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ORIGINAL RESEARCH

RHYTHM DISORDERS AND ELECTROPHYSIOLOGY

# Risk of New-Onset Atrial Fibrillation Associated With Targeted Treatment of Lymphoma

Amole Ojo, MD,[a] Ilan Goldenberg, MD,[a] Scott McNitt, MS,[a] Susan Schleede, MS,[a] Carla Casulo, MD,[b] Clive S. Zent, MD,[b] Jeremiah Moore, PharmD,[b] Mujtaba Soniwala, DO,[c] Mehmet K. Aktas, MD,[a] Saadia Sherazi, MD, MS[a]

## ABSTRACT

**BACKGROUND** Lymphoma treatment may be associated with new-onset atrial fibrillation (AF), especially among patients treated with Bruton tyrosine kinase inhibitors (BTKi).

**OBJECTIVES** The authors sought to assess the risk of new-onset AF, AF risk factors, and the impact of AF on mortality in patients with lymphoma and no history of AF.

**METHODS** The University of Rochester Medical Center Lymphoma Database was used to identify patients. The primary outcome was any AF episode identified using the International Classification of Diseases-10th Revision codes. Multivariable Cox regression was used to assess the risk of AF through the use of a time-dependent covariate for treatment overall as well as separate time-varying measures of BTKi (mainly ibrutinib) and non-BTKi treatment. The relative risk of all-cause mortality was determined using Cox proportional hazards analysis.

**RESULTS** Among 1,957 lymphoma patients, the rate of AF at 5-years following initiation of BTKi treatment was higher (25%) compared to those receiving non-BTKi therapy (8%), and those receiving no treatment (4%). Multivariable analysis showed that BTKi treatment was associated with pronounced increased risk for AF compared to no treatment (HR: 5.07 [95% CI: 2.88-8.90; $P < 0.001$]). Non-BTKi treatment was associated with an increased risk of AF compared to no treatment (HR: 1.82 [95% CI: 1.14-2.89; $P = 0.012$]). Risk factors for the development of AF included age ≥64 years, male sex, hypertension, and lymphoma treatment. New AF was associated with an increased risk for subsequent mortality (HR: 3.71 [95% CI: 2.59-5.31]).

**CONCLUSIONS** Patients undergoing lymphoma treatment, especially those with high-risk features, may benefit from AF surveillance. (JACC Adv 2023;2:100602) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Clinical Cardiovascular Research Center, University of Rochester Medical Center, Rochester, New York, USA; [b]James P. Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, New York, USA; and the [c]Department of Medicine, University of Rochester Medical Center, Rochester, New York, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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**ABBREVIATIONS AND ACRONYMS**

**AF** = atrial fibrillation

**BTKi** = Bruton tyrosine kinase inhibitors

**EMR** = electronic medical record

**RAAS** = renin-angiotensin-aldosterone system

**URMC** = University of Rochester Medical Center

According to the American Cancer Society, 80,470 new cases of non-Hodgkin lymphoma are estimated to be diagnosed in 2022 alone in the United States, and 20,250 people are estimated to die of these malignancies.[1] The development of Bruton tyrosine kinase inhibitors (BTKi) has revolutionized the treatment of some non-Hodgkin lymphomas with increased response rates, progression-free survival, and overall survival.[2-5] Unfortunately, targeted lymphoma treatment has been shown to be associated with atrial fibrillation (AF).[6-11] New-onset AF during lymphoma treatment is associated with worse outcomes in some studies.[8,12,13] However, previous studies included patients with prior history of AF.[7,12-14] Thus, there are limited data on the risk of new-onset AF, especially in those patients treated with BTKi treatment, and its impact on mortality. Furthermore, specific risk factors for new-onset AF development in this population have not been identified.

In this study, we aimed to: 1) determine the risk of new-onset AF after lymphoma treatment; 2) assess the risk of new-onset AF associated with BTKi treatment and non-BTKi treatment; 3) identify risk factors associated with new-onset AF in lymphoma patients; and 4) assess if new AF is associated with worse survival.

## METHODS

**UNIVERSITY OF ROCHESTER MEDICAL CENTER LYMPHOMA DISEASE.** Patients were identified from the University of Rochester Medical Center (URMC) Lymphoma Database. The URMC Lymphoma Database maintains a list of patients seen in the Lymphoma Service at the Wilmot Cancer Institute. All patients who were diagnosed with lymphoma and underwent evaluation between January 2013 and August 2019 were included. Patients received treatments under the guidance of hematologist using standard of care treatment protocols. Most patients with aggressive lymphoma undergo treatment at diagnosis. In contrast, many patients with indolent lymphomas can be observed without disease-specific treatment for variable durations before needing therapy.

