiation		Treatment Targets	
		SBP (mm Hg)	DBP (mm Hg)	SBP (mm Hg)	DBP (mm Hg)
High-Risk*	Clinical or sub-clinical CV disease; chronic kidney disease, 10-year global CV risk ≥15%; Age ≥75 years	≥130	NA	<120	NA
Diabetes**		≥130	≥80	<130	<80
Moderate-Risk**	Multiple risk factors and 10-year global CV risk 10-14%	≥140	≥90	<140	<90
Low-Risk**	No TOD or CV risk factors and 10-year global CV risk <10%	≥160	≥100	<140	<90

Table 4. Treatment Thresholds and Targets are Dependent on Underlying Cardiovascular Risk; *courtesy of Anthea Peters, MD and Sheri Koshman, MD, BScPharm, PharmD, ACPR, FCSHP*

Abbreviations: BP: blood pressure; **CV:** cardiovascular; **DBP:** diastolic blood pressure; **NA:** not available; **SBP:** systolic blood pressure; **TOD:** target organ damage.

* BP treatment threshold and target based on AOBP Automated Office BP (AOBP). This is performed with the patient unattended in a private room.
** BP treatment thresholds and targets based on Office BP Measurement (OBPM). These are measurements performed in the office using an electronic upper arm device with a provider in the room.

with CLL with a good prognosis. In addition to age, HTN is also a risk factor for the development of AF, for which patients on BTKi are at higher risk. Primary care providers and patients should be made aware that HTN is an AE associated with BTKi's and to be vigilant about monitoring for new or worsening HTN while on therapy.

History of HTN or development of HTN does not preclude treatment with BTKi's, and most patients can be treated with standard anti-hypertensive therapies, including diuretics, angiotensin-converting enzyme inhibitors (ACEI), or angiotensin receptor blockers (ARB), beta-blockers, and non-dihydropyridine calcium channel blockers.[33-35] Diltiazem and verapamil, both inhibitors of CYP3A, should be avoided due to drug-drug interaction with the risk of increasing levels of BTKi. Little data exists to identify the best HTN treatment options with BTKi; however, several agents may be required. In a retrospective study of 196 patients on BTKis (>90% CLL/SLL, 90% ibrutinib), 118 received treatment for preexisting HTN and 78 for *de novo* HTN after BTKi initiation[36]. The most effective drug combinations were beta-blockers and diuretic hydrochlorothiazide for those with prior HTN, and ACEis or ARB and hydrochlorothiazide for patients with *de novo* HTN.

Patients with a history of HTN do not need to be excluded from cBTKi's, but ibrutinib likely should be avoided.[33] In the case of grade ≥3 HTN, brief interruption of BTKi until HTN control is achieved, and then restarting potentially at a lower dose is an option; however, little data exists that this is a dose-related effect. Changing to acalabrutinib rather than zanubrutinib can also be considered. HTN rarely requires discontinuation of BTKi.[34] Fixed duration cBTKi combined with venetoclax likely does limit the development of HTN,[12] but due to the risk of sudden cardiac death with ibrutinib, specialists may prefer to await for funded options with second generation BTKi like AV or AVO following the recent publication of the AMPLIFY trial.[20]

It should be noted that the incidence of HTN tends to increase with age and may increase regardless of BTKi use in an elderly CLL population. This population also has many comorbidities, including AF, that increase their risk of CV disease over time.[37] In fact, it has also been shown that those with low-intermediate CLL-IPI risk are more likely to die of non-CLL-related causes, making it imperative that CV risks are assessed and addressed.[38] A difference in blood pressure of 10/5 mm Hg (to a nadir of SBP = 125 mm Hg) has been shown to decrease the risk of stroke, coronary heart disease, heart failure, and CV death in both primary and secondary prevention populations, indicating that even small elevations and subsequent drops can improve important cardiovascular outcomes.[39]

