Breaking barriers in rare disease research: a pilot trial of thromboprophylaxis with apixaban *versus* aspirin in *JAK2*-positive myeloproliferative neoplasms

JAK2-positive myeloproliferative neoplasms (MPN), including polycythemia vera (PV), essential thrombocythemia (ET), and pre-fibrotic myelofibrosis (pre-MF), are considered rare diseases, with an incidence of approximately 1-3 cases per 100,000 individuals per year.[1] They are characterized by an increased risk of thrombosis, including arterial and venous thrombosis, due to abnormal clonal hematopoiesis. Current thromboprophylaxis strategies, particularly for primary prevention, are largely based on extrapolation from broader cardiovascular studies, leaving significant gaps in knowledge specific to the MPN population. Low-dose aspirin is widely used for primary thromboprophylaxis, particularly in high-risk PV and ET.[2]

The classical and principal mutations in Philadelphia-negative MPN are *JAK2*^{V617F}, calreticulin (*CALR* exon 9), and *MPL*^{W515}. *JAK2* is present in almost all PV cases (96%) and in most ET/PMF/pre-MF cases (50-65%).[3-5] Through the presence of a common hematopoietic and endothelial progenitor cell harboring the *JAK2* mutation, both quantitative changes (increased proliferation of myeloid cells) and qualitative changes (increased interactions between endothelium, leucocytes, erythrocytes, and platelets) are observed.[6] The *JAK2* mutation is therefore associated with increased thrombotic risk, even when blood counts are normalized through other interventions. Thrombotic risk increases proportionally with *JAK2* allele burden.[7] These qualitative changes associated with the *JAK2* mutation (increased cellular interactions) are mostly mediated by the P-selectin pathway. Recently, it has been shown that the P-selectin-enhanced thrombus formation pathway leads to a clot that is not only platelet-rich, but also tissue factor- and fibrin-rich.[8] These observations suggest that anticoagulants, which inhibit the formation of thrombus via fibrin production, may play a central role in reducing the risk of thrombus formation in this patient population.

These unique pathophysiological features make it difficult to generalize findings from larger trials conducted in non-MPN populations. Therefore, dedicated MPN trials are essential to determine the most effective and safest treatment strategies tailored to the specific risks associated with these disorders. However, as *JAK2*-positive MPN are rare diseases, piloting feasibility of large-sample trials is key prior to embarking in long and costly studies.

This pilot trial was designed to assess the feasibility of conducting a larger, randomized study comparing apixaban and aspirin for primary thromboprophylaxis in patients with *JAK2*-positive MPN. The study aimed to evaluate recruitment rates, patient adherence, and retention, as well as to collect preliminary data on thrombotic and bleeding outcomes.

This was a multicenter, prospective, open-label, blinded endpoint pilot trial (*clinicaltrials gov. Identifier: NCT04243122*) conducted at three Canadian centers: Ottawa, Calgary, and Sherbrooke (recruitment period: February 2021 to October 2023). Adult patients with a confirmed diagnosis of PV, *JAK2*-positive EC, or *JAK2*-positive pre-MF, according to local clinical definitions, were eligible if they required low-dose aspirin for primary thromboprophylaxis. Patients with both incident diagnoses (diagnosed within 1 year) and prevalent disease were recruited.

Exclusion criteria included a contraindication to thromboprophylaxis, the need for a specific anticoagulant, or the use of non-aspirin antiplatelet agents. Eligible participants were randomized 1:1 to receive apixaban 2.5 mg twice daily or aspirin 81 mg daily for 6 months. Cytoreductive therapy, as indicated per guidelines, was allowed in both groups. Follow-up visits occurred at 3, 6, and 7 months after randomization.

The primary outcome of the study was the monthly recruitment rate per site. The trials processes, including potential participants identification practices (pre-screening), consenting practices, study medication distribution and accountability, and participant retention were also evaluated as secondary outcomes. Secondary clinical outcomes included thrombotic and bleeding complications, which were adjudicated by a blinded endpoint committee. The trial is reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement (*Online Supplementary Table S1*).

A total of 44 participants were recruited and randomized, with 22 in the apixaban arm and 22 in the aspirin arm. The baseline characteristics of the participants are summarized in Table 1 (Table 1). The mean age was 66.9 years in the apixaban group and 64.1 years in the aspirin group (P=0.66). Males comprised 54.5% of the apixaban group and 72.7% of the aspirin group (P=0.21). We recruited patients of different racial backgrounds, including White (N=38), Black (N=1), Asian (N=3), and individuals of other races (N=2). Incident cases were more common in the apixaban group (50% *vs*. 18.2%; P=0.03), but the use of cytoreductive therapy and baseline laboratory values were similar between groups.

Feasibility outcomes are detailed in Table 2. The overall recruitment rate was 0.8 patients per site per month, with 0.27 patients per site per month for incident cases. Adher-

ence to study medication was 96.5% (objective ≥80%), and all 44 participants completed the 6-month follow-up period (100% retention). No thrombotic or bleeding events have been observed.

This pilot trial demonstrated the feasibility of conducting a multicenter, randomized study comparing apixaban to aspirin for primary thromboprophylaxis in patients with *JAK2*-positive MPN. The recruitment rate met feasibility criteria, and patient retention and adherence were excellent.

Given the limited patient populations, conducting trials in rare diseases like MPN is inherently challenging. This difficulty is often compounded by a lack of diversity in trial enrollment. In MPN studies, this challenge is particularly pronounced, as most patients with MPN in North America are White. Racial and ethnic diversity could influence treatment efficacy or safety and understanding how these variations affect treatment response is essential for developing more personalized therapeutic strategies. Despite this challenge, our study achieved notable success in recruiting patients from diverse racial backgrounds. This success can serve as a model for the full-scale trial, emphasizing the importance of tailored recruitment strategies that engage diverse communities and address potential barriers to participation.

