Reappraisal of Cardiovascular Risk Factors in Patients With Chronic Myeloproliferative Neoplasms

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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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