Vascular Health and Risk Management

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REVIEW

Diagnosis and Management of Cardiovascular Risk in Patients with Polycythemia Vera

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Abstract: Polycythemia vera (PV) is a myeloproliferative neoplasm characterized by aberrant myeloid lineage hematopoiesis with excessive red blood cell and pro-inflammatory cytokine production. Patients with PV present with a range of thrombotic and hemorrhagic symptoms that affect quality of life and reduce overall survival expectancy. Thrombotic events, transformation into acute myeloid leukemia, and myelofibrosis are largely responsible for the observed mortality. Treatment of PV is thus primarily focused on symptom control and survival extension through the prevention of thrombosis and leukemic transformation. Patients with PV frequently experience thrombotic events and have elevated cardiovascular risk, including hypertension, dyslipidemias, obesity, and smoking, all of which negatively affect survival. To reduce the risk of thrombotic complications, PV therapy should aim to normalize hemoglobin, hematocrit, and leukocytosis and, in addition, identify and modify cardiovascular risk factors. Herein, we review what is currently known about the associated cardiovascular risk and propose strategies for diagnosing and managing patients with PV.

Plain Language Summary: Patients with the myeloproliferative neoplasm (MPN) polycythemia vera (PV) are at increased risk of cardiovascular (CV) events, including stroke, heart attacks, and peripheral arterial disease. High blood pressure, smoking, and dyslipidemia are common in MPN and contribute to the increased cardiovascular risk. Effectively controlling cardiovascular risk factors in PV, along with appropriate hematological therapy such as direct-acting oral anticoagulants alone or in combination with aspirin, may improve the outcomes of patients with PV, but further research is needed.

Keywords: cardiovascular risk, myeloproliferative neoplasms, polycythemia vera, thrombosis

Introduction

Polycythemia vera (PV) is a hematological disorder classified under myeloproliferative neoplasms (MPN) by the World Health Organization (WHO). Although there are seven subcategories under the MPN category, the term "MPN" is commonly reserved for the three pathological entities that lack the Philadelphia chromosome (Ph-) but carry mutations in the Janus kinase 2 (*JAK2*), calreticulin (*CALR)* or proto-oncogene, thrombopoietin receptor (*MPL)* genes. In addition to PV, these include essential thrombocythemia (ET), and primary myelofibrosis (PMF), and represent clonal proliferations arising in stem cells. The most frequent *JAK2* mutation associated with Ph-MPN is in exon 14 and is *JAK2V617F*.[1,2]

Clinical symptoms of PV include fatigue and itching, microvascular symptoms (eg headaches, visual disturbances, lightheadedness, paresthesia, and atypical chest discomfort), and features such as splenomegaly, hyperviscosity, leukocytosis, thrombocytosis, thrombotic and bleeding complications. PV may progress into acute myeloid leukemia or secondary myelofibrosis.[3]

Received: 30 August 2023
Accepted: 4 November 2023
Published: 22 November 2023

Patients with Ph-MPN frequently experience thrombotic events. A pooled prevalence of 20% for thrombotic events (either arterial 16.2% or venous 6.2%) at diagnosis of Ph-MPN (PV – 28.6%) was identified by a recent meta-analysis.[4] This included stroke (7.4%), transient ischemic attack (3.5%), acute ischemic heart disease (6.1%), acute peripheral ischemia (3.3%), deep vein thrombosis (3.4%) and pulmonary embolism (0.9%). Atypical anatomical site thromboses are also characteristic of Ph-MPN. They include splanchnic vein thrombosis or cerebral sinus thrombosis.[5]

In the European Collaboration on Low-dose Aspirin (ECLAP) study,[6] the most extensive PV epidemiological study conducted to date (N = 1638), thrombotic events were responsible for 41% of mortality (1.5 deaths/100 patients/year). They consisted mainly (70%) of arterial thrombosis (acute coronary syndromes, ischemic stroke, and peripheral arterial thrombosis). In this study, 587 patients (36%) had evidence of a thrombotic event at diagnosis, whereas 169 patients (10%) experienced a thrombosis during follow-up.

Heart or vascular disease and stroke are also observed in the general population and are correlated with cardiovascular (CV) risk factors, including weight control behaviors and smoking, and health factors such as blood pressure, cholesterol level, and glucose control. In the yearly update of heart disease, stroke, and CV risk factors that contribute to CV health, the American Heart Association (AHA) recently reported that the prevalence of CV risk factors observed in the general population was 13.3%, 41.4%, 32.8%, 46%, and 10.6% for smoking, obesity, total cholesterol ≥200 mg/dL, hypertension, and diabetes, respectively.[7]

It is not easy to critically appraise the relationship between PV and CV risks. The results obtained from studies of MPN patient cohorts have the advantage of analyzing real-world evidence and therefore produce reliable conclusions. However, in the case of thrombosis, which arises due to the interaction of many factors, it is not easy to understand which factor is primarily responsible for the thrombotic phenotype. Studies comparing PV/MPN patients with and without thrombosis could provide more precise information. However, the few such studies do not always allow comparisons between patients with similar characteristics, as MPNs are heterogeneous diseases characterized by different mutations and a diverse hematological picture. Retrospective analyses using data from electronic patient records often do not detail information on parameters such as blood pressure, weight, diabetes, smoking, mutation status, and therapy. Furthermore, there is some debate regarding whether elevated CV risk factors in patients with PV has a negative impact on clinical outcomes independent of factors such as advanced age, history of thrombosis, or leukocytosis. Cardiovascular risk factors are not incorporated into risk prognostication systems such as those of the European LeukemiaNet (ELN), who do not consider the evidence sufficiently robust to differentiate the risk in patients with PV versus that in the general population.[8,9]

Another risk of bias can be represented by the fact that patients with MPNs are subjected to more stringent check-ups than healthy individuals and it is, therefore, feasible that problems that would otherwise remain undiagnosed in the normal population are detected in the MPN population. For this reason, a higher number of subjects with CV conditions (stroke, heart attack, and peripheral arterial diseases) and a higher number of CV risk factors (obesity, hypertension, and diabetes) are observed in MPN patients than in age-matched controls.

