RESPONSE

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TO THE EDITOR:

Leukocytosis and thrombosis in polycythemia vera: can clinical trials settle the debate?

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We read with great interest and appreciated the letter by Ronner and colleagues[1] appearing in a recent issue of *Blood Advances*. Although these authors give recognition to our efforts to address a highly debated issue that could have implications in management of patients with polycythemia vera (PV), they also raise some important criticisms on the results of our meta-analysis.[2] We point out in our work that we followed best practices in systematic reviews of observational noninterventional studies,[3] and preregistered the detailed protocol for this work in the International Prospective Register of Systematic Reviews (PROSPERO)[4] (record no. CRD42019122292). Clearly, it is in the nature of this kind of study that some limitations apply, and, in their letter, Ronner et al correctly drew attention on some of these issues, which we would like to briefly address.

1. The aim of our meta-analysis was to obtain a consistent estimate of risk of major thrombosis in patients with essential thrombocythemia (ET) or PV relative to presence or absence of leukocytosis. We obtained estimates of relative risk by pooling both risk ratios (RR)/odds ratios (OR) and hazard ratios (HR). Ronner et al question this choice, remarking that RR/OR should ideally be converted to HR, using additional information (ie, the observed minus expected events and the variance, eventually derived from the number of events and the individual times to event of each study) before pooling them together. Whereas this criticism has merit, we would like to point out that in our selection, only 5 studies of 32 reported RR/OR instead of HR, and in those cases 1 or more of the aforementioned additional information needed to convert them into HR was not retrievable. However, assuming that proportionality of hazards was met in the primary studies, the difference between RR and HR should not be so large to significantly affect global estimates.
2. Another remark from the colleagues concerns the conflation of risks estimated based on leukocytosis present at diagnosis/enrollment and during follow-up, as in the case of the Cytoreductive Therapy in PV study that the authors appropriately referenced. However, as detailed in the PROSPERO protocol and in our article,[2] our primary analysis was clearly restricted to articles reporting leukocytosis at diagnosis or enrollment. We also carried out a sensitivity analysis that included those studies where leukocytosis was assessed during follow-up as well, but we highlight that this did not affect our primary analysis, which included only white blood cell counts measured at diagnosis or enrollment for the prediction of the first major thrombotic event considered overall.
3. The third point raised by Ronner et al is remarkable from a methodological point of view, so much so that the authors were led to perform a post hoc analysis on our data to address it. The matter concerns our reporting of interval estimates and the way we dealt with study heterogeneity; in particular, they suggest that the large heterogeneity we have seen would have called to report prediction intervals besides confidence intervals. We are aware that in meta-analyses of observational studies heterogeneity is an ever-present issue and limitation. To mitigate this limitation, we greatly reduced the sources of heterogeneity already at the level of study selection for the primary analysis, where, in fact, I^2 was low (11.5%) and not significantly different from 0. Exploring different subgroups in our sensitivity analyses, we detected various sources of heterogeneity, among them the most important being the type of myeloproliferative neoplasm (ET vs PV) and site of thrombosis (arterial vs venous). We opted to deal with this heterogeneity by adopting an adequate multivariable meta-regression model adjusting for these factors. We note that although our approach was preplanned and fully in line with the PROSPERO protocol, the choice of calculating prediction intervals, as suggested by Ronner et al, was inevitably made post hoc and guided by the results themselves.[4] Thus, it cannot be ruled out that prediction intervals adopted by Ronner et al, among many other possible approaches, might have provided overall estimates that are more in line with

their a priori assumptions. In any case, the prediction intervals as recalculated cover the null only in the case of PV, whereas our results on ET are more robust, as pointed out in the original paper.

The clinical implications of our meta-analysis do not conclude that leukocytosis has a causative role for all types of thrombosis in myeloproliferative neoplasms, and even less so in PV specifically. If such an association can be inferred, it holds mainly for ET and for arterial thrombosis. We agree with the authors that a well-designed prospective clinical trial would be needed to prove a role for leukocytosis in increasing the risk of thrombosis in PV. This issue was the object of a recent discussion we had during a consensus conference[5] in which it was deliberated that embarking in such a clinical trial would hardly be feasible, owing to the low rate of events expected when the comparator is an active cytoreductive drug. The alternative would be to test a cytoreductive drug that is active in reducing leukocytosis against phlebotomy only, but even so, the expected event rate would still be low. Perhaps some hints in this regard will be given by our ongoing LOW-PV clinical trial (NCT030030025) that is designed to test the efficacy of a ropeginterferon alfa-2b vs phlebotomy alone. Even so, it is unlikely that the number of events will grant statistical power to prove a correlation with leukocytosis. Given these difficulties, we underscore the conclusion of our consensus conference, in which the panel agreed that a large international well-structured database of individual patient data would be the best asset to give a definitive answer to this question because single studies used until now to tackle the issue have shown all of their limitations.

Contribution: T.B., A.C., and A.F. were equally responsible for this response to the commentary.

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