Patient demographics, clinical/pathological diagnosis, oncologic disease stage, and clinical trial enrollment are captured by careful review of medical records. Comorbid conditions including hypertension, diabetes mellitus, congestive heart failure, coronary artery disease, and history of arrhythmias were identified using electronic medical record (EMR) system. The International Classification of Diseases-10th Revision (ICD-10) codes were used to search the EMR for comorbid conditions. Echocardiographic data (specifically, left ventricular ejection fraction, left ventricular end-systolic volume, and left ventricular end-diastolic volume), when available, were extracted from the EMR.

The protocol for this study was approved by the Institutional Review Board at URMC, and the requirement for informed consent was waived.

**DEFINITIONS AND ENDPOINTS.** The database was searched for the type of lymphoma treatment each patient received, and they were broadly dichotomized as those receiving BTKi (90% ibrutinib; 10% acalabrutinib) and nonBTKi therapy. The non-BTKi treatments included combination chemotherapy regimens often containing anthracyclines, monoclonal antibodies, and other immune modulating therapy (Supplemental Table 1). Indications for BTKi treatment vs non-BTKi are largely determined by specific lymphoma diagnoses, and this class of drug is primarily used in patients with CLL/SLL, lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia), mantle cell lymphoma, and marginal zone lymphoma. The median duration of treatment in the BTKi group is 19.0 months (IQR of 23.3 months), while it was 23.8 months (IQR of 31.7 months) in the non-BTKi group.

The primary outcome was new incidence of AF occurring during study follow-up. ICD-10 codes for AF were used to identify cases of AF. Twenty-five percent of medical records were reviewed for data quality and accuracy among patients with arrhythmias. Follow-up was measured from 1 day after the date of lymphoma diagnosis (Supplemental Table 2) or on the day of the initial oncology visit. When this date was missing, the therapy start date was used for beginning of follow-up period for 2 patients (Supplemental Table 3). Patients with prior history of AF were excluded from the study analysis. Management of AF after diagnosis was at the discretion of the physicians taking care of the patients. Data about how the AF was managed was extracted from the EMR including changes in medications.

The secondary outcome was all-cause mortality after occurrence of AF. AF was defined as a time-dependent variable. Mortality data was obtained from the URMC lymphoma database, in which a research coordinator tracks mortality events for lymphoma patients who are managed in our institute, supplemented by data from EMR.

**STATISTICAL ANALYSIS.** Differences in patients' characteristics between those with no cancer

treatment, those who received BTKi treatment or non-BTKi treatment were compared using chi-square or Fisher exact tests for categorical variables and the Kruskal-Wallis nonparametric test for continuous variables. Simon and Makuch's nonparametric methodology was used to graphically display the time-dependent nature of lymphoma treatment and its relationship with the endpoint of AF. A time-dependent covariate for cancer treatments was estimated within the multivariable Cox proportional hazards regression model framework to assess the association of cancer treatment with the risk of AF relative to no treatment with follow-up time beginning at the time of lymphoma diagnosis. Similarly, time-dependent covariates for BTKi and non-BTKi treatments were estimated in multivariable Cox proportional hazards regression models to assess the risk of AF for these categories of treatment relative to no treatment.

Multivariable Cox proportional hazards regression modeling using a stepwise procedure was used to identify statistically significant clinical predictors of new-onset AF. These factors were included in the multivariable model to estimate the adjusted cause-specific hazard ratios for treatment. These factors were found to be age ≥64 years, male, and hypertension. Age was dichotomized at 64 years, as this was approximately the median as well as a clinically meaningful cutoff. Additionally, the relative risk of all-cause mortality associated with time-dependent AF was estimated in a multivariable Cox proportional hazards regression analysis, adjusting for the same factors used in the multivariable AF outcome model described above. Also, because the risk of all-cause mortality was substantial in this patient population, a competing risk of death model using the Fine-Gray methodology was estimated to examine if the subdistribution hazard ratio appeared substantially different. All statistical tests were 2-sided, and statistical significance was defined by a $P$ value <0.05. Statistical software SAS 9.4 was used for statistical analyses.

## RESULTS

Our study cohort consisted of 1,957 patients from the URMC Lymphoma Database without a history of known AF, 413 of whom had the diagnosis of CLL/SLL (21.1%). Table 1 shows baseline characteristics of study patients divided into 3 groups: no treatment; BTKi treatment (mainly ibrutinib); and non-BTKi treatment. The median age of study patients at lymphoma diagnosis was significantly lower among patients who received non-BTKi treatment (age 61 years) compared with those who did not receive treatment or received treatment with BTKi (age 64 and 65 years, respectively). Cardiovascular risk factors were evenly distributed among the 3 groups except for presence of coronary artery disease. The patients in the BTKi group are older and have a higher frequency of coronary artery disease (CAD). There was no statistically significant difference in the left ventricular end-diastolic volume across the 3 groups (Table 1).