Therefore, a multidisciplinary approach that considers not only the hematological features of the disease but also internist and cardiological ones should be implemented when managing patients with PV. Similarly to the paper recently published for essential thrombocythemia,[10] this review aims to assist in the multidisciplinary management of the PV patient.

Cardiovascular Risk Factors and Risk of Thrombosis in Polycythemia Vera

Evidence shows that conventional CV risk factors are frequent in patients with Ph-MPN (Table 1): arterial hypertension is reported in 39–70% of patients with PV,[6,11–13] diabetes mellitus in 7–16%,[6,12,13] dyslipidemia in 15–38%,[6,12,13] obesity in 7.5%,[13] and a smoking habit in 10–15%.[6,12,13] About three-quarters of patients with PV possess at least one CV risk factor and 37.7% have more than one CV risk factor.[12,13] The most dangerous complication of CV disease (CVD) is thrombosis[14] which is also a serious complication of PV.[3] However, how classical CV risk factors contribute to the incidence of thrombotic events in patients with Ph-MPN is not fully understood. In the ECLAP study, smoking, but not arterial hypertension or diabetes mellitus, was associated with a greater risk of arterial events during follow-up.[6] Other studies have shown that arterial hypertension represents an independent risk factor in patients with low-risk PV.[11] In

Table 1 Cardiovascular Risk Factors in Polycythemia Vera

Risk Factor	Notes	Reference
Polycythemia vera-specific:		
Clonal hematopoiesis	Epidemiological and experimental evidence supports the hypothesis that immune cell dysfunction mediated by clonal hematopoiesis is a risk factor for heart failure and CVD. Individuals with clonal hematopoiesis supported by the DNMT3A, TET2, ASXL1, or JAK2 (JAK2V617F) mutation are at increased risk of developing coronary heart disease after adjusting for classic CV risk factors.	[17,18]
Generic:		
Smoking	Smoking facilitates the phenomenon of atherosclerosis and thrombotic phenomena. The risk of CV events doubles in smokers. In individuals under age 50, smoking increases the risk of CV events by 4–5 times. Passive smoking increases CV risk by 30%.	[19]
Blood pressure	Arterial hypertension is the main risk factor for ischemic heart disease, heart failure, cerebrovascular diseases, atrial fibrillation, and chronic renal failure.	[19]
Cholesterol	High levels of LDL-C produce atherosclerosis and are correlated with high CV risk.	[20]
Body weight	Being overweight and obesity are both associated with an increased risk of CVD because of hypertension, dyslipidemia, insulin resistance, systemic inflammation and prothrombotic status which increase the incidence of CVD and secondary events.	[21]
Diabetes mellitus	Diabetes mellitus is a major risk factor for CVD, while CVD is the major cause of death in patients with diabetes mellitus.	[22]
Diet	Alimentary habits impact CV risk and the risk of other chronic diseases such as cancer.	[21]
Physical activity	Sedentary (<0.5 h/week of physical activity) lifestyle is recognized as one of the major CV risk factors.	[21]

Abbreviations: ASXL1, ASXL transcriptional regulator 1; CV, cardiovascular; CVD, cardiovascular disease; DNMT3A, DNA methyltransferase 3 alpha; JAK2, Janus kinase 2; LDL-C, low-density lipoprotein cholesterol; TET2, tet methylcytosine dioxygenase 2.

a Japanese real-world study, the presence of CV conditions (diabetes, hypertension, and hyperlipidemia) significantly increased the risk of thromboembolic events in both univariate and multivariate analyzes.[15] These results have also been confirmed in a Brazilian study.[16] Importantly, there is a significant worsening of survival as the number of CV risk factors in PV increases.[13]

Recently, studies have shown that hematopoietic and immune cells from the bone marrow play key roles in the onset and progression of CVD. Clonal expansion of bone marrow hematopoietic stem and progenitor cells carrying somatic gene mutations, described as clonal hematopoiesis, has been shown by genetic analysis to be common in healthy individuals not otherwise showing any hematologic disorders.[17,18,23] The finding is present in up to 10% of the general population and increases with age, and it is becoming apparent that clonal hematopoiesis is a significant risk factor for CVD as distinct from a cumulative incident risk of blood cancers. *JAK2V617F* and Tet methylcytosine dioxygenase 2 (*TET2*) are the most important mutations in clonal hematopoiesis. Hematopoietic cell clones that harbor *JAK2V617F* or *TET2* are associated with the pathogenesis of CVD (Table 1).[17,18,23]