Conclusions

Given its track record of causing HTN and cardiac AEs, including sudden cardiac deaths, the US Food and Drug Administration (FDA) updated its manual for ibrutinib to warn of cardiac safety issues in May 2022, and in 2023 ibrutinib was downgraded out of the preferred regimen category in the National Comprehensive Cancer Network Guidelines for CLL.[30] Relative to the very high rates of HTN caused by ibrutinib, acalabrutinib does carry a significantly lower risk. Zanubrutinib, on the other hand, does not appear to have a lower HTN risk but does have other advantages over ibrutinib. HTN is manageable and rarely necessitates discontinuation of BTKi. Fixed-duration novel agent combinations AV or AVO, as well as the non-covalent BTKi pirtobrutinib, are anticipated to cause a lower burden of CV risk, including HTN. Close collaboration with patients' family physician and perhaps cardio-oncology is essential for treatment and monitoring of HTN while hematologists optimize the anti-cancer effects.

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References

1. 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.
2. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5×11.pdf.
3. Byrd JC, Hillmen P, O'Brien S, et al. Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab. Blood 2019; 133(19): 2031-42.
4. 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.
5. Barr PM, Owen C, Robak T, et al. Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. *Blood Adv* 2022; 6(11): 3440-50.
6. 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.
7. 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.
8. Woyach JA, Perez Burbano G, Ruppert AS, et al. Follow-up from the A041202 study shows continued efficacy of ibrutinib regimens for older adults with CLL. *Blood* 2024; 143(16): 1616-27.
9. 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.
10. Shanafelt TD, Wang XV, Hanson CA, et al. Long-term outcomes for ibrutinib-rituximab and chemoimmunotherapy in CLL: updated results of the E1912 trial. *Blood* 2022; 140(2): 112-20.
11. Hillmen P, Pitchford A, Bloor A, et al. Ibrutinib and rituximab versus fludarabine, cyclophosphamide, and rituximab for patients with previously untreated chronic lymphocytic leukaemia (FLAIR): interim analysis of a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2023; 24(5): 535-52.
12. Kater AP, Owen C, Moreno C, et al. Fixed-Duration Ibrutinib-Venetoclax in Patients with Chronic Lymphocytic Leukemia and Comorbidities. *NEJM Evid* 2022; 1(7): EVIDoa2200006.
13. Caldeira D, Alves D, Costa J, Ferreira JJ, Pinto FJ. Ibrutinib increases the risk of hypertension and atrial fibrillation: Systematic review and meta-analysis. *PLoS* One 2019; 14(2): e0211228.
14. Gordon MJ, Jones JE, George B, et al. Long-term outcomes in patients with chronic lymphocytic leukemia treated with ibrutinib: Focus on hypertension and cardiovascular toxicity. *Cancer* 2023; 129(14): 2192-200.
15. Dickerson T, Wiczer T, Waller A, et al. Hypertension and incident cardiovascular events following ibrutinib initiation. *Blood* 2019; 134(22): 1919-28.
16. Ghia P, Pluta A, Wach M, et al. ASCEND: Phase III, Randomized Trial of Acalabrutinib Versus Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. *J Clin Oncol* 2020; 38(25): 2849-61.
17. Ghia P, Pluta A, Wach M, et al. Acalabrutinib Versus Investigator's Choice in Relapsed/Refractory Chronic Lymphocytic Leukemia: Final ASCEND Trial Results. *Hemasphere* 2022; 6(12): e801.
18. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. *Lancet* 2020; 395(10232): 1278-91.
19. Sharman JP, Egyed M, Jurczak W, et al. Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naive chronic lymphocytic leukemia. *Leukemia* 2022; 36(4): 1171-5.
20. Brown JR, Seymour JF, Jurczak W, et al. Fixed-Duration Acalabrutinib Combinations in Untreated Chronic Lymphocytic Leukemia. *N Engl J Med* 2025; 392(8): 748-62.
21. Brown JR, Byrd JC, Ghia P, et al. Cardiovascular adverse events in patients with chronic lymphocytic leukemia receiving acalabrutinib monotherapy: pooled analysis of 762 patients. *Haematologica* 2022; 107(6): 1335-46.
22. Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial. *J Clin Oncol* 2021; 39(31): 3441-52.
23. Seymour JF, Byrd JC, Ghia P, et al. Detailed safety profile of acalabrutinib vs ibrutinib in previously treated chronic lymphocytic leukemia in the ELEVATE-RR trial. *Blood* 2023; 142(8): 687-99.
24. Chen ST, Azali L, Rosen L, et al. Hypertension and incident cardiovascular events after next-generation BTKi therapy initiation. *J Hematol Oncol* 2022; 15(1): 92.
25. Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or Ibrutinib in Relapsed or Refractory Chronic Lymphocytic Leukemia. *N Engl J Med* 2023; 388(4): 319-32.
26. Shadman M, Munir T, Robak T, et al. Zanubrutinib Versus Bendamustine and Rituximab in Patients With Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Median 5-Year Follow-Up of SEQUOIA. *J Clin Oncol* 2024: JCO2402265.
27. Brown JR, Ghia P, Jurczak W, et al. Characterization of zanubrutinib safety and tolerability profile and comparison with ibrutinib safety profile in patients with B-cell malignancies: post-hoc analysis of a large clinical trial safety database. *Haematologica* 2024; 109(7): 2277-83.
28. Moslehi JJ, Furman RR, Tam CS, et al. Cardiovascular events reported in patients with B-cell malignancies treated with zanubrutinib. *Blood* Adv 2024; 8(10): 2478-90.
29. Kittai AS, Allan JN, James D, et al. An indirect comparison of acalabrutinib with and without obinutuzumab vs zanubrutinib in treatment-naive CLL. *Blood* Adv 2024; 8(11): 2861-9.
30. Yin S, Zheng X, Zhang W, et al. Efficacy and safety

