Cardiovascular toxicities associated with BTK inhibitors

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Disclosures

Speakers bureau: BeiGene, AstraZeneca, Novartis

Board: BeiGene, Bristol Myers Squibb, Novartis

Honoraria: Bristol Myers Squibb

Grants: Bristol Myers Squibb, Novartis, French Federation of Cardiology, Heart and Research Foundation, INSERM, National Research Agency

INSERM, French National Institute of Health and Medical Research.

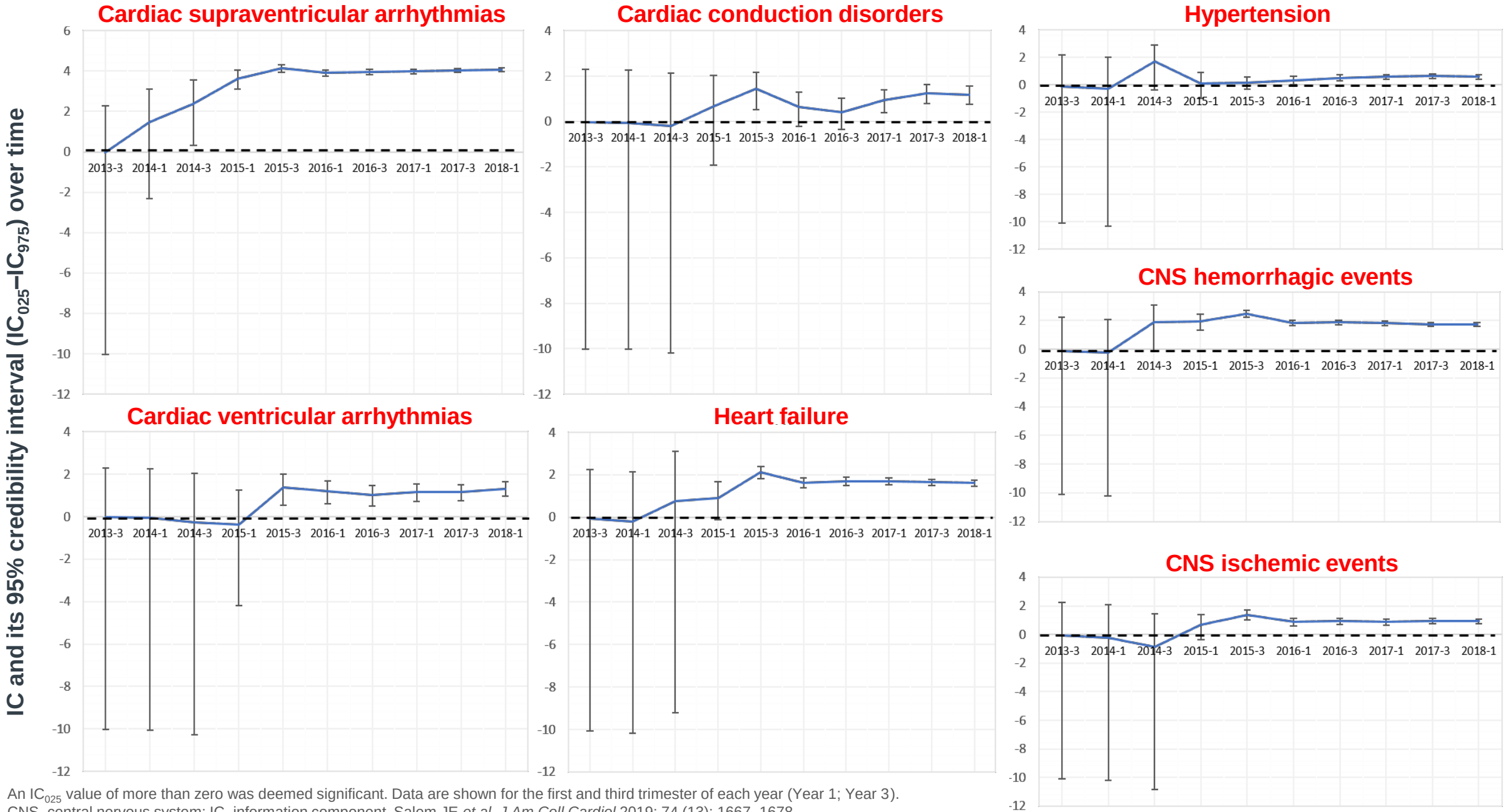
Cardiovascular toxicities associated with ibrutinib

- Ibrutinib cardiovascular adverse drug reactions identified using the international pharmacovigilance database VigiBase
  - **16,343,451 safety case reports**

	Until January 2018	Ibrutinib, n (%)	IC_{025}
FDA FDA	**Cardiac supraventricular arrhythmias**	**959** (7.07%)	**3.97**
	CNS hemorrhagic events	**505** (3.72%)	**1.63**
New signal	**Heart failure**	**363** (2.67%)	**1.46**
FDA	**Cardiac ventricular arrhythmias**	**70** (0.52%)	**0.96**
New signal	**Cardiac conduction disorders**	**50** (0.37%)	**0.76**
New signal	**CNS ischemic events**	**254** (1.87%)	**0.73**
FDA	**Hypertension**	**295** (2.17%)	**0.40**
	Cardiac valve disorders	30 (0.22%)	−0.07
	Myocardial infarction	149 (1.10%)	−0.11
	Cardiac death or shock	131 (0.97%)	−0.13
	Venous thromboembolic events	108 (0.80%)	−0.34
	Vascular neoplasms	2 (0.01%)	−2.72
	Pulmonary hypertension	19 (0.14%)	−1.14
	Hyperglycemia, diabetes	112 (0.83%)	−1.07
	Torsade de pointes / QT prolongation	9 (0.07%)	−2.01
	Myocarditis	2 (0.01%)	−3.61
	Dyslipidemia	14 (0.10%)	−2.75

CNS, central nervous system; IC_{025}, information component and its 95% credibility interval lower end.
Salem JE *et al*. *J Am Coll Cardiol* 2019; 74 (13): 1667–1678.

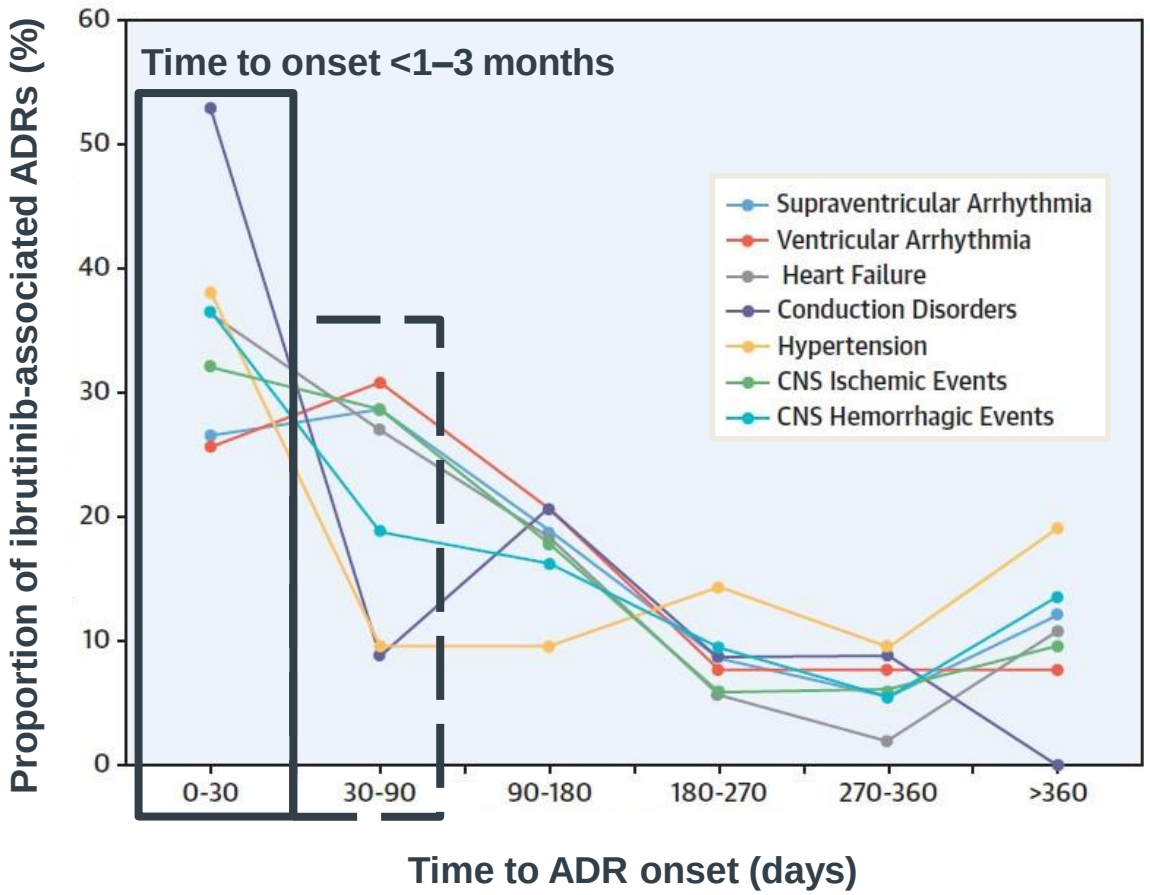
Cardiovascular fatalities associated with ibrutinib



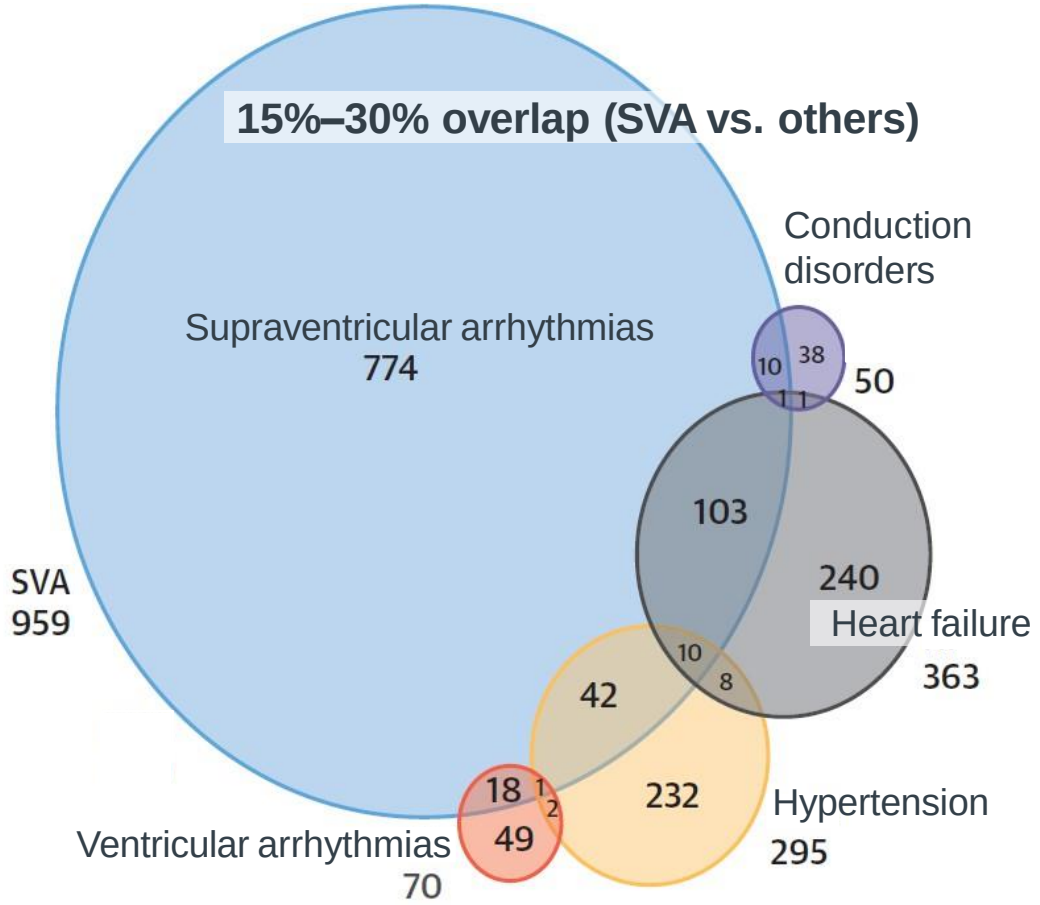
An IC_{025} value of more than zero was deemed significant. Data are shown for the first and third trimester of each year (Year 1; Year 3).
CNS, central nervous system; IC, information component. Salem JE *et al*. *J Am Coll Cardiol* 2019; 74 (13): 1667–1678.

Cardiovascular toxicities associated with ibrutinib

Time to ADR onset associated with ibrutinib



Overlap of cardiovascular ADRs associated with ibrutinib in VigiBase*



*Overlap between supraventricular arrhythmias, VAs, CDs, HF, and hypertension; overlap between VA and CD (n=1) or VA and HF (n=7) are not displayed.
ADR, adverse drug reaction; CD, conduction disorder; CNS, central nervous system; HF, heart failure; SVA, supraventricular arrhythmia; VA, ventricular arrhythmia.
Salem JE *et al*. *J Am Coll Cardiol* 2019; 74 (13): 1667–1678.