The risk of arterial thrombotic events in PV is higher than that for venous events.[24] The accepted risk factors for thrombosis are "age >60" and "past thrombotic events".[25] In fact, the two factors allow for the classification of patients into low-risk (in the absence of both factors) or high-risk (in their presence), guiding therapeutic choices. In a study conducted by the International Working Group on Myeloproliferative Neoplasms Research and Treatment, prior arterial events, hyperlipidemia, and hypertension were predictive of future arterial events. By contrast, prior venous events, leukocytosis $\geq 11 \times 10^9$/L, and a major hemorrhagic event predicted future venous events. Arterial thrombosis was associated with age ≥60 years, hypertension, diabetes, hyperlipidemia, and a normal karyotype, whereas venous thrombosis was associated with age ≤60 years, palpable splenomegaly, female sex, and a history of major

hemorrhage.[26] In some studies, the allele burden of the *JAK2V617F* variant has been identified as a potential risk factor for thrombosis in MPN patients.[27]

In the absence of further evidence, it seems intuitive to conclude that patients with Ph-MPN need to be assessed to identify classical modifiable CV risk factors (smoking, hypercholesterolemia, arterial hypertension), with the scope of optimizing their baseline risk profile, to which the excess risk caused by the hematological disease is added.

Cardiovascular Risk Assessment

The 2021 guidelines issued by the European Association of Preventive Cardiology/European Society of Cardiology (EAPC/ESC) recommend systematic global CVD risk assessment in persons with any major vascular risk factor (such as family history of premature CVD or familial hypercholesterolemia, smoking, arterial hypertension, diabetes mellitus, raised lipid levels, obesity, or in those with comorbidities increasing CVD risk; recommendation Class I, evidence level A).[21] Given that PV patients have an excess of 1.7% thrombotic events per patient/year at follow-up, even when treated according to the best standard of antithrombotic therapy (phlebotomy and acetylsalicylic acid; ASA),[28] PV should be considered a comorbidity that increases CV risk, comparable to other disorders increasing CV risk, such as diabetes mellitus and chronic kidney disease (CKD).

Therefore, we propose to stratify the CV risk in patients with PV, similarly to what was done in other hematological disorders (eg chronic myelogenous leukemia)[29] according to the EAPC/ESC guidelines.[21]

An initial evaluation of CV risk is done on the basis of anamnesis (Table 2). In particular, data on the presence of CVD and major risk factors (history of a CV event, diabetes mellitus, peripheral arteriopathy, CKD, resistant arterial hypertension, atrial fibrillation and left ventricle hypertrophy) must be collected. Also, the factors that modify CV risk must be identified. These include a family history of CVD, obesity, physical inactivity, psychiatric disease, autoimmune or inflammatory disorders, the use of antivirals, and obstructive sleep apnea syndrome. Risk assessment is further performed with the use of laboratory and instrumental examinations (Table 3). For patients with no CVD, CKD or diabetes mellitus, the Systematic COronary Risk Estimation 2 (SCORE2) algorithm estimates the 10-year risk of fatal/non-fatal CVD events in apparently healthy individuals aged 40–69. For individuals over 69, SCORE2-Older Persons (SCORE2-OP) is used.[30]

A comprehensive assessment of CV risk factors is at the basis of patient management, aiming at diminishing risk. CV risk assessment should be performed annually.[31]

Measures to Modify Cardiovascular Risk and Risk of Thrombosis

Modifying the CV risk profile in PV patients includes lifestyle modifications and pharmaceutical management of arterial hypertension and dyslipidemias (Figure 1).

Lifestyle Modifications

Stopping smoking is the most important of all CV risk-reducing measures. Smoking has been shown to reduce treatment response and overall survival in MPN,[32] and the EAPC/ESC 2021 guidelines recommend that all smokers should be convinced to quit smoking, with similar benefits seen when passive smoking ceases. Patients should also be instructed on a correct diet (reduced saturated fat, salt, and sugar, increased dietary fiber) and alcohol consumption limitations. Moreover, patients must be encouraged to engage in regular physical exercise and control their weight.[21]

Arterial Hypertension

While no specific guidelines exist for treating hypertension in PV patients, lifestyle modifications are recommended for all patients. The ESC/European Society of Hypertension (ESH) 2018 guidelines recommend that patients with PV and arterial hypertension should be treated with angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II receptor antagonists (ARB) with or without calcium channel blockers to obtain a blood pressure reduction to the target of <130 (or less if tolerated)/80 mmHg. The therapeutic goal for arterial hypertension may vary according to the patient's age with comorbidities (Table 4). Data analysis of hypertensive PV patients in the ECLAP study showed that patients treated with an ACE-I had a significantly lower need for cytoreductive therapy than those using other antihypertensive agents. The

Table 2 Cardiovascular Risk Determination Based on Anamnesis with Indications of Who Should Treat the patient[21]