**TABLE 1 Baseline Characteristics of Patients: No Treatment vs BTKi Treatment vs Non-BTKi Treatment**

| | No Treatment (n = 901) | BTKi (n = 197) | Non-BTKi (n = 859) | *P* Value |
|---|---|---|---|---|
| Age, y | 64 (55-72) | 65 (57-73) | 61 (50-70) | <0.001 |
| Female | 390 (43) | 70 (36) | 375 (44) | 0.101 |
| Hypertension | 213 (24) | 54 (27) | 236 (27) | 0.156 |
| Hyperlipidemia | 195 (22) | 51 (26) | 217 (25) | 0.150 |
| Diabetes | 81 (9) | 22 (11) | 92 (11) | 0.406 |
| Coronary artery disease | 63 (7) | 26 (13) | 71 (8) | 0.016 |
| Heart failure | 21 (2) | 3 (2) | 28 (3) | 0.279 |
| NT-proBNP | 1,169.5 ± 1762.8 | 719.6 ± 908.4 | 865.2 ± 1,165.6 | 0.334 |
| LVEF* | 62.8 ± 15.6 | 63.2 ± 10.9 | 65.1 ± 8.0 | 0.897 |
| LVESV* | 48.8 ± 39.8 | 45.9 ± 15.8 | 40.7 ± 19.4 | 0.512 |
| LVEDV* | 119.3 ± 48.0 | 125.9 ± 29.4 | 113.1 ± 33.2 | 0.377 |
| Ibrutinib | 0 | 177 (90) | 0 | <0.001 |
| Anthracycline-based chemo | 0 | 0 | 81 (9) | <0.001 |
| Anthracycline-based chemo plus immune MAB | 0 | 0 | 401 (47) | <0.001 |
| MAB/immune-based chemo (no anthracycline) | 0 | 0 | 273 (32) | <0.001 |
| Other chemo (not anthracycline, BTKi or immune MAB) | 0 | 0 | 104 (12) | <0.001 |
| Anticoagulation | 131 (15) | 41 (21) | 187 (22) | <0.001 |
| Beta-blockers | 141 (16) | 40 (20) | 146 (17) | 0.271 |
| Antiarrhythmic medications | 165 (18) | 34 (17) | 233 (27) | <0.001 |

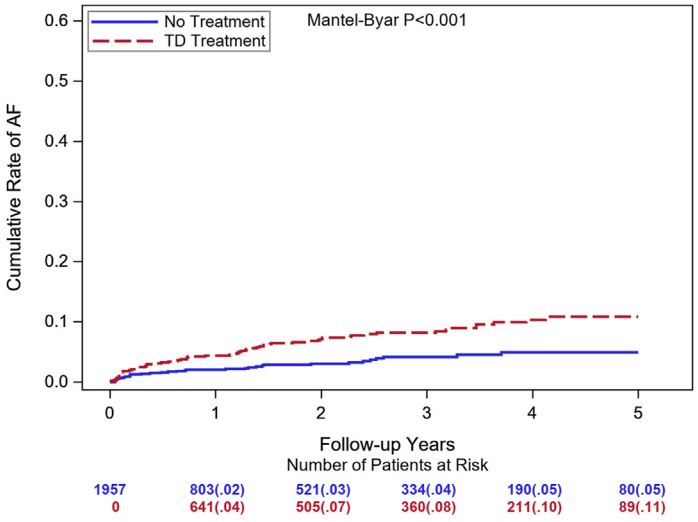
Values are median (IQR), n (%), or mean ± SD. *Echocardiographic data only available for 97 patients.

AF = atrial fibrillation; BTKi = Bruton tyrosine kinase inhibitors; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; MAB = monoclonal antibody; NT-proBNP = N-terminal pro-brain natriuretic peptide.

**RISK OF NEW AF ASSOCIATED WITH LYMPHOMA TREATMENT.** Simon and Makuch survival analysis showed that the overall rate of new-onset AF at 5-years following the initiation of any lymphoma treatment in patients without prior history of AF was significantly higher (11%) compared to no treatment (5%) ($P$ for the overall difference during follow-up <0.001) (Figure 1). Importantly, separation in the cumulative rates of AF appeared immediately after initiation of lymphoma treatment and continued for 5 years.

Consistent with these univariate findings, lymphoma treatment was associated with a significantly increased risk of AF compared to no treatment (HR: 2.31; 95% CI: 1.51-3.55; $P < 0.001$) (Table 2).

**FIGURE 1 Cumulative Probability of AF: Time-Dependent Treatment vs No Treatment**




AF = atrial fibrillation.

### RISK OF AF BY LYMPHOMA TREATMENT SUBTYPE.

Simon and Makuch survival analysis showed that the rate of new-onset AF at 5 years following the initiation of BTKi treatment (mainly ibrutinib) was significantly higher (25%) compared to no treatment (4%), with sustained and continued separation in event rates throughout follow-up (*P* for the overall difference during follow-up <0.001) (Central Illustration).

Consistent with the univariate findings, multivariable analysis showed that BTKi treatment was associated with an increased risk for AF compared to no treatment (HR: 5.07 [95% CI: 2.88-8.90; $P < 0.001$]).

