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Abstract: Cardiovascular (CV) risk factors are important contributors to thrombotic risk in the general population and in patients with chronic myeloproliferative neoplasms (MPNs). However, the role of CV risk factors is often masked by other disease features that have a strong prognostic impact regarding thrombotic risk in MPN patients. This review summarizes the contemporary knowledge and aspects that have not been addressed or lack consensus in the medical community. We propose multidisciplinary care for MPN patients with CV comorbidities and provide future directions that may be needed to appropriately manage CV risk factors in MPNs.

Introduction

Philadelphia chromosome–negative chronic myeloproliferative neoplasms (MPNs) are a group of bone marrow cancers comprising essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis (MF). MPNs are characterized by excessive proliferation of 1 or more mature myeloid cell lineages; the presence of mutually exclusive driver mutations in the Janus kinase 2 (*JAK2*), calreticulin (*CALR*), or thrombopoietin receptor (*MPL*) genes; splenomegaly; constitutional symptoms; variable degrees of bone marrow fibrosis; and the propensity to progress to secondary (post-PV or post-ET) MF and acute myeloid leukemia (AML).[1-4] In addition to increased myeloproliferation, constitutive activation and dysregulation of the JAK-signal transducer and activator of the transcription (STAT) signaling pathway causes aberrant synthesis of various inflammatory cytokines. These cytokines are the driving force of the MPN

clone expansion[5] and disease progression,[6] and are partly responsible for the development of cardiovascular (CV) disease in MPN patients.[7] Higher blood viscosity, blood cell activation, formation of leukocyte-platelet complexes, increased synthesis of neutrophil extracellular traps and different procoagulant factors, endothelial dysfunction, and overproduction of microparticles and reactive oxygen species (ROS) are important factors associated with atherosclerosis and thrombosis in MPN patients.[8-10] However, the MPN clone may also produce cardioprotective cytokines.[11]

The risk of thrombosis is significantly higher in MPN patients compared with the general population,[12] and up to one-third of MPN patients may experience a thrombotic event during the disease course.[13] The cumulative incidence of thrombotic events is estimated to be 3.5 per 100 person-years in PV patients, and 2.5 per 100 person-years in ET and MF patients.[14] For example, in the ECLAP randomized clinical trial (RCT), mortality owing to CV events accounted for 45% of all deaths in PV patients.[14]

In contrast to PV and ET, where thrombotic risk is the mainstay of prognostication and treatment, thrombotic risk in MF is often underappreciated. This is mostly attributed to the fact that prognostication and treatment strategies in MF primarily focus on estimating and minimizing the risk of death, respectively. As a result, a proper understanding of the incidence and risk factors for thrombosis may be obscured. Nevertheless, thrombotic risk in MF is not negligible, especially among patients with post-PV MF, and may be associated with similar risk factors as in ET and PV.[15-17] Owing to the tendency for CV complications and disease progression, the overall survival (OS) of all MPN patients is worse than that in the age- and sex-matched general population.[18,19] This finding is of particular concern in the case of young MPN patients, who are likely to develop disease- and therapy-related complications during their lifetime.[20]

In this review, we summarize contemporary knowledge and aspects of CV disease that have not been addressed or where there is a lack of consensus within the medical community. Additionally, we propose future directions that may be needed to appropriately manage CV risk factors in MPNs.

Current Risk Stratification and Treatment of MPNs

The most important prognostic factors for future thrombotic events in patients with MPNs are age older than 60 years and prior thrombotic events. PV patients who present with either one of these 2 factors are classified as high-risk.[21] In ET, the presence of the *JAK2* mutation is additionally used to construct 4 risk categories in the Revised International Prognostic Score of Thrombosis for Essential Thrombocythemia (R-IPSET-thrombosis): very low (age ≤60 years, no prior thrombosis, and the absence of the *JAK2* mutation), low (age ≤60 years, no prior thrombosis, with the *JAK2* mutation present), intermediate (age >60 years, without prior thrombosis and without the *JAK2* mutation) and high-risk (prior thrombosis or age >60 years with the presence of the *JAK2* mutation).[22,23] Patients with MF are usually risk-stratified regarding the risk of death by applying the Dynamic International Prognostic Scoring System (DIPSS). The DIPSS is a robust tool that enables risk prognostication for MF patients, taking into consideration age, white blood cell count, hemoglobin, the presence of constitutional symptoms, and peripheral blasts.[24] Although more recent prognostic systems for MF incorporate cytogenetic and molecular data,[25-27] performing these tests is costly, and the necessary infrastructure may be unavailable in all clinical settings. With regard to CV risk, an interaction between low-risk status based on the International Prognostic Scoring System (IPSS) and the presence of the *JAK2* mutation appears to exist, suggesting the necessity to intervene in lower-risk MF patients.[28] The Myelofibrosis Secondary to PV and ET Prognostic Model (MYSEC-PM) is applied to post-PV and post-ET patients with secondary MF for optimal prognostication.[29]

Currently, the proposed risk-adapted therapy in MPNs includes low-dose aspirin for all PV and low- to high-risk ET patients, whereas cytoreduction, typically with hydroxyurea or interferon (IFN), is usually recommended for high-risk ET and PV patients only.[1,30] The use of aspirin in *CALR*-mutated low-risk ET patients is not recommended, as it does not seem to mitigate the risk of thrombosis and may increase the risk of bleeding.[31] Patients with PV are also regularly phlebotomized to maintain hematocrit levels below 45%, because achieving this level significantly lowers the risk of adverse CV events in the CYTO-PV RCT.[32] It is not known if *JAK2*-mutated patients without PV should also be phlebotomized if their hematocrit levels are above 45%. Patients with MF classified as intermediate-2/high-risk are at high risk for death and are considered for allogeneic stem cell transplant. Treatment with JAK inhibitors, such as ruxolitinib (Jakafi, Incyte), is usually recommended before the procedure and for elderly or unfit patients.[33,34] The benefits of JAK2 inhibitors may be more pronounced among patients with less advanced MF features.[35,36] In general, a different cytoreductive agent should be considered in cases of drug intolerance or lack of efficacy.[37,38] Ruxolitinib may be a reasonable choice in patients with PV who have hydroxyurea resistance or intolerance.[39,40] Even low-risk MPN

patients may benefit from specific therapy if they present with symptoms and require frequent phlebotomy.[21]

