

To the editor:

The risk of atrial fibrillation with ibrutinib use: a systematic review and meta-analysis

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Ibrutinib is an irreversible inhibitor of Bruton tyrosine kinase in the B-cell receptor signaling pathway. In randomized trials, ibrutinib is effective as first-line treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) (compared with chlorambucil),¹ for relapsed/refractory CLL/SLL (compared with ofatumumab or combined with bendamustine/rituximab),^{2,3} or for relapsed/refractory mantle cell lymphoma (compared with temsirolimus),⁴ with promising results in the treatment of Waldenström macroglobulinemia.⁵ It is anticipated that ibrutinib will become an important part of the therapeutic armamentarium for these conditions. Randomized trials suggest that ibrutinib may increase the risk of atrial fibrillation (AF) as compared with chlorambucil¹ or ofatumumab.² In the general population, AF is strongly associated with heart failure and arterial thromboembolism, which result in substantial morbidity and mortality. There is uncertainty over the magnitude of the increase in AF risk attributable to ibrutinib because the absolute numbers of incident AF cases are small in individual studies.

We undertook a systematic review and meta-analysis to (1) estimate the magnitude of the increase in AF risk among ibrutinib recipients, as compared with alternative therapies and (2) quantify the frequency of AF reported among ibrutinib recipients. We searched MEDLINE and EMBASE, and proceedings from the American Society of Hematology, the European Haematology Association, and the American Society of Clinical Oncology for articles describing AF rates in recipients of ibrutinib. The following search terms were used: ibrutinib; imbruvica; or PCI-32765. Animal studies, case reports, case series (ie, that reported on consecutive AF cases), cross-sectional studies, editorials, phase I/dose-finding studies, and conference abstracts more than 12 months old were excluded.

Two independent reviewers screened the articles' titles and abstracts for eligibility. Cases of disagreement were resolved by a third reviewer. Papers identified after title and abstract screening were obtained in full. When data from the same cohort of participants were presented in different papers, only the manuscript with the larger sample size was included in the meta-analysis. The following data were extracted from eligible full text manuscripts: design, disease, sample size, treatments, participant age and sex, follow-up duration, AF rates, and where reported, AF ascertainment strategies, past history of cardiovascular disease, AF, or hypertension.

Statistical analysis was performed using STATA 14 (StataCorp, College Station, TX). To evaluate the increase in the risk of incident AF, the primary meta-analytic approach was a fixed effects model using the Mantel-Haenszel method. A sensitivity analysis was performed using a DerSimonian and Laird random effects model. Heterogeneity of studies was evaluated by Cochran's Q and the I² statistic. Pooled AF rates were estimated as follows: we multiplied the median follow-up duration by the sample size. Crude study-specific AF rates were then

calculated by dividing the number of incident AF cases by the total number of person-months follow-up. AF rates were then pooled using the "metaprop" command in STATA, which computes the pooled estimates after the Freeman-Tukey double arcsine transformation to stabilize the variances.

The search strategy yielded 1871 unique abstracts. Thirty-nine full text manuscripts and 44 conference abstracts were reviewed. Of these 83 papers, 63 were excluded because they lacked data on the occurrence of AF (n = 45), did not study ibrutinib (n = 2), were dose-finding studies (n = 1) or case series (n = 1), or included data that were presented in another included manuscript (n = 14). Thus, 20 manuscripts, reporting on the occurrence of AF in individuals treated with ibrutinib, contributed to the meta-analysis (Table 1).⁶⁻²¹ Four of these studies were randomized controlled trials, 10 phase II studies, one prospective cohort study, and 5 retrospective cohort studies. In total, 14 studies included CLL/SLL patients; 5 studies included mantle cell lymphoma patients; 2 studies included Waldenström macroglobulinemia patients, and one study included follicular lymphoma patients.

Among the 4 randomized trials of ibrutinib, the pooled relative risk (95% confidence interval, CI) of AF associated with ibrutinib as compared with the comparator was 3.9 (2.0-7.5, $P < .0001$) according to the fixed effects model (Figure 1). By the random effects model, the pooled relative risk (95% CI) of AF in ibrutinib recipients was 3.5 (1.8-6.9, $P < .0001$). The I² statistic for heterogeneity was 0%, and the heterogeneity χ^2 was 1.74 ($P = .6$), suggesting homogeneity of results among the randomized trials. Over median follow-ups of up to 26 months, the pooled rate (95% CI) of AF among ibrutinib recipients among all 20 studies cited was 3.3 (2.5-4.1) per 100 person-years. The pooled rate (95% CI) of AF among participants receiving the nonibrutinib therapy in the 4 randomized trials included was 0.84 (0.32-1.6) per 100 person-years.

