JACC: CARDIOONCOLOGY VOL. 6, NO. 2, 2024

ORIGINAL RESEARCH

Artificial Intelligence Electrocardiography to Predict Atrial Fibrillation in Patients With Chronic Lymphocytic Leukemia

Georgios Christopoulos, MD,[a] Zachi I. Attia, PhD,[a] Sara J. Achenbach, MS,[b] Kari G. Rabe, MS,[b] Timothy G. Call, MD,[c] Wei Ding, MD, PhD,[c] Jose F. Leis, MD, PhD,[d] Eli Muchtar, MD,[c] Saad S. Kenderian, MD,[c] Yucai Wang, MD, PhD,[c] Paul J. Hampel, MD,[c] Amber B. Koehler, PA-C,[c] Neil E. Kay, MD,[c] Prashant Kapoor, MD,[c] Susan L. Slager, PhD,[b,c] Tait D. Shanafelt, MD,[e] Peter A. Noseworthy, MD,[a] Paul A. Friedman, MD,[a] Joerg Herrmann, MD,[a,*] Sameer A. Parikh, MD[c,*]

ABSTRACT

BACKGROUND The use of an artificial intelligence electrocardiography (AI-ECG) algorithm has demonstrated its reliability in predicting the risk of atrial fibrillation (AF) within the general population.

OBJECTIVES This study aimed to determine the effectiveness of the AI-ECG score in identifying patients with chronic lymphocytic leukemia (CLL) who are at high risk of developing AF.

METHODS We estimated the probability of AF based on AI-ECG among patients with CLL extracted from the Mayo Clinic CLL database. Additionally, we computed the Mayo Clinic CLL AF risk score and determined its ability to predict AF.

RESULTS Among 754 newly diagnosed patients with CLL, 71.4% were male (median age = 69 years). The median baseline AI-ECG score was 0.02 (range = 0-0.93), with a value ≥0.1 indicating high risk. Over a median follow-up of 5.8 years, the estimated 10-year cumulative risk of AF was 26.1%. Patients with an AI-ECG score of ≥0.1 had a significantly higher risk of AF (HR: 3.9; 95% CI: 2.6-5.7; $P < 0.001$). This heightened risk remained significant (HR: 2.5; 95% CI: 1.6-3.9; $P < 0.001$) even after adjusting for the Mayo CLL AF risk score, heart failure, chronic kidney disease, and CLL therapy. In a second cohort of CLL patients treated with a Bruton tyrosine kinase inhibitor (n = 220), a pretreatment AI-ECG score ≥0.1 showed a nonsignificant increase in the risk of AF (HR: 1.7; 95% CI: 0.8-3.6; $P = 0.19$).

CONCLUSIONS An AI-ECG algorithm, in conjunction with the Mayo CLL AF risk score, can predict the risk of AF in patients with newly diagnosed CLL. Additional studies are needed to determine the role of AI-ECG in predicting AF risk in CLL patients treated with a Bruton tyrosine kinase inhibitor. (J Am Coll Cardiol CardioOnc 2024;6:251-263)

From the [a]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota, USA; [b]Department of Quantitative Health Sciences, Mayo Clinic, Rochester, Minnesota, USA; [c]Division of Hematology, Mayo Clinic, Rochester, Minnesota, USA; [d]Division of Hematology and Medical Oncology, Mayo Clinic, Scottsdale, Arizona, USA; and the [e]Department of Medicine, Stanford University, Palo Alto, California, USA. *Drs Herrmann and Parikh contributed equally to this work.
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.

Manuscript received August 14, 2023; revised manuscript received February 26, 2024, accepted February 27, 2024.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2024.02.006

JACC: CARDIOONCOLOGY, VOL. 6, NO. 2, 2024
APRIL 2024:251–263

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AI = artificial intelligence

ACI-ECG = artificial intelligence echocardiography

BTKi = Bruton tyrosine kinase inhibitor

CLL = chronic lymphocytic leukemia

ECG = electrocardiography

Chronic lymphocytic leukemia (CLL) is 1 of the most common types of adult leukemia in the Western world, with an estimated 18,740 new diagnoses reported in the United States in 2023.[1] CLL is a disease associated with advancing age, typically diagnosed around 72 years of age, and exhibits a 2:1 incidence ratio in males compared with females.[1] Concurrently, atrial fibrillation (AF) demonstrates a high prevalence both within the general population and specifically among individuals with CLL, carrying a high risk of heart failure, stroke, recurrent hospitalization, and heightened overall morbidity and mortality.[2] The prevalence of AF is substantial, estimated at 2.3% in individuals older than 40 years and 5.9% in those older than 65 years in the general population.[3]

In a previous investigation, we demonstrated that within a large cohort of patients with CLL (n = 2,444, median age = 65 years) seen within 12 months of diagnosis at Mayo Clinic in Rochester, Minnesota, the prevalence of AF was approximately 6%.[4] Among patients who did not have AF at the time of CLL diagnosis, the risk of incident AF over time was approximately 1% per year. Through a comprehensive multivariable analysis, several variables emerged as significant contributors to an increased risk of incident AF, including age, male sex, hypertension, and valvular heart disease. Using a weighted risk model, we constructed a predictive model, the Mayo Clinic CLL AF score, for developing incident AF, stratifying patients into 4 groups with 10-year rates of incident AF ranging from 4% to 33% and achieving a C-statistic of 0.699.[4] Additionally, other risk factors such as prior AF, heart failure, or left atrial enlargement have also been identified as being associated with an increased incidence of AF in patients with CLL.[4-7]

The clinical relevance of the risk of developing AF in patients with CLL is demonstrated by the established association between treatment with Bruton tyrosine kinase inhibitors (BTKis) and an increased risk of future AF.[8-14] Given the significant morbidity associated with AF, the development of a simple and readily available clinical tool for risk stratification in patients with CLL would be useful, particularly in determining candidacy for BTKi-based therapy and predicting the risk of future arrhythmias.

Recently, artificial intelligence (AI) has been applied to 12-lead electrocardiography (ECG) to predict predisposition (risk) even in the presence of normal sinus rhythm.[15] The artificial intelligence electrocardiography (AI-ECG) software generates a probability output for future AF documentation, ranging from 0 to 1 (0%-100%). A high score or probability can be used to serve as an alert to the clinician, indicating that the patient is at risk for concurrent or future AF. This could trigger additional screening or extended monitoring for AF. Early AF diagnosis holds the potential to prevent systemic embolism and stroke through timely anticoagulation and, particularly in the CLL population, aids in selecting CLL therapies with lower arrhythmogenic potential.

The AI algorithm, developed through an analysis using a convolutional neural network of over 600,000 electrocardiograms, has learned to recognize nuances in ECG tracing, often imperceptible to the human eye, for effective AF prediction. Subsequent application of the AI algorithm in prospective cohorts demonstrated its ability to predict AF. Specifically, in a recent population-based study involving 1,936 patients, an AI-ECG score exceeding 0.5 at baseline was associated with AF development in 21.5% of patients at 2 years and 52.2% at 10 years.[16] The discriminatory ability of the AI model, calculated in the same study, was 0.69. Building on these promising results, the current study aimed to investigate the predictive capability of AI-ECG in stratifying the risk of AF in patients with CLL.

METHODS

PATIENT COHORTS AND BASELINE AI-ECG AF SCORE. The Mayo Clinic CLL database, comprising patients with CLL seen at Mayo Clinic in Rochester, Minnesota, who allow for the use of their clinical records for research purposes,[17-19] served as the primary source. Within this database, we identified previously untreated patients who did not have a history of AF between January 1, 1995, and June 8, 2020. A second cohort included CLL patients treated with BTKi therapy, with baseline defined as the date of BTKi initiation.

