haematologica
Journal of the Ferrata Storti Foundation

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

by Miriam Kimpton, Sonia Cerquozzi, Dominique Toupin, Jean-Chistrophe Ianotto, Pierre Villeneuve, Deborah M. Siegal, Marc Carrier and Aurélien Delluc

Received: April 9, 2026.
Accepted: April 30, 2026.

Citation: Miriam Kimpton, Sonia Cerquozzi, Dominique Toupin, Jean-Chistrophe Ianotto, Pierre Villeneuve, Deborah M. Siegal, Marc Carrier and Aurélien Delluc. Breaking barriers in rare disease research: a pilot trial of thromboprophylaxis with apixaban versus aspirin in JAK2-Positive myeloproliferative neoplasms. Haematologica. 2026 May 7. doi: 10.3324/haematol.2026.301040 [Epub ahead of print]

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

Miriam Kimpton[1], Sonia Cerquozzi[2], Dominique Toupin[3], Jean-Christophe Ianotto[4], Pierre Villleneuve[1], Deborah M. Siegal[1], Marc Carrier[1], Aurélien Delluc[1]

[1]Department of Medicine, The Ottawa Hospital, University of Ottawa, and The Ottawa Hospital Research Institute, Ottawa, Canada
[2]Cumming School of Medicine, University of Calgary, Calgary, Canada
[3]Service d'hémato-oncologie, Département de médecine, Centre hospitalier universitaire de Sherbrooke, Sherbrooke, Canada
[4]Service d'Hématologie et d'Hémostase Clinique, Institut De Cancéro-Hématologie, INSERM, UMR1304, GETBO, Centre hospitalier universitaire de Brest, Brest France; France intergroupe des néoplasies myéloprolifératives (FIM), Paris, France.

Manuscript word count: 1110
References: 8
Tables: 2

Corresponding author
Aurélien Delluc, MD, PhD
Ottawa Hospital Research Institute – University of Ottawa
501 Smyth Road, Ottawa, ON, Canada, K1H 8L6
E-mail: adelluc@toh.ca

Acknowledgements
A. Delluc holds the Chair on Innovative strategies in venous thromboembolism, Department of Medicine, University of Ottawa.

Conflicts of interest
None

Funding
CanVECTOR 2019 pilot trials competition
R.K. Smiley 2019 Grant from the Canadian Society of Hematology
Association médicale universitaire de l'Hôpital Montfort – Subventions « Projets de recherche »

Authors' 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 critical review of the manuscript.

Trial registration

ClinicalTrials.gov identifier: NCT04243122

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.

Dear Editors,

JAK2-positive myeloproliferative neoplasms (MPNs), 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 MPNs are JAK2V617F, calreticulin (CALR exon 9), and MPL W515. JAK2 is present in almost all PV cases (96%) and in most ET/PMF/PreMF cases (50-65%) (3-5). Through the presence of a common hematopoietic and endothelial progenitor cell harbouring 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-postive MPNs 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 MPNs. 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 (NCT04243122) conducted at three Canadian centers: Ottawa, Calgary, and Sherbrooke. Adult patients with a confirmed diagnosis of polycythemia vera, JAK2-positive essential thrombocythemia, or JAK2-positive pre-fibrotic myelofibrosis, 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 (Supplementary Table 1).

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. Adherence 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 MPNs. The recruitment rate met feasibility criteria, and patient retention and adherence were excellent.

Given the limited patient populations, conducting trials in rare diseases like MPNs 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 MPNs 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 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 MPNs 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 (NCT05198960).

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.

Table 1: baseline characteristics of the trial participants by study arm

	Apixaban n=22	**Aspirin n=22**	**p-value**
Age year 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			
White n (%)	20 (90.9)	18 (81.8)	0.38
Black n (%)	1 (4.5)	0	
Asian n (%)	1 (4.5)	2 (9.1)	
Other n (%)	0	2 (9.1)	
MPN characteristics			
JAK2 pre-MF n (%)	1 (4.5)	0	0.54
JAK2ET n (%)	10 (45.5)	12 (54.5)	
PV n (%)	11 (50)	10 (45.5)	
Incident case n (%)	11 (50)	4 (18.2)	0.03
Cytoreductive therapy n (%)	20 (90.9)	17 (77.3)	0.22
Hydroxyurea n (%)	16 (72.7)	15 (68.2)	0.74
Interferon n (%)	1 (4.5)	1 (4.5)	1
Ruxolitinib n (%)	2 (9.1)	0	0.15
Phlebotomy n (%)	10 (45.5)	8 (36.4)	0.54
Baseline labs			
HGB g/l mean ± SD	133 ± 32	144 ± 19	0.17
WBC $x10^9$/L mean ± SD			
PLAT $x10^9$/L (mean ± SD)	389 ±221	418 ± 200	0.65
Serum Creatinine µmol/L mean ± SD	81 ± 23	88 ± 33	0.42

MPN: myeloproliferative neoplasm; JAK2 pre-MF: pre-myelofibrosis; JAK2ET: essential thrombocythemia ; PV: Polycythemia Vera; HGB: hemoglobin; WBC: white blood cells; PLAT: platelets; 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%

