

Response to “Cardiovascular adverse events in patients with chronic lymphocytic leukemia receiving acalabrutinib monotherapy: pooled analysis of 762 patients”

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Received: October 14, 2021.

Accepted: November 5, 2021.

Citation: Andrea Visentin and Livio Trentin. Response to “Cardiovascular adverse events in patients with chronic lymphocytic leukemia receiving acalabrutinib monotherapy: pooled analysis of 762 patients”. Haematologica. 2021 Nov 18. doi: 10.3324/haematol.2021.280199. [Epub ahead of print]

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Response to “Cardiovascular adverse events in patients with chronic lymphocytic leukemia receiving acalabrutinib monotherapy: pooled analysis of 762 patients”

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Keywords: chronic lymphocytic leukemia, acalabrutinib, ibrutinib, atrial fibrillation

running title: don't forget the Italian score

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0039 049 821 2298

words 464/1000

Table 1

references: 9/10

Disclosure:

LT received research funding by Janssen, participated to scientific board organized by Janssen, AstraZeneca and Gilead; AV participated to scientific board organized by Janssen and Gilead, speaker bureau for AstraZeneca.

Author contribution

AV and LT review literature and wrote the letter.

Dear editor,

we read with great interest the study by Brown J. et al(1) analyzing the cardiovascular events during acalabrutinib treatment within 4 clinical trials. After a median time of acalabrutinib treatment of 24.9 months in the pooled analysis, 38 out of 762 CLL patients developed AF and/or atrial flutter (15 with treatment naive and 23 with relapsed/refractory CLL)(1). Rates of AF decrease over time, but was higher among patients with prior history of arrhythmia as well as in elderly patients.

BTK inhibitors are widely used for the treatment of B-cell malignancies, including chronic lymphocytic leukemia (CLL). Continuous treatment with the first in class BTK inhibitor, ibrutinib, has been associated with increased incidence of cardiovascular events like atrial fibrillation (AF), atrial flutter and new onset or worse previous arterial hypertension compared to the control healthy population(2-4).

The risk of developing ibrutinib-induced AF can be predicted by some AF risk scores developed(3, 5-7). As reported in Table 1, i) the Framingham score is based on age, male sex, body mass index, systolic pressure, treatment for hypertension, PR interval, significant murmur, heart failure(3); ii) the Shanafelt score includes age, gender, valvular heart disease and hypertension(6); iii) the Italian score includes age, gender, non-valvular cardiopathy, valvular heart disease, hypo/hyperthyroidism, chronic lung diseases, diabetes mellitus and previous grade 3-4 infections(5). In addition, the colleagues from the Mayo clinic analyzed the incidence and management of AF among 290 CLL patients treated with ibrutinib(8). After a median time on ibrutinib of 19 months, authors concluded that all the three scores were able to identify patients with an increased risk to develop AF but “based on lower Akaike information criteria (AIC), the Italian score (AIC = 513) was best able to predict risk of treatment-emergent AF versus the Mayo CLL risk score (AIC = 524) and the Framingham risk score (AIC = 530)”(8).

However, in the paper by Brown et al only the Shanafelt risk score was applied to acalabrutinib treated patients(1).

Given the non-inferiority of the Italian AF score, or slightly better prediction accuracy, we would like to suggest to stratify and compare the cumulative incidence of AF of acalabrutinib-treated patients with both scores.

Recently updated results from the Elevate RR trial has been published(9). This pivotal phase III clinical trial compared acalabrutinib vs ibrutinib in relapsed-refractory patients with high-risk cytogenetics, displaying the superimposable efficacy but a better safety profile of acalabrutinib in the management of CLL patients compared to ibrutinib(9). In particular AF, hypertension, diarrhea, arthralgia and muscle spasms were lower in the acalabrutinib arm, while headache and cough were more common with acalabrutinib than ibrutinib arm(9). Whether second generation BTK inhibitor, like acalabrutinib, decreases AF rate to all class of risk, in particular to score ≥ 5 , compared to ibrutinib is unknown but is a relevant unmet clinical need.

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Table 1. Atrial Fibrillation scores.

Variables	Framingham score	Shanafelt score	Italian's score
Age	X	X	X
Male	X	X	X
Body mass index	X		
Systolic pressure	X		
Treatment for hypertension	X		
EKG PR interval	X		
Heart murmur	X		
Heart failure	X		
Valvular hear disease		X	X
Hypertension		X	
Cardiopathy			X
Hypo/hyper-thyroidism			X
Chronic lung disease			X
diabetes mellitus			X
G3-4 infections			X