Patient characteristics, including age, sex, history of hypertension, and valvular heart disease, along with CLL-specific markers such as absolute lymphocyte count, Rai stage, immunoglobulin heavy chain gene variable region (*IGHV*) mutation status, cytogenetic abnormalities detected by fluorescence in situ hybridization, and CLL international prognostic index risk score, were obtained from the Mayo Clinic CLL database. The Mayo Clinic CLL AF score, ranging from 0 to 7 points, was calculated using the following criteria: 2 points for ages 65 to 74 years or 3 points for ages 75 years or older, 1 point for male, 2 points for valvular heart disease, and 1 point for hypertension.[4] Patients with incident AF were identified through chart review using International Classification of

Diseases-9th Revision and -10th Revision codes, and the diagnosis was confirmed by 12-lead ECG. This approach is similar to our prior publications,[4,18] and the identification occurred during the patients' longitudinal care at our institution, without the implementation of special surveillance strategies for AF detection. In addition, covariates such as body mass index, history of sleep apnea, coronary artery disease, heart failure, chronic kidney disease, and diabetes mellitus were abstracted from the electronic health record for each patient.

DEVELOPMENT OF THE AI-ECG ALGORITHM. The probability of AF was determined through a convolutional neural network trained on a substantial ECG database. Detailed information on the derivation and validation of the AI algorithm has been previously reported.[15] In brief, the network was developed using the Keras Framework with a Tensorflow backend (Google) and Python. The analysis of the 12-lead ECG focused on the inclusion of 8 independent leads (leads I, II, and V1-6). The network dissected ECG information from these leads into a matrix featuring spatial and temporal axes. Convolutional layers were sequentially applied to the temporal axis, which contains time and morphologic features, enabling the detection of features of AF in sinus rhythm that may be undetectable to the human eye.

Although the specific features recognized by the artificial platform are not reported, various abnormalities of the P-wave such as the PR interval, P axis, R-wave amplitude, and fractionation have been implicated in increasing the likelihood of AF[20] and may have contributed to the learning process. The AI-ECG algorithm was applied to all patients in this study, with the baseline AI-ECG probability of AF calculated based on the nearest ECG collected within 10 years before CLL diagnosis (CLL cohort) or 10 years before the initiation of ibrutinib therapy (BTKi cohort).

STATISTICAL ANALYSIS. Descriptive statistics are used to present baseline demographic characteristics using median and range or 25th and 75th percentiles (Q1-Q3) as appropriate. Patients were dichotomized based on their AI-ECG AF score at baseline; they were categorized as having a positive ECG (AI-ECG AF score $\geq$0.1) or a negative ECG (AI-ECG AF score $<$0.1). The selection of 0.1 as the threshold of ECG positivity was determined based on previous observations indicating the optimal balance between sensitivity and specificity.[15] After this dichotomization, cumulative incidence curves were constructed, accounting for death as a competing risk using Gray's method, to demonstrate the incidence of AF over time based on positive vs negative baseline AI-ECG.

TABLE 1 Characteristics of the Study Population

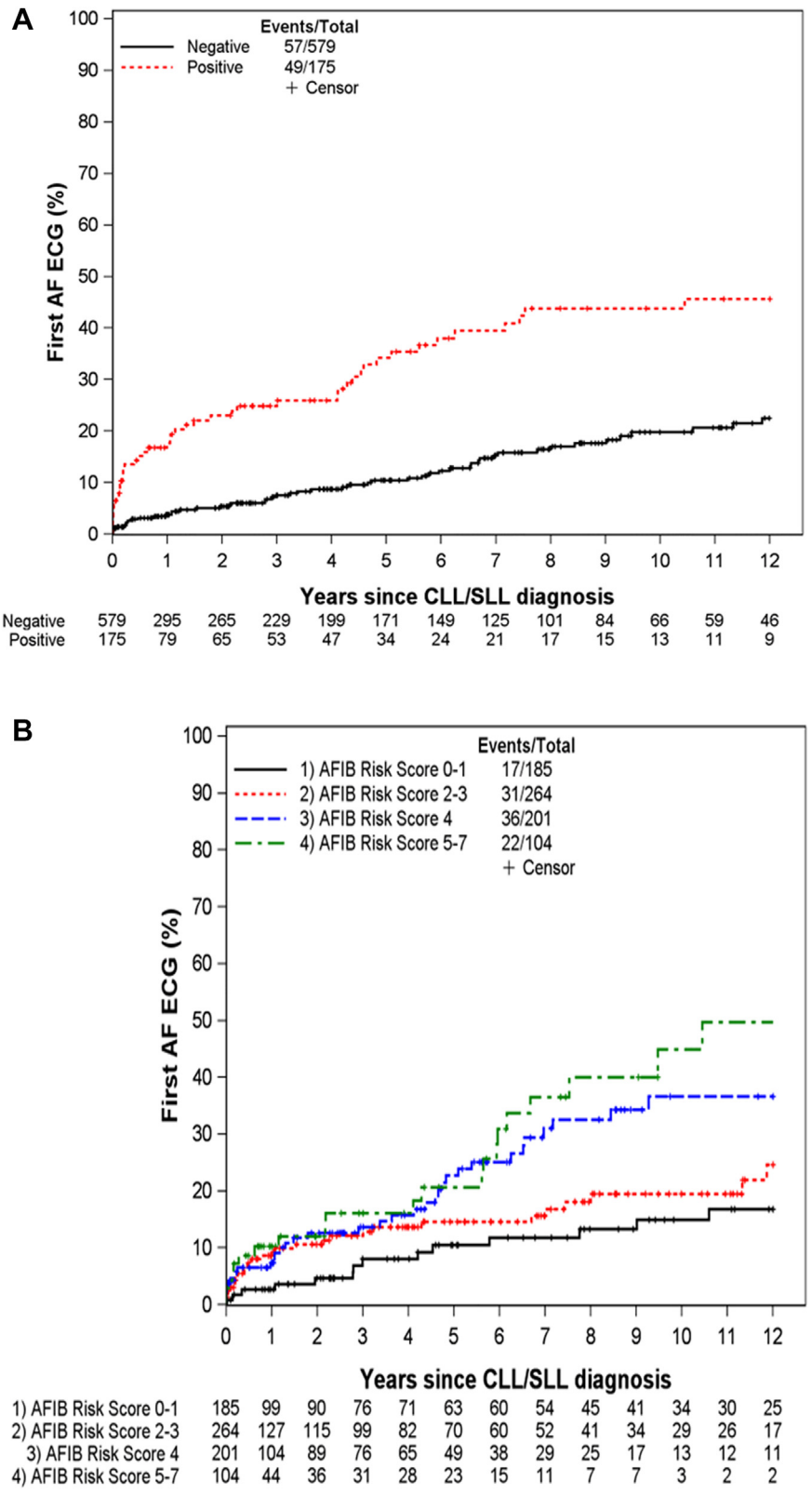
	Previously Untreated CLL Patients (n = 754)	Patients Treated With BTKi[a] (n = 220)
Median age at baseline, y	69 (25-95)	69 (35-89)
Male	538 (71.4)	156 (70.9)
Median absolute lymphocyte count, $\times 10^9$/L	10.8 (0.4-958.4)	47.1 (0.5-436.4)
Rai stage		
0	344 (45.7)	27 (12.3)
I-II	329 (43.8)	79 (35.9)
III-IV	79 (10.5)	114 (51.8)
Missing	2	0
IGHV mutation status		
Mutated	213 (49.7)	44 (23.4)
Unmutated	216 (50.3)	144 (76.6)
Missing	325	32
FISH		
del 13q	198 (38.7)	55 (27.5)
Negative or trisomy 12	230 (45.0)	67 (33.5)
del11q or del17p	83 (16.2)	78 (39.0)
Missing	243	20
CLL-IPI risk group		
Low risk, 0-1	115 (30.2)	1 (0.7)
Intermediate risk, 2-3	117 (30.7)	17 (11.2)
High risk, 4-6	130 (34.1)	108 (71.1)
Very high risk, 7-10	19 (5.0)	26 (17.1)
Missing	373	68
Hypertension	345 (45.8)	108 (49.1)
Valvular heart disease	59 (7.8)	41 (18.6)
Median days from AI-ECG to CLL diagnosis or start of ibrutinib	7 (0-3,649)	366 (0-3,514)
AI-ECG baseline score $\geq$0.1	175 (23.2)	42 (19.1)
Mayo Clinic CLL AF score[b]		
0-1	185 (24.5)	57 (25.9)
2-3	264 (35.0)	60 (27.3)
4	201 (26.7)	53 (24.1)
5-7	104 (13.8)	50 (22.7)