Cardiac supraventricular arrhythmia associated with ibrutinib

US FDA label and meta-analyses of randomized clinical trials:[1]

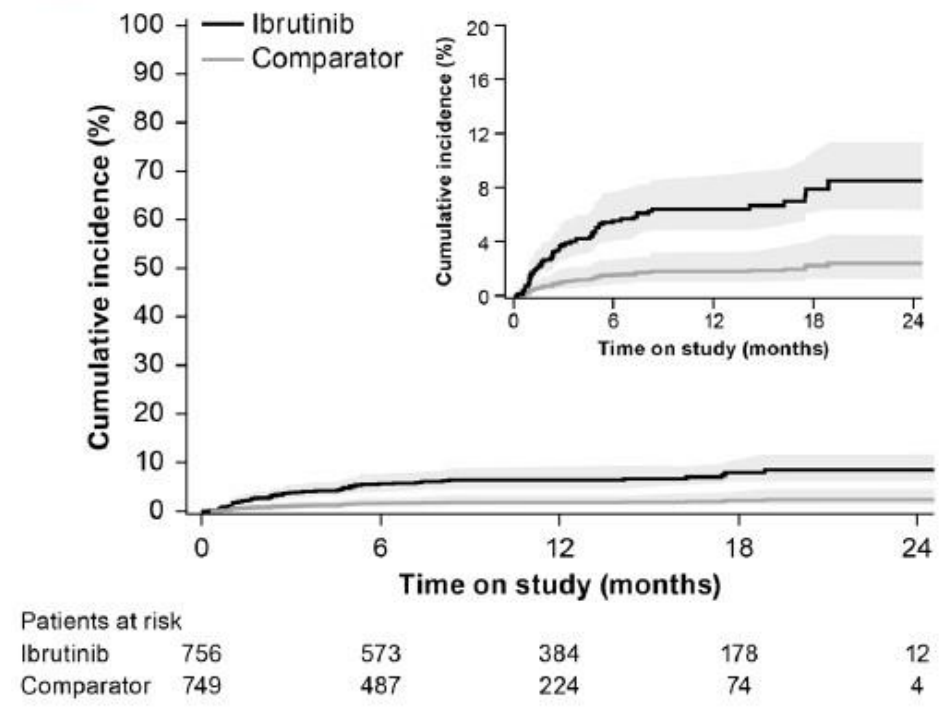
- **6.5%** after **17 months**
- **13.8%** at **36 months** (3.7% SAEs)

In real-life cohorts:[2]

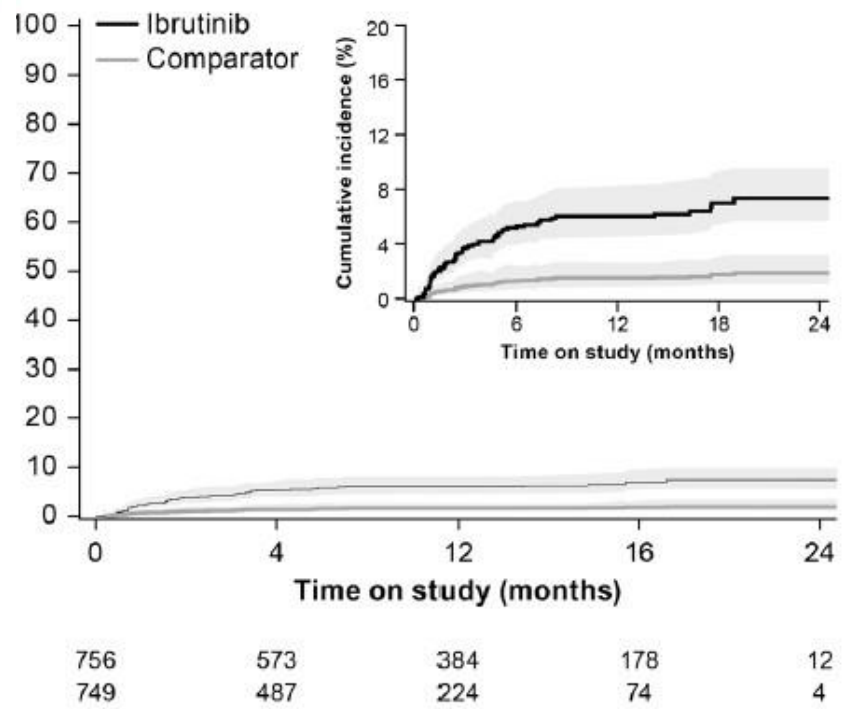
- **38% at 2 years**

Cumulative incidence (95% CI) of atrial fibrillation with ibrutinib vs. comparator[1]

Unadjusted analysis



Adjusted for competing events*



*Death and progressive disease.
CI, confidence interval; FDA, Food and Drug Administration; SAE, serious adverse event.
1. Brown JR *et al*. *Haematologica* 2017; 102 (10): 1796–1805. 2. Baptiste F *et al. Open Heart* 2019; 6 (1): e001049.

Cardiac supraventricular arrhythmia associated with ibrutinib: Extended analysis

US FDA label and meta-analyses of randomized clinical trials:[1]

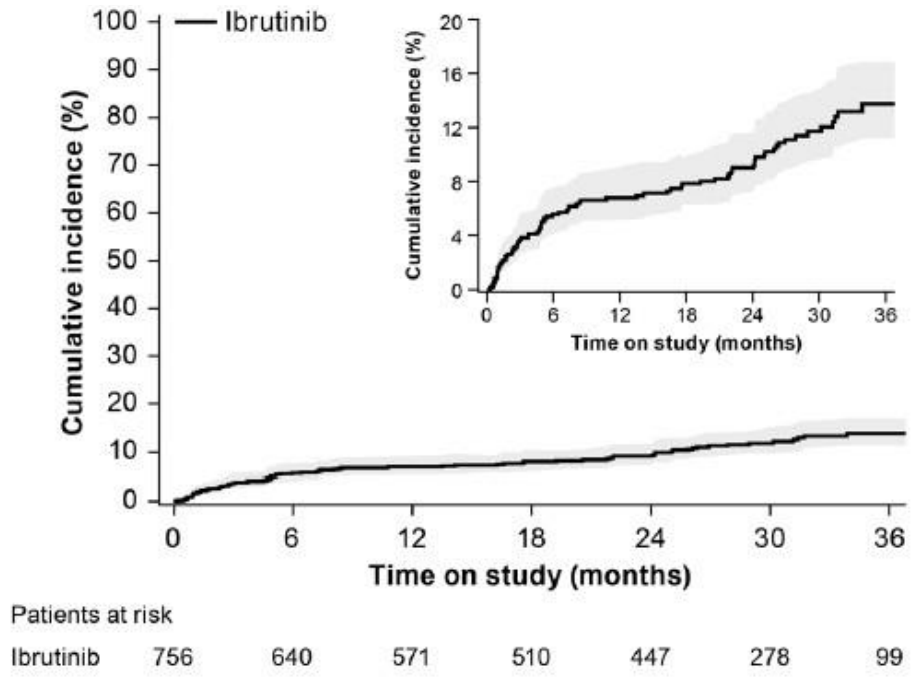
- **6.5%** after **17 months**
- **13.8%** at **36 months** (3.7% SAEs)

In real-life cohorts:[2]

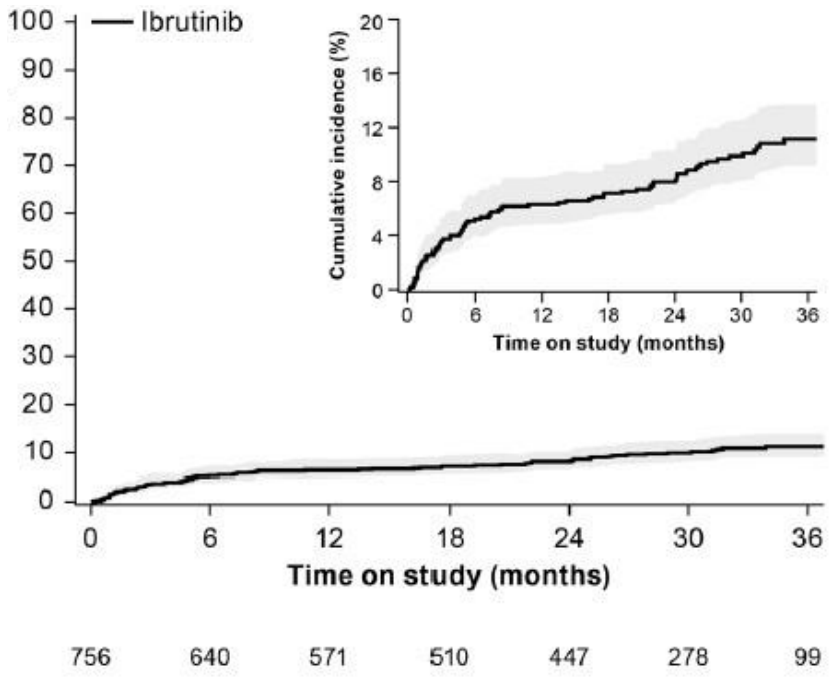
- **38% at 2 years**

Cumulative incidence (95% CI) of atrial fibrillation with ibrutinib: Extended analysis[1]

Unadjusted analysis



Adjusted for competing events*



*Death and progressive disease.
CI, confidence interval; FDA, Food and Drug Administration; SAE, serious adverse event.
1. Brown JR *et al*. *Haematologica* 2017; 102 (10): 1796–1805. 2. Baptiste F *et al. Open Heart* 2019; 6 (1): e001049.

Other cardiac AEs with ibrutinib

CNS hemorrhagic events

- In clinical trials, subdural (extra-cerebral) hematoma occurred in 1%–2% of patients[1]
- Case reports of hemorrhagic conversion of ischemic stroke, subarachnoid hemorrhage, and vitreous hemorrhage[2]

Cardiac ventricular arrhythmia[1]

- In clinical trials, Grade ≥3 VA occurred in ~0.2% of patients
- No QT prolongation

Hypertension[1]

- In clinical trials, any grade hypertension occurred in ~10%–20% of patients (Grade 3–4: 4%–13%)

Heart failure[3]

Kinase	IC_{50}, nM
	Ibrutinib
BTK	1.5 ± 0.2 (n=4)
ERBB2	6.4 ± 1.8 (n=3)
ERBB4	3.4 ± 1.3 (n=3)

?? Anti-HER2

Conduction disorders[4]

	n (%)
Atrioventricular block ≥2nd degree	27 (54)
Bundle branch block	13 (26)
Atrioventricular block 1st degree	5 (10)

AE, adverse event; CNS, central nervous system; IC_{50}, concentration required for 50% inhibition; VA, ventricular arrhythmia.

1. Pharmacyclics LLC. IMBRUVICA capsules, tablets, oral suspension – prescribing information; August 2022. 2. Shatzel JJ *et al*. *J Thromb Haemost* 2017; 15 (5): 835–847.
3. Byrd JC *et al*. *N Engl J Med* 2016; 374: 323–332 (supplementary). 4. Salem JE *et al*. *J Am Coll Cardiol* 2019; 74 (13): 1667–1678 (supplementary).

Initial case presentation: Mrs. F

Patient

- 76-year-old female

Cancer history

- CLL diagnosed 8 years ago
- In remission for 6 years after rituximab and bendamustine
- Second-line ibrutinib (420 mg/day)

Laboratory studies

- Lymphocytes: 33.8 × 10^9/L
- Hemoglobin: 11.6 g/dL

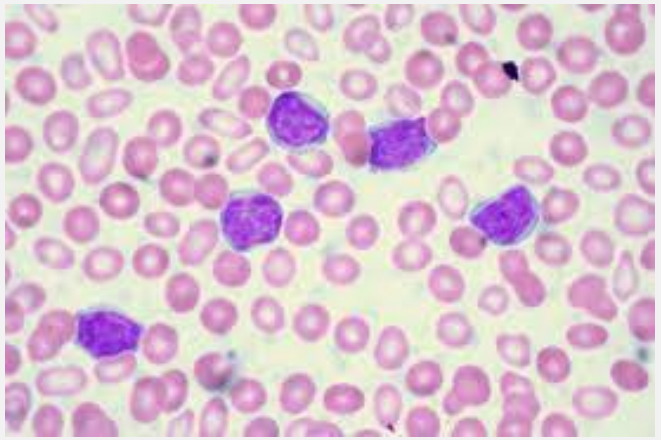
Cardiovascular risk factors

- HIV ~30 years
- Active smoker
- Pre-diabetes
- Blood pressure: 138/70 mmHg
- HR: 49 bpm
- BMI: 25.7 kg/m²