of new-generation Bruton tyrosine kinase inhibitors in chronic lymphocytic leukemia/small lymphocytic lymphoma: a systematic review and meta-analysis. *Ann Hemato*l 2024; 103(7): 2231-44.
31. Lyon AR, Lopez-Fernandez T, Couch LS, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J Cardiovasc Imaging* 2022; 23(10): e333-e465.
32. Rabi DM, McBrien KA, Sapir-Pichhadze R, et al. Hypertension Canada's 2020 Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children. *Can J Cardiol* 2020; 36(5): 596-624.
33. Soumerai JD, Barrientos JC, Ahn IE, et al. Consensus Recommendations from the 2024 Lymphoma Research Foundation Workshop on Treatment Selection and Sequencing in CLL or SLL. *Blood* Adv 2024.
34. Quartermaine C, Ghazi SM, Yasin A, et al. Cardiovascular Toxicities of BTK Inhibitors in Chronic Lymphocytic Leukemia: JACC: CardioOncology State-of-the-Art Review. J*ACC CardioOncol* 2023; 5(5): 570-90.
35. Awan FT, Addison D, Alfraih F, et al. International consensus statement on the management of cardiovascular risk of Bruton's tyrosine kinase inhibitors in CLL. *Blood* Adv 2022; 6(18): 5516-25.
36. Samples L, Voutsinas J, Fakhri B, et al. Hypertension treatment for patients receiving ibrutinib: a multicenter retrospective study. *Blood* Adv 2024; 8(9): 2085-93.
37. Larsson K, Mattsson M, Ebrahim F, Glimelius I, Hoglund M. High prevalence and incidence of cardiovascular disease in chronic lymphocytic leukaemia: a nationwide population-based study. *Br J Haematol* 2020; 190(4): e245-e8.
38. Wang Y, Achenbach SJ, Rabe KG, et al. Cause of death in patients with newly diagnosed chronic lymphocytic leukemia (CLL) stratified by the CLL-International Prognostic Index. *Blood Cancer J* 2021; 11(8): 140.
39. Mancia G, Facchetti R, Quarti-Trevano F, Grassi G. Reproducibility and Treatment Effect on Office and Ambulatory Pressure Relation. *Hypertension* 2025; 82(1): 126-35.
40. 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.
41. 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.
42. Brown JR, Eichhorst B, Lamanna N, et al. Sustained benefit of zanubrutinib vs ibrutinib in patients with R/R CLL/SLL: final comparative analysis of ALPINE. *Blood* 2024; 144(26): 2706-17.
43. Tam CS, Brown JR, Kahl BS, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. *Lancet Oncol* 2022; 23(8): 1031-43.

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