Former Databases and Contemporary Definitions and Treatments for CV Comorbidities in MPNs

A variety of generic CV risk factors have been extensively investigated in patients with MPNs, including arterial hypertension,[22,41-51] diabetes mellitus (DM),[14,32,41-43,45-47,49,50] smoking,[42,43,45,46,49,50,52-56] hyperlipidemia,[44] chronic kidney disease,[57-59] hyperuricemia,[60,61] obesity, and cachexia.[62] They were evaluated as individual entities, grouped with other CV risk factors, or as a cumulative comorbidity burden.

In contrast to R-IPSET-thrombosis,[22,23] the original IPSET-thrombosis[63] included several CV risk factors (arterial hypertension, DM, and smoking) and was validated in prefibrotic MF.[64] However, although the presence of CV risk factors[41-49] and the higher number of comorbidities[62] may increase the thrombotic risk and potentially reduce life expectancy in MPNs, these factors are not included in the current risk prognostication systems. The absence of prognostic recognition of CV risk factors and other comorbidities is primarily attributed to inconsistent results,[22,46,50] inclusion of patients from different diagnostic periods and follow-up times, heterogeneity in the definitions of CV risk factors and thrombotic events, inclusion of a small number of patients with specific CV risk factors, and different statistical approaches and other variables, which may be confounding factors in retrospective analyses.

The disadvantage of using large datasets from registries to evaluate CV risk factors is the large time span of evaluation and the consequent heterogeneity in patients considering the definition and treatment of CV comorbidities. Studies in cohorts of MPN patients that investigated the thrombotic risk included stored biological samples or baseline clinical data with follow-up time spanning more than 30 years. Definitions, criteria, and diagnostic cut-offs for all CV comorbidities profoundly changed during this extended period. These changes may affect the validity of the conclusions regarding how comorbidities (as per the diagnostic criteria of that time) contributed to thrombotic risk compared with the present criteria. For example, in 1995, an RCT[65] set the threshold for DM as fasting glucose greater than 7.8 mmol/L (140 mg/dL) and a high lipid profile as total cholesterol greater than 6.2 mmol/L (240 mg/dL), but these cut-off values are currently considered unacceptable. Also, more potent agents used to target different CV comorbidities, such as statins, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and others, were developed through the years and have profoundly changed the prognosis associated with specific comorbidities in the general population. Thus, we do not know whether conclusions about the efficacy and safety of specific drugs based on datasets that are more than 20 years old are accurate in contemporary MPN cohorts when compared with placebo plus best of care, according to today's standards.

Another issue with retrospective registries is that CV comorbidities were often defined at any time during the follow-up period. In these cases, patients included during later study periods had more detailed medical information, whereas those with missing data were often coded as not having a comorbidity. This approach misclassifies some of the patients with comorbidities. The same may apply to mutation testing and exposure to specific drugs.

Ideally, firm evidence is generated from RCTs that enables prospective follow-up and predefined protocols, procedures, and outcomes. The main disadvantages of RCTs are the potential lack of representative patients from real life (who may not fulfill the predefined study inclusion/exclusion criteria but still need medical care), the short follow-up period needed to observe enough events to appropriately power the statistical analyses (especially in low-risk patients), and the focus of the evaluation on selected outcomes. Additionally, major clinical outcomes, such as thrombotic events, are quite infrequent in MPN patients treated with contemporary cytoreductive treatments in recent RCTs.[33,40,66,67] As a result, the statistical power of these studies to assess the potential antithrombotic effect of different cytoreductive treatments is limited.

For the aforementioned reasons, the current MPN treatment guidelines do not recommend the presence of CV risk factors as an indication for cytoreductive treatment in otherwise low-risk patients. Nevertheless, aggressive control of generic CV risk factors in all MPN patients is recommended with the administration of twice-daily aspirin and consideration of cytoreduction in low-risk patients with persistently high CV risk, provided that primary CV prevention strategies have already been implemented.[21,37,38]

Lack of Generalized Traditional Prognostic Scores and the Need for New Surrogate Markers of Thrombotic Risk

Retrospective analyses of registry datasets have demonstrated that the prognostic scoring systems developed for CV prognostication in the general population, such as the CHA2DS2-VASC in atrial fibrillation or the simplified Pulmonary Embolism Severity Index (sPESI)

in pulmonary embolism, may perform suboptimally in MPN patients.[68,69] These scoring systems account for specific comorbidities and reflect the cumulative comorbidity burden in the final score. Instead, it appears that MPN-related factors may play a more important role during risk prognostication of MPN patients. For all the aforementioned reasons, it may not be the number of particular comorbidities per se, but the extent of their control that is more important on how these comorbidities contribute to the overall thrombotic risk.[70]

Many biologic biomarkers that were directly measured or derived have recently emerged as prognostically relevant in the prognosis of MPN patients. Parameters that can be easily obtained from the complete blood count analysis, such as red blood cell distribution width,[71-74] lymphocyte and neutrophil count and percentage, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio,[75-77] and estimated plasma volume status,[78,79] are highly useful. These non-MPN specific variables bear prognostic importance regarding the thrombotic risk in persons with CV comorbidities from the general population.[80] However, caution regarding the interpretation of the former biomarkers is needed given the large number of factors that may affect them and their substantial inter- and intra-individual variability.[81] Although it may be difficult to interpret what exactly these parameters represent biologically, they were consistently associated with undesirable clinical outcomes in multiple independent datasets. These observations were recently further supported by artificial intelligence through a machine-learning model identifying red blood cell distribution width, lymphocyte percentage, and neutrophil percentage as parameters with strong prognostic properties regarding thrombotic risk in hydroxyurea-treated PV patients.[82] Nevertheless, additional research is still needed to fully understand whether clinical decisions can rely on these surrogate markers of thrombotic risk.