Treatment

- HIV triple drug therapy
- Aspirin 75 mg/day

Baseline pre-ibrutinib

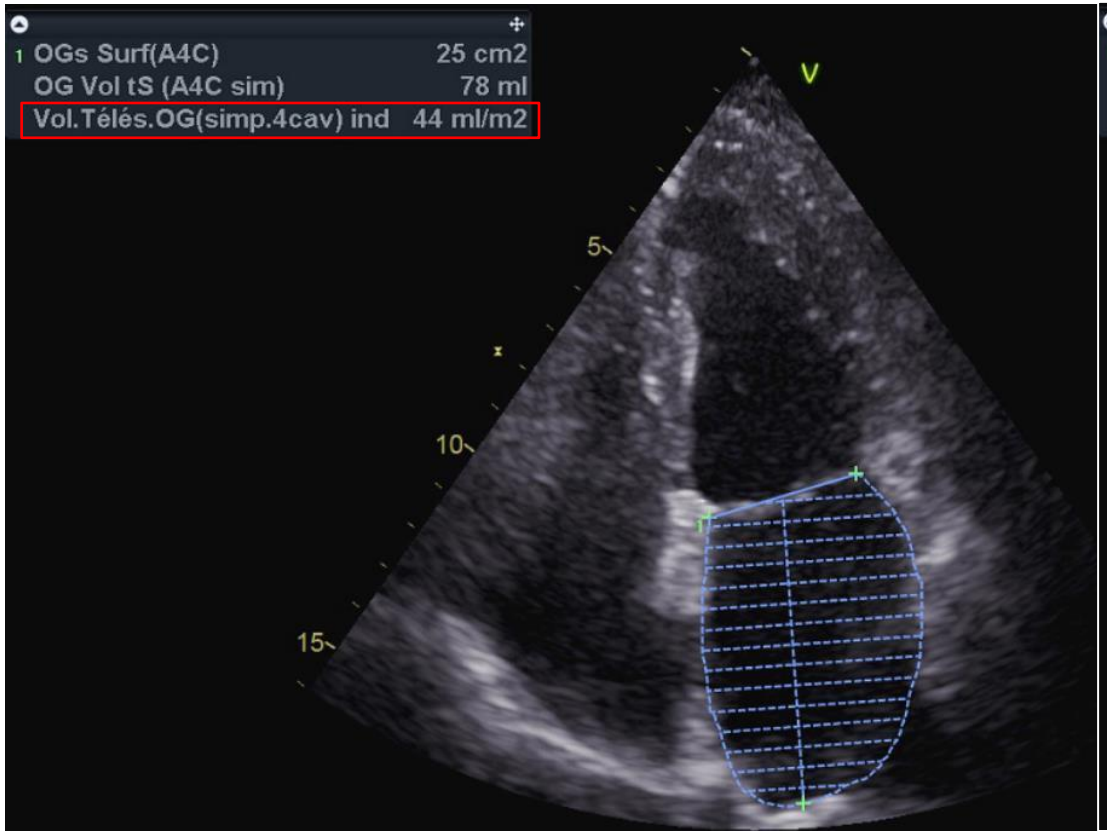


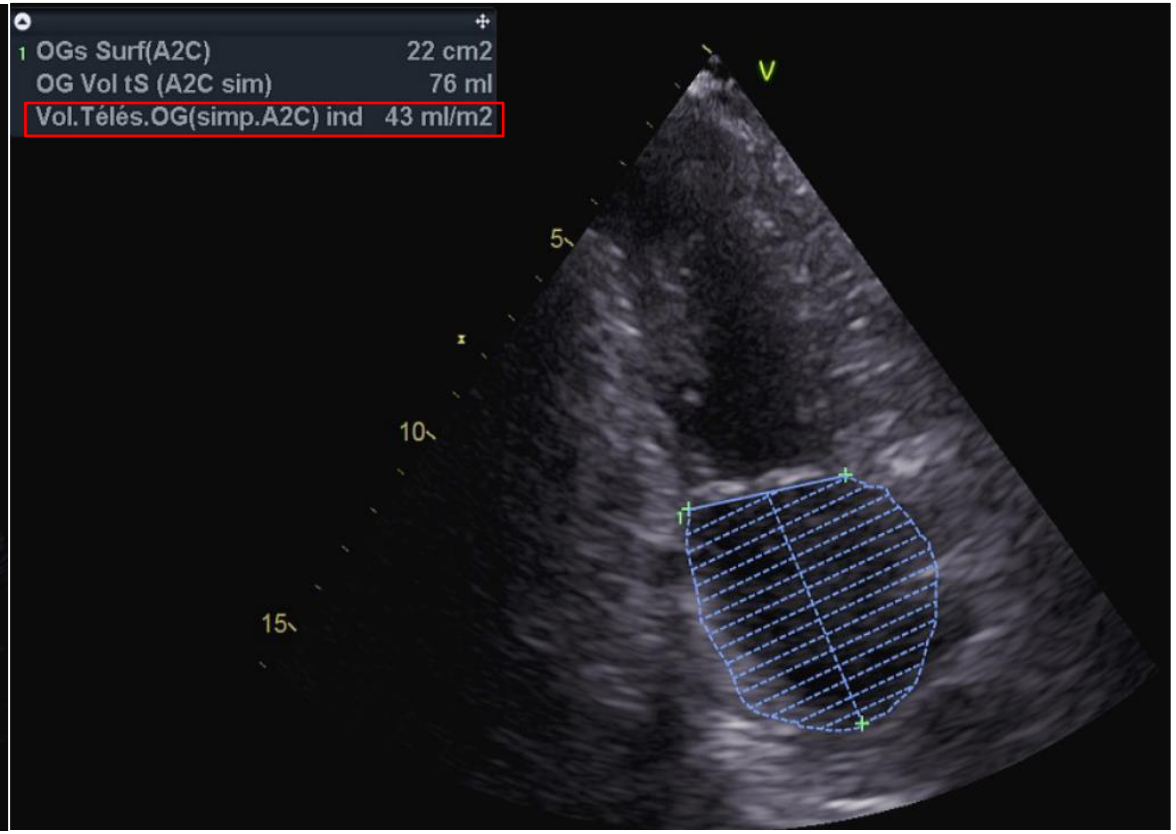
The information included in this presentation should be interpreted as related to this individual case rather than as a general statement about the properties of the medicines under discussion.

BMI, body mass index; bpm, beats per minute; CLL, chronic lymphocytic leukemia; HR, heart rate.

Mrs. F: Baseline echocardiography

- Normal left ventricular ejection fraction, diameter, and volumes; no hypertrophy
- No valve abnormalities
- Normal right ventricle and no pulmonary hypertension
- **Left atrial dilatation, LAVI: 44 mL/m²**

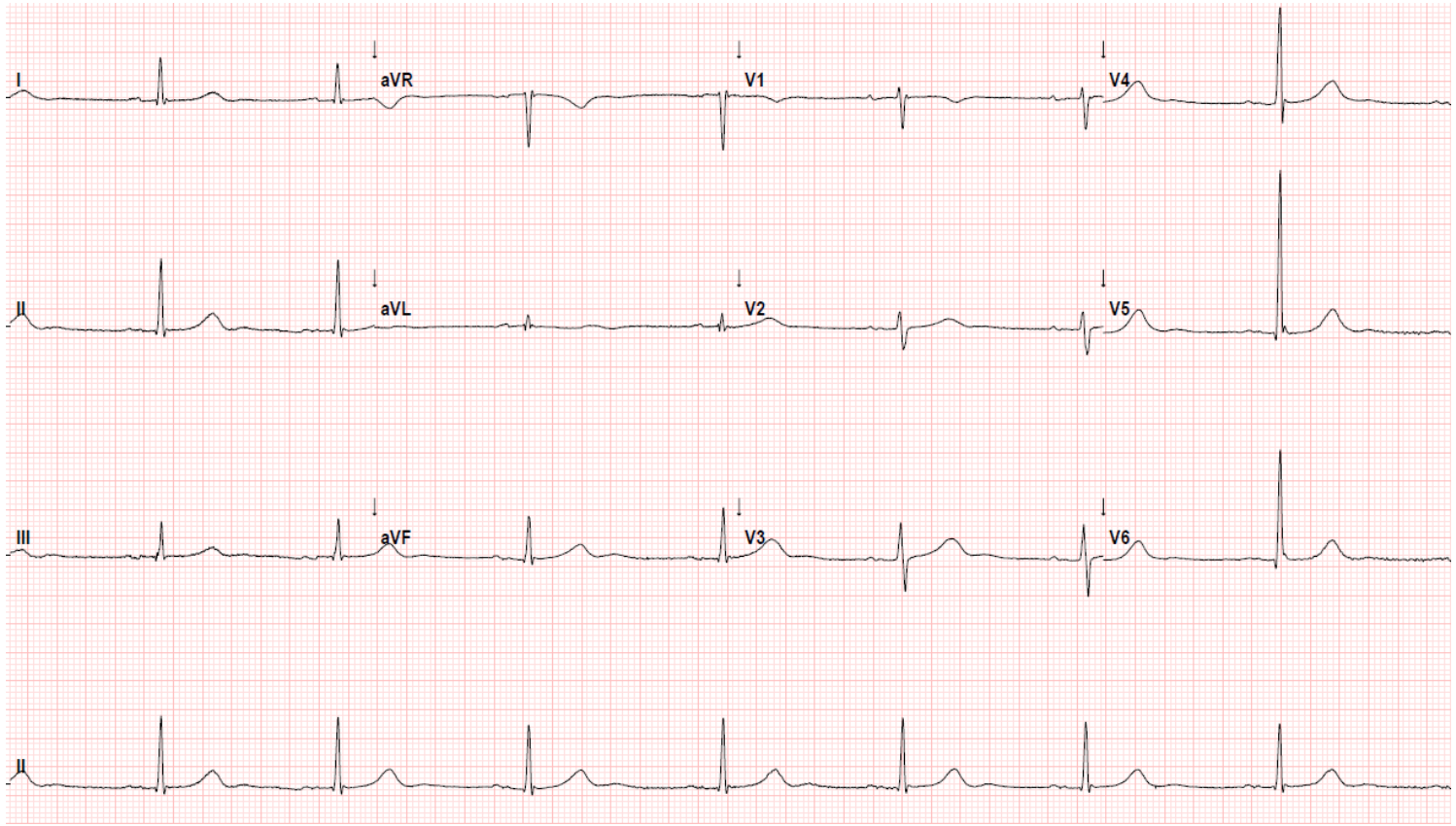


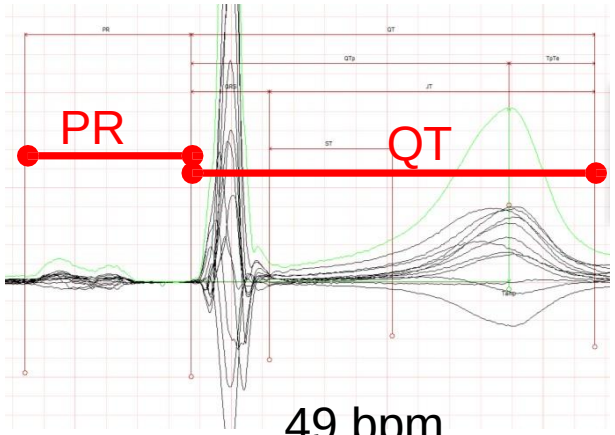


LAVI, left atrial volume index.

Mrs. F: Prior to ibrutinib treatment

Sinus rhythm, first-degree atrioventricular block
Grade 2 long QT





49 bpm

QT	517 ms
PR	213 ms
QRS	100 ms
JT	417 ms
ST	157 ms
Tamp	913 uV
QTp	407 ms
TpTe	110 ms
QTcB	465
QTcF	482

Blood pressure: 138/70 → Monitoring

bpm, beats per minute.

Left atrial abnormality

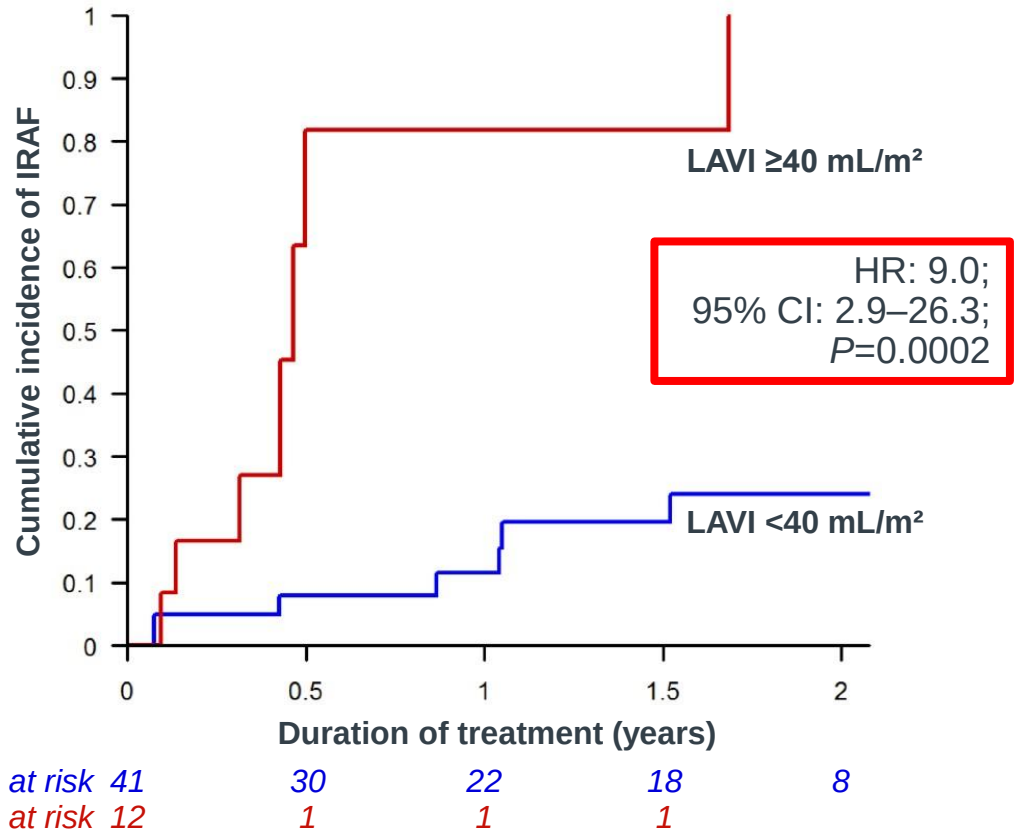
Cardiovascular characteristics associated with ibrutinib-associated atrial fibrillation[1]

Variable	OR (95% CI)	*P*-value
Left atrial abnormality*	6.6 (1.5–29.2)	0.01
Baseline hypertension	1.6 (0.3–8.2)	0.59
Baseline coronary artery disease	1.7 (0.2–14.2)	0.61
Age	1.0 (0.94–1.1)	0.63

ECG as a predictor of ibrutinib-associated atrial fibrillation[1]

Characteristic	Value, %	95% CI, %
Sensitivity	79	54–94
Specificity	71	49–87
Positive likelihood ratio	2.7	1.4–5.3
Negative likelihood ratio	0.30	0.1–0.74
Positive predictive value	68	45–86
Negative predictive value	81	58–95

LAVI ≥40 mL/m² as a predictor of ibrutinib-associated atrial fibrillation[2]