This analysis suggests that ibrutinib consistently increases the risk of incident AF compared with alternative therapies. The incidence rates of AF observed in the general adult population have been previously described. Among 7983 community-dwelling adults aged 60-64 years screened by electrocardiogram twice during a mean 6.9 years, the incidence (95% CI) of AF was 0.55 (0.42-0.71) per 100 person-years.²² In the Framingham study, AF incidence was measured by annual questionnaires, by annual electrocardiograms, and from hospital records. The incidence of AF among men aged 65-74 years was 1.8 per 100 person-years, and among women aged 65-74 years was 1.0 per 100 person-years.²³ Thus the rate of AF among ibrutinib recipients is substantially higher than the incidence rate observed among the general population. The mechanism(s) by which ibrutinib may promote AF are unknown. Although Bruton tyrosine kinase and tec protein kinases, which are inhibited by ibrutinib, are expressed in cardiac tissue,^{24,25} further research is needed to elucidate specific molecular pathways.

Table 1. Included manuscripts

Author	Study design	Malignancy	Treatment	Age (y)	Sample size*	Comparator	Median follow-up (mo)	AF in ibrutinib recipients	AF in control group
Chanan-Khan ³	RCT	CLL/SLL	Non-first line	Median 64, range 31-86	289 ibrutinib; 289 control	Placebo	17	21	7
Burger ¹	RCT	CLL/SLL	First line	Median 73, range 65-90	136 ibrutinib; 133 controls	Chlorambucil	18.4	8	1
Byrd ²	RCT	CLL/SLL	Non-first line	Median 67, range 30-88	195 ibrutinib; 196 controls	Ofatumumab	9.4	6	0
Dreyling ⁴	RCT	MCL	Non-first line	Median 68, IQR 13	139 ibrutinib; 141 controls	Temsirolimus	20	5	2
Byrd ⁶	Phase II, single arm	CLL/SLL	Non-first line	Median 66, range 37-82	85	—	20.9	3	—
Byrd ⁷	Phase II, single arm	CLL/SLL	Both first line and non-first line	Median 68, range 37-84	132	—	36	8	—
Dimopoulos ⁸	Phase II, single arm	Waldenström	Non-first line	Median 67, range 47-90	31	—	7.7	0	—
Farooqui ⁹	Phase II, single arm	CLL/SLL	Both first line and non-first line	Not stated	86	—	28	14	—
Fowler ¹⁰	Phase II, single arm	Follicular lymphoma	First line	Median 58, range 32-84	60	—	10.2	1	—
O'Brien ¹¹	Phase II, single arm	CLL	Both first line and non-first line	Median 68, range 37-84	94	—	25	7	—
Stilgenbauer ¹²	Phase II, single arm	CLL	Non-first line	Median 64	144	—	11.5	11	—
Jaglowski ¹³	Phase II, single arm	CLL/SLL/PLL	—	N = 31 aged ≥65	71	—	12.5	6	—
Wang ¹⁴	Phase II, single arm	MCL	Non-first line	Median 67, range 45-86	50	—	16.5	7	—
Wang ¹⁵	Phase II, single arm	MCL	Non-first line	Median 68, range 40-84	111	—	26.7	12	—
Parikh ¹⁶	Retrospective cohort	CLL	Both first line and non-first line	Not stated	11 treatment-naïve; 124 relapsed/refractory	—	2.8 treatment-naïve; 6.4 relapsed/refractory	2 treatment-naïve; 1 relapsed/refractory	—
Sandoval-Sus ¹⁷	Retrospective cohort	CLL/SLL	Non-first line	Median 62, range 36-80	54	—	9.1	2	—
Romisher ¹⁸	Retrospective cohort	CLL/MCL	Not stated	Median 65, range 47-83	32	—	Not stated	5	—
Cheah ¹⁹	Retrospective cohort	MCL	Non-first line	Median 69, range 35-84	42	—	10.7	2	—
Hansson ²⁰	Retrospective cohort	CLL/SLL	Non-first line	Median 69	92	—	6.8	3	—
Gustine ²¹	Retrospective cohort	Waldenström	Both first line and non-first line	Median 66, range 30-93	112	—	11.8	6	—

IQR, interquartile range; MCL, mantle cell lymphoma; RCT, randomized controlled trial; —, not applicable.
 *Except where otherwise stated, numbers refer to number of ibrutinib recipients.