Values are n, median (range), or n (%). [a]187 patients with ibrutinib monotherapy, 22 patients with ibrutinib/Rituxan, and 11 patients with ibrutinib/obinutuzumab. [b]The Mayo Clinic CLL AF score, ranging from 0 to 7 points, was calculated using the following criteria: 2 points for ages 65 to 74 years or 3 points for ages 75 years or older, 1 point for male, 2 points for valvular heart disease, and 1 point for hypertension.

AF = atrial fibrillation; AI-ECG = artificial intelligence echocardiography; BTKi = Bruton tyrosine kinase inhibitor; CLL = chronic lymphocytic leukemia; CLL-IPI = chronic lymphocytic leukemia international prognostic index; *IGHV* = immunoglobulin heavy chain gene variable region.

Univariable and multivariable Cox proportional hazards models using subdistribution hazards (death not censored) were fitted to calculate the HR and 95% CI for the risk of AF based on baseline AI-ECG positivity. Similar analyses were performed after stratifying patients based on the Mayo Clinic CLL AF score. Discrimination was assessed using the C-statistic (area under the curve), with a C-statistic $>$0.7 considered relevant at the individual patient level. Variables that showed significance in the univariable models but were not included as part of the Mayo CLL AF score were included in the multivariable models. Linearity and nonproportional hazards assumptions for Cox models were tested and verified using the R

FIGURE 1 Risk of AF in Untreated CLL Patients



(A) The risk of atrial fibrillation (AF) in previously untreated chronic lymphocytic leukemia (CLL) patients based on baseline artificial intelligence echocardiography positivity. (B) The risk of AF in previously untreated CLL patients based on the Mayo CLL AF risk score. AFIB = atrial fibrillation; ECG = electrocardiography; SLL = small lymphocytic lymphoma.

functions coxph and cox.zph (R Foundation for Statistical Computing). Sensitivity analyses were also performed by restricting results to patients with a baseline ECG available within 1, 3, or 5 years of CLL diagnosis or BTKi therapy initiation.

A P value ≤0.05 was considered statistically significant. Statistical analyses were performed with SAS version 9.4 (SAS Institute) and R 4.2.2 (R Foundation for Statistical Computing). The Mayo Clinic Institutional Review Board approved this study.

RESULTS

PATIENT COHORT. Table 1 presents baseline characteristics for 754 newly diagnosed CLL patients. The median time between the baseline ECG and CLL diagnosis was 7 days (range = 0-3,649 days). The median follow-up duration was 5.8 years (range = 0.01-24.7 years). Among the cohort, 106 CLL patients developed incident AF. The overall estimated 2-, 5-, and 10-year risk of AF in the entire cohort was 10.0% (95% CI: 7.6%-13.1%), 16.6% (95% CI: 13.4%-20.7%), and 26.1% (95% CI: 21.7%-31.4%), respectively.

AI-ECG AND MAYO CLINIC CLL RISK SCORE FOR AF. The median baseline AI-ECG score was 0.02 (Q1-Q3: 0.00-0.09; range = 0-0.93). Among 754 CLL patients, 579 (76.8%) had a baseline AI-ECG score <0.1 (median = 0.01, range = 0.00-0.09), and 175 (23.2%) had a baseline ECG score ≥0.1 (median = 0.24, range = 0.10-0.94). Among patients with an AI-ECG score ≥0.1, the estimated 2-, 5-, and 10-year risk of AF was 23.0% (95% CI: 16.7%-31.7%), 34.2% (95% CI: 26.2%-44.5%), and 43.8% (95% CI: 34.8%-55.2%), respectively. In contrast, among patients with an AI-ECG score <0.1, the estimated 2-, 5-, and 10-year risk of AF was 5.4% (95% CI: 3.5%-8.4%), 10.4% (95% CI: 7.5%-14.6%), and 19.8% (95% CI: 15.1%-25.9%), respectively (Figure 1A).

A positive baseline AI-ECG significantly increased the incidence of AF during follow-up (HR: 3.9; 95% CI: 2.6-5.7; $P < 0.001$, Table 2), and the C-statistic for predicting AF risk with AI-ECG was 0.66 (95% CI: 0.61-0.71). Stratified by the Mayo Clinic AF risk score, the 10-year estimated risk of AF was 15.0% (95% CI: 8.9%-25.2%), 19.5% (95% CI: 13.5%-28.1%), 36.7% (95% CI: 27.3%-49.3%), and 44.9% (95% CI: 30.9%-65.2%) in patients with Mayo Clinic AF risk scores of 0 to 1, 2 to 3, 4, and 5+, respectively (Figure 1B), and the C-statistic for the Mayo CLL AF risk score was 0.62 (95% CI: 0.57-0.67).

In multivariable analysis, the 2 highest risk categories of the Mayo CLL AF clinical risk score (AF risk score 4 vs score 0-1; HR: 2.0; 95% CI: 1.2-3.6; $P = 0.013$; AF risk score 5+ vs score 0-1; HR: 2.1; 95% CI: 1.1-4.1; $P = 0.030$) and the start of BTKi therapy (as a time-dependent variable; HR: 4.6, 95% CI: 2.6-8.2; $P < 0.001$) remained independent risk factors for AF along with the AI-ECG score (HR: 2.5; 95% CI: 1.6-3.9; $P < 0.001$) (Table 2). The combination of AI-ECG and the Mayo Clinic AF risk score improved the C-statistic for AF risk prediction to 0.71 (95% CI: 0.66-0.76).

We next stratified the AF rates in subgroups of patients with positive and negative baseline AI-ECG based on the Mayo Clinic AF risk score. Among the 175 patients with a baseline AI-ECG score ≥0.1 (Figure 2A), the 10-year risk estimates were 45.8% (95% CI: 16.2%-100.0%), 44.0% (95% CI: 27.1%-71.6%), 43.1% (95% CI: 29.8%-62.2%), and 44.2% (95% CI: 27.6%-71.0%) for AF risk scores of 0 to 1, 2 to 3, 4, and 5+, respectively. Among the 579 patients with a baseline AI-ECG score <0.1 (Figure 2B), the 10-year estimates were 12.9% (95% CI: 7.1%-23.4%), 13.8% (95% CI: 8.3%-22.9%), 32.7% (95% CI: 20.5%-52.2%), and 50.4% (95% CI: 24.5%-100.0%) for AF risk scores of 0 to 1, 2 to 3, 4, and 5+, respectively.

