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Krečak, Ivan; Verstovsek, Srdan; Lucijanić, Marko

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Authors: Ivan Krecak, [1,2*], Srdan Verstovsek,[3] Marko Lucijanic [4,5]

Affiliations:

[1] Department of Internal Medicine, General Hospital of Sibenik-Knin County, Sibenik, Croatia

[2] Faculty of Medicine, University of Rijeka, Rijeka, Croatia

[3] Kartos Therapeutics, Redwood City, California, USA

[4] Divison of Hematology, University Hospital Dubrava, Zagreb, Croatia

[5] School of Medicine, University of Zagreb, Zagreb, Croatia

***Corresponding author**
Ivan Krecak, MD, PhD
e-mail: krecak.ivan@gmail.com
Department of Internal Medicine
General Hospital of Sibenik-Knin County
Stjepana Radića 83, 22000 Sibenik, Croatia

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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 strong prognostic impact regarding thrombotic risk in MPN patients. In this review, we summarized 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 which may be needed to appropriately manage CV risk factors in MPNs.

Keywords: myeloproliferative neoplasm; arterial hypertension; cardiovascular risk factor; diabetes mellitus; hyperlipidemia; smoking; chronic kidney disease

Introduction

Philadelphia-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 one or more mature myeloid cell lineages, presence of mutually exclusive driver mutations in the Janus Kinase 2 (JAK2), calreticulin (*CALR*) or thrombopoetin 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 (SMF) and acute myeloid leukemia (AML) [1,2,3,4]. Besides increased myeloproliferation, constitutive activation and dysregulation of the JAK-signal transducer and activator of 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 when compared to 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 3.5/100 person-years in PV, and 2.5/100 person-years in ET and MF patients [14]. For example, in the European Collaboration on Low-dose Aspirin (ECLAP) randomized clinical trial (RCT), the mortality due 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 patients is often underappreciated. This is mostly attributed to the fact that prognostication and treatment strategies in MF are primarily directed at estimating and minimizing the risk of death, respectively; as a result, proper understanding of the incidence and risk factors for thrombosis may be obscured. Nevertheless, thrombotic risk in MF is not negligible, especially among post-PV MF patients, and may be associated with similar risk factors as in ET and PV [15-17]. Due to the tendency for CV complications and disease progression, overall survival (OS) in all MPN patients is worse than 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 consensus is lacking in the medical community, and propose future directions which may be needed to appropriately manage CV risk factors in MPNs.

Current risk stratification and treatment of MPNs

The most important prognostic factors of future thrombotic events in MPN patients are age >60 years and prior thrombotic events. PV patients presenting either one of these two factors are classified as "high-risk" [21]. In ET, the presence of JAK2 mutation is additionally used to construct four risk categories in the Revised International Prognostic Score of Thrombosis in Essential Thrombocythemia (R-IPSET): very low (age ≤60 years, no prior thrombosis, and the absence of JAK2 mutation), low (age ≤60 years, no prior thrombosis, with JAK2 mutation present), intermediate (age >60 years, without prior thrombosis and without JAK2 mutation) and high-risk (prior thrombosis or age >60 years with the presence of 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 enabling risk prognostication of MF patients taking into consideration age, white blood cell count, hemoglobin, presence of constitutional symptoms, and peripheral blasts [24]. Although more recent prognostic systems for MF incorporate cytogenetic and molecular data [25-27], performance of these tests is costly, and the infrastructure may be unavailable at all clinical settings. With respect to CV risk, there seems to be an interaction between low-risk DIPSS and presence of JAK2 mutation, suggesting the necessity to intervene in lower risk MF patients [28]. The Myelofibrosis Secondary to Polycythemia and Thrombocythemia Prognostic Model (MYSEC-PM) is applied in post-PV and post-ET SMF patients 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 hydroxyurea (HU) or interferons (IFNs), is usually recommended in 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 <45%, because achieving this level significantly lowered the risk of adverse CV events in the Cytoreductive Therapy for PV (CYTO-PV), a randomized controlled trial (RCT) [32]. It is not known if JAK2 mutated patients without PV should also be phlebotomized if they have hematocrit levels above 45%. Patients with MF classified as intermediate-2/high-risk are at high risk of death and are considered for allogeneic stem cell transplant. Treatment with JAK inhibitors, such as ruxolitinib, is usually recommended prior to the procedure and in 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 PV patients who have HU-

resistance/intolerance [39,40]. Even low-risk MPN patients may benefit from specific therapy if they present with symptoms and require frequent phlebotomies [21].