Another challenge encountered during this pilot trial was the occurrence of the COVID-19 pandemic that significantly impacted recruitment. In the pandemic era, several changes were enacted, with the support of our local Research Ethics Board, to allow for the resumption of participant

Table 1. Baseline characteristics of the trial participants by study arm.

Characteristics	Apixaban N=22	Aspirin N=22	*P*
Age, years, mean ± SD	66.9±1.8	64.1±2.3	0.66
Male sex, N (%)	12 (54.5)	16 (72.7)	0.21
Weight, kg, mean ± SD	77.4±14.7	81.9±19.7	0.40
Race, N (%) White Black Asian Other	 20 (90.9) 1 (4.5) 1 (4.5) 0	 18 (81.8) 0 2 (9.1) 2 (9.1)	 0.38 - - -
MPN characteristics, N (%) *JAK2* pre-MF *JAK2*ET PV	 1 (4.5) 10 (45.5) 11 (50)	 0 12 (54.5) 10 (45.5)	 0.54 - -
Incident case, N (%)	11 (50)	4 (18.2)	0.03
Cytoreductive therapy, N (%) Hydroxyurea Interferon Ruxolitinib Phlebotomy	20 (90.9) 16 (72.7) 1 (4.5) 2 (9.1) 10 (45.5)	17 (77.3) 15 (68.2) 1 (4.5) 0 8 (36.4)	0.22 0.74 1 0.15 0.54
Baseline laboratory values, mean ± SD HGB, g/L WBC, x10^9/L PLT, x10^9/L Serum creatinine, μmol/L	 133±32 - 389±221 81±23	 144±19 - 418±200 88±33	 0.17 - 0.65 0.42

HGB: hemoglobin; *JAK2* pre-MF: pre-myelofibrosis; *JAK2*ET: essential thrombocythemia; MPN: myeloproliferative neoplasm; PLT: platelets; PV: polycythemia vera; WBC: white blood cells; SD: standard deviation.

Table 2. Feasibility outcomes and interpretation.

Outcome	Present trial	GREEN-GO	AMBER-AMEND	RED-STOP
Recruitment	Total: 0.8 patient/site/month Incident cases: 0.27 patient/site/month	>80% (0.42-0.52 patient/site/month)	30-80% (0.16-0.41 patient/site/month)	<30% (0-0.15 patient/site/month)
Adherence	≥96.5% (43 patients)	>80%	50-80%	<50%
Retention	100% (44 patients)	>90%	70-90%	<70%

recruitment. Such changes included pivoting to a remote consent instead of in person consent, changing to virtual research follow up visits (in keeping with the standard of care for medical appointments at our institution at that time), and using a drug shipping service for the distribution of the study medication. Despite the challenges associated with the COVID-19 pandemic, this forced adoption of new processes and technologies within the research environment has generally led to greater efficiency and flexibility. Where appropriate based on the need to preserve research participant safety for a given trial, such procedures are now well integrated in research guidance documents (ICH E6(R3) guideline; TCPS2).

This pilot study confirms the feasibility of recruiting and retaining patients with *JAK2*-positive MPN for a full-scale randomized trial comparing apixaban and aspirin aimed at determining the optimal thromboprophylactic strategy in this population. Currently, a full-size trial assessing the efficacy and safety of low-dose DOAC compared to low-dose aspirin is underway in France and Canada (*clinicaltrails gov. Identifier: NCT05198960*).

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Contributions

MK, MC, and AD obtained funding, designed and performed the research, analyzed data, performed data analysis, and wrote the manuscript. SC, DT, JCI, and DMS performed the research, interpreted the data, and provided critically reviewed of the manuscript.

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Data-sharing statement

De-identified individual participant data underlying the results reported in this article are available upon reasonable request to the corresponding author. Requests will be reviewed by the study steering committee and may require a data sharing agreement in accordance with institutional policies.

References

1. Srour SA, Devesa SS, Morton LM, et al. Incidence and patient survival of myeloproliferative neoplasms and myelodysplastic/myeloproliferative neoplasms in the United States, 2001-12. Br J Haematol. 2016;174(3):382-396.
2. Barbui T, Barosi G, Birgegard G, et al. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. J Clin Oncol. 2011;29(6):761-770.
3. Rumi E, Pietra D, Ferretti V, et al. JAK2 or CALR mutation status defines subtypes of essential thrombocythemia with substantially different clinical course and outcomes. Blood. 2014;123(10):1544-1551.
4. Campbell PJ, Scott LM, Buck G, et al. Definition of subtypes of essential thrombocythaemia and relation to polycythaemia vera based on JAK2 V617F mutation status: a prospective study. Lancet. 2005;366(9501):1945-1953.
5. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-2405.
6. Guadall A, Lesteven E, Letort G, et al. Endothelial cells harbouring the JAK2V617F mutation display pro-adherent and pro-thrombotic features. Thromb Haemost. 2018;118(9):1586-1599.
7. Vannucchi AM, Antonioli E, Guglielmelli P, et al. Prospective identification of high-risk polycythemia vera patients based on JAK2(V617F) allele burden. Leukemia. 2007;21(9):1952-1959.
8. Guy A, Gourdou-Latyszenok V, Le Lay N, et al. Vascular endothelial cell expression of JAK2(V617F) is sufficient to promote a pro-thrombotic state due to increased P-selectin expression. Haematologica. 2019;104(1):70-81.