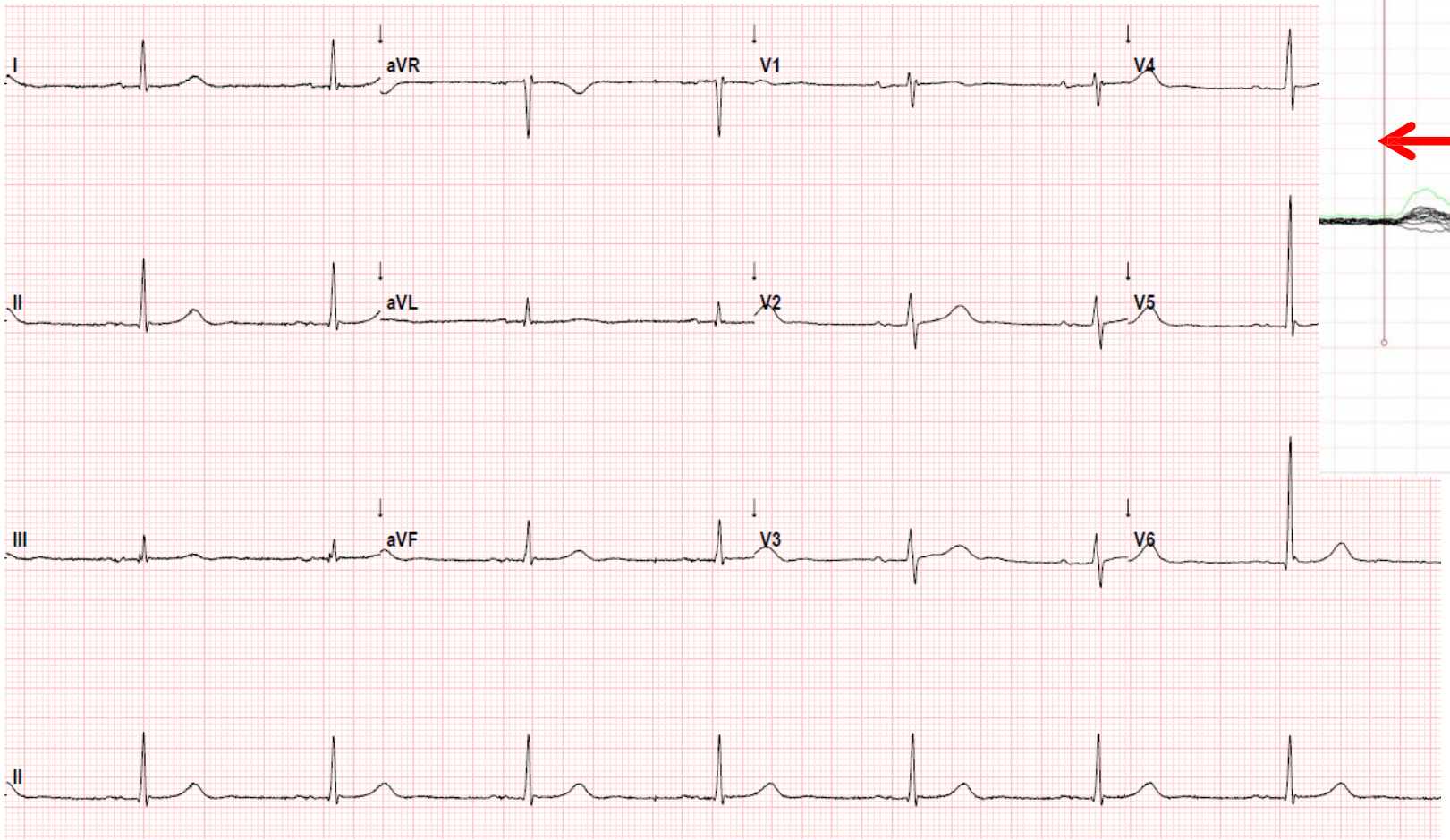


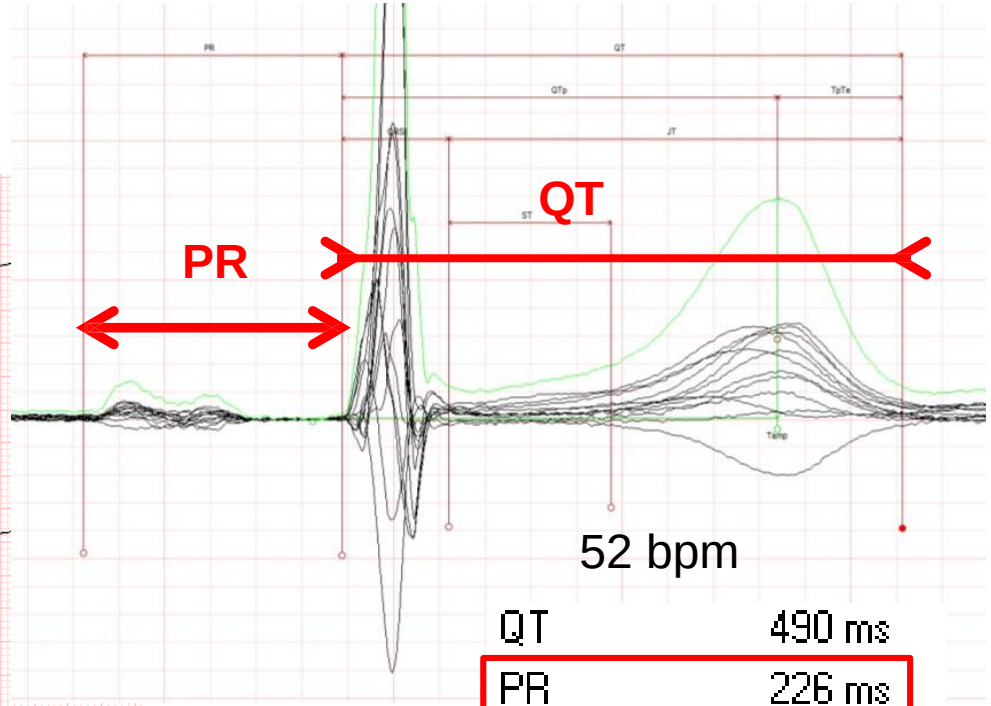
Mrs. F: PR: 213 ms / LAVI: 44 mL/m²

*Lead II-bifed P wave, with 40 ms between peaks for 2.5 mm wide, 100 ms in duration; lead V1-biphasic P wave with terminal portion 40 ms in duration or 1 mm deep; PR interval 200 ms (intra-atrial conduction delay).
CI, confidence interval; ECG, electrocardiogram; HR, hazard ratio; IRAF, ibrutinib-related atrial fibrillation; LAVI, left atrial volume index; OR, odds ratio; PR, PR interval.

1. Mato AR *et al. Cancer Biol Ther* 2018; 19 (1): 1–2. 2. Baptiste F *et al. Open Heart* 2019; 6 (1): e001049.

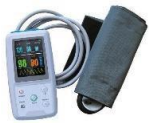
Mrs. F: 1 month after ibrutinib treatment





52 bpm

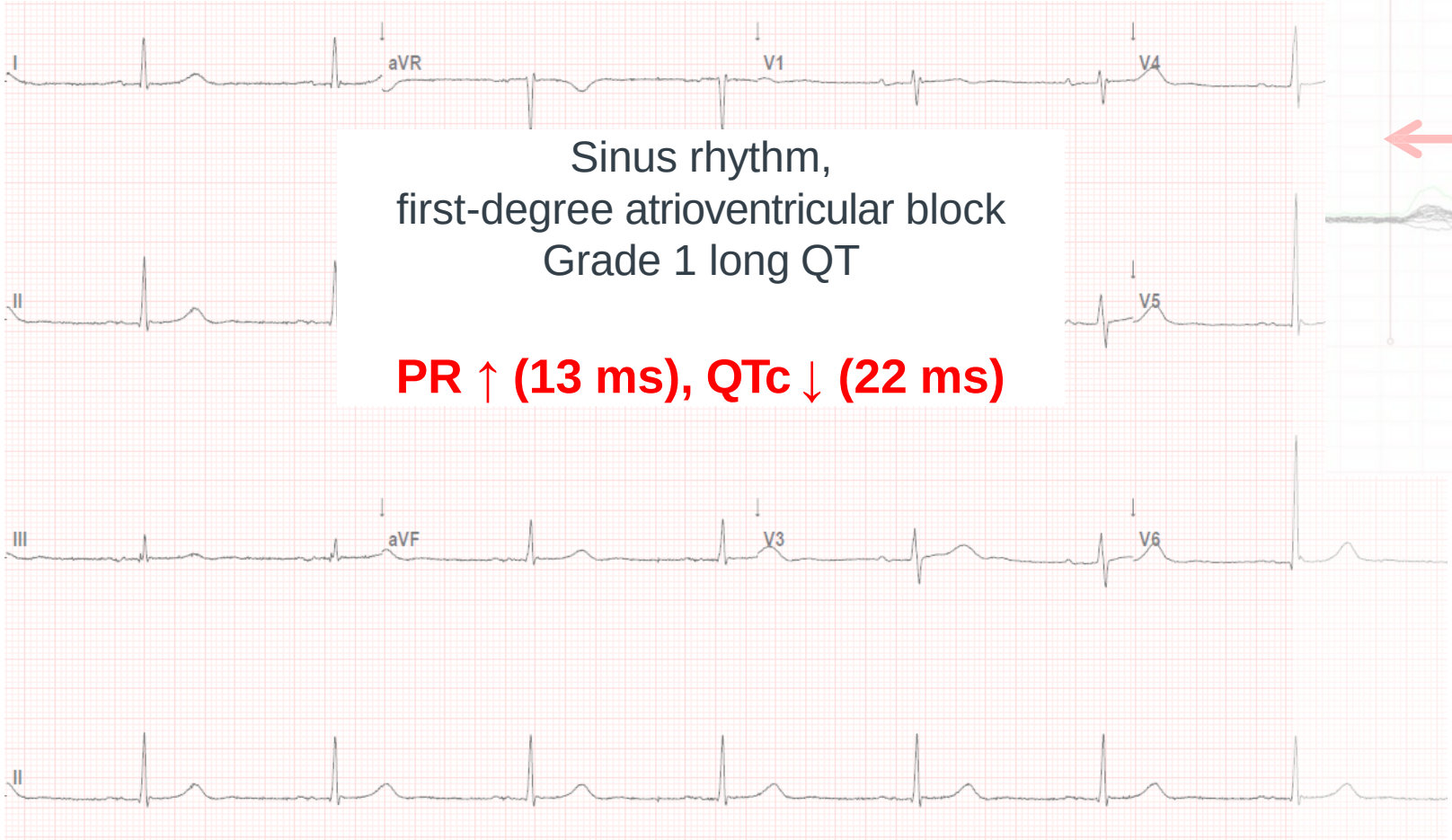
QT	490 ms
PR	226 ms
QRS	93 ms
JT	397 ms
ST	142 ms
Tamp	793 uV
QTp	381 ms
TpTe	109 ms
QTcB	445
QTcF	460



Blood pressure: 149/72 → Perindopril 5 mg/day, amlodipine 5 mg/day

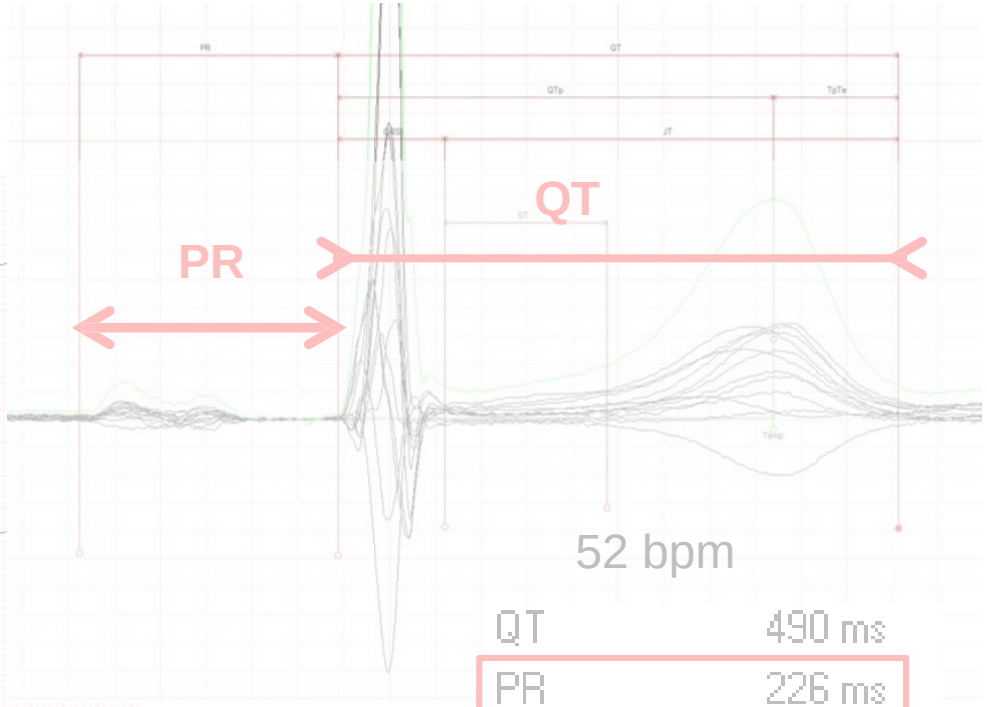
bpm, beats per minute.

Mrs. F: 1 month after ibrutinib treatment



Sinus rhythm,
first-degree atrioventricular block
Grade 1 long QT

PR ↑ (13 ms), QTc ↓ (22 ms)



QT	490 ms
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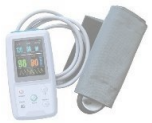
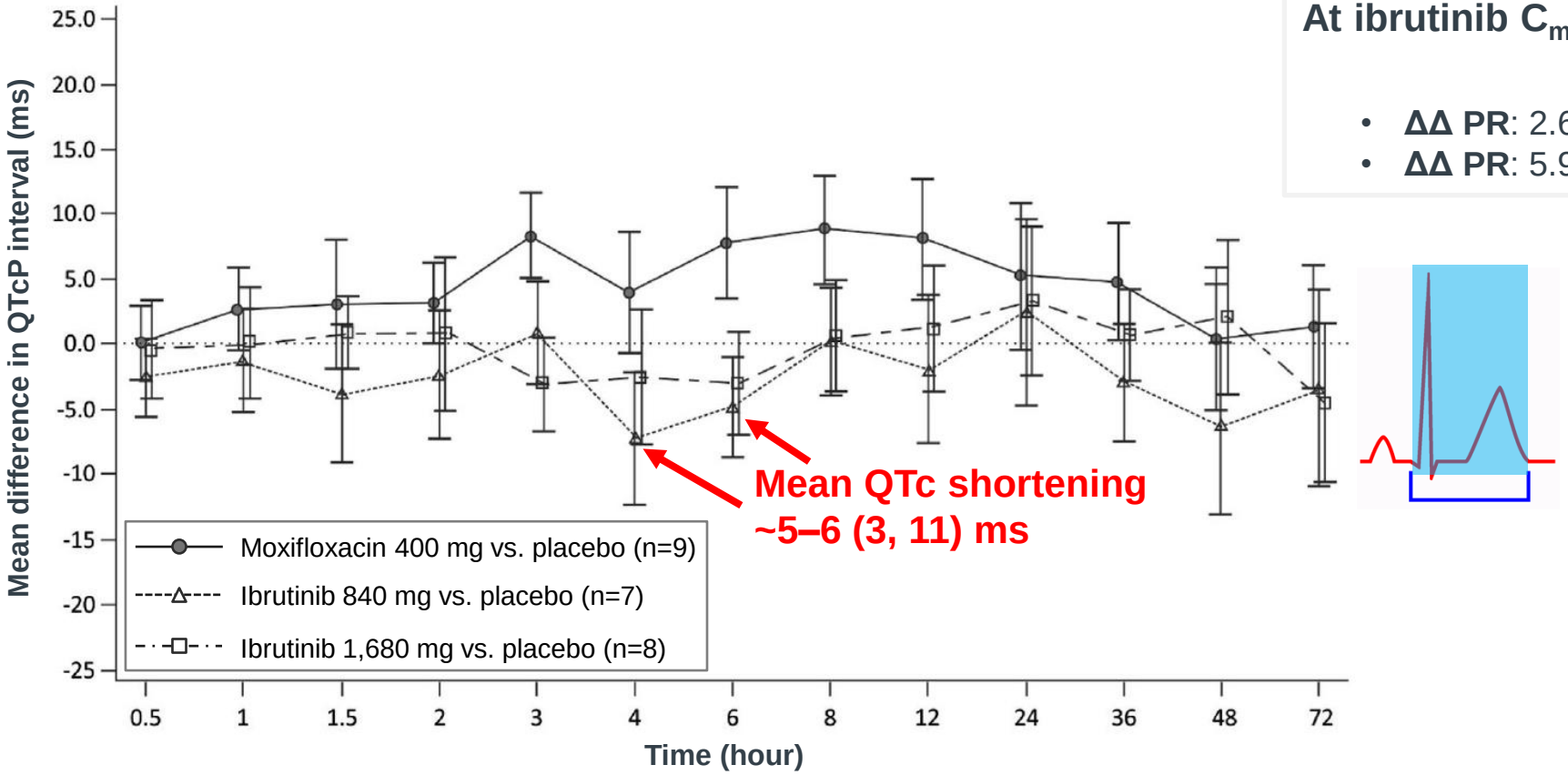


Blood pressure: 149/72 → Perindopril 5 mg/day, amlodipine 5 mg/day

bpm, beats per minute; QTc, corrected QT interval.