Anamnesis	Yes?	Risk level	Treater
Past myocardial infarction	□	**Very high risk**	**Referral to a specialist cardiology/hypertension center**
Coronary or other arterial revascularization procedures	□		
ACS and other arterial atherosclerotic occlusions	□		
Past stroke or transient ischemic attack	□		
Aorta aneurism	□		
Peripheral artery disease	□		
Diabetes mellitus:	□		
• With organ damage (proteinuria)	□		
• With other major risk factor:	□		
✓ uncontrolled grade 3 hypertension			
✓ severe dyslipidemia			
✓ smoking			
Severe CKD (GFR<30 mL/min/1.73 m^2)	□		
Age <50 years and SCORE2 ≥7.5%	□		
Age 50–69 years and SCORE2 ≥10.0%	□		
Age ≥70 years and SCORE2-OP ≥15.0%	□		
Markedly elevated single risk factor:	□	**High risk**	**Consider a referral to a specialist cardiology/ hypertension center**
• Uncontrolled grade 3 hypertension			
• Severe dyslipidemia			
• Smoking			
Diabetes mellitus:	□		
• Without organ damage (without proteinuria or neuropathy)	□		
• Duration ≥10 years			
• With additional risk factor			
Moderate CKD (GFR 30–59 mL/min/1.73 m^2)	□		
Age <50 years and SCORE2 2.5–7.49%	□		
Age 50–69 years and SCORE2 5–9.99%	□		
Age ≥70 years and SCORE2-OP 7.5–14.99%	□		
TT echocardiogram:			
Left ventricular hypertrophy (LVMi >95 g/m^2 [F] or ≥115 g/m^2 [M])	□		
GLS > –18% or EF <52/54 M/F or altered kinetics	□		
Resistant hypertension (not controlled by 3 drugs including a diuretic at full dose)	□		
Diabetes mellitus:	□	**Moderate risk**	**GP**
Type 1 and age <35 years			
Type 2 and age <50 years			
Diabetes duration >10 years, without additional risk factors			
Age <50 years and SCORE2 <2.5%	□	**Low risk**	**GP**
Age 50–69 years and SCORE2 <5.0%	□		
Age ≥70 years and SCORE2-OP <7.5%	□		

Notes: Very High Risk High Risk Moderate Risk Low Risk.

Abbreviations: ACS, acute coronary syndrome; CKD, chronic kidney disease; EF, ejection fraction; F, female; GFR, glomerular filtration rate; GLS, global longitudinal strain; GP, general practitioner; LVMi, left ventricular mass index; M, male; SCORE2, Systematic COronary Risk Evaluation 2; SCORE2-OP, Systematic COronary Risk Evaluation 2 in Older Persons; TT, transthoracic.

authors suggested a possible role of ACE-I is controlling the marrow renin-angiotensin system, which has a role in the mechanisms of erythropoiesis and is activated in clonal forms.[33,34] This link with renin-angiotensin system expression in bone marrow may also partly explain reductions in thrombotic complications observed in PV patients with arterial hypertensive treated with ACE-I or ARB.[35] ACE inhibitors have also been shown to improve kidney function in PV patients, as evidenced by improvements in estimated glomerular filtration rate, suggesting renoprotective properties.[36]

Table 3 Laboratory and Instrumental Examinations to Assess Cardiovascular Risk

First-line hemato-chemical examinations
Creatinine, Na and K
Creatinine clearance
Total cholesterol
HDL-C
Triglycerides
Glycemia
HbA1c (in patients with diabetes mellitus)
Albuminuria/creatininuria (to be carefully evaluated in patients with plasma cell dyscrasias)
Uricemia, iron levels
Instrumental examinations
Electrocardiogram
Echocardiogram with the assessment of systolic function and of the left ventricle mass
Home blood pressure monitoring
ABPM in patients with arterial hypertension

Abbreviations: ABPM, ambulatory 24-hour blood pressure monitoring; HbA1c, glycated hemoglobin; HDL-C, high density lipoprotein cholesterol; K, potassium; Na, sodium.

The use of ACE-I is to be preferred in patients with PV and arterial hypertension if no contraindications exist. A beta-blocker can be added (or maintained, as in the case of coexisting ischemic heart disease) in order to obtain the blood pressure target.[37] In the presence of diabetes mellitus, microalbuminuria, or frank proteinuria, antihypertensive agents that act on the renin-angiotensin system are preferred.[37] There are no data on the safety of diuretics in patients with PV; however, it may be prudent to limit their use in patients with elevated hematocrit (Ht) values. In the case of resistant hypertension, after evaluating compliance and excluding other secondary causes, further therapeutic possibilities are represented by introducing mineralocorticoid receptor antagonists (spironolactone/canrenone) or alpha-1 blockers.

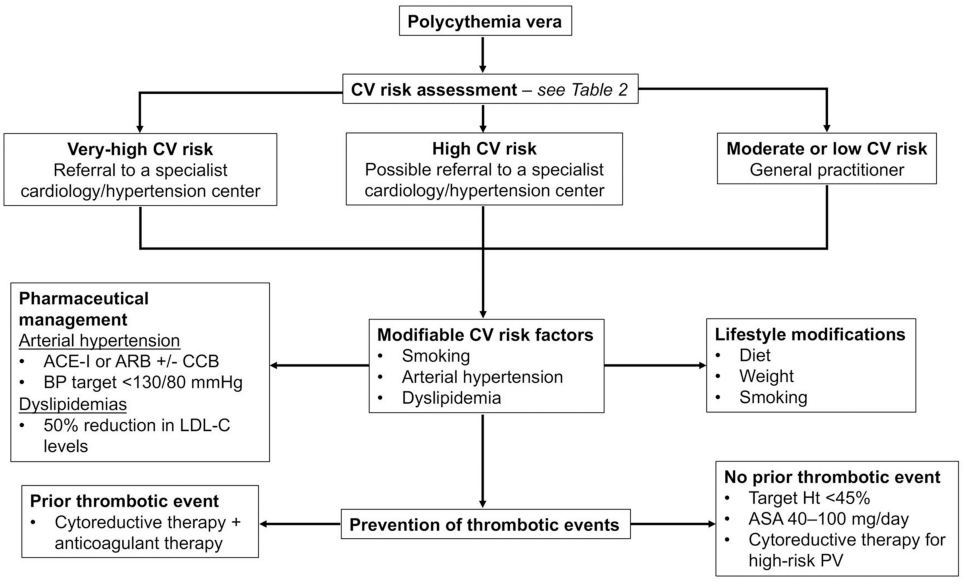

Figure 1 Flow diagram for the diagnosis and management of the cardiovascular risk profile and prevention of thrombotic events in patients with PV.
Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor antagonists; ASA, acetylsalicylic acid; BP, blood pressure; CCB, calcium channel blockers; CV, cardiovascular; Ht, hematocrit; LDL-C, low density lipoprotein cholesterol; PV, polycythemia vera.