Former databases and contemporary definitions and treatments for cardiovascular comorbidities in MPNs

A variety of generic CV risk factors were extensively investigated in MPN pateints, including arterial hypertension (AH) [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 (CKD) [57-59], hyperuricemia [60,61], and obesity and cachexia [62]. They were evaluated either as individual entities, grouped with other CV risk factors, or as a cumulative comorbidity burden.

In contrast to R-IPSET[22,23], the original IPSET [63] included CV risk factors - AH, 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 have the potential to reduce life expectancy in MPNs, these factors have not been formally 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 for evaluation of CV risk factors is the large timespan of evaluation and the consequent heterogeneity in patients considering the definition and treatment of CV comorbidities. Studies on 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 of time. These changes may affect the validity of the conclusions regarding the way that comorbidities (considered with the diagnostic criteria of that time) contributed to thrombotic risk compared to the present criteria. For example, in 1995, an RCT [65] set the threshold for DM as fasting glucose >7.8 mmol/L (140 mg/dL) and a high lipid profile when the total cholesterol >6.2 mmol/L (240 mg/dL); however, currently, these cut-off values are 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 (ACE) 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 >20 year-old datasets are accurate in contemporary MPN cohorts when compared to "placebo plus best of care" according to today's standards.

Another issue with retrospective registries is that CV comorbidities were often been defined at *any time* during the follow-up period. In these cases, the 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 patients bearing a comorbidity. The same may apply for mutation testing and exposure to specific drugs.

Ideally, firm evidence is generated from RCTs that enable prospective follow-up, pre-defined protocols, procedures, and outcomes. On the other hand, 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, were quite infrequent in MPN patients treated with contemporary cytoreductive treatments in more recent RCTs [33,40,66,67]; thus, limiting the statistical power to assess the potential antithrombotic effect of different cytoreductive treatments.

Due to 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 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 demonstrated that the prognostic scoring systems developed for CV prognostication in the general population, such as the CHA2DS2-VASC in atrial fibrillation (AF) or 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].

A number of 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 (RDW) [71-74], lymphocyte and neutrophil count and percentage, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) [75-77], estimated plasma volume status (ePVS) [78,79], are very useful. These are non-MPN specific variables, which bear prognostic importance regarding the thrombotic risk in persons with CV comorbidities from the general population [80]. However, caution regarding 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 RDW, lymphocyte and neutrophil percentage as parameters with strong prognostic properties regarding thrombotic risk in HU-treated PV patients [82]. Nevertheless, additional research is still needed to fully understand whether clinical decisions can rely on these surrogates 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, which were 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 (100 mg daily) in comparison to placebo. However, the same trial did not demonstrate significant benefit regarding overall or CV mortality as isolated outcomes.

Aspirin is currently recommended to 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) [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 due to other comorbid conditions where aspirin is considered a standard of care. Per recent guidelines, PV and ET patients stratified to 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, these surrogate measurements of thrombotic risk did not translate into reduced thrombotic risk, and randomized or real-life data demonstrating its usefulness 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 secondary prevention of thrombotic events and is strongly recommended in this context [88]. However, until recently, aspirin was widely used for the purpose of primary prevention of thrombotic events in the general population based on convincing early evidence, i.e., early RCTs of aspirin use in primary prevention of CV complications showed benefit in large populations with 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 only be considered as a primary prevention strategy of CV complications in patients who are at increased CV risk but after a comprehensive discussion with the patient regarding the benefits versus the increased risk of bleeding [91].