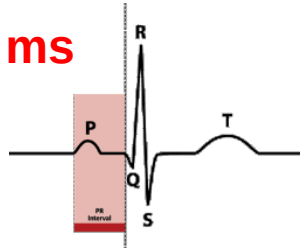
Ibrutinib does not prolong the QT interval in healthy individuals

Single-dose challenge vs. placebo



Mean PR increase ~3–6 (1, 11) ms

At ibrutinib C_{max}



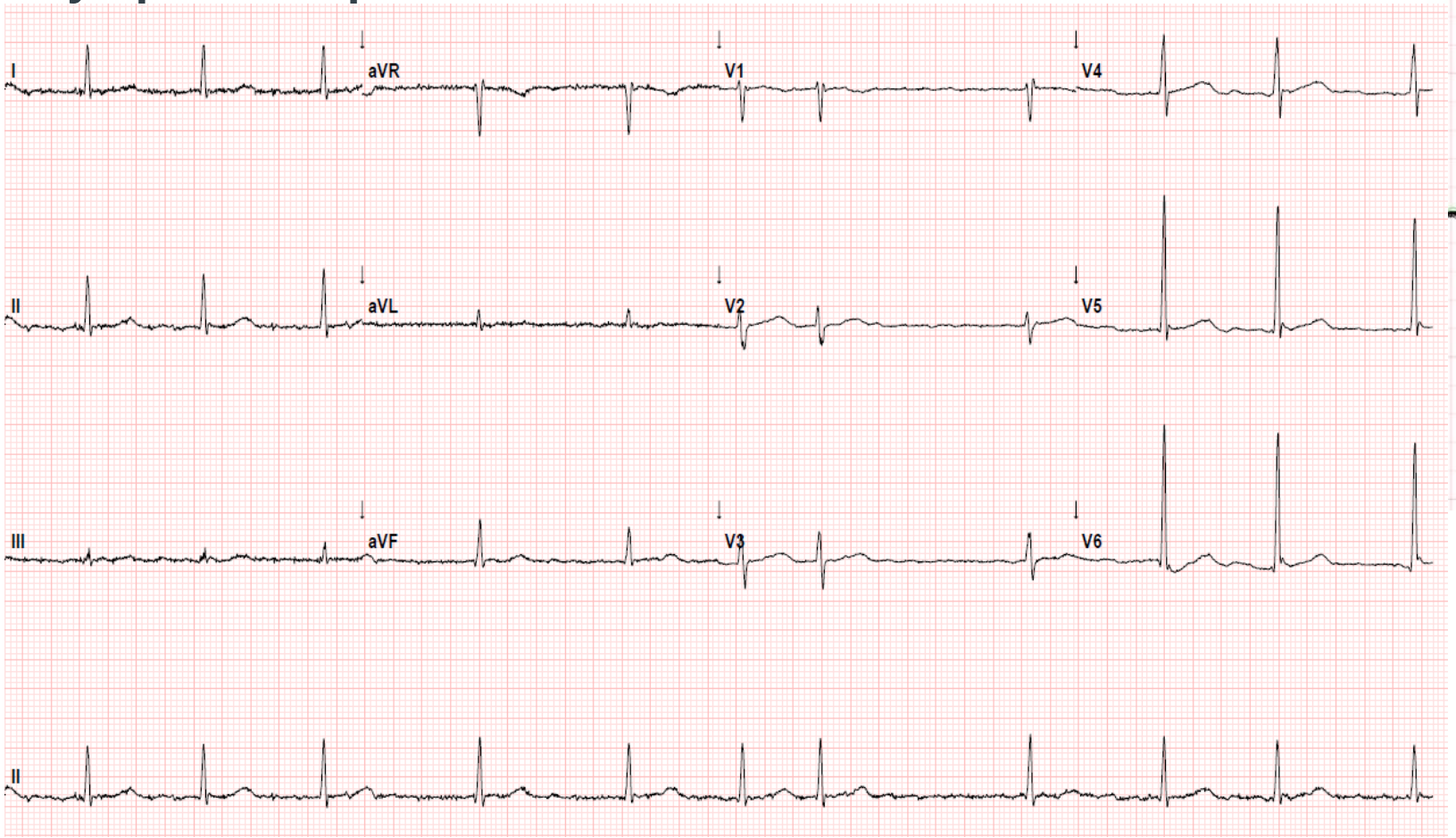
- **ΔΔ PR**: 2.63 ms IC_{90} (−0.01 to 5.27); 840 mg
- **ΔΔ PR**: 5.94 ms IC_{90} (1.29–10.58); 1,680 mg

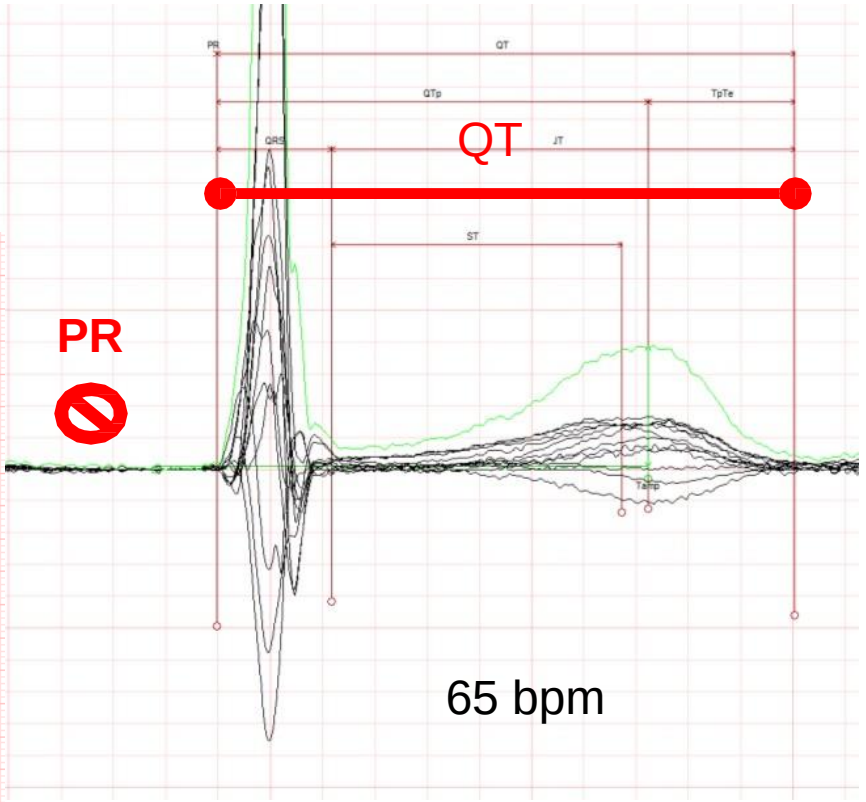
C_{max}, maximum blood plasma concentration; IC_{90}, concentration required for 90% inhibition; PR, PR interval; QTc, corrected QT interval; QTcP, QTc prolongation.

de Jong *et al. Cancer Chemother Pharmacol* 2017; 80 (6): 1227–1237.

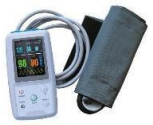
Mrs. F: 3 months after ibrutinib treatment

Asymptomatic persistent atrial fibrillation





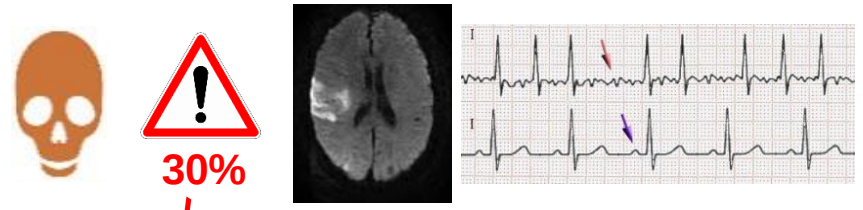
QT	442 ms
PR	[illegible]
QRS	88 ms
JT	354 ms
ST	222 ms
Tamp	373 uV
QTp	330 ms
TpTe	112 ms
QTcB	465
QTcF	457



Blood pressure: 144/73 → Perindopril 10 mg/day, amlodipine 5 mg/day

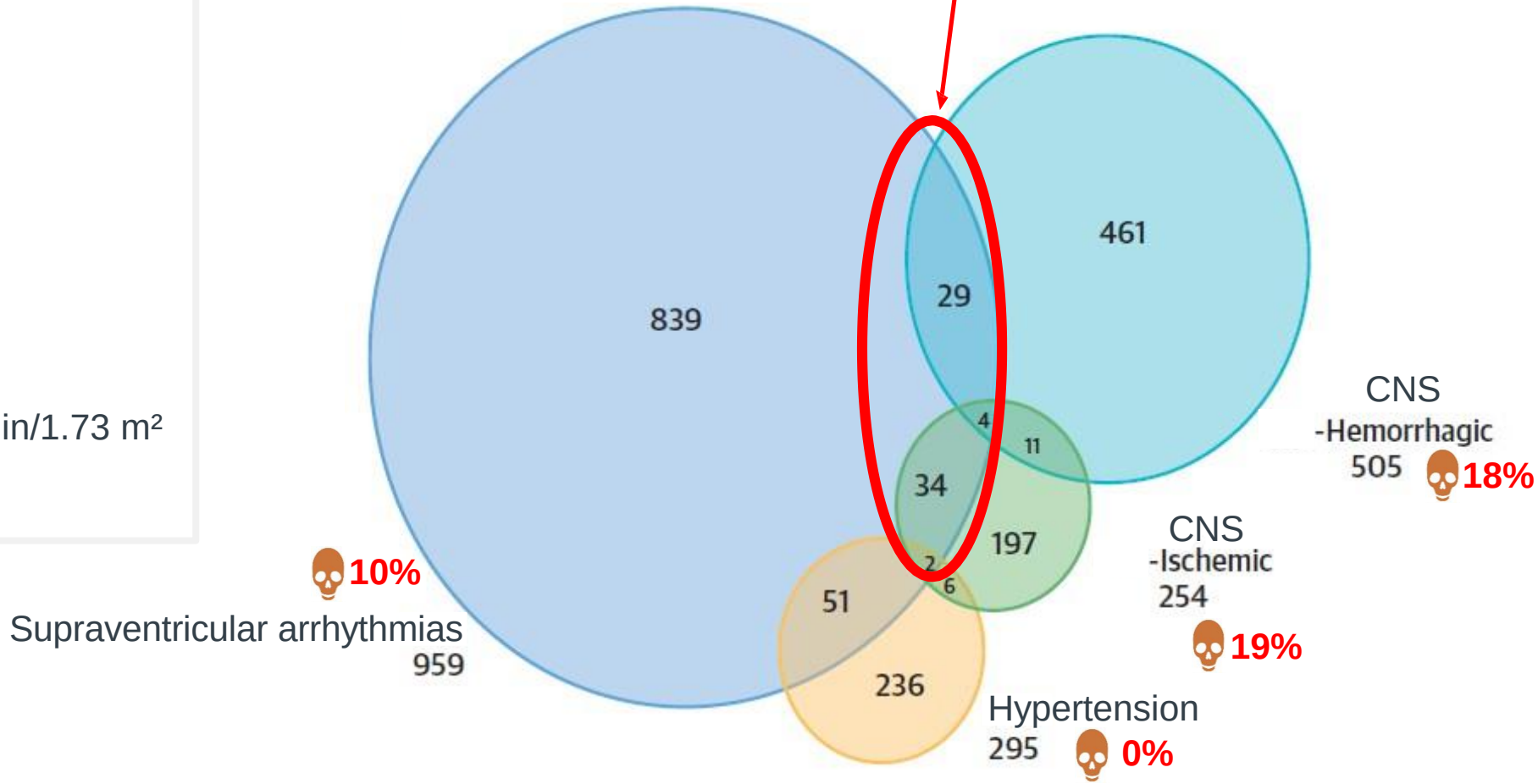
bpm, beats per minute.

Overlap and fatalities: 10%–30% fatalities



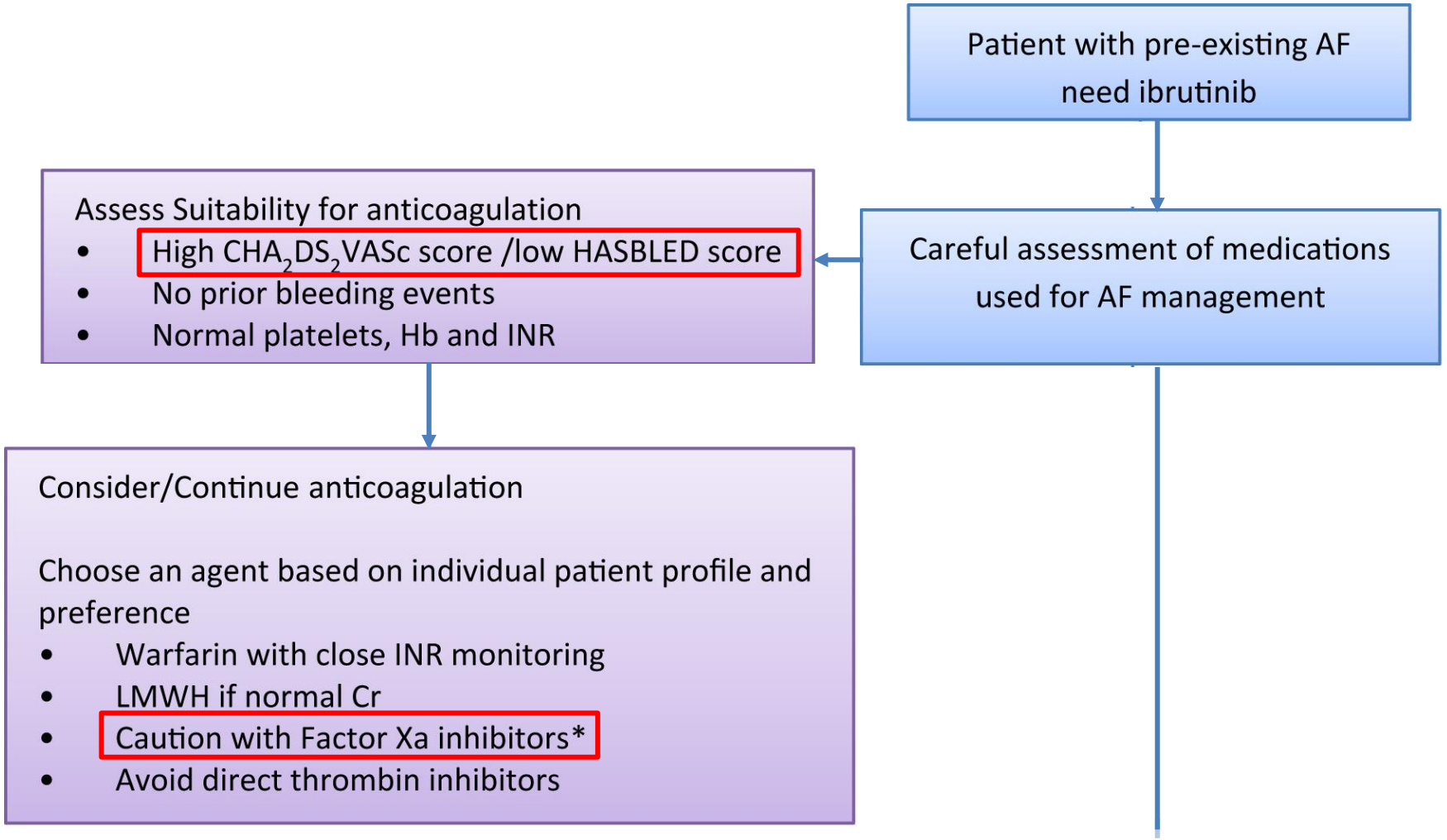
Mrs. F

- **CHA_2DS_2-VASC: 5**
- **HAS-BLED: 3**
- Hemoglobin: 13 g/dL
- Platelets: 132 × 10^9 g/dL
- Leukocytes: 11.5 × 10^9 g/dL
- INR: 1
- Creatinine clearance: 60 mL/min/1.73 m²
- On aspirin 75 mg/day



CHA_2DS_2-VASC, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65–74 years, sex category; CNS, central nervous system; HAS-BLED, hypertension, abnormal renal or liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol; INR, international normalized ratio.
Salem JE *et al*. *J Am Coll Cardiol* 2019; 74 (13): 1667–1678.