Table 4 Therapeutic Goals for Modifiable Cardiovascular Risk Factors

Risk Factor	Target	Notes
Systolic blood pressure		
18–65 years	**130 mmHg**	Standard target
>65 years	**130–139 mmHg**	If tolerated
Diastolic blood pressure	**70–79 mmHg**	
LDL-C target[a]		
	<100 mg/dL	Patients with moderate CV risk or young patients with diabetes mellitus duration <10 years without other risk factors
	<70 mg/dL	Patients with high CV risk or diabetes mellitus without target organ damage
	<55 mg/dL	Patients with very high CV risk or diabetes mellitus with target organ damage or severe CKD or established atherosclerotic CVD
Triglycerides	**<150 mg/dL**	
Fasting glycemia	**<110 mg/dL**	
HbA1c	**<6.5%**	

Notes: [a]In patients with high and very high CV risk, at least a 50% reduction is required.
Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol.

Dyslipidemias

Similar to the lack of specific guidelines for treating arterial hypertension in patients with PV, no such guidelines exist for the treatment of dyslipidemias. ESC/European Atherosclerosis Society (EAS) established therapeutic goals for the treatment of dyslipidemias according to the level of low-density lipoprotein cholesterol (LDL-C) (Table 4).[38] Given that patients with PV have a higher risk of CV events than patients without PV, we believe they should be treated more aggressively than currently recommended for patients in the same risk class without PV. Indeed, there is evidence that LDL-C levels <70 mg/dL (1.8 mmol/L) may be an appropriate therapeutic goal in moderate CV risk PV patients, rather than just in those at high CV risk or with diabetes mellitus.[39] Regardless, lifestyle modifications must be introduced as a first-line measure in the case of dyslipidemias. If needed, according to the ESC/EAS guidelines, the initial therapeutic approach is based on the use of highly potent statins. High-potency statins are expected to provide a 50% reduction in LDL-C levels. If targets are not reached, ezetimibe is added, and if this fails, inhibitors for proprotein convertase subtilisin/kexin type 9 may be used according to the risk of the patient (Figure 2).

There is substantial variability in the response to lipid-modifying treatment. The use of predefined therapeutic targets may help patient-doctor communication and increase treatment adherence.[38]

Thrombosis Prophylaxis Specific to Polycythemia Vera

Primary prevention in PV is focused on the interventions necessary to reduce the risk of developing thrombosis in patients who have never experienced a thrombotic event (Table 5). A randomized clinical trial showed the antithrombotic value of maintaining Ht below 45%.[40] Therefore, phlebotomy (or erythropheresis) is recommended in patients with PV, with the aim of maintaining Ht <45%. In patients who are intolerant to phlebotomy (ie individuals who experienced 2 episodes of post-phlebotomy syncope despite appropriate management or those who have blood or needle phobia leading to treatment avoidance) or in those with inadequate Ht control with phlebotomies (ie a need for ≥6 phlebotomies per year for at least 2 years in the maintenance phase after reaching Ht concentrations <45% in the induction phase), cytoreductive therapy should be considered.[9,41,42] A lower Ht target level may be preferred in specific clinical situations (eg pregnancy or past history of splanchnic vein thrombosis).[43] Primary prophylaxis with low-dose ASA 40–100 mg/day should be introduced in all low-risk PV patients in addition to phlebotomy.[2] ASA twice daily may be considered in patients with inadequate control of microvascular symptoms who present CV risk factors, especially hypertension, or those with leukocytosis.[2] However, further controlled studies are necessary to confirm the superiority of twice-daily versus once-daily dosing of ASA.