CONSORT 2025 checklist of information to include when reporting a randomised trial*

Section / Topic	No	CONSORT 2025 checklist item description	Reported on page no.
Title and abstract			
Title and structured abstract	1a	Identification as a randomised trial	Title page
	1b	Structured summary of the trial design, methods, results, and conclusions	NA
Open science			
Trial registration	2	Name of trial registry, identifying number (with URL) and date of registration	2
Protocol and statistical analysis plan	3	Where the trial protocol and statistical analysis plan can be accessed	3
Data sharing	4	Where and how the individual de-identified participant data (including data dictionary), statistical code and any other materials can be accessed	NA
Funding and conflicts of interest	5a	Sources of funding and other support (e.g., supply of drugs), and role of funders in the design, conduct, analysis and reporting of the trial	Title page
	5b	Financial and other conflicts of interest of the manuscript authors	Title page
Introduction			
Background and rationale	6	Scientific background and rationale	2
Objectives	7	Specific objectives related to benefits and harms	2
Methods			
Patient and public involvement	8	Details of patient or public involvement in the design, conduct and reporting of the trial	2-3
Trial design	9	Description of trial design including type of trial (e.g., parallel group, crossover), allocation ratio, and framework (e.g., superiority, equivalence, non-inferiority, exploratory)	2-3
Changes to trial protocol	10	Important changes to the trial after it commenced including any outcomes or analyses that were not prespecified, with reason	NA
Trial setting	11	Settings (e.g., community, hospital) and locations (e.g., countries, sites) where the trial was conducted	2
Eligibility criteria	12a	Eligibility criteria for participants	3
	12b	If applicable, eligibility criteria for sites and for individuals delivering the interventions (e.g., surgeons, physiotherapists)	NA

Intervention and comparator	13	Intervention and comparator with sufficient details to allow replication. If relevant, where additional materials describing the intervention and comparator (e.g., intervention manual) can be accessed	3
Outcomes	14	Pre-specified primary and secondary outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome	2
Harms	15	How harms were defined and assessed (e.g., systematically, non-systematically)	2
Sample size	16a	How sample size was determined, including all assumptions supporting the sample size calculation	2
	16b	Explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	17a	Who generated the random allocation sequence and the method used	NA
	17b	Type of randomisation and details of any restriction (e.g., stratification, blocking and block size)	NA
Allocation concealment mechanism	18	Mechanism used to implement the random allocation sequence (e.g., central computer/telephone; sequentially numbered, opaque, sealed containers), describing any steps to conceal the sequence until interventions were assigned	NA
Implementation	19	Whether the personnel who enrolled and those who assigned participants to the interventions had access to the random allocation sequence	NA
Blinding	20a	Who was blinded after assignment to interventions (e.g., participants, care providers, outcome assessors, data analysts)	2
	20b	If blinded, how blinding was achieved and description of the similarity of interventions	2
Statistical methods	21a	Statistical methods used to compare groups for primary and secondary outcomes, including harms	3
	21b	Definition of who is included in each analysis (e.g., all randomised participants), and in which group	3
	21c	How missing data were handled in the analysis	NA
	21d	Methods for any additional analyses (e.g., subgroup and sensitivity analyses), distinguishing prespecified from post-hoc	NA
Results			
Participant flow, including flow diagram	22a	For each group, the numbers of participants who were randomly assigned, received intended intervention, and were analysed for the primary outcome	3 and Table 1
	22b	For each group, losses and exclusions after randomisation, together with reasons	3
Recruitment	23a	Dates defining the periods of recruitment and follow-up for outcomes of benefits and harms	2
	23b	If relevant, why the trial ended or was stopped	NA

Intervention and comparator delivery	24a	Intervention and comparator as they were actually administered (e.g., where appropriate, who delivered the intervention/comparator, how participants adhered, whether they were delivered as intended [fidelity])	2
	24b	Concomitant care received during the trial for each group	2
Baseline data	25	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed, outcomes and estimation	26	For each primary and secondary outcome, by group: ● the number of participants included in the analysis ● the number of participants with available data at the outcome time point ● result for each group, and the estimated effect size and its precision (such as 95% confidence interval) ● for binary outcomes, presentation of both absolute and relative effect size	Table 2 and page 3
Harms	27	All harms or unintended events in each group	3
Ancillary analyses	28	Any other analyses performed, including subgroup and sensitivity analyses, distinguishing pre-specified from post-hoc	3
Discussion			
Interpretation	29	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	3
Limitations	30	Trial limitations, addressing sources of potential bias, imprecision, generalisability, and, if relevant, multiplicity of analyses	3

*We strongly recommend reading this statement in conjunction with the CONSORT 2025 Explanation and Elaboration and/or the CONSORT 2025 Expanded Checklist for important clarifications on all the items. We also recommend reading relevant CONSORT extensions. See www.consort-spirit.org.

Citation: Hopewell S, Chan AW, Collins GS, Hróbjartsson A, Moher D, Schulz KF, et al. CONSORT 2025 Statement: updated guideline for reporting randomised trials. BMJ. 2025; 388:e081123. https://dx.doi.org/10.1136/bmj-2024-081123.