Anticoagulation strategy



Mrs. F

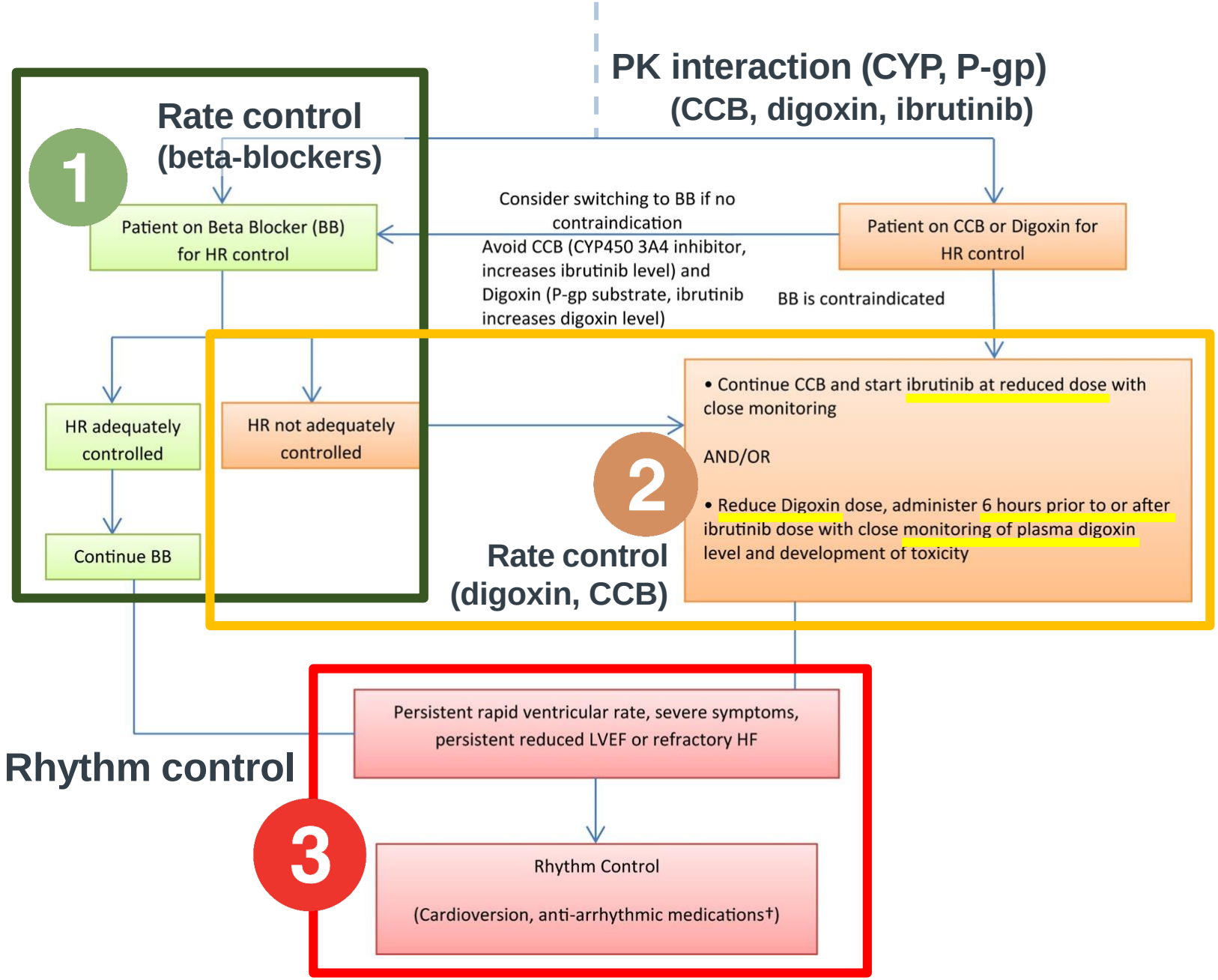
- **Apixaban** 5 mg* twice daily
  - Weight >60 kg (70 kg)
  - Age <80 years (76)
  - Creatinine <133 µmol/L (93)
- **Stop aspirin**
- **Therapeutic drug monitoring**
  - Anti-Xa levels (C_{max}, C_{min}) in expected range

*Factor Xa inhibitor interacts with ibrutinib and increases the bleeding risk (ibrutinib P-glycoprotein inhibitor). Factor Xa or ibrutinib dose reduction may be considered based on individual case.
AF, atrial fibrillation; CHA_2DS_2-VASC, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65–74 years, sex category; C_{max}, maximum blood plasma concentration; C_{min}, minimum blood plasma concentration; Cr, creatinine; HAS-BLED, hypertension, abnormal renal or liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol; Hb, hemoglobin; INR, international normalized ratio; LMWH, low-molecular-weight heparin.
Ganatra S *et al. JACC Clin Electrophysiol* 2018; 4 (12): 1491–1500.

Rate vs. rhythm control

Mrs. F

- Heart rate: 60–70 bpm spontaneously
- **Rate control**
- **No anti-arrhythmic agent**

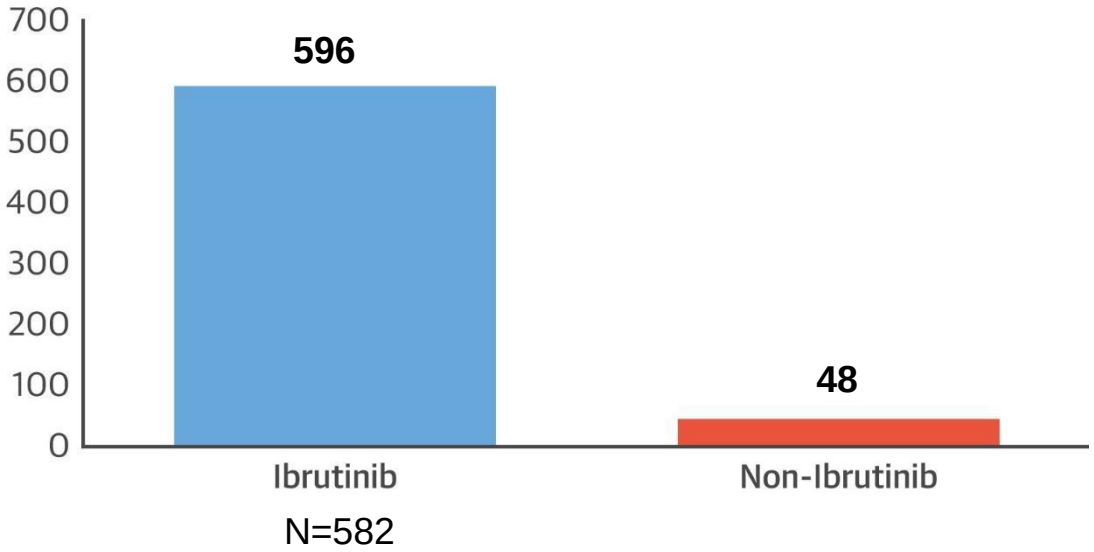


†Amiodarone interacts with ibrutinib and increases the risk of ibrutinib-associated adverse events. Temporary withholding of ibrutinib or dose reduction might be considered.
bpm, beats per minute; CCB, calcium channel blocker; CYP, cytochrome P450; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; P-gp, P-glycoprotein; PK, pharmacokinetic.
Ganatra S *et al. JACC Clin Electrophysiol* 2018; 4 (12): 1491–1500.

VA following ibrutinib initiation for lymphoid malignancies

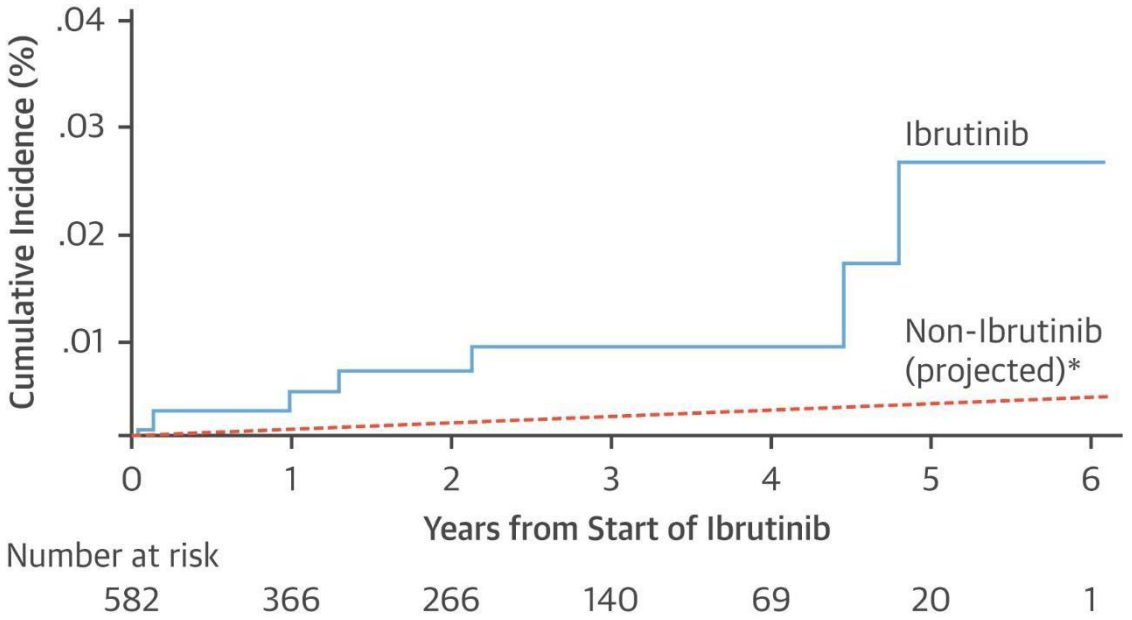
In published clinical trials,
VA occurred
~0.2% Grade ≥3[1]

VA incidence rate per 100,000 person-years[2]



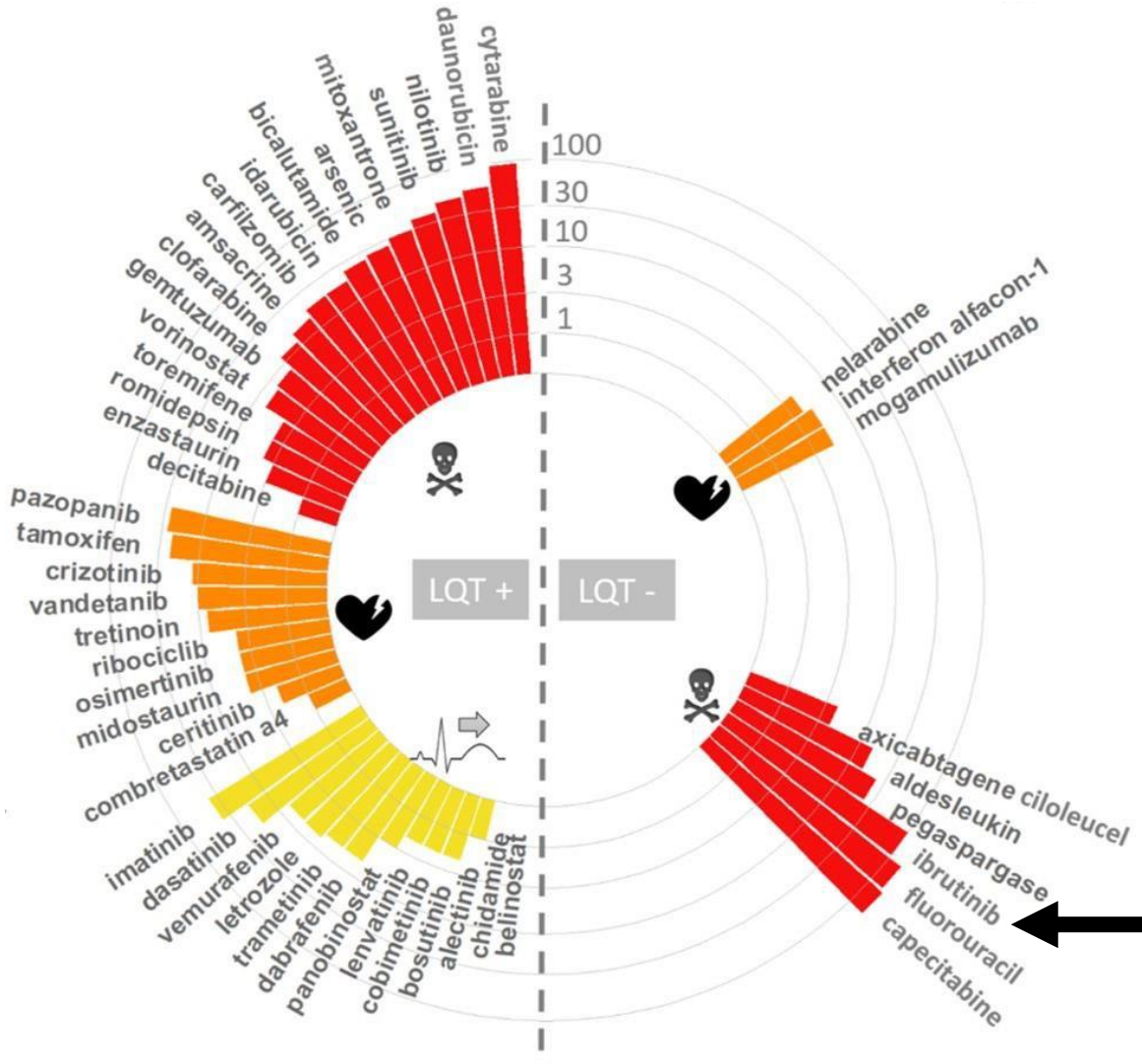
N=582

Cumulative incidence of VAs over time[2]



*Assumes a linear event rate over time.
FDA, Food and Drug Administration; VA, ventricular arrhythmia.
1. Pharmacyclics LLC. IMBRUVICA capsules, tablets, oral suspension – prescribing information; August 2022. 2. Guha A *et al*. *J Am Coll Cardiol* 2018; 72 (6): 697–698.