Aspirin: Former and Recent Considerations

Aspirin is universally prescribed to PV patients as the primary prophylactic to prevent thrombotic events, based on the results of the ECLAP RCT published in 2004.[83] The ECLAP trial demonstrated lower cumulative rates of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from CV causes with low-dose aspirin treatment at 100 mg daily vs placebo. However, the same trial did not demonstrate significant benefits regarding overall or CV mortality as isolated outcomes. Aspirin is currently recommended for all PV patients if not contraindicated.[38] Similarly, guidelines for ET treatment recommend aspirin to the majority of patients (to all except very–low-risk patients defined by the R-IPSET-thrombosis),[84] based on extrapolated and retrospective data. Although there are no guidelines explicitly recommending aspirin, patients with MF are often treated with aspirin because it was initiated during earlier prefibrotic MPN stages or owing to other comorbid conditions where aspirin is considered a standard of care. Per recent guidelines, PV and ET patients are stratified into higher risk groups, and those with CV comorbidities are considered candidates for aspirin twice daily.[21] These recommendations are based on the demonstration of more potent inhibition of platelets in MPN patients with twice- and triple-daily dosing of aspirin.[85] Nevertheless, there is currently no evidence suggesting that these surrogate measurements of thrombotic risk may translate into reduced thrombotic risk, as randomized or real-life data demonstrating the usefulness of twice- or triple-daily aspirin are still lacking. In MPN patients, aspirin is currently considered an agent that reduces thrombotic risk and does not have anti- or pro-myeloproliferative activity.[86,87]

Aspirin has a definitive beneficial role in the secondary prevention of thrombotic events and is strongly recommended in this context.[88] However, until recently, aspirin was widely used for the primary prevention of thrombotic events in the general population based on convincing early evidence. Specifically, early RCTs of aspirin use in the primary prevention of CV complications showed benefit in large populations, with a small increase in major bleeding risk.[89] Aspirin has analgesic properties, and there are a number of indirect indicators of its benefits (both regarding CV complications and malignant diseases) in the literature, mostly based on retrospective studies. Nevertheless, the role of aspirin in the context of primary prevention has been revisited in the last few years.[90] Thus, current recommendations for patients with DM suggest that aspirin should be considered as a primary prevention strategy for CV complications only in patients who are at increased CV risk, and only after a comprehensive discussion with the patient regarding the benefits vs the increased risk of bleeding.[91]

Four large primary prevention trials performed in recent years have revealed additional considerations. The ASPREE RCT, which was designed to evaluate dementia-free and disability-free survival, randomized a total of 19,114 healthy elderly patients to either aspirin at 100 mg daily or placebo. The study did not find a benefit in these outcomes, but the investigators were surprised to see an increased mortality rate with aspirin use that was driven by a higher incidence of cancer-related death.[92] This was the first large-scale RCT that evaluated the role of aspirin in elderly patients and profoundly questioned its properties. The ASCEND RCT randomized 15,480 patients with DM to aspirin at 100 mg daily or placebo and showed

lower rates of serious vascular events (myocardial infarction, stroke or transient ischemic attack, or death from any vascular cause) and higher rates of major bleeding with aspirin, without survival benefit.[93] The ARRIVE RCT randomized 12,546 middle-aged and older adults at intermediate risk for atherosclerotic CV disease without DM to aspirin or placebo and did not find a significant difference in the number of CV events or survival between the groups, but reported a 2-fold increase in the risk of gastrointestinal bleeding with aspirin.[94] The TIPS-3 RCT randomized (using a 2×2×2 factorial design) 5713 patients without CV disease but with elevated CV risk; the patients received a polypill containing statins and antihypertensive medications or placebo daily, aspirin at 75 mg or placebo daily, and vitamin D or placebo monthly. The study showed that the group treated with both the polypill plus aspirin had a lower CV risk, and improved survival and similar bleeding rates compared with the placebo; also, no significant differences were observed for aspirin only compared with placebo regarding CV outcomes, death, and bleeding.[95] In the aforementioned first 3 trials, concomitant use of statins and antihypertensive medications was high and smoking rates were low, suggesting that aspirin may not exert beneficial effects in patients potently treated for CV comorbidities.

In light of the new studies questioning the benefits of aspirin for disease prevention in the general population, the role and dosing of aspirin in preventing thrombotic events in MPN patients should be critically reevaluated as well. It is questionable if the ECLAP study would report similar conclusions regarding thrombotic endpoints in cohorts treated with novel therapies for MPNs and CV comorbidities.

Peculiarities of CV Risk Factors in MPN Patients

The optimal management of CV risk factors in MPN patients is currently unknown and usually mirrors the experience of the general population. The underlying pathophysiologic mechanisms of CV risk factors in MPN patients are also strongly affected by high cellular proliferation, increased metabolic turnover, and significant inflammatory burden associated with MPNs. Therefore, the optimal treatment of CV risk factors in MPNs may also need to take into account these specificities. Here, we would like to briefly mention several important aspects regarding each CV risk factor in MPN patients.