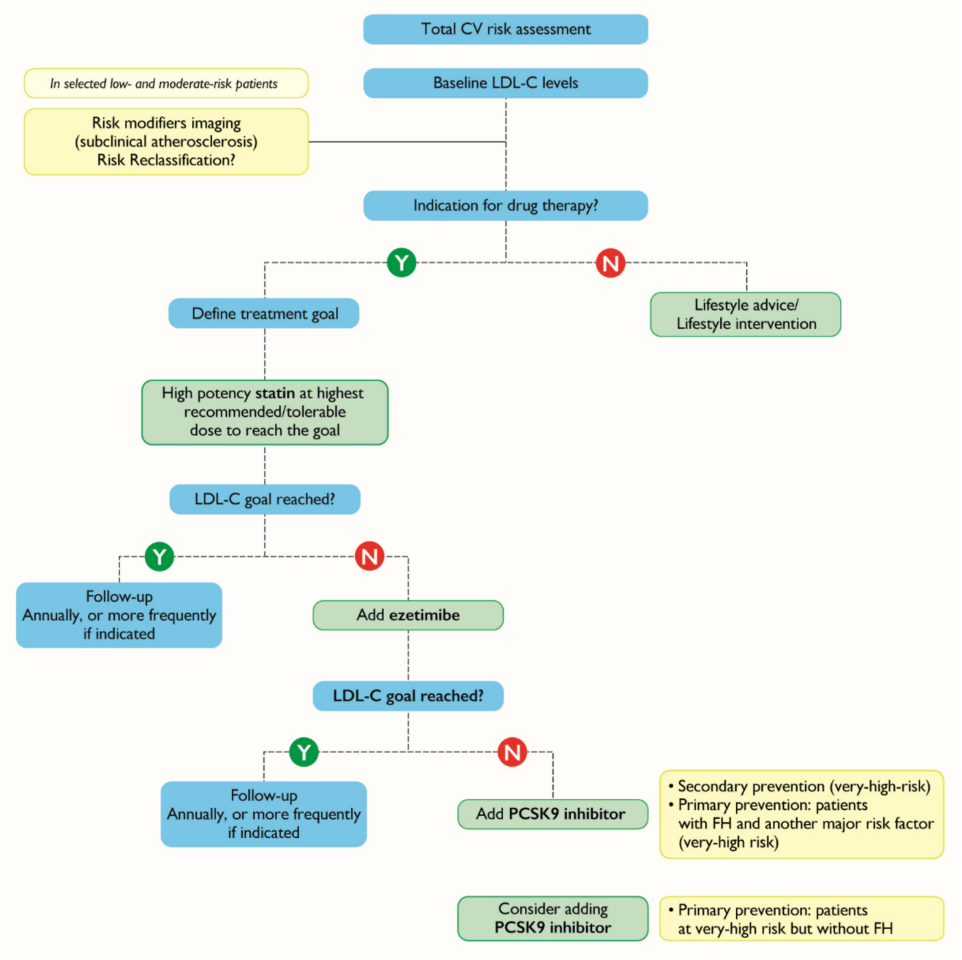

Figure 2 The algorithm for the sequential introduction of cholesterol lowering therapy.
Notes: Adapted with permission from Oxford University Press. Mach F, Baigent C, Catapano AL et al 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41(1):111–188. The European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines, permission conveyed through Copyright Clearance Center, Inc.[38]
Abbreviations: CV, cardiovascular; FH, familial hypercholesterolemia; LDL-C, low density lipoprotein cholesterol; N, no; PCSK9, proprotein convertase subtilisin/kexin type 9; Y, yes.

Moreover, based on ELN 2021 recommendations, cytoreductive therapy should also be considered to reduce the risk of thrombosis in progressive (at least 100% increase if baseline count is $<10 \times 10^9$ cells/L or at least 50% increase if baseline count is $>10 \times 10^9$ cells/L) and persistent (leukocyte count $>15 \times 10^9$ cells/L confirmed at 3 months) leukocytosis or in extreme thrombocytosis ($>1500 \times 10^9$ platelets/L), disease-related bleeding manifestations irrespective of the platelet count, or both situations.[9]

Secondary Thrombosis Prevention

Secondary prevention is a set of measures introduced to individuals who have already had a CV event (eg myocardial infarction, angina, myocardial revascularization, stroke, transient ischemic attack, peripheral arterial disease of lower limbs or carotids, or revascularization procedures) in order to reduce the risk of recurrent events, improve survival and quality of life.[21,45] All patients are strongly encouraged to participate in a cardiologic rehabilitation program.

In MPN patients with a history of arterial and/or venous thrombosis, it is crucial to act on modifiable CV risk factors (as described above) and to estimate the individual risk of thrombosis and hemorrhage.[3,46] In patients with high CV risk and previous thrombosis, cytoreductive therapy in addition to ASA should also be considered (Table 5).[37,47] The acute treatment of organ-specific arterial thrombosis (stroke, acute myocardial infarction, peripheral artery disease) is no different in patients with an MPN from the general population except for the addition of cytoreductive therapy and

Table 5 Primary and Secondary Prevention of Thrombotic Events in Polycythemia Vera

Clinical Feature	Intervention
Primary prophylaxis	
All PV patients	ASA
Unless	
vWF activity <30%	Consider holding ASA
Platelet >1 million	Consider holding ASA
Ht ≥45%	Phlebotomy/cytoreduction to target Ht <45%
High-risk PV (age >60 years/past thrombosis)	Cytoreduction
Secondary prophylaxis	
All patients	Cytoreduction
Typical VTE	Consider indefinite VKA for most patients, ASA if not on VKA
Atypical VTE	Indefinite VKA and DOAC
Arterial thrombosis	ASA

Notes: Adapted with permission from Springer Nature. Martin K. Risk factors for and management of MPN-associated bleeding and thrombosis. *Curr Hematol Malig Rep*. 2017;12(5):389–396.[44]

Abbreviations: ASA, acetylsalicylic acid; DOAC, direct oral anticoagulant; Ht, hematocrit; PV, polycythemia vera; VKA, vitamin K antagonists; VTE, venous thromboembolism; vWf, von Willebrand factor.