Absolute number of ventricular arrhythmias*



ESC European Society of Cardiology
European Heart Journal (2021) **42**, 3915–3928
doi:10.1093/eurheartj/ehab362

CLINICAL RESEARCH
Arrhythmias

Anticancer drug-induced life-threatening ventricular arrhythmias: a World Health Organization pharmacovigilance study

Joe-Elie Salem [1,2]*, Lee S. Nguyen [1,3], Javid J. Moslehi[2], Stéphane Ederhy[4], Bénédicte Lebrun-Vignes [1,5], Dan M. Roden [2,6], Christian Funck-Brentano [1], and Paul Gougis[1]

Positive signals for

SD and VA ± LQT

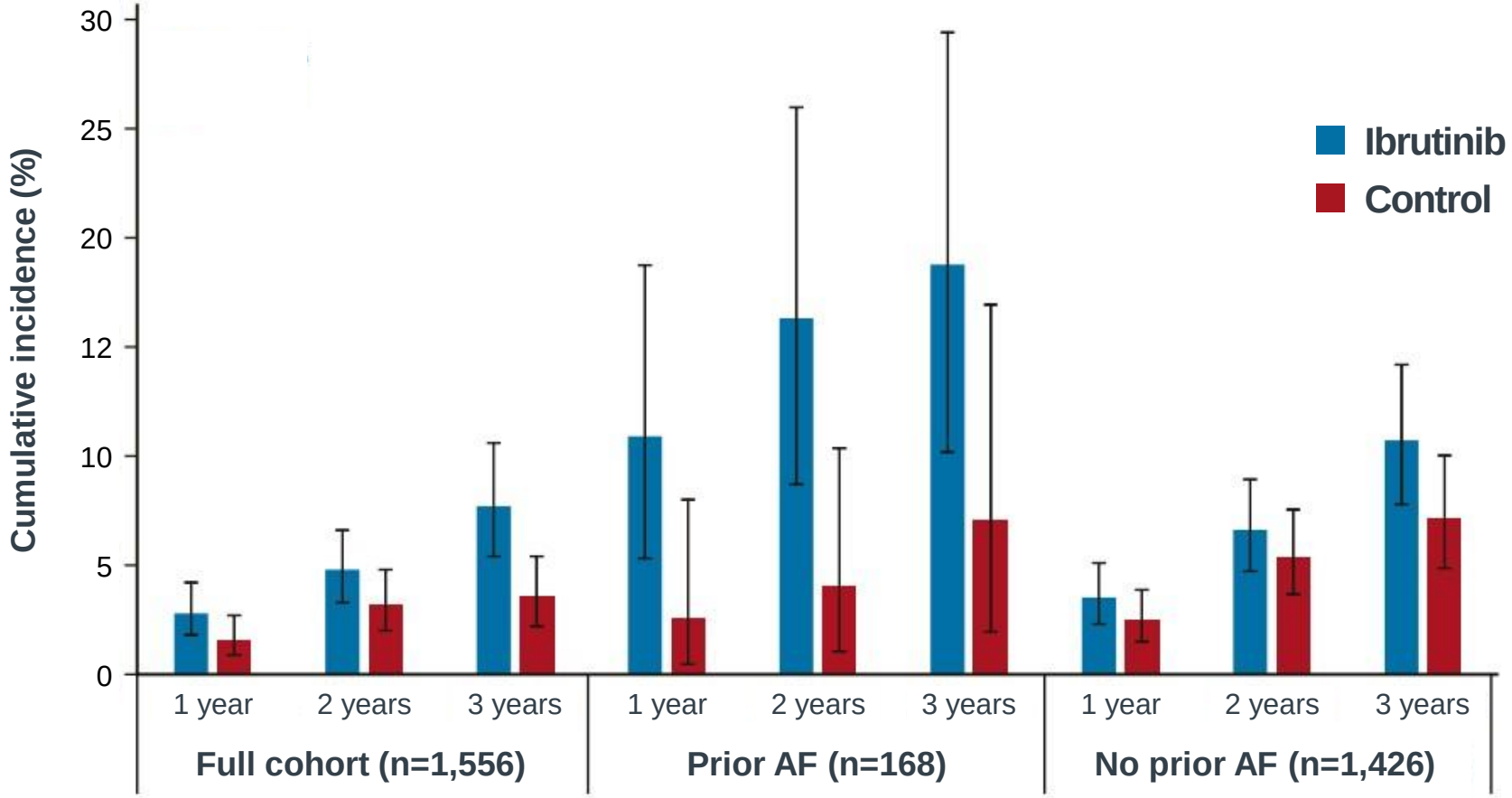
VA/TdP ± LQT, not SD

LQT but not VA/TdP/SD

*NTdP included in NVA.
LQT, long QT; NTdP, number of TdP; NVA, number of VA; SD, sudden death; TdP, torsade de pointes; VA, ventricular arrhythmia. Salem JE *et al. Eur Heart J* 2021; 42: 3915–3928.

Heart failure following ibrutinib initiation for CLL

Cumulative incidence of heart failure at 1, 2, and 3 years in ibrutinib-treated patients with CLL and matched CLL controls unexposed to ibrutinib*, †

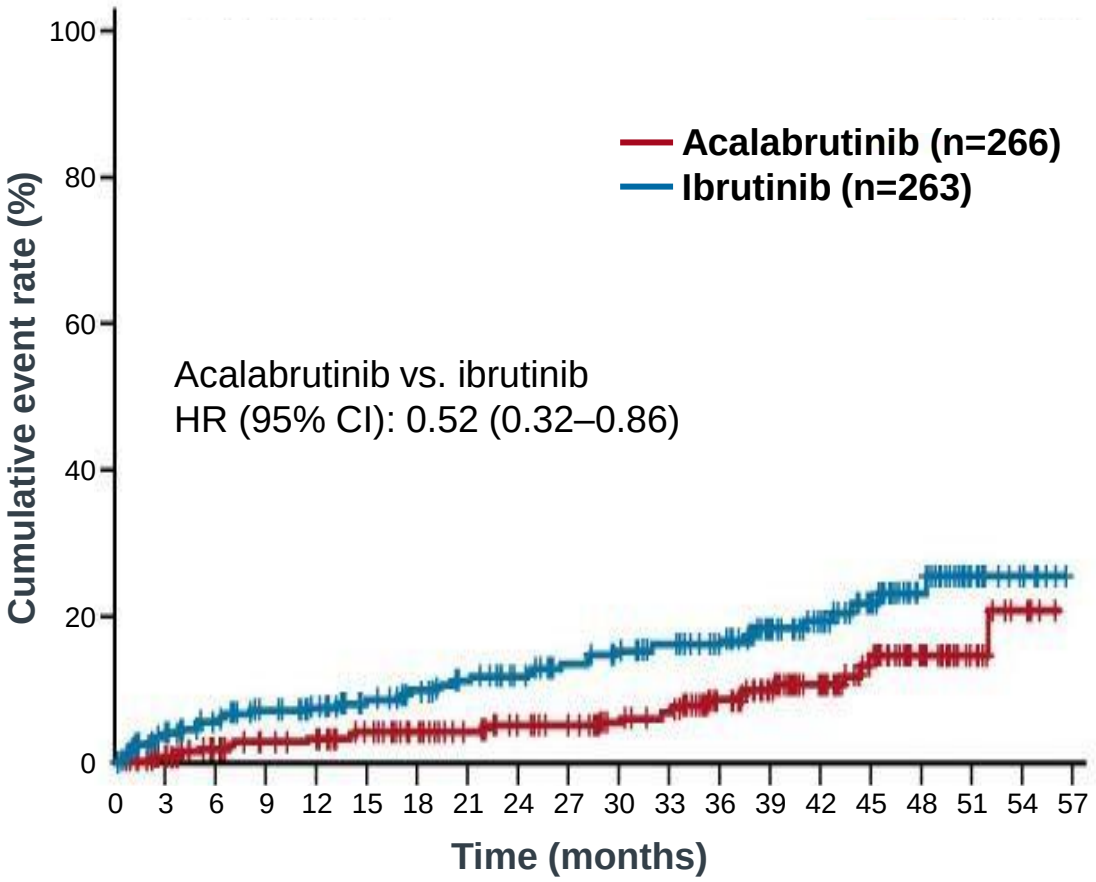


*Patients were matched on prior AF, age ≥66 years, exposure to DOAC or other anticoagulants, and the logit of the propensity score for receiving ibrutinib. †Error bars represent 95% CIs.
AF, atrial fibrillation; CI, confidence interval; DOAC, direct oral anticoagulant.
Abdel-Qadir H *et al. J Clin Oncol* 2021; 39 (31): 3453–3462.