Simon and Makuch survival analysis showed that the rate of new-onset AF at 5-years following the initiation of non-BTKi treatment was also significantly higher (8%) compared to no treatment (5%) though to a lesser extent, with sustained separation in event rates throughout follow-up (*P* for the overall difference during follow-up = 0.012) (Central Illustration).

Consistent with the univariate findings, multivariable analysis showed that non-BTKi treatment was associated with an increased risk for AF compared to no treatment (HR: 1.82 [95% CI: 1.14-2.89; $P = 0.012$]).

**TABLE 2 Independent AF Risk Factors During Lymphoma Treatment**

| | HR | 95% CI | *P* Value |
|---|---|---|---|
| Any Lymphoma treatment vs no treatment | 2.31 | 1.51-3.55 | <0.0001 |
| By lymphoma treatment subtype* | | | |
| BTKi vs no treatment | 5.07 | 2.88-8.90 | <0.0001 |
| Non-BTKi vs no treatment | 1.82 | 1.14-2.89 | 0.012 |
| BTKi vs Non-BTKi | 2.79 | 1.62-4.80 | 0.0002 |
| Age ≥64 y | 2.81 | 1.79-4.40 | <0.0001 |
| Male | 1.79 | 1.17-2.75 | 0.008 |
| Hypertension | 1.69 | 1.12-2.55 | 0.013 |

*Obtained from a separate multivariate model that included subtypes of lymphoma treatment.
AF = atrial fibrillation; BTKi = Bruton tyrosine kinase inhibitors.

### ADDITIONAL RISK FACTORS FOR NEW-ONSET AF IN LYMPHOMA PATIENTS.

Multivariable analysis identified 3 independent risk factors associated with increased risk of AF during lymphoma treatment with both BTKi (mainly ibrutinib) and non-BTKi: age ≥64 years (HR: 2.81 [95% CI: 1.79-4.40; $P < 0.001$]); male (HR: 1.79 [95% CI: 1.17-2.75; $P = 0.008$]); and hypertension (HR: 1.69 [95% CI: 1.12-2.55; $P = 0.013$]) (Table 2).

### SURVIVAL AFTER DEVELOPMENT OF NEW-ONSET AF IN LYMPHOMA PATIENTS.

Over the study period, a total of 306 patients died: 103 (11%) in the no-treatment group, 46 (23%) in the BTKi group, and 157 (18%) in the non-BTKi group. Multivariable analysis for the endpoint of all-cause mortality showed that the development of AF among lymphoma patients without a history of AF was associated with nearly a pronounced increased risk of subsequent mortality (adjusted hazard ratio for all-cause mortality: 3.71 (95% CI: 2.59-5.31; $P < 0.001$). Of note, the risk of death following the development of AF was consistent regardless of lymphoma therapy type (*P* for new-onset AF-by-treatment interaction = 0.76). The cumulative rates of death following development of AF in all the patients regardless of therapy and in those who were treated with BTKi (mainly ibrutinib) are shown in Figures 2 and 3 respectively. The association between mortality and AF onset was regardless of treatment with HRs of 2.83 (95% CI: 1.25-6.38), 3.98 (95% CI: 2.51-6.33), and 3.95 with BTKi treatment, non-BTKi treatment, and without treatment, respectively.