Arterial hypertension in MPN patients has less variation during blood pressure measurements, a higher occurrence of non-dipper phenotype, and a lower sympathetic nervous system activity.[96,97] On the other hand, arterial hypertension may also diminish after the start of phlebotomy, even in non-MPN patients.[98,99]

DM is either insufficiently recognized or is a less common CV comorbidity in MPNs. This is a particular concern owing to the detrimental effects of DM on CV health in the general population. Additionally, optimal levels of glycated hemoglobin (HbA1c) for the diagnosis and treatment of DM in MPN patients are still not established. HbA1c values may be affected by high cellular turnover and other MPN-specific features and therapies.[100,101] In recent years, SGLT2 inhibitors have been shown to possess favorable cardioprotective and renoprotective properties in the general population[102]; however, they have not been extensively tested in MPNs. These drugs have been associated with the occurrence of secondary polycythemia and an increase in thrombotic risk and hemoglobin/hematocrit levels during phlebotomy, similarly to Chuvash polycythemia.[103] Moreover, a small case series has shown that the use of SGLT2 inhibitors may also unmask an underlying MPN, often with a high thrombotic risk, calling for diagnostic MPN exclusion in patients who develop polycythemia during SGLT2 treatment.[104]

Smoking-induced inflammation and its carcinogenic potential may promote the development of MPNs,[105] impair treatment responses, and negatively affect survival.[106]

Many MPN patients have hypocholesterolemia, which is hypothesized to be a consequence of high lipid membrane utilization in the proliferating cells. Low-density lipoprotein (LDL) values of less than 1.8 mmol/L have been associated with a lower incidence of thrombotic events and may have the strongest discriminatory properties regarding thrombotic risk in PV and ET patients.[44] Interestingly, this cut-off value corresponds to that of target LDL levels for the treatment of high-risk persons in the general population.[107]

Chronic kidney disease is highly prevalent among MPN patients and was shown to bear high thrombotic risk for both arterial and venous thrombotic events in MPNs.[57-59] This is of particular interest owing to its possible association with MPN-related glomerulopathy, which is the MPN manifestation at the level of glomeruli.[108]

Hyperuricemia reflects higher cellular turnover, nutritional habits, and worse kidney function, and is associated with the occurrence of gout and increased CV risk among MPN patients.[60,61,109] Owing to a lack of recognition by current treatment guidelines and the unknown optimal treatment target levels, urate-lowering therapies are usually prescribed on an individual basis.

Obesity and cachexia, which are on opposite sides of the body mass index spectrum, carry specific risks in MPN patients. It is unclear whether more favorable outcomes associated with higher body mass index may reflect the absence of cachexia, or the so-called obesity

paradox.[62] Obesity induces inflammation and may promote carcinogenesis. Biomarkers associated with cachexia reflect negatively on the outcomes of MPN patients[75,110] and can be reverted with specific therapies,[35] which calls for more clinical trials specifically focusing on nutritional support in MPNs. Notably, the use of ruxolitinib in MF patients has been associated with muscle mass improvement,[35] weight gain, and an increase in total cholesterol and low-density lipoprotein levels. Total cholesterol levels during ruxolitinib treatment generally did not exceed 6.2 mmol/L (240 mg/dL), and low-density lipoprotein levels typically did not exceed 4 mmol/L (160 mg/dL).[111] These observations have suggested a favorable disease-modifying activity of ruxolitinib on metabolic and nutritional measures in MF patients without substantially affecting the risk of hyperlipidemia.

Conclusion and Perspectives

Thrombotic risk dominates MPN prognostication and treatment, and multidisciplinary care may be needed to adequately control CV comorbidities in MPN patients. Currently, CV risk factors are not included in the well-established MPN-specific prognostic scores for a variety of reasons. It should be pointed out, however, that CV comorbidities may share common pathophysiologic mechanisms with MPNs and may require simultaneous and focused medical care. Significant advances in the understanding of the molecular biology of MPNs have led to the development of integrated clinical and molecular prognostic scores that have provided more refined prognostication in patients. Introduction of targeted treatments in MPNs, such as JAK inhibitors (eg, ruxolitinib, fedratinib [Inrebic, Bristol-Myers Squibb], and momelotinib) and the more-potent and less-toxic IFN formulations (eg, ropeginterferon alfa-2b-njft [Besremi, PharmaEssentia]), has revolutionized the therapeutic landscape in MPNs. Unfortunately, diagnostic and MPN-specific therapeutic advancements may have also caused CV comorbidities to occasionally leave the primary focus of hematologists.

Exploratory post-hoc analyses of the current RCTs in which treatment responses and clinical outcomes of MPN patients are stratified according to CV risk factors would be a great way to start. Also, multi-institutional international collaborations (eg, big data) with the help of new technologies (eg, artificial intelligence) may represent an exciting approach to creating MPN-specific risk scores for particular CV comorbidities and determining the optimal target values of different metabolic parameters (eg, LDL, HbA1c, or serum uric acid) in MPN patients. Finally, RCTs in MPN patients using contemporary and potent medications (eg, statins, PCSK9 inhibitors, angiotensin-converting enzyme inhibitors, and SGLT2 inhibitors) for the treatment of different CV comorbidities (on top of MPN-specific treatments) may be needed to establish new standards of care.

Disclosures

Dr Verstovsek is an employee of Kartos Therapeutics. Drs Krecak, Verstovsek, and Lucijanic have no competing interests to declare.