Overall, the results remained consistent when considering only newly diagnosed CLL patients who

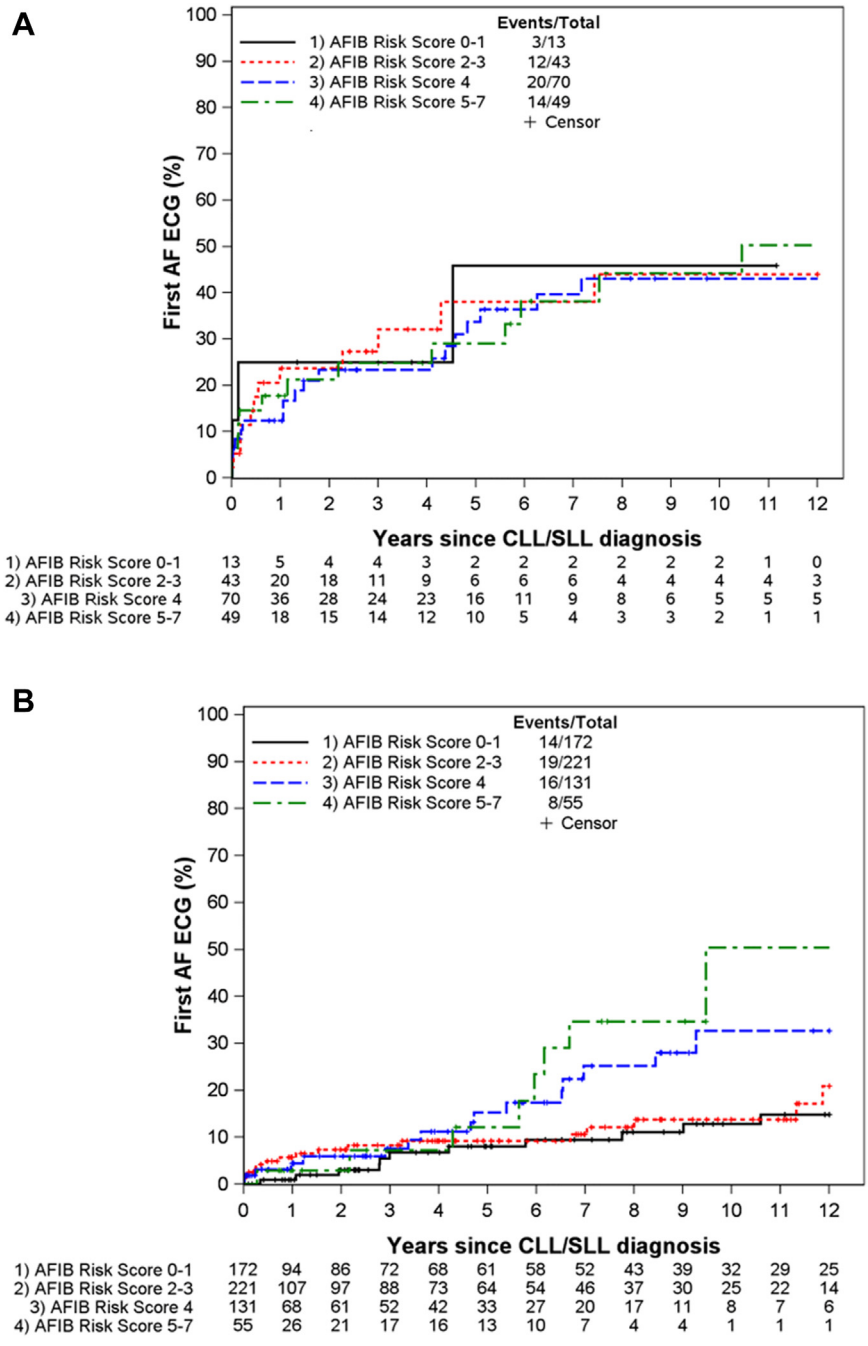
TABLE 2 Cox Regression Analysis in Untreated CLL

Previously Untreated CLL (n = 754) Parameter	Univariable		Multivariable	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age at diagnosis per 10-y increase	1.7 (1.4-2.1)	<0.001	–	–
Male	1.7 (1.04-2.8)	0.034	–	–
Hypertension before CLL diagnosis	1.1 (0.8-1.6)	0.598	–	–
Valvular heart disease prior to CLL diagnosis	2.4 (1.4-4.0)	0.001	–	–
Mayo CLL AF risk group[a]				
AF risk score 0-1	Reference		Reference	
AF risk score 2-3	1.8 (0.98-3.3)	0.059	1.4 (0.8-2.4)	0.269
AF risk score 4	3.0 (1.7-5.5)	<0.001	2.0 (1.2-3.6)	0.013
AF risk score 5-7	4.4 (2.3-8.5)	<0.001	2.1 (1.1-4.1)	0.030
Positive AI-ECG, threshold ≥0.1	3.9 (2.6-5.7)	<0.001	2.5 (1.6-3.9)	<0.001
Sleep apnea	1.8 (0.99-3.2)	0.054	–	–
Coronary artery disease	1.2 (0.8-1.9)	0.430	–	–
Heart failure	4.5 (2.6-7.8)	<0.001	2.0 (1.02-3.7)	0.043
Chronic kidney disease	2.3 (1.1-5.0)	0.035	1.4 (0.6-3.5)	0.469
Diabetes mellitus	1.4 (0.9-2.2)	0.183	–	–
BMI, n = 628	1.0 (0.97-1.04)	0.839	–	–
CLL treatment, time-dependent variable	1.0 (0.7-1.6)	0.891	–	–
CLL treatment with BTKi, time-dependent variable	4.3 (2.5-7.4)	<0.001	4.6 (2.6-8.2)	<0.001

Because age, sex, hypertension, and history of valvular heart disease are already incorporated into the calculation of the Mayo CLL AF score, these variables are not separately included in the multivariable analyses. [a]The Mayo Clinic CLL AF score, ranging from 0 to 7 points, was calculated using the following criteria: 2 points for ages 65 to 74 years or 3 points for ages 75 years or older, 1 point for male, 2 points for valvular heart disease, and 1 point for hypertension.

BMI = body mass index; other abbreviations as in Table 1.