Four large primary prevention trials performed in the last few years revealed additional considerations. The ASPREE RCT randomized a total of 19,114 healthy elderly patients to aspirin (100 mg daily) or placebo, which were administered to evaluate dementia-free and disability-free survival. The study did not find benefit in the outcomes but surprisingly, the investigators reported an increased mortality associated with aspirin use, driven by 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 the properties of aspirin. The ASCEND RCT randomized 15,480 patients with DM to aspirin (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, without survival benefit [93]. The ARRIVE RCT randomized 12,546 middle-aged and older adults at intermediate risk for atherosclerotic CV disease without DM and did not find a significant difference in the number of CV events or survival between the groups, but reported twofold increase in the gastrointestinal bleeding risk [94]. The TIPS-3 RCT randomized (using a 2x2x2 factorial design) 5,713 patients without CV disease but with elevated CV risk; the patients received a polypill containing statins and antihypertensive medications or placebo daily, aspirin (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 to the placebo; also, no significant differences were observed for aspirin only compared to placebo regarding CV outcomes, death, and bleeding [95]. In the aforementioned first three 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.

Considering the new studies questioning the benefits of aspirin in prevention of diseases in the general population, the role and dosing of aspirin in preventing thrombotic events in

MPN patients should be critically re-evaluated 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 cardiovascular risk factors in MPN patients

The optimal management of CV risk factors in MPN patients is currently unknown and usually mirrors the experience from the general population. The underlying pathophysiological 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.

AH in MPN patients has less variation during blood pressure measurements, higher occurrence of non-dipper phenotype and lower sympathetic nervous system activity [96,97]. On the other hand, AH may also diminish after the start of phlebotomies, 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 due to 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].

Smoking-induced inflammation and its carcinogenic potential may promote the development of MPNs [102], impair treatment responses, and negatively affect survival [103].

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 <1.8 mmol/L are associated with 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 [104].

CKD is highly prevalent among MPN patients and was shown to bear high trombotic risk for both arterial and venous thrombotic events in MPNs [57-59]. This is of particular interest due to its possible association with MPN-related glomerulopathy, the MPN manifestation at the level of glomeruli [105].

Hyperuricemia reflects higher cellular turnover, nutritional habits and kidney function, and is associated with the occurrence of gout and increased CV risk among MPN patients [60,61,106]. Due to lack of recognition by current treatment guidelines and the unknown optimal treatment target levels, urate-lowering therapies are usually prescribed to MPN patients on an individual basis.

Obesity and cachexia, on the different sides of body mass index (BMI) spectrum, bear specific risks in MPN patients. It is unclear whether more favorable outcomes associated with higher BMI 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 outcomes of MPN patients [75,107] and can be reverted with specific therapies [35], calling for clinical trials specifically focusing on nutritional support in MPNs.

Conclusion and perspectives

Thrombotic risk dominates the 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 into the well established MPN-specific prognostic scores due to a variety of reasons which we have elaborated above. It should be pointed out, however, that CV comorbidities may share common pathophysiological mechanisms with MPNs and require simultaneous and focused medical care. Significant advances in the understanding of the molecular biology in MPNs have led to development of integrated clinical and molecular prognostic scores which have provided a more refined prognostication of MPNs. Introduction of targeted treatments in MPNs, such as JAK inhibitors (i.e., ruxolitinib, fedratinib, momelotinib), and more potent and less toxic IFNs (i.e., ropeginterferon-alfa2b) has revolutionized the therapeutic landscape in MPNs. Unfortunately, diagnostic and MPN-specific therapeutic progresses may have also caused CV comorbidities to occasionally leave the primary focus of hematologists.

Exploratory post hoc analyses of the current RCT where treatment responses and clinical outcomes of MPN patients are stratified according to particular CV risk factors would be a great way to start. Also, multi-institutional international collaborations ("big data") with the help of new technologies (i.e, artificial intelligence) may represent an exciting approach to create MPN-specific risk scores for particular CV comorbidities and to determine the optimal target values of different metabolic parameters (i.e., LDL, Hba1c, or serum uric acid) in MPN patients. Finally, RCT in MPN patients using contemporary and potent medications (i.e., statins, PCSK9 inhibitors, ACE inhibitors, SGLT2 inhibitors and others) for the treatment of different CV comorbidities (on top of MPN-specific treatments) may be needed to establish new standards of care.

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