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References

1. Krecak I, Lucijanic M, Verstovsek S. Advances in risk stratification and treatment of polycythemia vera and essential thrombocythemia. *Curr Hematol Malig Rep*. 2022;17(5):155-169.
2. Tefferi A. Primary myelofibrosis: 2023 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2023;98(5):801-821.
3. Pasca S, Chifotides HT, Verstovsek S, Bose P. Mutational landscape of blast phase myeloproliferative neoplasms (MPN-BP) and antecedent MPN. *Int Rev Cell Mol Biol*. 2022;366:83-124.
4. Shahin OACH, Chifotides HT, Bose P, Masarova L, Verstovsek S. Accelerated phase of myeloproliferative neoplasms. *Acta Haematol*. 2021;144(5):484-499.
5. Fleischman AG, Aichberger KJ, Luty SB, et al. TNFα facilitates clonal expansion of JAK2V617F positive cells in myeloproliferative neoplasms. *Blood*. 2011;118(24):6392-6398.
6. Gleitz HFE, Benabid A, Schneider RK. Still a burning question: the interplay between inflammation and fibrosis in myeloproliferative neoplasms. *Curr Opin Hematol*. 2021;28(5):364-371.
7. Hasselbalch HC, Bjørn ME. MPNs as inflammatory diseases: the evidence, consequences, and perspectives. *Mediators Inflamm*. 2015;2015:102476.
8. Cervantes F, Arellano-Rodrigo E, Alvarez-Larrán A. Blood cell activation in myeloproliferative neoplasms. *Haematologica*. 2009;94(11):1484-1488.
9. Barbui T, Finazzi G, Falanga A. Myeloproliferative neoplasms and thrombosis. *Blood*. 2013;122(13):2176-2184.
10. Leiva O, Hobbs G, Ravid K, Libby P. Cardiovascular disease in myeloproliferative neoplasms: *JACC: CardioOncology* State-of-the-Art Review. *JACC Cardiooncol*. 2022;4(2):166-182.
11. Lucijanic M, Livun A, Tupek KM, et al. Heat shock protein 27 (HSP27/HSPB1) expression is increased in patients with primary and secondary myelofibrosis and may be affecting their survival. *Leuk Lymphoma*. 2017;58(10):2497-2500.
12. Hultcrantz M, Björkholm M, Dickman PW, et al. Risk for arterial and venous thrombosis in patients with myeloproliferative neoplasms: a population-based cohort study. *Ann Intern Med*. 2018;168(5):317-325.
13. Pemmaraju N, Gerds AT, Yu J, et al. Thrombotic events and mortality risk in patients with newly diagnosed polycythemia vera or essential thrombocythemia. *Leuk Res*. 2022;115:106809.
14. Barbui T, Carobbio A, De Stefano V. Thrombosis in myeloproliferative neoplasms during cytoreductive and antithrombotic drug treatment. *Res Pract Thromb Haemost*. 2022;6(1):e12657.
15. Lucijanic M, Krecak I, Soric E, et al. Patients with post polycythemia vera myelofibrosis might experience increased thrombotic risk in comparison to primary and post essential thrombocythemia myelofibrosis. *Leuk Res*. 2022;119:106905.
16. Kc D, Falchi L, Verstovsek S. The underappreciated risk of thrombosis and bleeding in patients with myelofibrosis: a review. *Ann Hematol*. 2017;96(10):1595-1604.
17. Barbui T, Carobbio A, Cervantes F, et al. Thrombosis in primary myelofibrosis: incidence and risk factors. *Blood*. 2010;115(4):778-782.
18. Tefferi A, Rumi E, Finazzi G, et al. Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study. *Leukemia*. 2013;27(9):1874-1881.