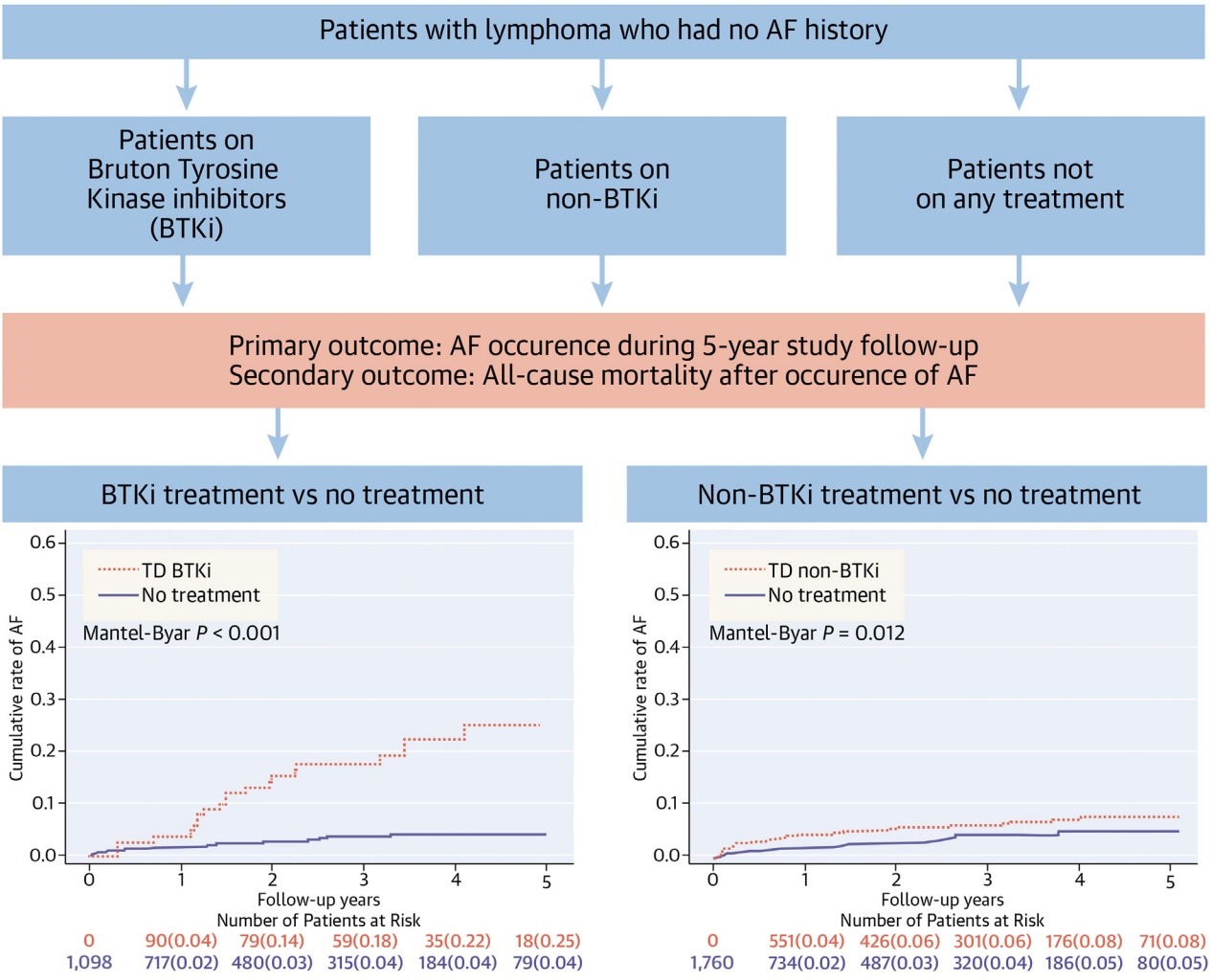
### MANAGEMENT OF NEW-ONSET AF IN LYMPHOMA PATIENTS.

Some of these patients were managed with use of beta blockers, while others were started on antiarrhythmic medications (Table 1). Only 53% of the patients diagnosed with AF were started on anticoagulation.

## DISCUSSION

In this study, we found that the rate of new AF at 5-years following the initiation of lymphoma treatment was higher in patients receiving treatment (11%)

**CENTRAL ILLUSTRATION** **Atrial Fibrillation Risk During Targeted Lymphoma Treatment in Patients Without Prior History of Atrial Fibrillation**

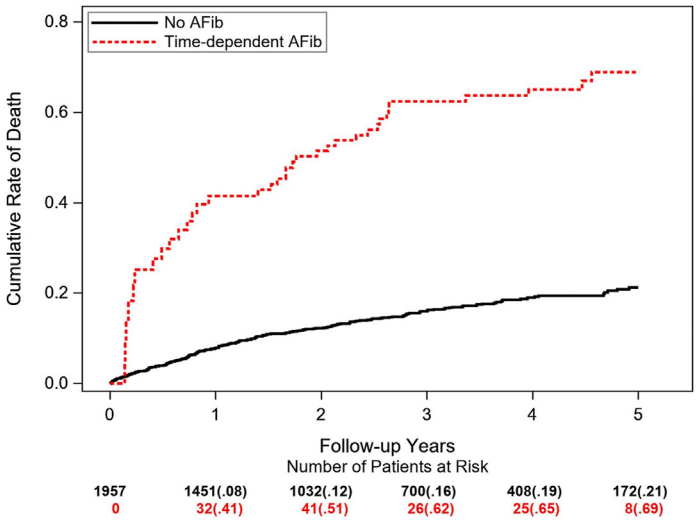



**Ojo A, et al. JACC Adv. 2023;2(8):100602.**

compared to those not receiving treatment (5%). BTKi treatment (mainly ibrutinib) was associated with a 5.1-times increased risk for AF compared to no treatment, whereas non-BTKi treatment was associated with only a 1.8-times increased risk compared to no treatment. The risk of developing AF following initiation of BTKi treatment appeared early and remained elevated in long-term follow-up, reaching 25% at 5 years of follow-up. Age ≥64 years, male sex, and hypertension were independent risk factors for AF in lymphoma patients, in addition to lymphoma treatment with BTKi and non-BTKi agents. These data suggest that monitoring patients with lymphoma and these risk factors may be of value, as new-onset AF was associated with nearly a 4-times increased risk of mortality.