phlebotomy (Table 5). Antiplatelet agents together with cytoreduction are typically used in patients with a history of an arterial thrombotic event, while in PV patients who have experienced a venous episode, anticoagulants are administered.[48] Secondary prophylaxis with ASA is usually done at 100 mg/day, although 200 mg/day (100 mg twice daily), otherwise recommended in high-risk essential thrombocythemia, may be administered to some patients.[3] There is no specific anticoagulant recommended for MPN patients by the existing guidelines.[49] Results from small retrospective studies show that the overall incidence of new thrombotic and hemorrhagic events in patients treated with vitamin K antagonists (VKAs) and direct-acting oral anticoagulants (DOACs) were comparable (reviewed in).[48] Currently, their use must be decided case-by-case based on individual characteristics.[50] Analysis of data from 494 MPN patients with ET (52%) or PV (48%) in the Italian Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) registry revealed that VKA treatment reduced the recurrence of venous thromboembolic events (VTE), with a hazard ratio of 0.32 and a VTE-related bleeding risk of 0.9%).[51]

A 2018 study showed the merits of associating antithrombotic drugs with cytoreductive therapy in secondary prevention. In this study, MPN patients, who had experienced an ischemic stroke or transient ischemic attack and were subsequently treated with ASA or oral anticoagulants and cytoreduction.[52] The composite incidence of recurrent ischemic stroke, transient ischemic attack, myocardial infarction and CV death was lower in these patients than that reported in the general population without an increased risk of major bleeding.[52]

However, evidence for the use of DOAC in MPNs predominantly comes from small retrospective studies. Of interest, the prospective AIRPORT-MPN study is comparing thrombosis prophylaxis with low-dose ASA with or without cytoreductive therapy with the DOAC apixaban, with or without cytoreductive therapy, in patients with MNP (ClinicalTrials.gov Identifier: NCT04243122).

A recently-published retrospective study reported data from MPN patients treated with DOAC or VKA. Patients had venous (87.3%) and arterial (12.7%) thromboses; 45 of 71 patients were treated with a VKA, and 26 received a DOAC.[53] There were no significant differences in bleeding episodes between the two groups, although the prevalence of recurrent thromboses were more frequent in patients treated with VKA (35%) than DOAC (0%, $p = 0.0003$).

Recently, Barbui et al conducted an international, multicenter, real-world observational study in 442 MPN patients with atrial fibrillation and VTE receiving treatment with a DOAC.[54] After estimating the incidence and risk factors for thrombotic and bleeding complications, they concluded that DOACs and VKAs had a largely similar risk-benefit profile for preventing VTE in patients with MPN. However, the concomitant use of hydroxyurea may be a compounding factor in the apparent favorable efficacy of DOAC in the prevention of ischemic cerebrovascular events in atrial fibrillation, as

hydroxyurea is an independent protective factor against recurrence in MPN. However, a significant bleeding tendency is associated with dabigatran in primary myelofibrosis.[54]

Nevertheless, given the ease of administration and improved patient convenience, DOACs could be considered an alternative to VKAs as antithrombotic prophylaxis.

In patients affected by venous thromboembolism and thrombocytopenia, anticoagulant therapy using low molecular weight heparin must be modified in individuals with a platelet count <50,000 platelets/mm^3; half of the recommended dose should be prescribed if platelet count ranges from 25,000–50,000/mm^3, and no anticoagulation therapy should be used in patients with a platelet count <25,000/mm^3.[55,56] The duration of necessary anticoagulation in PV is still under study.[48]

Thrombophilia screening (eg testing for mutations in genes coding for factor II, factor V, factor VIII, antithrombin, protein C, protein S, activated protein C resistance, lupus anticoagulant, anticardiolipin antibodies or anti-B2 glycoprotein 1 antibodies, and homocysteine) does not change the management of the patient and should only be considered in selected patients.[57] If suspected, a search for lupus anticoagulant, anticardiolipin or anti-beta-2 glycoprotein 1 antibodies should be performed. For patients with a confirmed diagnosis of antiphospholipid antibody syndrome (APS) requiring long-term anticoagulation to prevent recurrent thrombosis, the 2019 ESC and American Society of Hematology (ASH) guidelines do not recommend the use of DOACs. However, evidence-based guidelines developed by the European League Against Rheumatism (EULAR), the British Society for Haematology (BSH), and the International Society on Thrombosis and Haemostasis (ISTH) recommend warfarin as the first-choice treatment for this indication.[58–60] They also propose that DOACs may be considered in certain situations, specifically in patients already stably anticoagulated with a DOAC, those on low-quality anticoagulation while on warfarin, those unwilling or unable to undergo standard international normalized ratio monitoring, and patients with contraindications to or having experienced serious adverse events while on warfarin. Warfarin is recommended for patients with arterial APS or triple positivity, although DOACs may be considered for those with venous APS and single or double positivity.[58–60]

Management of Specific Pathologies

Acute Ischemic Heart Disease

Lifestyle modifications and close blood pressure monitoring should be done in all ischemic heart disease patients. Pharmacological therapy should include an ACE-I combined with a beta-blocker in patients with heart failure or left ventricular ejection fraction ≤40% (Class I recommendation, evidence level A) and statins to achieve target LDL-C levels. Table 6 includes details of antiplatelet treatment modalities in patients who had an ST-elevation myocardial infarction, non-ST-elevation myocardial infarction and/or an aortocoronary bypass.[61]

Table 6 Antiplatelet Therapy in Patients with Acute Ischemic Heart Disease Who Had an ST-Elevation Myocardial Infarction, Non-ST-Elevation Myocardial Infarction or Aortocoronary Bypass