19. Tefferi A, Guglielmelli P, Larson DR, et al. Long-term survival and blast transformation in molecularly annotated essential thrombocythemia, polycythemia vera, and myelofibrosis. *Blood*. 2014;124(16):2507-2513.
20. Abu-Zeinah K, Saadeh K, Silver RT, Scandura JM, Abu-Zeinah G. Excess mortality in younger patients with myeloproliferative neoplasms. *Leuk Lymphoma*. 2023;64(3):725-729.
21. Tefferi A, Barbui T. Polycythemia vera: 2024 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2023;98(9):1465-1487.
22. Barbui T, Vannucchi AM, Buxhofer-Ausch V, et al. Practice-relevant revision of IPSET-thrombosis based on 1019 patients with WHO-defined essential thrombocythemia. *Blood Cancer J*. 2015;5(11):e369.
23. Haider M, Gangat N, Lasho T, et al. Validation of the revised International Prognostic Score of Thrombosis for Essential Thrombocythemia (IPSET-thrombosis) in 585 Mayo Clinic patients. *Am J Hematol*. 2016;91(4):390-394.
24. Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). *Blood*. 2010;115(9):1703-1708.
25. Tefferi A, Guglielmelli P, Nicolosi M, et al. GIPSS: genetically inspired prognostic scoring system for primary myelofibrosis. *Leukemia*. 2018;32(7):1631-1642.
26. Guglielmelli P, Lasho TL, Rotunno G, et al. MIPSS70: mutation-enhanced international prognostic score system for transplantation-age patients with primary myelofibrosis. *J Clin Oncol*. 2018;36(4):310-318.
27. Mora B, Guglielmelli P, Kuykendall A, et al. Prediction of thrombosis in post-polycythemia vera and post-essential thrombocythemia myelofibrosis: a study on 1258 patients. *Leukemia*. 2022;36(10):2453-2460.
28. Barbui T, Ghirardi A, Carobbio A, et al. Increased risk of thrombosis in JAK2 V617F-positive patients with primary myelofibrosis and interaction of the mutation with the IPSS score. *Blood Cancer J*. 2022;12(11):156.
29. Passamonti F, Giorgino T, Mora B, et al. A clinical-molecular prognostic model to predict survival in patients with post polycythemia vera and post essential thrombocythemia myelofibrosis. *Leukemia*. 2017;31(12):2726-2731.
30. Krecak I, Skelin M, Verstovsek S. Evaluating ropeginterferon alfa-2b for the treatment of adults with polycythemia vera. *Expert Rev Hematol*. 2023;16(5):305-316.
31. Alvarez-Larrán A, Pereira A, Guglielmelli P, et al. Antiplatelet therapy versus observation in low-risk essential thrombocythemia with a CALR mutation. *Haematologica*. 2016;101(8):926-931.
32. Marchioli R, Finazzi G, Specchia G, et al; CYTO-PV Collaborative Group. Cardiovascular events and intensity of treatment in polycythemia vera. *N Engl J Med*. 2013;368(1):22-33.
33. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med*. 2012;366(9):799-807.
34. Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med*. 2012;366(9):787-798.
35. Lucijanic M, Galusic D, Soric E, et al. Ruxolitinib treatment improves muscle mass in patients with myelofibrosis. *Ann Hematol*. 2021;100(4):1105-1106.
36. Palandri F, Al-Ali HK, Guglielmelli P, Zuurman MW, Sarkar R, Gupta V. Benefit of early ruxolitinib initiation regardless of fibrosis grade in patients with primary myelofibrosis: a post hoc analysis of the single-arm phase 3b JUMP study. *Cancers (Basel)*. 2023;15(10):2859.
37. Barbui T, Tefferi A, Vannucchi AM, et al. Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet. *Leukemia*. 2018;32(5):1057-1069.
38. Marchetti M, Vannucchi AM, Griesshammer M, et al. Appropriate management of polycythaemia vera with cytoreductive drug therapy: European LeukemiaNet 2021 recommendations. *Lancet Haematol*. 2022;9(4):e301-e311.
39. Harrison CN, Nangalia J, Boucher R, et al. Ruxolitinib versus best available therapy for polycythemia vera intolerant or resistant to hydroxycarbamide in a randomized trial. *J Clin Oncol*. 2023;41(19):3534-3544.
40. Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. *N Engl J Med*. 2015;372(5):426-435.
41. Mancuso S, Santoro M, Accurso V, et al. Cardiovascular risk in polycythemia vera: thrombotic risk and survival: can cytoreductive therapy be useful in patients with low-risk polycythemia vera with cardiovascular risk factors? *Oncol Res Treat*. 2020;43(10):526-530.
42. Cerquozzi S, Barraco D, Lasho T, et al. Risk factors for arterial versus venous thrombosis in polycythemia vera: a single center experience in 587 patients. *Blood Cancer J*. 2017;7(12):662.
43. Sørensen AL, Knudsen TA, Skov V, et al. Smoking impairs molecular response, and reduces overall survival in patients with chronic myeloproliferative neoplasms: a retrospective cohort study. *Br J Haematol*. 2021;193(1):83-92.
44. Krečak I, Holik H, Coha B, et al. Low-density lipoprotein (LDL) and the risk of thrombotic events in essential thrombocythemia and polycythemia vera. *Ann Hematol*. 2021;100(5):1335-1336.
45. Lekovic D, Gotic M, Sefer D, Mitrovic-Ajtic O, Cokic V, Milic N. Predictors of survival and cause of death in patients with essential thrombocythemia. *Eur J Haematol*. 2015;95(5):461-466.
46. Furuya C, Hashimoto Y, Morishita S, et al. Reevaluation of cardiovascular risk factors for thrombotic events in 580 Japanese patients with essential thrombocythemia. *J Thromb Thrombolysis*. 2023;55(2):263-272.
47. Lekovic D, Gotic M, Milic N, et al. The importance of cardiovascular risk factors for thrombosis prediction in patients with essential thrombocythemia. *Med Oncol*. 2014;31(10):231.
48. Horvat I, Boban A, Zadro R, et al. Influence of blood count, cardiovascular risks, inherited thrombophilia, and JAK2 V617F burden allele on type of thrombosis in patients with Philadelphia chromosome negative myeloproliferative neoplasms. *Clin Lymphoma Myeloma Leuk*. 2019;19(1):53-63.
49. Barbui T, Carobbio A, Rumi E, et al. In contemporary patients with polycythemia vera, rates of thrombosis and risk factors delineate a new clinical epidemiology. *Blood*. 2014;124(19):3021-3023.
50. Krečak I, Morić Perić M, Zekanović I, et al. No impact of the increased number of cardiovascular risk factors on thrombosis and survival in polycythemia vera. *Oncol Res Treat*. 2021;44(4):201-203.
51. Găman MA, Kipkorir V, Srichawla BS, Dhali A, Găman AM, Diaconu CC. Primary arterial hypertension and drug-induced hypertension in Philadelphia-negative classical myeloproliferative neoplasms: a systematic review. *Biomedicines*. 2023;11(2):388.
52. Landolfi R, Di Gennaro L, Barbui T, et al; European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP). Leukocytosis as a major thrombotic risk factor in patients with polycythemia vera. *Blood*. 2007;109(6):2446-2452.
53. Watson KV, Key N. Vascular complications of essential thrombocythaemia: a link to cardiovascular risk factors. *Br J Haematol*. 1993;83(2):198-203.
54. Randi ML, Fabris F, Cella G, Rossi C, Girolami A. Cerebral vascular accidents in young patients with essential thrombocythemia: relation with other known cardiovascular risk factors. *Angiology*. 1998;49(6):477-481.
55. Jantunen R, Juvonen E, Ikkala E, Oksanen K, Anttila P, Ruutu T. The predictive value of vascular risk factors and gender for the development of thrombotic complications in essential thrombocythemia. *Ann Hematol*. 2001;80(2):74-78.
56. Stein BL, Rademaker A, Spivak JL, Moliterno AR. Gender and vascular complications in the JAK2 V617F-positive myeloproliferative neoplasms. *Thrombosis*. 2011;2011:874146.
57. Krečak I, Holik H, Martina MP, Zekanović I, Coha B, Gverić-Krečak V. Chronic kidney disease could be a risk factor for thrombosis in essential thrombocythemia and polycythemia vera. *Int J Hematol*. 2020;112(3):377-384.
58. Lucijanic M, Galusic D, Krecak I, et al. Reduced renal function strongly affects survival and thrombosis in patients with myelofibrosis. *Ann Hematol*. 2020;99(12):2779-2785.
59. Gecht J, Tsoukakis I, Kricheldorf K, et al. Kidney dysfunction is associated with thrombosis and disease severity in myeloproliferative neoplasms: implications from the German Study Group for MPN Bioregistry. *Cancers (Basel)*. 2021;13(16):4086.
60. Krečak I, Lucijanić M, Gverić-Krečak V, Duraković N. Hyperuricemia might promote thrombosis in essential thrombocythemia and polycythemia vera. *Leuk Lymphoma*. 2020;61(7):1744-1747.
61. Lucijanic M, Krecak I, Galusic D, et al. Higher serum uric acid is associated with higher risks of thrombosis and death in patients with primary myelofibrosis. *Wien Klin Wochenschr*. 2022;134(3-4):97-103.
62. Benevolo G, Elli EM, Bartoletti D, et al. Impact of comorbidities and body mass index on the outcome of polycythemia vera patients. *Hematol Oncol*. 2021;39(3):409-418.
63. Barbui T, Finazzi G, Carobbio A, et al. Development and validation of an International Prognostic Score of thrombosis in World Health Organization-essential thrombocythemia (IPSET-thrombosis). *Blood*. 2012;120(26):5128-5133.
64. Guglielmelli P, Carobbio A, Rumi E, et al. Validation of the IPSET score for thrombosis in patients with prefibrotic myelofibrosis. *Blood Cancer J*. 2020;10(2):21.
65. Cortelazzo S, Finazzi G, Ruggeri M, et al. Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. *N Engl J Med*. 1995;332(17):1132-1136.