**NEW-ONSET AF DEVELOPMENT DURING LYMPHOMA TREATMENT.** Our findings are consistent with recent studies that demonstrate an increased risk of AF with contemporary lymphoma treatments.[8,13-15] Lentz et al[15] found the incidence of AF was 11.9% after a median 154-day ibrutinib exposure. In another study by Reda et al,[14] the incidence of AF was 16.3% after a median of 8 months. However, prior studies included patients with prior history of AF. A unique feature of our study is the exclusion of patients with prior history of AF. This is the first assessment of "pure" new AF onset associated with cancer treatment. Our study

**FIGURE 2 Cumulative Rate of Death Following AF Development Regardless of Therapy**




AF = atrial fibrillation.

also found an increased risk of AF associated with BTKi treatment (mainly Ibrutinib) of 25% at 5 years of follow-up. Furthermore, we found that AF risk was associated with non-BTKi treatment. It is worth noting that there were more patients with CAD among those treated with BTKi compared to those treated with non-BTKi and those who did not receive treatment. The results remained the same after adjusting for CAD. In addition to therapies, we identified risk factors associated with new-onset AF that can be used in clinical practice.

The exact mechanism for the increased risk of AF with ibrutinib treatment is not known. A potential mechanism is the inhibition of protective phosphoinositide 3-kinase (PI3K)-Akt pathway.[16] This pathway is a critical regulator of cardiac protection under stress conditions. Ibrutinib, via BTK, targets the α-subunit of PI3K (p110α), which is the predominant PI3K isoform expressed in cardiovascular tissues. Loss of the α-subunit of PI3K (p110α) activity can lead to AF both in murine and human models,[16] whereas increased PI3K (p110α) activity dramatically decreased atrial fibrosis.[17] Ibrutinib also irreversibly inhibits 19 other kinases that contain cysteine residues homologous to Cys-481 in BTK including Tec protein, interleukin-2-inducible T-cell kinase, and T-cell X chromosome kinase. These pharmacodynamic features may be responsible for ibrutinib-related AF events that are not typically observed in BTK-deficient patients. Early evidence suggests that the second-generation BTKi, acalabrutinib, has a significantly lower risk of AF compared to Ibrutinib, and this may reflect the fact that it is a more selective BTK inhibitor.[17] Xiao et al reported that inhibition of C-terminal Src kinase was the strongest candidate for ibrutinib-associated AF. Treatment of mice with ibrutinib for 4 weeks leads to inducible AF, left atrial enlargement, myocardial fibrosis, and inflammation. This was reproduced in mice lacking BTK. But not in mice treated with acalabrutinib, a more specific BTKi, demonstrating an off-target side effect.[18] Cardiac-specific C-terminal Src kinase knockout in mice led to increased AF, left atrial enlargement, fibrosis, and inflammation, phenocopying Ibrutinib treatment.[18]

Proposed hypotheses for mechanisms via which anthracyclines can induce AF include direct and indirect effects on cardiac ion channels, activation of pro-inflammatory pathways, and accumulation of reactive oxygen species.[19,20] Proposed mechanisms for AF onset associated with treatment with monoclonal antibodies include induction of immune-mediated destruction of cardiomyocytes, inhibition of NRG-1/Erb signaling, and a cytokine release syndrome.[20] Patients who are undergoing lymphoma treatment may also experience some issues that may predispose them to AF, including electrolyte disorders, volume depletion, large volume infusion, and increased sympathetic tone due to pain.

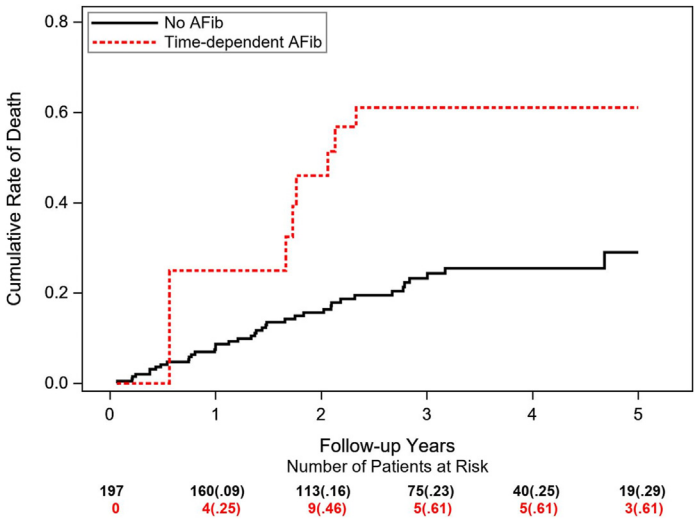
**ADDITIONAL RISK FACTORS FOR NEW-ONSET AF IN LYMPHOMA PATIENTS.** Among patients treated for lymphoma, age ≥64 years was an independent risk factor for AF onset, although the pathophysiologic mechanisms by which aging increases the likelihood of AF is poorly understood. The atrial myocardium undergoes both electrical and structural remodeling with age. A longer time during which atria are exposed to other risk factors such as congestive heart failure also plays a role in the association of age and AF onset.[21] Across all age groups, the incidence of AF is higher in men than in women.[22] It is not clear if this difference is due to sex or underdiagnosis of AF in women. The difference may also be due to higher incidence of other AF risk factors in men compared to women. The degree of shortening of atrial effective refractory period in response to rapid atrial pacing has been reported to be significantly less in premenopausal women compared with postmenopausal women and age-matched men, suggesting the protective role of estrogen.[23] Over time, hypertension is associated with an increase in atrial pressure and/or volume overload, and diastolic dysfunction. These may lead to atrial dilatation and fibrosis—the