FIGURE 2 Risk of AF in Untreated CLL Patients Based on AI-ECG Score

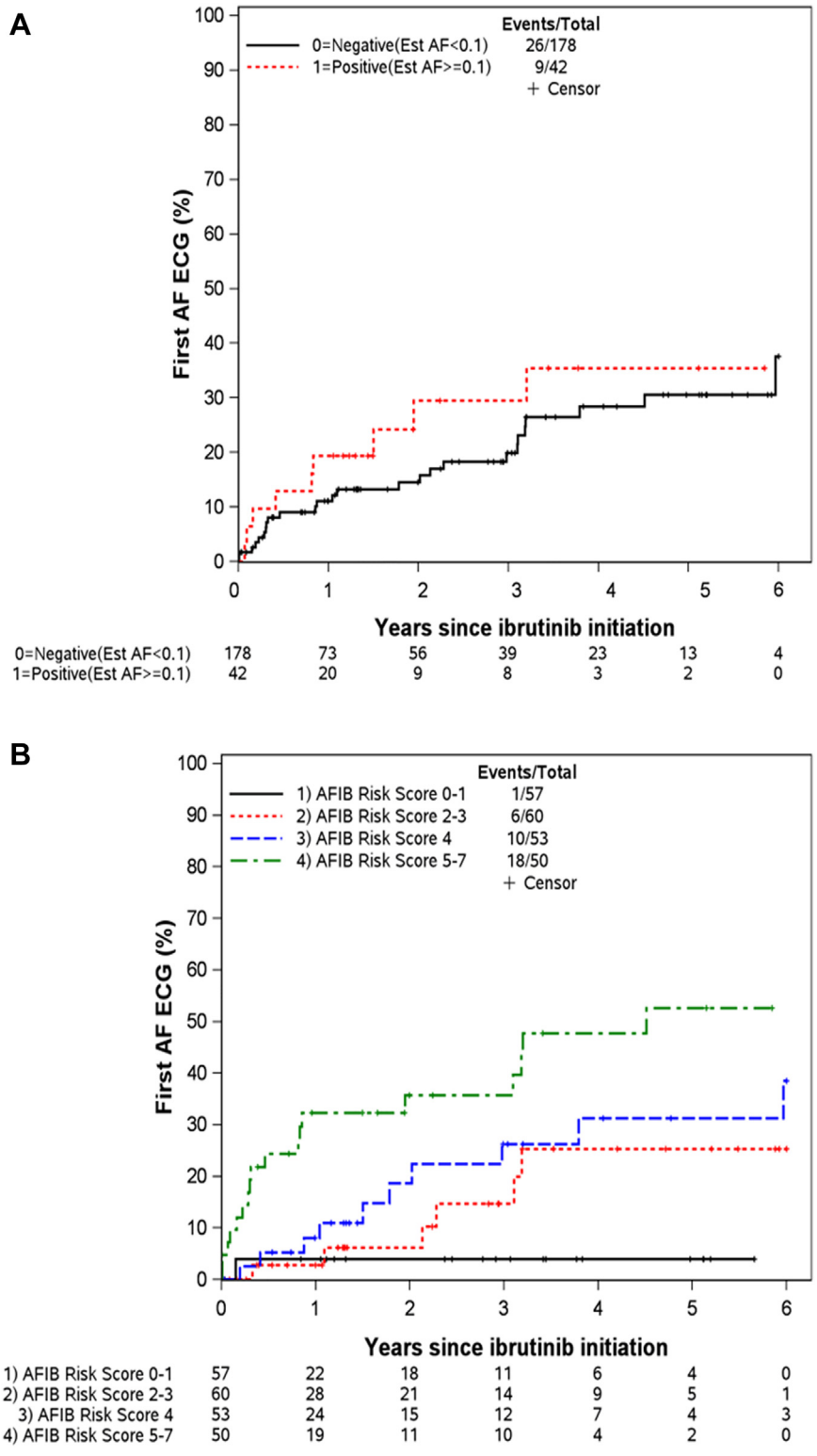


(A) The risk of AF in previously untreated CLL patients with a baseline artificial intelligence echocardiography (AI-ECG score) ≥0.1 (n = 175) based on the Mayo CLL AF risk score. (B) The risk of AF in previously untreated CLL patients with a baseline AI-ECG score <0.1 (n = 579) based on the Mayo CLL AF risk score. Abbreviations as in Figure 1.

had a baseline ECG available within 5 years (n = 658), within 3 years (n = 597), or within 1 year (n = 519) of CLL diagnosis; however, detailed data for these subsets are not presented.

CLL PATIENTS UNDERGOING BTKi THERAPY. We identified a cohort of 220 CLL patients who received BTKi therapy and had a baseline ECG available within 10 years of treatment start (Table 1) (64 patients

FIGURE 3 Risk of AF in CLL Patients Treated With BTKi



(A) The risk of AF in CLL patients treated with Bruton tyrosine kinase inhibitor (BTKi) based on baseline AI-ECG positivity. (B) The risk of AF in patients treated with BTKi based on the Mayo CLL AF risk score. Abbreviations as in Figure 1.

TABLE 3 Cox Regression Analysis in CLL Patients Treated With BTKi

CLL Patients Treated With BTKi (n = 220) Parameter	Univariable	
	HR (95% CI)	*P* Value
Age at diagnosis per 10-y increase	1.8 (1.2-2.7)	0.004
Male sex	1.5 (0.7-3.5)	0.321
Hypertension before CLL diagnosis	3.3 (1.5-7.2)	0.004
Valvular heart disease before CLL diagnosis	3.4 (1.7-6.7)	<0.001
Mayo CLL AF risk group[a]		
AF risk score 0-1	Reference	
AF risk score 2-3	4.4 (0.5-36.8)	0.168
AF risk score 4	8.2 (1.0-64.7)	0.046
AF risk score 5-7	18.8 (2.5-141.0)	0.004
Positive AI-ECG, threshold ≥0.1	1.7 (0.8-3.6)	0.191
Sleep apnea	1.6 (0.8-3.4)	0.213
Coronary artery disease	0.9 (0.5-1.8)	0.784
Heart failure	1.8 (0.6-5.2)	0.264
Chronic kidney disease	1.3 (0.6-2.9)	0.509
Diabetes mellitus	1.0 (0.5-2.1)	0.901
BMI, n = 196	1.0 (0.97-1.1)	0.296

[a]The Mayo Clinic CLL AF score, ranging from 0 to 7 points, was calculated using the following criteria: 2 points for ages 65 to 74 years or 3 points for ages 75 years or older, 1 point for male, 2 points for valvular heart disease, and 1 point for hypertension.

Abbreviations as in Tables 1 and 2.

overlapped with the larger newly diagnosed CLL cohort). The median time from pretreatment ECG to the start of BTKi therapy was 366 days (range = 0-3,514 days), and the median baseline AI-ECG score was 0.02 (Q1-Q3: 0.01-0.07, range = 0-0.84).

Overall, the 2-year and 5-year risk estimates of incident AF were 17.6% (95% CI: 21.1%-25.7%) and 31.8% (95% CI: 23.5%-42.9%), respectively. A pretreatment AI-ECG score ≥0.1 had a 1.7-fold increased incidence of AF during follow-up (95% CI: 0.8-3.6; $P = 0.19$), and the C-statistic for predicting AF risk with AI-ECG alone was 0.55 (95% CI: 0.47-0.64). The estimated 2-year and 5-year risks of AF were 29.5% (95% CI: 15.8%-55.2%) and 35.5% (95% CI: 19.8%-63.4%), respectively, among patients with an AI-ECG score ≥0.1 compared with 14.5% (95% CI: 9.0%-23.3%) and 30.6% (95% CI: 21.5%-43.7%), respectively, among those with an AI-ECG score <0.1 (Figure 3A).

Stratified by the Mayo Clinic AF risk score, patients with scores of 0 to 1, 2 to 3, 4, and 5+ had estimated 5-year AF risks of 4.0% (95% CI: 0.6%-28.4%), 25.3% (95% CI: 12.1%-53.1%), 31.2% (95% CI: 17.5%-55.7%), and 52.6% (95% CI: 36.7%-75.4%), respectively (Figure 3B).

In univariable analyses, there was no significant association between baseline AI-ECG and an increased risk of AF. However, the 2 highest Mayo Clinic AF risk score categories were found to be associated with an increased risk of AF compared with the lowest risk group (Table 3). The results remained consistent when analyzing patients with available 12-lead ECG within 3 years (n = 161) or 5 years (n = 195) before the start of BTKi therapy; detailed results are not presented.

However, restricting the analysis to include only those patients with a 12-lead ECG obtained within 12 months of BTKi initiation (n = 110) revealed that the AI-ECG score was statistically significant in univariable analysis (HR: 2.8; 95% CI:1.2-6.9; $P = 0.021$). In multivariable analysis, after adjusting for age, hypertension, and valvular heart disease, this risk was attenuated, and the AI-ECG score was no longer significantly associated with a higher risk (HR: 2.2; 95% CI: 0.9-5.4; $P = 0.084$). The C-statistics for the Mayo CLL AF risk score alone and the combined scores of AI-ECG and Mayo CLL AF in predicting AF in CLL patients treated with BTKi were 0.73 (95% CI: 0.64-0.81) and 0.73 (95% CI: 0.64-0.82), respectively.