66. Barbui T, Vannucchi AM, De Stefano V, et al. Ropeginterferon alfa-2b versus phlebotomy in low-risk patients with polycythaemia vera (Low-PV study): a multicentre, randomised phase 2 trial. *Lancet Haematol*. 2021;8(3):e175-e184.
67. Kiladjian JJ, Klade C, Georgiev P, et al; PROUD-PV Study Group. Long-term outcomes of polycythemia vera patients treated with ropeginterferon alfa-2b. *Leukemia*. 2022;36(5):1408-1411.
68. Leiva O, Jenkins A, Rosovsky RP, Leaf RK, Goodarzi K, Hobbs G. Predictors of increased risk of adverse cardiovascular outcomes among patients with myeloproliferative neoplasms and atrial fibrillation. *J Cardiol*. 2023;81(3):260-267.
69. Krečak I, Grohovac D, Vučenović Bašić N, et al. Clinical presentation, treatment patterns, and outcomes of pulmonary embolism in patients with chronic myeloproliferative neoplasms [published online March 21, 2023]. *Thromb Res*. doi:10.1016/j.thromres.2023.03.004.
70. Krecak I, Sabljic A, Lucijanic M. Understanding and modifying thrombotic risk in patients with myeloproliferative neoplasms. *J Cardiol*. 2023;81(6):586.
71. Lucijanic M, Pejsa V, Jaksic O, et al. The degree of anisocytosis predicts survival in patients with primary myelofibrosis. *Acta Haematol*. 2016;136(2):98-100.
72. Krečak I, Krečak F, Gverić-Krečak V. High red blood cell distribution width might predict thrombosis in essential thrombocythemia and polycythemia vera. *Blood Cells Mol Dis*. 2020;80:102368.
73. Lucijanic M, Krecak I, Verstovsek S, et al. Higher red blood cell distribution width predicts thrombosis risk in primary and secondary myelofibrosis. *Ann Hematol*. 2022;101(6):1355-1357.
74. Verstovsek S, De Stefano V, Heidel FH, et al. US Optum Database Study in polycythemia vera patients: thromboembolic events (TEs) with hydroxyurea (HU) vs ruxolitinib switch therapy and machine-learning model to predict incidence of TEs and HU failure [ASH abstract 1659]. *Blood*. 2019;134(1)(suppl).
75. Lucijanic M, Veletic I, Rahelic D, et al. Assessing serum albumin concentration, lymphocyte count and prognostic nutritional index might improve prognostication in patients with myelofibrosis. *Wien Klin Wochenschr*. 2018;130(3-4):126-133.
76. Lucijanic M, Cicic D, Stoos-Veic T, et al. Elevated neutrophil-to-lymphocyte-ratio and platelet-to-lymphocyte ratio in myelofibrosis: inflammatory biomarkers or representatives of myeloproliferation itself? *Anticancer Res*. 2018;38(5):3157-3163.
77. Krečak I, Holik H, Morić Perić M, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as prognostic biomarkers in polycythemia vera. *Int J Lab Hematol*. 2022;44(4):e145-e148.
78. Krečak I, Zekanović I, Holik H, Morić Perić M, Coha B, Gverić-Krečak V. Estimating plasma volume using the Strauss-derived formula may improve prognostication in polycythemia vera. *Int J Lab Hematol*. 2022;44(2):e69-e71.
79. Lucijanic M, Krecak I, Soric E, et al. Higher estimated plasma volume status is associated with increased thrombotic risk and impaired survival in patients with primary myelofibrosis. *Biochem Med (Zagreb)*. 2023;33(2):020901.
80. Felker GM, Allen LA, Pocock SJ, et al; CHARM Investigators. Red cell distribution width as a novel prognostic marker in heart failure: data from the CHARM Program and the Duke Databank. *J Am Coll Cardiol*. 2007;50(1):40-47.
81. Lippi G, Plebani M. Red blood cell distribution width (RDW) and human pathology. One size fits all. *Clin Chem Lab Med*. 2014;52(9):1247-1249.
82. Verstovsek S, Krečak I, Heidel FH, et al. Identifying patients with polycythemia vera at risk of thrombosis after hydroxyurea initiation: the polycythemia vera-advanced integrated models (PV-AIM) project. *Biomedicines*. 2023;11(7):1925.
83. Landolfi R, Marchioli R, Kutti J, et al; European Collaboration on Low-Dose Aspirin in Polycythemia Vera Investigators. Efficacy and safety of low-dose aspirin in polycythemia vera. *N Engl J Med*. 2004;350(2):114-124.
84. Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2021 update on diagnosis, risk-stratification and management. *Am J Hematol*. 2020;95(12):1599-1613.
85. Mainoli B, Duarte GS, Costa J, Ferreira J, Caldeira D. Once- versus twice-daily aspirin in patients at high risk of thrombotic events: systematic review and meta-analysis. *Am J Cardiovasc Drugs*. 2021;21(1):63-71.
86. Lucijanic M, Skelin M, Kusec R. Second primary malignancies in myeloproliferative neoplasms and the role of aspirin. *Leukemia*. 2019;33(10):2554.