structural and electrical changes needed for development of AF. Renin-angiotensin-aldosterone system activation and hypertension are closely linked. Components of the renin-angiotensin-aldosterone system have been shown to promote AF.[24] It is of note that treatment with ibrutinib has been associated with development of hypertension, which indirectly increases the risk of AF associated with treatment with ibrutinib.[25-28]

**CLINICAL IMPLICATIONS OF AF DEVELOPMENT DURING LYMPHOMA TREATMENT.** In our study, new-onset AF is associated with worse survival, similar to other studies that have found worse outcomes with AF onset during lymphoma treatment.[29] In our study, new-onset AF was associated with worse survival regardless of treatment group (BTKi, non-BTKi, or no treatment). It is well established that AF increases risk of death by increasing the risk of embolic strokes. It is also well known that development of AF may be a surrogate marker for worsening clinical status of patients, so that patients die from exacerbation or worsening of a different condition and not from complications related to AF. In our study, it is more likely that AF was a surrogate marker for worsening clinical status of the patients and less likely to be the direct cause of mortality.

**STUDY LIMITATIONS.** Our study has several limitations. Our study is a single-center observational study, and diagnoses are based on ICD-10 codes. We do not have data about metabolic derangements and electrolyte abnormalities that might have helped trigger AF. We do not have information on left atrial size for all the patients, and we also do not have information on P-wave length that could have provided more information about AF risk. We do not have data on the incidence of cardiomyopathy during treatment that might have predisposed to development of AF. Echocardiograms were not routinely repeated. All arrhythmic episodes included in this study were symptomatic, requiring physician contact, thereby possibly reducing ascertainment bias. The only way to ascertain asymptomatic episodes of AF is to do a long-term monitoring, but this was not part of the database. Hence, the possibility of an ascertainment bias remains. In our study, as in likely any other observational analyses of nonrandomized treatment interventions, there always remains the risk of confounding, even when numerous important clinical factors have been adjusted for in multivariable modeling. It is also important to note that our database does not capture data about functional capacity.

**FIGURE 3** Cumulative Rate of Death Following AF Development in Those Treated With BTKi (Mainly Ibrutinib)




AF = atrial fibrillation.

## CONCLUSIONS

Our study shows a significant risk of AF after initiation of lymphoma treatment with either BTKi (mainly ibrutinib in our study) or non-BTKi therapy, although the risk is higher in patients treated with BTKi. We identified simple clinical variables associated with new AF during or following lymphoma treatment. Patients undergoing treatment for lymphoma, especially those identified to be at a higher risk, may benefit from AF surveillance during and after treatment even when they have no AF history.

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**ADDRESS FOR CORRESPONDENCE:** Dr Amole Ojo, Clinical Cardiovascular Research Center, University of Rochester Medical Center, 265 Crittenden Blvd., Box 653, Rochester, New York 14642, USA. E-mail: amole_ojo@urmc.rochester.edu.

## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Targeted lymphoma treatment in patients without prior history of AF is associated with an increased risk of AF. Development of AF during lymphoma treatment is associated with reduced survival.

**TRANSLATIONAL OUTLOOK:** Patients undergoing targeted lymphoma treatment, especially those identified to be at a higher risk, may benefit from AF surveillance during and after treatment even when they have no AF history. Future studies are needed to discover how the risk of AF associated with targeted lymphoma treatment can be reduced.

## REFERENCES

**1.** American Cancer Society. Non-Hodgkin's lymphoma. Accessed July 7, 2022. https://cancerstatisticscenter.cancer.org/#!/cancer-site/Non-Hodgkin%20lymphoma

**2.** Byrd JC, Furman RR, Coutre SE, 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;26:3918-3927.

**3.** Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med*. 2019;381:432-443.

**4.** 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;34:787-798.

**5.** Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;373:2425-2437.

**6.** Shanafelt TD, Parikh SA, Noseworthy PA, et al. Atrial fibrillation in patients with chronic lymphocytic leukemia (CLL). *Leuk Lymphoma*. 2017;58:1630-1639.

**7.** Thompson PA, Lévy V, Tam CS, et al. Atrial fibrillation in CLL patients treated with ibrutinib. An international retrospective study. *Br J Haematol*. 2016;175:462-466.