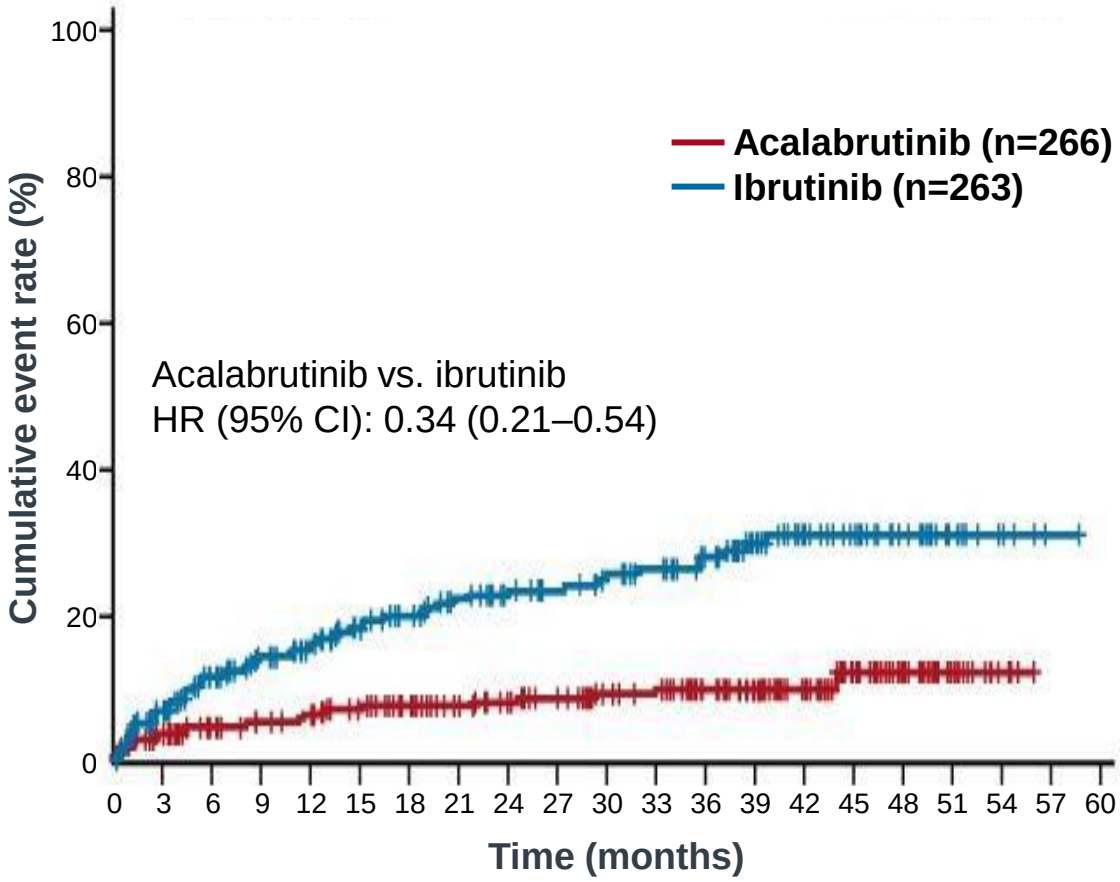
Next-generation BTK inhibitors

Cardiac events for acalabrutinib vs. ibrutinib in R/R CLL

Time to atrial fibrillation/flutter



Time to hypertension

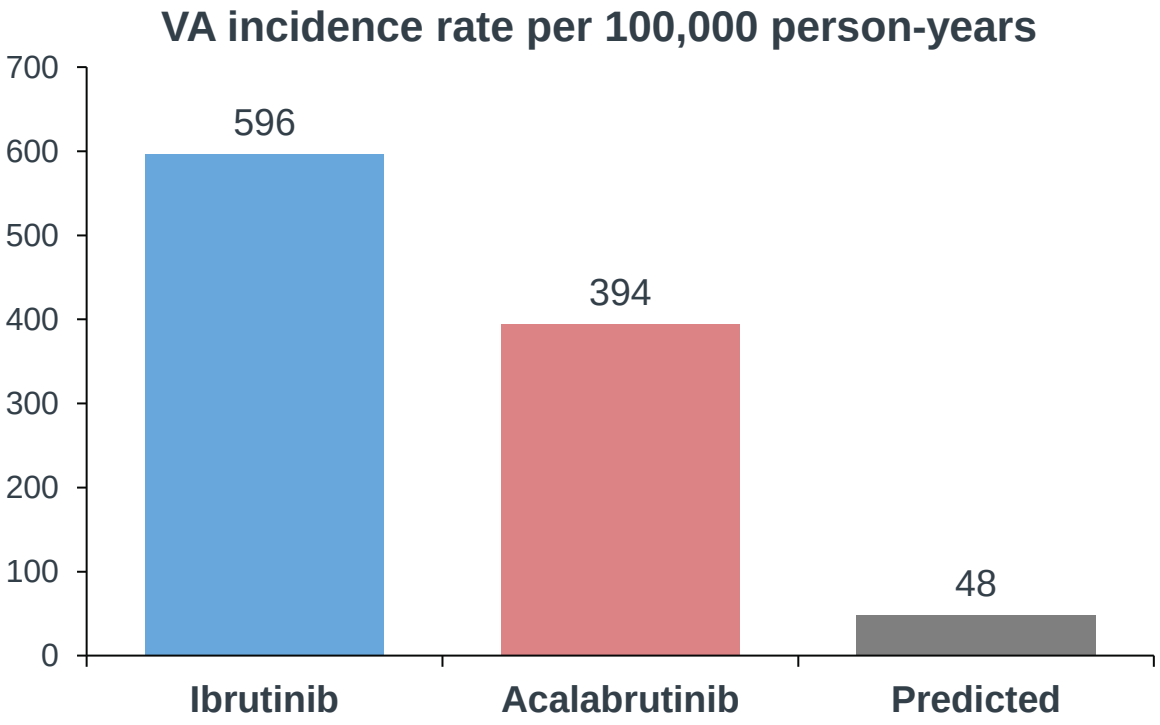


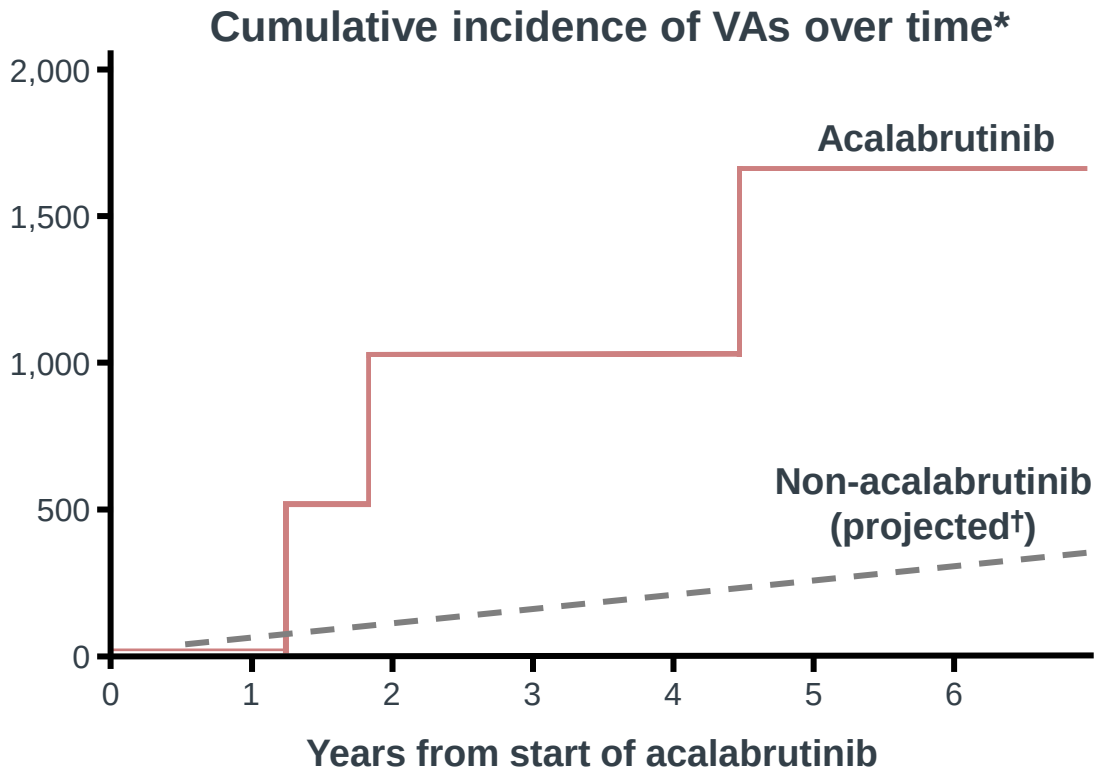
CLL, chronic lymphocytic leukemia; R/R, relapsed/refractory.
Byrd JC *et al*. *J Clin Oncol* 2021; 39 (31): 3441–3452.

Ventricular arrythmia events following acalabrutinib initiation

US-based epidemiological study

- 290 consecutive hematologic malignancy patients treated with acalabrutinib from 2014 to 2020



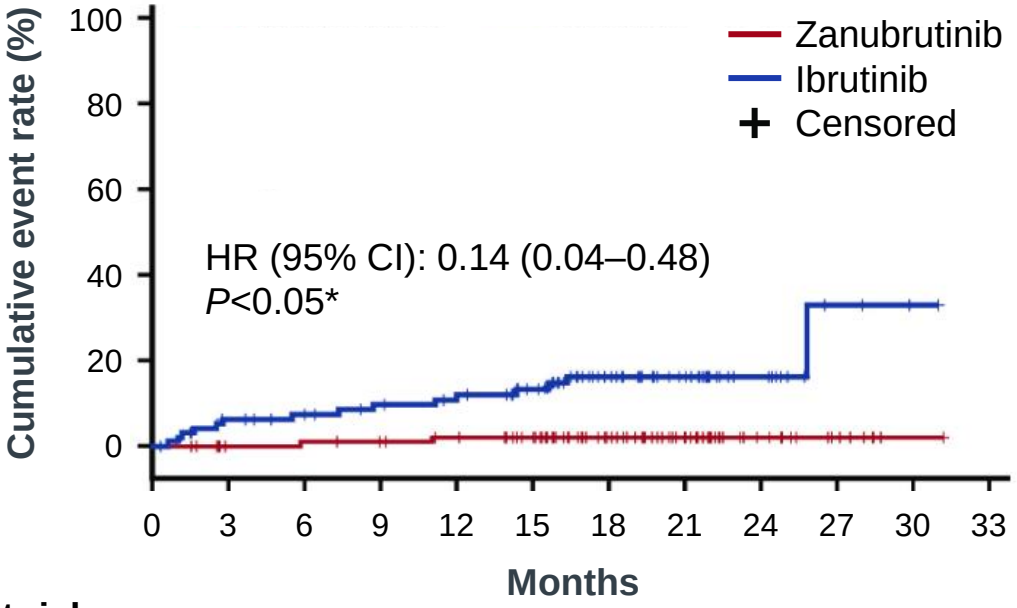


*Those without prior ibrutinib use or structural heart disease. †Assumes a linear event rate over time.
VA, ventricular arrythmia.
Gambril J *et al*. *Circulation* 2022; 146: A12000.

Time to atrial fibrillation/flutter and hypertension in the ASPEN trial in WM

Zanubrutinib vs. ibrutinib

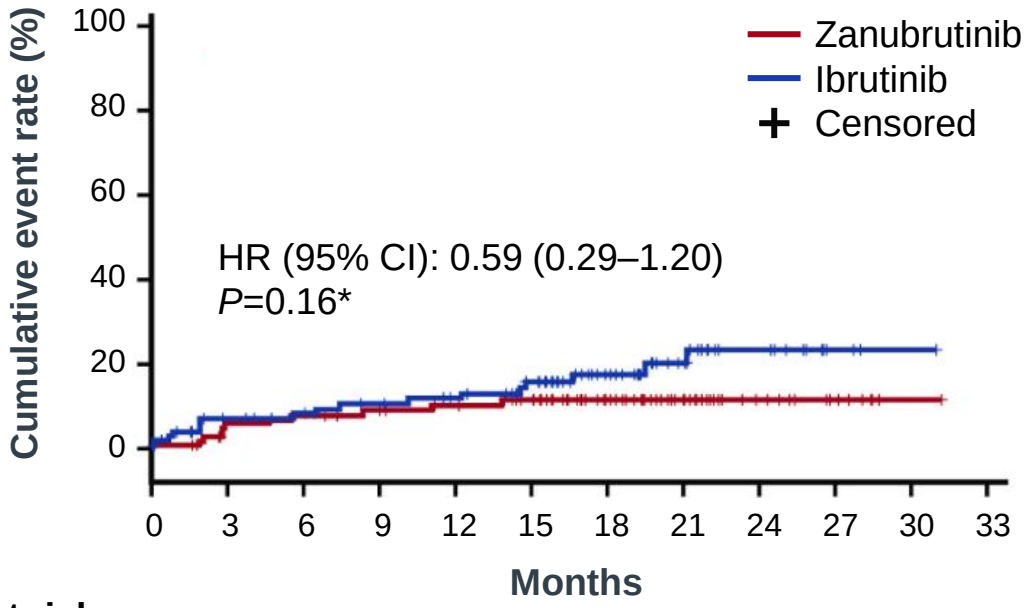
Time to atrial fibrillation/flutter



No. at risk

Zanubrutinib	101	95	94	92	89	81	57	34	15	7	1	0
Ibrutinib	98	87	83	78	74	66	46	28	13	3	1	0

Time to hypertension



No. at risk

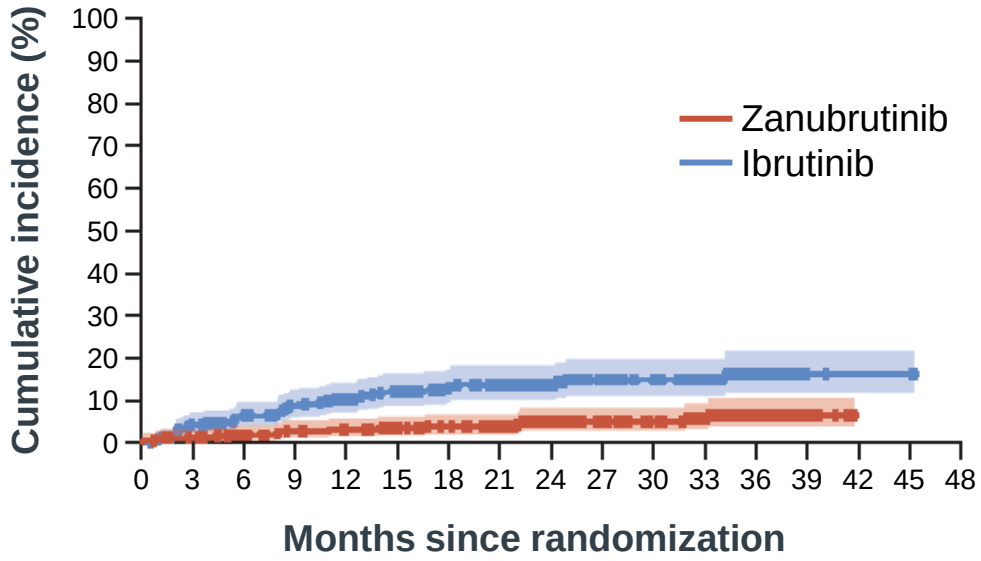
Zanubrutinib	101	90	88	84	81	73	51	28	14	7	1	0
Ibrutinib	98	84	80	75	71	61	42	24	11	3	1	0

*Descriptive purposes only.
CI, confidence interval; HR, hazard ratio; WM, Waldenström's macroglobulinemia.
Tam CS *et al*. *Blood* 2020; 136 (18): 2038–2050.

Time to atrial fibrillation/flutter and hypertension in the ALPINE study in CLL

Zanubrutinib vs. ibrutinib

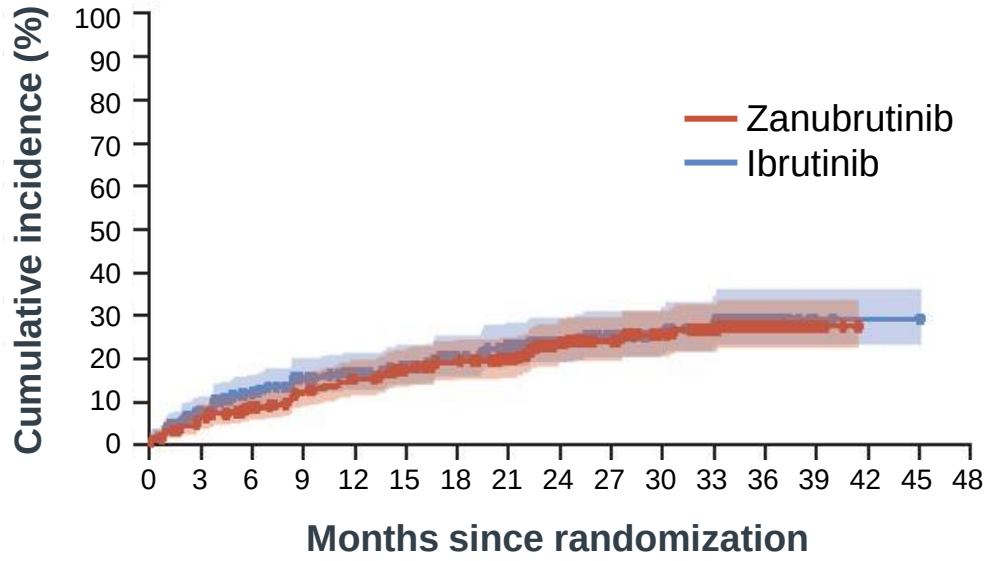
Time to atrial fibrillation/flutter



No. at risk

Zanubrutinib	324	302	288	268	199	148	51	10	0		
Ibrutinib	324	278	247	211	153	108	40	3	2	1	0

Time to hypertension



No. at risk

Zanubrutinib	324	280	248	221	157	115	35	6	0		
Ibrutinib	324	254	222	186	129	84	28	3	2	1	0

CLL, chronic lymphocytic leukemia.

Brown JR *et al*. *N Engl J Med* 2023; 388: 319–332.

Conclusions (1/2)

- Cardiac supraventricular arrhythmias and hypertension are the most frequent cardiovascular complications observed with BTK inhibitors
- In a prospective multicenter cohort study with systematic cardio-oncology follow-up, the risk of ibrutinib-related atrial fibrillation was 38% at 2 years (>15-fold the risk in the general population)[1]
  - Most cases occurred in asymptomatic patients within the first 6 months of ibrutinib initiation, justifying standardized and close monitoring during this period
- Management is based on reducing the risk of:
  - Thromboembolic and heart failure risks
  - BTK inhibitor arrest

1. Baptiste F *et al*. *Open Heart* 2019; 6 (1): e001049.

Conclusions (2/2)

- The risk of atrial fibrillation depends on the off-target kinome (CSK) of the drugs and is lower in new-generation BTK inhibitor trials (to be confirmed in real life)
- Risk of other cardiovascular issues (heart failure, ventricular arrhythmias, sudden death) with BTK inhibitors deserves further evaluation
- **Close cooperation between cardiologists and hematologists is needed to better manage patients with CLL treated with BTK inhibitors**

CLL, chronic lymphocytic leukemia; CSK, C-terminal Src kinase.