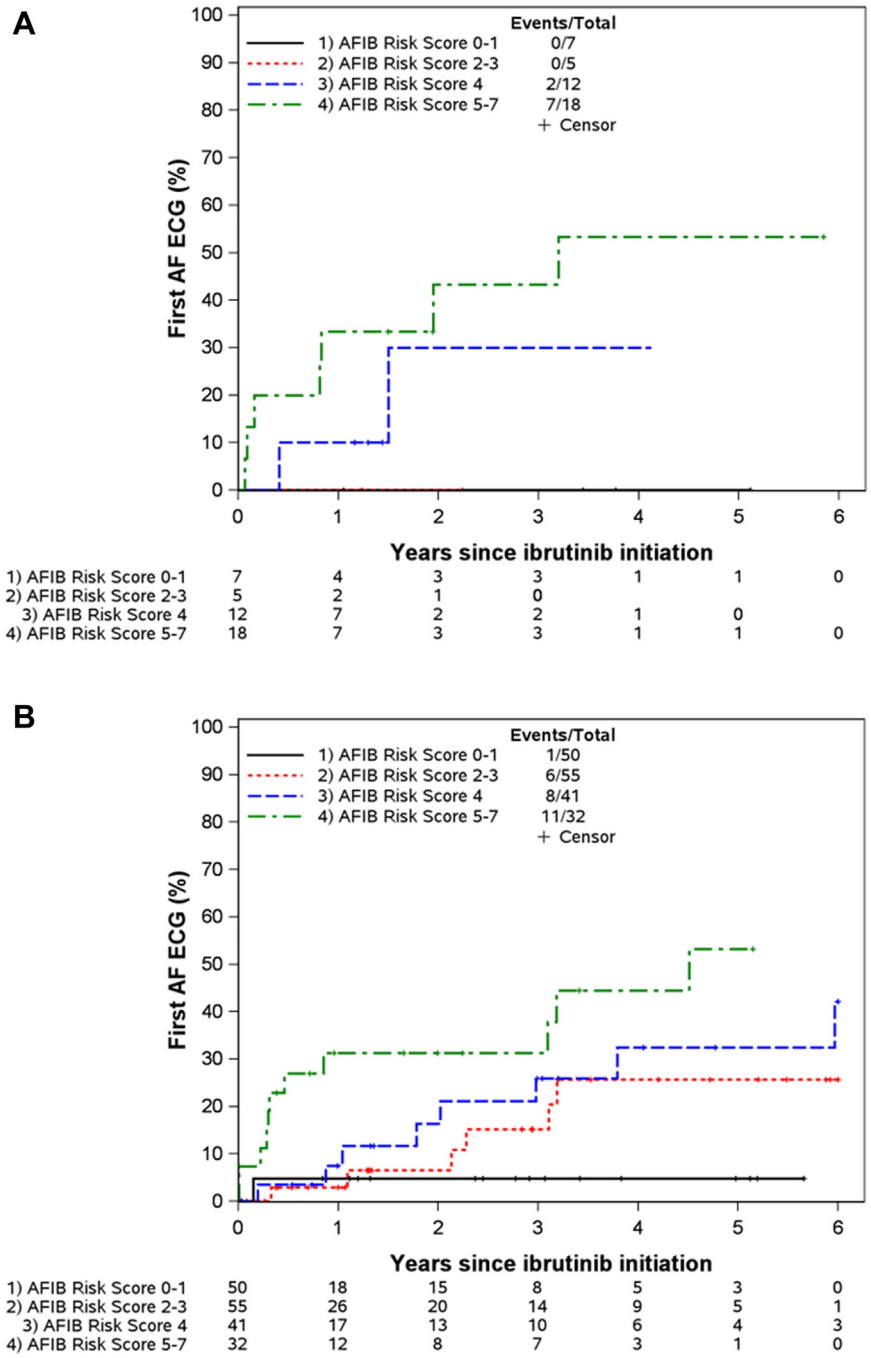
The Mayo Clinic AF risk score effectively stratified AF risk in both patient subgroups—those with a positive and those with a negative AI-ECG readout. Among the 42 patients with a baseline AI-ECG score ≥0.1 (Figure 4A), the 2-year risk estimates of AF were 0% (95% CI: 0.0%-0.0%), 0% (95% CI: 0.0%-0.0%), 30.0% (95% CI: 7.1%-100.0%), and 43.3% (95% CI: 22.0%-85.5%) for AF risk scores of 0 to 1, 2 to 3, 4, and 5+, respectively. However, these results are not reliable given the small sample size (ie, 9 events among 42 patients).

Among the 178 patients with a baseline AI-ECG score <0.1, the 5-year risks of AF were 4.8% (95% CI: 0.7%-33.8%), 25.7% (95% CI: 12.4%-53.5%), 32.4% (95% CI: 16.8%-62.4%), and 53.3% (95% CI: 32.4%-87.4%) for AF risk scores of 0 to 1, 2 to 3, 4, and 5+, respectively (Figure 4B). The AI-ECG score was not significant (HR: 2.2; 95% CI: 0.2-24.1; $P = 0.526$) after adjusting for the Mayo CLL AF score to predict the risk of AF.

DISCUSSION

The estimated risk of AF incidence is approximately 1% per year in patients with newly diagnosed CLL.[4] Various factors such as older age, male sex, valvular heart disease, and hypertension have all been independently demonstrated to be associated with an increased risk of AF, and these factors have been integrated into the Mayo Clinic CLL AF risk score.[4] In addition to patient-related risk factors, BTKi therapy such as ibrutinib has been known to increase the risk of AF in patients with CLL.[8-14] Although patients with BTKi-associated AF may continue therapy with dose interruption or dose reduction, the incidence of AF in

FIGURE 4 Atrial Fibrillation Risk in CLL by Mayo CLL AF Score



(A) The risk of atrial fibrillation in previously untreated CLL patients according to the Mayo CLL AF risk score with baseline AI-ECG score of ≥0.1 (n = 42). (B) The risk of atrial fibrillation in CLL patients treated with BTKi according to the Mayo CLL AF risk score who have a baseline AI-ECG score of <0.1 (n = 178). BTKi = Bruton tyrosine kinase inhibitor; AF = atrial fibrillation; AI-ECG = artificial intelligence - electrocardiogram; CLL = chronic lymphocytic leukemia.

JACC: CARDIOONCOLOGY, VOL. 6, NO. 2, 2024
APRIL 2024:251–263

CENTRAL ILLUSTRATION **Atrial Fibrillation Risk in Chronic Lymphocytic Leukemia Patients Based on the Mayo Chronic Lymphocytic Leukemia Atrial Fibrillation Score**

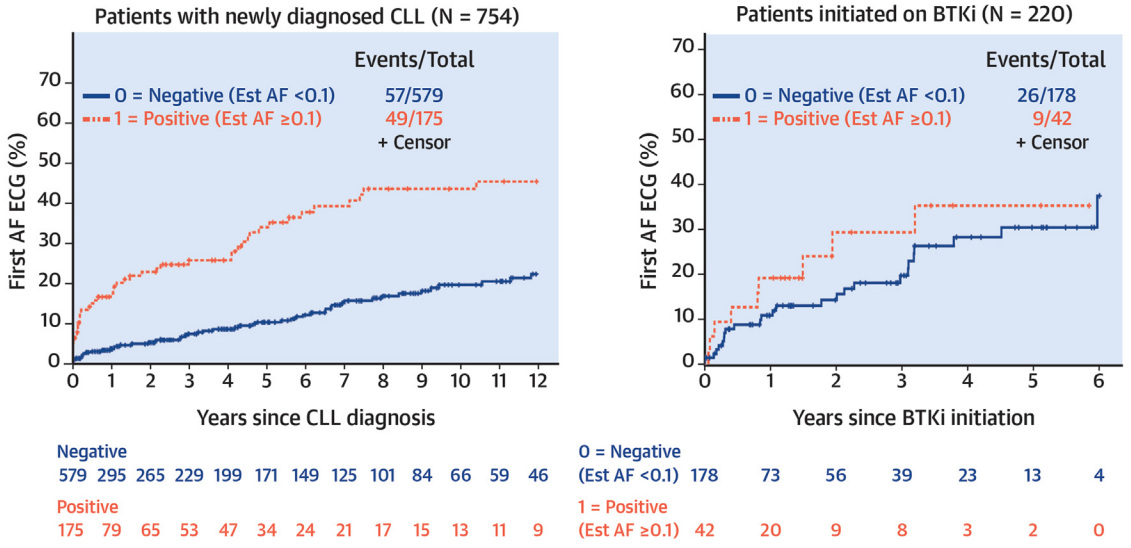
Probability of atrial fibrillation (AF) based on AI-ECG or Mayo Clinic AF risk score