A number of caveats should be acknowledged in interpreting these data. No study reported methods for identifying AF cases. Because allocation was masked in only one of the randomized trials of ibrutinib,³

bias in the detection of AF between the ibrutinib and comparator arms may have occurred. Furthermore, in populations at high risk for AF (but without known AF), the yield of AF increases with the intensity of

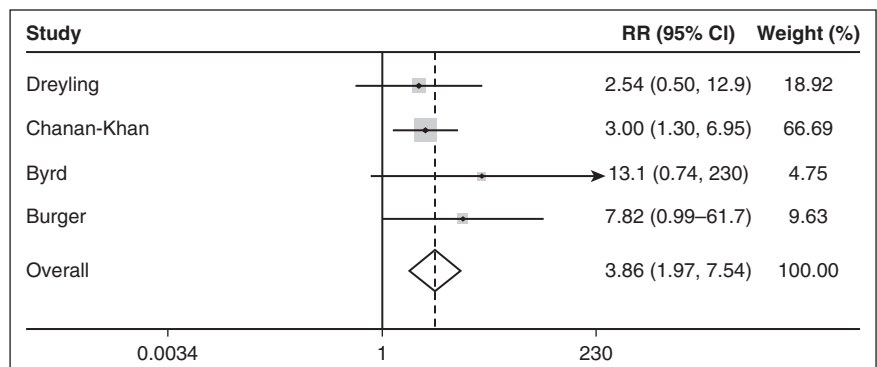


Figure 1. Forest plot of the fixed effects relative risk (RR) of AF in ibrutinib recipients as compared with alternative therapy.

surveillance. Therefore, if screening for AF was not conducted in an intensive or systematic manner, the rates of AF reported in the present meta-analysis may underestimate the true rates. The baseline prevalence of AF was reported in only 2 studies in this meta-analysis. We cannot exclude the possibility that the increase in the risk of incident AF observed in the ibrutinib arms of the randomized trials is simply an unmasking of preexisting AF. Given the limited duration of follow-up in studies to date, it is uncertain whether the rate of AF will remain constant over time, or whether it will reduce or increase with prolonged ibrutinib use.

Patients treated with ibrutinib should be closely monitored for the development of AF, which is associated with a 5-fold increased risk of ischemic stroke, a leading cause of morbidity and mortality, in the general population. Further research is necessary to determine the frequency with which AF affects ibrutinib recipients, the temporal relationship between duration of ibrutinib exposure and AF occurrence, predictors of AF among ibrutinib recipients, the thromboembolic risk in ibrutinib recipients who develop AF (especially given the antiplatelet effect of ibrutinib), and how they should optimally be managed.

*D.P.L. and F.C. contributed equally to this study.

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Contribution: D.P.L. conceived the study idea, designed the study, collected data, performed statistical analysis, and drafted the manuscript. F.C. designed the study, collected data, and revised the manuscript. C.H. designed the study and revised the manuscript. A.D. collected data. J.S.H. interpreted the data and revised the manuscript. G.F. interpreted the data and revised the manuscript. D.S. designed the study, collected data, and revised the manuscript.