87. Barbui T, Ghirardi A, Vannucchi AM, Marchetti M, De Stefano V; MPN-K authors. Reply to: second primary malignancies in myeloproliferative neoplasms and the role of aspirin. *Leukemia*. 2020;34(4):1208-1209.
88. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140(11):e596-e646.
89. Davidson KW, Barry MJ, Mangione CM, et al; US Preventive Services Task Force. Aspirin Use to Prevent Cardiovascular Disease: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2022;327(16):1577-1584.
90. Berger JS. Aspirin for primary prevention-time to rethink our approach. *JAMA Netw Open*. 2022;5(4):e2210144.
91. American Diabetes Association Professional Practice Committee. 10. Cardiovascular disease and risk management: standards of medical care in diabetes-2022. *Diabetes Care*. 2022;45(suppl 1):S144-S174.
92. McNeil JJ, Nelson MR, Woods RL; ASPREE Investigator Group. Effect of aspirin on all-cause mortality in the healthy elderly. *N Engl J Med*. 2018;379(16):1519-1528.
93. Bowman L, Mafham M, Wallendszus K, et al; ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med*. 2018;379(16):1529-1539.
94. Gaziano JM, Brotons C, Coppolecchia R, et al; ARRIVE Executive Committee. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2018;392(10152):1036-1046.
95. Yusuf S, Joseph P, Dans A, et al; International Polycap Study 3 Investigators. Polypill with or without aspirin in persons without cardiovascular disease. *N Engl J Med*. 2021;384(3):216-228.
96. Akdi A, Özeke Ö, Karanfil M, et al. Diurnal rhythm of blood pressure in patients with polycythemia vera. *Blood Press Monit*. 2020;25(2):69-74.
97. Jóźwik-Plebanek K, Dobrowolski P, Lewandowski J, et al. Blood pressure profile, sympathetic nervous system activity, and subclinical target organ damage in patients with polycythemia vera. *Pol Arch Intern Med*. 2020;130(7-8):607-614.
98. Zidek W, Tenschert W, Karoff C, Vetter H. Treatment of resistant hypertension by phlebotomy. *Klin Wochenschr*. 1985;63(16):762-764.
99. Xiong XJ, Wang PQ, Li SJ. Blood-letting therapy for hypertension: a systematic review and meta-analysis of randomized controlled trials. *Chin J Integr Med*. 2019;25(2):139-146.
100. Ren Q, Lv X, Yang L, et al. Erythrocytosis and performance of HbA1c in detecting diabetes on an oxygen-deficient plateau: a population-based study. *J Clin Endocrinol Metab*. 2020;105(4):e1612-e1620.
101. Karsegard J, Wicky J, Mensi N, Caulfield A, Philippe J. Spurious glycohemoglobin values associated with hydroxyurea treatment. *Diabetes Care*. 1997;20(7):1211-1212.
102. Tsai WC, Hsu SP, Chiu YL, et al. Cardiovascular and renal efficacy and safety of sodium-glucose cotransporter-2 inhibitors in patients without diabetes: a systematic review and meta-analysis of randomised placebo-controlled trials. *BMJ Open*. 2022;12(10):e060655.
103. Gangat N, Abdallah M, Szuber N, et al. Sodium-glucose co-transporter-2 inhibitor use and JAK2 unmutated erythrocytosis in 100 consecutive cases. *Am J Hematol*. 2023;98(7):E165-E167.
104. Gangat N, Alkhateeb H, Reichard K, Tefferi A. Sodium-glucose co-transporter-2 inhibitor therapy and unmasking of JAK2-mutated myeloproliferative neoplasm: a Mayo Clinic series of nine consecutive cases [published online July 20, 2023]. *Am J Hematol*. doi:10.1002/ajh.27034.
105. Hasselbalch HC. Smoking as a contributing factor for development of polycythemia vera and related neoplasms. *Leuk Res*. 2015;39(11):1137-1145.
106. Daltro De Oliveira R, Soret-Dulphy J, Zhao L-P, et al. Interferon-alpha (IFN) therapy discontinuation is feasible in myeloproliferative neoplasm (MPN) patients with complete hematological remission [ASH abstract 483]. *Blood*. 2020;136(1)(suppl).
107. Mach F, Baigent C, Catapano AL, et al; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41(1):111-188.
108. Lucijanic M, Krecak I, Kusec R. Renal disease associated with chronic myeloproliferative neoplasms. *Expert Rev Hematol*. 2022;15(2):93-96.
109. Yu T, Weinreb N, Wittman R, Wasserman LR. Secondary gout associated with chronic myeloproliferative disorders. *Semin Arthritis Rheum*. 1976;5(3):247-256.
110. Tefferi A, Nicolosi M, Penna D, et al. Development of a prognostically relevant cachexia index in primary myelofibrosis using serum albumin and cholesterol levels. *Blood Adv*. 2018;2(15):1980-1984.
111. Mesa RA, Verstovsek S, Gupta V, et al. Effects of ruxolitinib treatment on metabolic and nutritional parameters in patients with myelofibrosis from COMFORT-I. *Clin Lymphoma Myeloma Leuk*. 2015;15(4):214-221.e1.