Newly diagnosed chronic lymphocytic leukemia (CLL) (N = 754)
5-year estimated AF risk: 16.6%

CLL patients who received BTKi therapy (N = 220)
5-year estimated AF risk: 31.8%

Predictors of AF (N = 754)	HR (95%CI)	*P* value
Mayo CLL AF risk group		
AF Risk Score 0-1	Reference	
AF Risk Score 2-3	1.4 (0.8-2.4)	0.269
AF Risk Score 4	2.0 (1.2-3.6)	0.013
AF Risk Score 5-7	2.1 (1.1-4.1)	0.030
Positive AI-ECG (threshold ≥0.1)	2.5 (1.6-3.9)	<0.001
HF	2.0 (1.02-3.7)	0.043
Chronic kidney disease	1.4 (0.6-3.5)	0.469
BTKi	4.6 (2.6-8.2)	<0.001

Stratification of cumulative AF incidence by AI-ECG



- AI-ECG can independently predict AF risk in untreated newly diagnosed CLL patients, but not in CLL patients starting BTKi therapy
- Mayo CLL AF risk score can risk stratify in both CLL cohorts and can further risk stratify newly diagnosed CLL patients with a negative (low) probability of AF by AI-ECG

Christopoulos G, et al. J Am Coll Cardiol CardioOnc. 2024;6(2):251-263.

The figure (left) shows the risk of atrial fibrillation (AF) in previously untreated chronic lymphocytic leukemia (CLL) patients with a baseline artificial intelligence electrocardiography (AI-ECG) score ≥0.1 (n = 42) based on the Mayo CLL AF risk score. The Figure (right) shows the risk of AF in CLL patients treated with Bruton tyrosine kinase inhibitor (BTKi) with a baseline AI-ECG score <0.1 (n = 178) based on the Mayo CLL AF risk score. The table represents the multivariable associations between clinical factors and AF risk in 754 patients with newly diagnosed CLL.

these patients negatively affects CLL outcomes and increases mortality.[18] As a result, clinical AF risk stratification of patients is important to choosing BTKi-based vs alternative therapy. As shown here and in our previous work,[18] the Mayo Clinic AF risk score is able to stratify AF risk in newly diagnosed patients with CLL and in those undergoing BTKi therapy.

AI-ECG has emerged as a new tool for predicting AF risk in the general population. In our original study,[15] the optimal cutoff for AF risk was a probability value of 0.1, effectively balancing sensitivity and specificity. In clinical practice, adjusting the AI-ECG threshold allows for tailored use—a lower threshold for high sensitivity, such as determining the tolerance of cardiotoxic therapy from an arrhythmia standpoint, and a higher threshold for high specificity, indicating prohibitive risk and suggesting alternative treatments.

It is important to note that, based on the derivation study by Attia et al,[15] an AI-ECG output of 0.1 reflects a 10% AF probability within 30 days of obtaining the ECG, potentially underestimating AF incidence over the course of years. However, our AI-ECG algorithm, based on the pretherapy (baseline) 12-lead ECG, effectively discriminated patients at high and low risk of AF over several years. In fact, in the overall CLL patient cohort, a positive AI-ECG readout independently predicted future AF risk, even after adjusting for the Mayo Clinic CLL AF score. Thus, although the original AI-ECG algorithm was derived in a noncancer population, its application to patients with CLL proves beneficial in discriminating patients at high and low risk of AF. Factors other than the AI-ECG score that were independently associated with an increased risk of AF included the Mayo CLL AF score (comprising age, history of hypertension, and valvular heart disease) and heart failure. Furthermore, receipt of BTKi, acting as a time-dependent variable, independently increased the risk of AF.

In contrast to the general CLL cohort, a baseline AI-ECG score ≥0.1 did not demonstrate predictive ability for developing AF in patients with CLL starting on BTKi. Several factors may contribute to the limited predictive ability of AI-ECG in this subgroup, including an insufficient sample size and limited follow-up duration, because the number of patients at risk significantly decreased after 2 years of follow-up. Furthermore, the median time of ECG acquisition to treatment initiation was considerably longer in the BTKi cohort compared with the newly diagnosed CLL cohort (median = 366 vs 7 days). Indeed, when we focused on the BTKi-treated patients who had a 12-lead ECG obtained within 12 months of BTKi initiation, the AI-ECG score had a numerically higher risk of AF, although this was not significant in multivariable analysis. Experimental studies have shown that ibrutinib increases the risk of AF through an off-target effect on c-src (Proto-oncogene tyrosine-protein kinase Src), potentially introducing an element of AF risk not accounted for in the AI algorithm training.

Finally, we recognize that AF is highly heterogenous, and it is conceivable that "provoked" AF, such as postoperative AF[21] or the AF induced by BTKi in this study, may not be accurately predicted using an AI model initially trained on the general population. To gain a more accurate understanding of the predictive power of this technology in such scenarios, additional studies are needed. These studies should specifically train the AI-ECG model using a large cohort of BTKi-treated patients with extended follow-up.

STUDY LIMITATIONS. Limitations to consider include the retrospective and single-center nature of this study, which may limit the generalizability of the findings to other settings. In addition, the inclusion of patients with CLL with baseline ECG obtained up to 10 years before diagnosis or the start of BTKi therapy raises questions about whether closer baseline ECG could provide additional predictive value, and further studies are warranted in this regard. Although limiting the analyses to baseline ECG within 1 to 5 years did not change the overall results, the clinical ascertainment of the 12-lead ECG during routine care may introduce bias by including individuals at higher risk of cardiovascular outcomes, including AF. Finally, all BTKi-treated patients in this study received ibrutinib, the first-in-class BTKi. Whether similar results extend to other covalent BTKis, such as zanubrutinib and acalabrutinib, or noncovalent BTKis, such as pirtobrutinib and nemtabrutinib, remains to be determined.

CONCLUSIONS

AI-ECG demonstrated its predictive value for future AF in untreated newly diagnosed patients with CLL, providing complementary information to the Mayo CLL AF risk score (**Central illustration**). However, its predictive ability was not observed in newly diagnosed patients with CLL receiving BTKi therapy. Prospective studies are needed to determine the algorithm's efficacy in risk stratifying AF for patients undergoing various BTKi therapies, allowing for optimization of the algorithm. Such advancements could help guide management decisions for patients with CLL who are at a higher risk of AF than the general population.