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References

- Burger JA, Tedeschi A, Barr PM, et al; RESONATE-2 Investigators. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. *N Engl J Med*. 2015;373(25):2425-2437.
- Byrd JC, Brown JR, O'Brien S, et al; RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med*. 2014;371(3):213-223.
- Chanan-Khan A, Cramer P, Demirkan F, et al; HELIOS investigators. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. *Lancet Oncol*. 2016;17(2):200-211.
- Dreyling M, Jurczak W, Jerkeman M, et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. *Lancet*. 2016; 387(10020):770-778.
- Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenström's macroglobulinemia. *N Engl J Med*. 2015;372(15): 1430-1440.
- Byrd JC, O'Brien S, James DF. Ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2013;369(13):1278-1279.
- Byrd JC, Furman RR, Coutre SE, et al. Three-year follow-up of treatment-naïve and previously treated patients with CLL and SLL receiving single-agent ibrutinib. *Blood*. 2015;125(16):2497-2506.
- Dimopoulos MA, Trotman J, Tedeschi A, et al. Ibrutinib therapy in rituximab-refractory patients with Waldenström's macroglobulinemia: initial results from an international, multicenter, open-label phase 3 substudy (iNNOVATE™) [abstract]. *Blood*. 2015;126(23). Abstract 2745.
- Farooqui M, Valdez J, Soto S, Bray A, Tian X, Wiestner A. Atrial fibrillation in CLL/SLL patients on ibrutinib [abstract]. *Blood*. 2015;126(23). Abstract 2933.
- Fowler N, Nastoupil L, De Vos S, et al. Ibrutinib plus rituximab in treatment-naïve patients with follicular lymphoma: results from a multicenter, phase 2 study [abstract]. *Blood*. 2015;126(23). Abstract 470.
- O'Brien S, Coutre S, Furman RR, et al. Durable responses including complete responses in CLL following long term treatment with single-agent ibrutinib 420 mg [abstract]. *Clin Lymphoma Myeloma Leuk*. 2015;15(suppl 2):S23. Abstract 300.
- Stilgenbauer S, Jones JA, Coutre SE, et al. Results from the phase 2 RESONATETM-17 trial: Efficacy and safety of Ibrutinib in patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma with Del17p [abstract]. *Oncol Res Treat*. 2015;38(suppl 5):92. Abstract V291.
- Jagłowski SM, Jones JA, Nagar V, et al. Safety and activity of BTK inhibitor ibrutinib combined with ofatumumab in chronic lymphocytic leukemia: a phase 1b/2 study. *Blood*. 2015;126(7):842-850.
- Wang ML, Lee H, Chuang H, et al. Ibrutinib in combination with rituximab in relapsed or refractory mantle cell lymphoma: a single-centre, open-label, phase 2 trial. *Lancet Oncol*. 2016;17(1):48-56.
- Wang ML, Blum KA, Martin P, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. *Blood*. 2015;126(6):739-745.
- Parikh SA, Chaffee KR, Call TG, et al. Ibrutinib therapy for chronic lymphocytic leukemia (CLL): an analysis of a large cohort of patients treated in routine clinical practice [abstract]. *Blood*. 2015;126(23). Abstract 2935.
- Sandoval-Sus JD, Chavez JC, Dalia S, et al. Outcomes of patients with relapsed/refractory chronic lymphocytic leukemia after ibrutinib discontinuation outside clinical trials: a single institution experience [abstract]. *Blood*. 2015; 126(23). Abstract 2945.
- Romisher A, Carver J, Schuster SJ, et al. Bruton's tyrosine kinase inhibition is associated with manageable cardiac toxicity [abstract]. *Blood*. 2015;126(23). Abstract 4529.
- Cheah CY, Chihara D, Romaguera JE, et al. Patients with mantle cell lymphoma failing ibrutinib are unlikely to respond to salvage chemotherapy and have poor outcomes. *Ann Oncol*. 2015;26(6):1175-1179.
- Hansson L, Winqvist M, Asklid A, et al. Real-world results on ibrutinib in patients with relapsed or refractory chronic lymphocytic leukemia (CLL): Data from 97 Swedish patients treated in a compassionate use program [abstract]. *Blood*. 2015;126(23). Abstract 1745.
- Gustine JN, Meid K, Dubeau TE, Treon SP, Castillo JJ. Atrial fibrillation associated with ibrutinib in Waldenström macroglobulinemia. *Am J Hematol*. 2016;91(6):E312-E313.
- Heeringa J, van der Kuip DA, Hofman A, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J*. 2006;27(8): 949-953.
- Psaty BM, Manolio TA, Kuller LH, et al. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation*. 1997;96(7):2455-2461.
- 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.
- Ekman N, Lymboussaki A, Väström I, Sarvas K, Kaipainen A, Alitalo K. Bmx tyrosine kinase is specifically expressed in the endocardium and the endothelium of large arteries. *Circulation*. 1997;96(6):1729-1732.

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