**8.** Archibald WJ, Rabe KG, Kabat BF, et al. Atrial fibrillation in patients with chronic lymphocytic leukemia (CLL) treated with ibrutinib: risk prediction, management, and clinical outcomes. *Ann Hematol*. 2021;100:143-155.

**9.** Leong DP, Caron F, Hillis C, et al. The risk of atrial fibrillation with ibrutinib use: a systematic review and meta-analysis. *Blood*. 2016;128:138-140.

**10.** Ganatra S, Sharma A, Shah S, et al. Ibrutinib-associated atrial fibrillation. *JACC Clin Electrophysiol*. 2018;4:1491-1500.

**11.** Yun S, Vincelette ND, Acharya U, Abraham I. Risk of atrial fibrillation and bleeding diathesis associated with ibrutinib treatment: a systematic review and pooled analysis of four randomized controlled trials. *Clin Lymphoma Myeloma Leuk*. 2017;17:31-37.e13.

**12.** Salem JE, Manouchehri A, Bretagne M, et al. Cardiovascular toxicities associated with ibrutinib. *J Am Coll Cardiol*. 2019;74:1667-1678.

**13.** Andrea V, Marina D, Francesca Romana M, et al. A Scoring system to predict the risk of atrial fibrillation in chronic lymphocytic leukemia and its validation in a cohort of ibrutinib-treated patients. *Blood*. 2018;132:3118.

**14.** Reda G, Fattizzo B, Cassin R, et al. Predictors of atrial fibrillation in ibrutinib-treated CLL patients: a prospective study. *J Hematol Oncol*. 2018;11:79.

**15.** Lentz R, Feinglass J, Ma S, Akhter N. Risk factors for the development of atrial fibrillation on ibrutinib treatment. *Leuk Lymphoma*. 2019;60:1447-1453.

**16.** McMullen JR, Boey EJ, Ooi JY, Seymour JF, Keating MJ, Tam CS. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. *Blood*. 2014;124:3829-3830.

**17.** Alexandre J, Moslehi JJ, Bersell KR, Funck-Brentano C, Roden DM, Salem J-E. Anticancer drug-induced cardiac rhythm disorders: current knowledge and basic underlying mechanisms. *Pharmacol Ther*. 2018;189:89-103.

**18.** Xiao L, Salem JE, Clauss S, et al. Ibrutinib-mediated atrial fibrillation attributable to inhibition of C-terminal Src kinase. *Circulation*. 2020;142(25):2443-2455.

**19.** Binah O, Cohen IS, Rosen MR. The effects of adriamycin on normal and ouabain-toxic canine Purkinje and ventricular muscle fibers. *Circ Res*. 1983;53:655-662.

**20.** Tamargo J, Caballero R, Delpón E. Cancer chemotherapy and cardiac arrhythmias: a review. *Drug Saf*. 2015;38:129-152.

**21.** Wasmer K, Eckardt L, Breithardt G. Predisposing factors for atrial fibrillation in the elderly. *J Geriatr Cardiol*. 2017;14:179-184.

**22.** Ohlmeier C, Mikolajczyk R, Haverkamp W, Garbe E. Incidence, prevalence, and antithrombotic management of atrial fibrillation in elderly Germans. *Europace*. 2013;15:1436-1444.

**23.** Bidoggia H, Maciel JP, Capalozza N, et al. Sex differences on the electrocardiographic pattern of cardiac repolarization: possible role of testosterone. *Am Heart J*. 2000;140:678-683.

**24.** Cardin S, Li D, Thorin-Trescases N, Leung TK, Thorin E, Nattel S. Evolution of the atrial fibrillation substrate in experimental congestive heart failure: angiotensin-dependent and -independent pathways. *Cardiovasc Res*. 2003;60:315-325.

**25.** Dickerson T, Wiczer T, Waller A, et al. Hypertension and incident cardiovascular events following ibrutinib initiation. *Blood*. 2019;134(22):1919-1928.

**26.** Jones J, George B, Peterson CB, et al. Long-term effects of ibrutinib on blood pressure in patients with chronic lymphocytic leukemia (CLL). *J Clin Oncol*. 2019;37(15_suppl):e19009.

**27.** Lee DH, Hawk F, Seok K, et al. Association between ibrutinib treatment and hypertension. *Heart*. 2022;108:445-450.

**28.** Roeker LE, Sarraf Yazdy M, Rhodes J, et al. Hypertension in patients treated with ibrutinib for chronic lymphocytic leukemia. *JAMA Netw Open*. 2019 Dec 2;2(12):e1916326.

**29.** Amioka M, Sairaku A, Ochi T, et al. Prognostic significance of new-onset atrial fibrillation in patients with non-Hodgkin's lymphoma treated with anthracyclines. *Am J Cardiol*. 2016;118:1386-1389.

**KEY WORDS** atrial fibrillation, Bruton tyrosine kinase inhibitors, lymphoma treatment, risk factors

**APPENDIX** For supplemental tables, please see the online version of this paper.