JACC: CARDIOONCOLOGY, VOL. 6, NO. 2, 2024
APRIL 2024:251–263

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Herrmann was supported National Institutes of Health/NCI (RO1 CA233610), Miami Heart Research Institute, and Mayo Clinic Department of Cardiovascular Medicine. This research was supported in part by the Henry J. Predolin Foundation. IP related to AI-ECG algorithm for AF risk has been licensed to Anumana (potential equity/royalty relationship). Dr Ding has received research funding from Merck and DTRM; and has served on the Advisory Boards of Merck and Octapharma (no personal compensation). Dr Kenderian is an inventor on patents in the field of CAR immunotherapy that are licensed to Novartis (through an agreement between Mayo Clinic, University of Pennsylvania, and Novartis), Humanigen (through Mayo Clinic), Morphosys (through Mayo Clinic), Tolero (through Mayo Clinic), and Mettaforge (through Mayo Clinic); has received research funding from Kite, Gilead, Juno, Celgene, Novartis, Humanigen, MorphoSys, Tolero, Sunesis, Leahlabs; and Lentigen; has participated in consultancy with Torque, Leahlabs, and Kiniksa; has participated in scientific advisory board meetings of Juno, Kite, and Humanigen; and has participated in data safety monitoring board meetings of Humanigen. Dr Wang has received research funding (to the institution) from Incyte, InnoCare, Novartis, LOXO Oncology, Eli Lilly, MorphoSys, Novartis, Genentech, and Genmab; has served on the Advisory Boards (compensation to institution) of Eli Lilly, LOXO Oncology, TG Therapeutics, Incyte, InnoCare, Kite, Jansen, BeiGene; has served as a consultant (compensation to institution) to Innocare and AbbVie; and has received honorarium (to institution) from Kite. Dr Kay has served on the Advisory Boards for AbbVie, AstraZeneca, BeiGene, Behring, Boehringer Ingelheim Pharmaceuticals Inc, Dava Oncology, Janssen, Juno Therapeutics, and Pharmacyclics; has served on the Data Safety Monitoring Committee for Agios Pharm, AstraZeneca, Bristol-Myers Squibb Celgene, and Dren Bio Janssen; and has received research funding from: AbbVie, Acerta Pharma, Bristol Meyer Squib, Celgene, Genentech, Pharmacyclics, Sunesis, and Vincerx. Dr Kappor has served as a consultant for Sanofi and Cellectar; has received research funding from Sanofi, Janssen, Amgen, GlaxoSmithKline, Takeda, and AbbVie; and has received honoraria from Celgene, Janssen, Takeda, Karyopharm, Beigene, and AbbVie. Dr Shanafelt has received research support to his institution from Genentech, AbbVie, and Pharmacyclics. Dr Herrmann has served on the Advisory Board for AstraZenca, Astellas, and Pfizer; and has received royalties from Elsevier, Inc. Dr Parikh has received research funding to his institution from Janssen, AstraZeneca, Merck, and Genentech for clinical studies in which Dr Parikh is a principal investigator; and has received honoraria to his institution from Pharmacyclics, Merck, AstraZeneca, Janssen, BeiGene, Genentech, Amgen, MingSight Pharmaceuticals, TG Therapeutics, NovalGen Limited, Kite Pharma, and AbbVie for his participation in consulting activities/advisory board meetings. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. This research was previously presented as an abstract at the American Society of Hematology Scientific Sessions in 2020, December 7, 2020, virtual poster session.

ADDRESS FOR CORRESPONDENCE: Dr Sameer A. Parikh, Division of Hematology, Mayo Clinic, Rochester, Minnesota 55905, USA. E-mail: Parikh.Sameer@mayo.edu. OR Dr Joerg Herrmann, Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota 55905, USA. E-mail: herrmann.joerg@mayo.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The application of artificial intelligence to standard 12-lead electrocardiograms identified patients with chronic lymphocytic leukemia at increased risk of future atrial fibrillation independent of other known risk factors.

TRANSLATIONAL OUTLOOK: The identification of patients with an increased risk of future atrial fibrillation may provide valuable clinical information, especially in guiding therapy selection for patients with chronic lymphocytic leukemia. However, to strengthen our conclusions, external validation of these findings from independent data sets is required.

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin*. 2021;71(1):7–33. https://doi.org/10.3322/caac.21654

2. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001;285(18):2370–2375. https://doi.org/10.1001/jama.285.18.2370

3. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med*. 1995;155(5):469–473.

4. Shanafelt TD, Parikh SA, Noseworthy PA, et al. Atrial fibrillation in patients with chronic lymphocytic leukemia (CLL). *Leuk Lymphoma*. 2017;58(7):1630–1639. https://doi.org/10.1080/10428194.2016.1257795

5. Visentin A, Deodato M, Mauro FR, et al. A scoring system to predict the risk of atrial fibrillation in chronic lymphocytic leukemia. *Hematol Oncol*. 2019;37(4):508–512. https://doi.org/10.1002/hon.2655

6. Lentz R, Feinglass J, Ma S, Akhter N. Risk factors for the development of atrial fibrillation on ibrutinib treatment. *Leuk Lymphoma*. 2019;60(6):1447–1453. https://doi.org/10.1080/10428194.2018.1533129

7. 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(1):79. https://doi.org/10.1186/s13045-018-0626-0

8. 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(25):3829–3830. https://doi.org/10.1182/blood-2014-10-604272

9. 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. https://doi.org/10.1371/journal.pone.0211228

10. Baptiste F, Cautela J, Ancedy Y, et al. High incidence of atrial fibrillation in patients treated with ibrutinib. *Open Heart*. 2019;6(1):e001049. https://doi.org/10.1136/openhrt-2019-001049

11. Ganatra S, Sharma A, Shah S, et al. Ibrutinib-associated atrial fibrillation. *J Am Coll Cardiol EP*. 2018;4(12):1491–1500. https://doi.org/10.1016/j.jacep.2018.06.004

12. Jiang L, Li L, Ruan Y, et al. Ibrutinib promotes atrial fibrillation by inducing structural remodeling and calcium dysregulation in the atrium. *Heart Rhythm*. 2019;16(9):1374–1382. https://doi.org/10.1016/j.hrthm.2019.04.008

13. 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(1):138–140. https://doi.org/10.1182/blood-2016-05-712828

14. Rasmussen KM, Patil V, Burningham Z, Yong C, Sauer BC, Halwani AS. Atrial fibrillation and bleeding in patients with chronic lymphocytic leukemia treated with ibrutinib in the Veterans Health Administration. *Fed Pract*. 2020;37(suppl 2):S44–S49.

15. Attia ZI, Noseworthy PA, Lopez-Jimenez F, et al. An artificial intelligence-enabled ECG algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction. *Lancet*. 2019;394(10201):861–867. https://doi.org/10.1016/S0140-6736(19)31721-0

16. Christopoulos G, Graff-Radford J, Lopez CL, et al. Artificial intelligence-electrocardiography to predict incident atrial fibrillation: a population-based study. *Circ Arrhythm Electrophysiol*. 2020;13(12):e009355. https://doi.org/10.1161/CIRCEP.120.009355

17. Hampel PJ, Call TG, Rabe KG, et al. Disease flare during temporary interruption of ibrutinib therapy in patients with chronic lymphocytic leukemia. *Oncologist*. 2020;25(11):974–980. https://doi.org/10.1634/theoncologist.2020-0388

18. 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(1):143–155. https://doi.org/10.1007/s00277-020-04094-3

19. Koehler AB, Leung N, Call TG, et al. Incidence and risk of tumor lysis syndrome in patients with relapsed chronic lymphocytic leukemia (CLL) treated with venetoclax in routine clinical practice. *Leuk Lymphoma*. 2020;61(10):2383–2388. https://doi.org/10.1080/10428194.2020.1768384

20. German DM, Kabir MM, Dewland TA, Henrikson CA, Tereshchenko LG. Atrial fibrillation predictors: importance of the electrocardiogram. *Ann Noninvasive Electrocardiol*. 2016;21(1):20–29. https://doi.org/10.1111/anec.12321

21. Siontis KC, Noseworthy PA, Arghami A, et al. Use of artificial intelligence tools across different clinical settings. *Circ Cardiovasc Qual Outcomes*. 2021;14(9):e008153. https://doi.org/10.1161/CIRCOUTCOMES.121.008153

KEY WORDS **artificial intelligence, atrial fibrillation, chronic lymphocytic leukemia, electrocardiography**