# Response to Comment on: "Cardiovascular adverse events in patients with chronic lymphocytic leukemia receiving acalabrutinib monotherapy: pooled analysis of 762 patients"

I would like to thank Drs. Visentin and Trentin for their insightful response to our recently published article entitled "Cardiovascular adverse events in patients with chronic lymphocytic leukemia receiving acalabrutinib monotherapy: pooled analysis of 762 patients."[1] In their response, Drs. Visentin and Trentin suggest an analysis of our pooled cardiovascular data for acalabrutinib using the Italian atrial fibrillation (AF) risk score[2] in addition to the analysis that we reported using the Shanafelt AF risk score.[1] They refer to the report by Archibald and colleagues,[3] which compared the risk of AF with ibrutinib using three prediction tools: the Framingham Heart Study AF score,[4] the Mayo chronic lymphocytic leukemia (CLL) AF score (also known as the Shanafelt AF risk score),[5] and the Italian AF risk score.[2] That analysis demonstrated good performance of all three tools based on clear separation of time to AF in each risk group; however, based on lower Akaike information criteria (estimate of prediction error), the Italian AF risk score was best able to predict risk of developing AF.[3] We agree that additional data assessing risk of AF are needed in the context of Bruton tyrosine kinase inhibitor therapy, particularly in high-risk patient subgroups.

In our pooled analysis of acalabrutinib data,[1] we analyzed the incidence of *de novo* AF/flutter according to Shanafelt AF risk category in order to be consistent with a previous analysis demonstrating increased incidence and risk of *de novo* AF with increasing Shanafelt AF risk category in ibrutinib-treated patients.[6] The Shanafelt AF risk category (0–1, 2–3, 4, and ≥5) is based on factors that were independently associated with AF in their cohort: older age (2 points for age 65–74 years; 3 points for age ≥75 years), male sex (1 point), valvular heart disease (2 points), and hypertension (1 point).[1,5] Our analysis of acalabrutinib data showed a notable increase in AF incidence only among patients with the highest Shanafelt risk scores, with an incidence of 13% reported for Shanafelt risk category ≥5 compared with 2% to 5% for the lower Shanafelt risk categories (0–4).[1] While these data suggested that the incidence of AF by Shanafelt risk category was lower for acalabrutinib compared with data previously reported for ibrutinib (Shanafelt risk categories ≥5 [15%] and 0–4 [4% to 9%]),[6] our findings indicate that the lower risk categories may be less informative for assessing AF risk in the context of acalabrutinib therapy. Compared with the Shanafelt AF risk score, the Italian AF risk score (categories: 0, 1-2, 3-4, and ≥5) weights older age less heavily (>65 years: 1 point), uses the same weighting for male sex (1 point) and valvular disease (2 points), excludes hypertension, and includes several additional factors that reflect comorbidities relevant to AF in this population (cardiomyopathy: 3 points; hyperthyroidism: 1 point; chronic lung disease: 1 point; diabetes mellitus: 1 point; and severe infections: 1 point).[2,3]

Given the potential for greater stratification of higher-risk patients using the Italian score, we agree that a comparative analysis of the Shanafelt AF risk score and the Italian AF risk score using data from our pooled cardiovascular safety analysis of acalabrutinib in patients with CLL is of interest. We are currently assessing these data.

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### Disclosures

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# References


1. Brown JR, Byrd JC, Ghia P, et al. Cardiovascular adverse events in patients with chronic lymphocytic leukemia receiving acalabrutinib monotherapy: pooled analysis of 762 patients. Haematologica. 2022;107(6):1335-1346.
2. 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.
3. 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. 2020;100(1):143-155.
4. Wiczer TE, Levine LB, Brumbaugh J, et al. Cumulative incidence, risk factors, and management of atrial fibrillation in patients receiving ibrutinib. Blood Adv. 2017;1(20):1739-1748.
5. Shanafelt TD, Parikh SA, Noseworthy PA, et al. Atrial fibrillation in patients with chronic lymphocytic leukemia (CLL). Leuk Lymphoma. 2017;58(7):1630-1639.
6. Brown JR, Moslehi J, O'Brien, et al. Characterization of atrial fibrillation adverse events reported in ibrutinib randomized controlled registration trials. Haematologica. 2017;102(10):1796-1805.