Clinical Situation	Intervention
All patients:	• 75–100 mg/day ASA (or 75 mg/day clopidogrel)
PCI to place a stent:	• DAPT with 75–325 mg/day ASA + 75 mg/day clopidogrel (or prasugrel 10 mg/day if <75 years and >60 kg, or 90 mg BID ticagrelor) for 6 months if chronic coronary syndrome, 12 months if ACS (can be reduced if high bleeding risk case by case) • single antiplatelet therapy thereafter
PCI to place a stent with atrial fibrillation or flutter:	• Oral anticoagulation (VKA or DOAC) + DAPT (100 mg/day ASA + 75 mg/day clopidogrel) for up to 1 month depending on hemorrhagic risk. • oral anticoagulation (DOAC/VKA) + single antiplatelet therapy (ASA or clopidogrel) until 1 year • oral anticoagulation thereafter
PCI to place a stent and intraventricular thrombosis:	• VKA for 6 months until complete resolution of the thrombosis. The duration of DAPT should be decided on a case-by-case basis

Abbreviations: ACS, acute coronary syndrome; ASA, acetylsalicylic acid; BID, twice daily; DAPT, double antiplatelet therapy; DOAC, direct oral anticoagulant; PCI, percutaneous coronary intervention; VKA, vitamin K antagonists.

Ischemic Stroke or Transient Ischemic Attack

In patients who have had ischemic strokes or a transient ischemic attack, antiplatelet therapy with ASA at a dose of 100 mg/day is recommended to prevent secondary events.[62]

Deep Vein Thrombosis

Anticoagulation therapy effectively prevents the recurrence of deep vein thrombosis and reduces the risk of thromboembolic events by up to two times compared with untreated patients. The duration of anticoagulant therapy must be established based on the patient's characteristics, the risk of thrombosis recurrence, MPN activity, ongoing treatments, and on the individual's risk of bleeding. Experts recommend indefinite anticoagulant therapy in the context of atypical thrombosis, including splanchnic vein thrombosis and cerebral venous sinuses thrombosis.[5,44,63]

Conclusion

Ph-MPN are associated with an increased CV risk independent of the presence of conventional CV risk factors. High blood pressure, smoking, and dyslipidemia are common in MPN and contribute to an increased risk of CV events. Identifying patients at very high risk of fatal CV events is necessary to introduce early co-management by hematologists, cardiologists, and metabolic disease specialists. The definition of CV risk class (% fatal events at 10 years) based on the appropriate ESC scores is necessary to define the thresholds and intensity of intervention on pharmacologically modifiable risk factors, such as hypercholesterolemia, glucose metabolism, and blood pressure, and on risk factors modifiable with lifestyle, such as weight, diet, and smoking. Strict control of CV risk factors, in association with appropriate hematological therapy, may improve outcomes of patients with Ph-MPN. Further studies will clarify if the combination of ASA and DOAC could improve the management of patients with MPN at high risk of relapse. However, CVD characteristics in MPN may differ from those in the general population, and optimal thresholds for metabolic in these diseases have not been fully elucidated.[64] MPN-specific treatment goals may be necessary to optimize risk factor management in these patients.

Abbreviations

ABPM, ambulatory 24-hour blood pressure monitoring; ACE-I, angiotensin converting enzyme inhibitors; ACS, acute coronary syndrome; APS, antiphospholipid antibody syndrome; ARB, angiotensin II receptor antagonists; ASA, acetylsalicylic acid; ASH, American Society of Hematology; ASXL1, ASXL transcriptional regulator 1; BID, twice daily; BSH, British Society for Haematology; CALR, calreticulin; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DAPT, double antiplatelet therapy; DNMT3A, DNA methyltransferase 3 alpha; DOAC, direct oral anticoagulant; EAPC, European Association of Preventive Cardiology; EAS, European Atherosclerosis Society; ECLAP, European Collaboration on Low-dose Aspirin Study; EF, ejection fraction; ELN, European LeukemiaNet; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ET, essential thrombocythemia; EULAR, European League Against Rheumatism; F, female; FH, familial hypercholesterolemia; GFR, glomerular filtration rate; GLS, global longitudinal strain; GP, general practitioner; HbA1c, glycated hemoglobin; HDL-C, high density lipoprotein cholesterol; Ht, hematocrit; ISTH, International Society on Thrombosis and Haemostasis; JAK2, janus kinase 2; K, potassium; LDL-C, low-density lipoprotein cholesterol; LVMi, left ventricular mass index; M, male; MPL, proto-oncogene thrombopoietin receptor; MPN, myeloproliferative neoplasms; Na, sodium; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin type 9; Ph-, Philadelphia chromosome; PMF, primary myelofibrosis; PV, polycythemia vera; SCORE2, systematic coronary risk estimation 2; SCORE2-OP, systematic coronary risk estimation-older persons; TET2, tet methylcytosine dioxygenase 2; TT, transthoracic; VKA, vitamin K antagonists; VTE, venous thromboembolism; vWF, von Willebrand factor; WHO, World Health Organization.

Acknowledgments

The authors would like to thank Dr Alicja M. Gruszka, MD, PhD, for providing medical writing assistance on behalf of Springer Healthcare Communications, Arneak Kooner of Springer Healthcare Communications and Ray Hill and

Melanie Gatt on behalf of Springer Healthcare Communications for providing styling assistance prior to submission. This medical writing and editorial assistance was funded by Novartis Farma SpA.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The authors have not received fees or financial compensation for their participation in this article.

Disclosure

G.B. has been on the advisory board, and been a speaker for Novartis, Janssen, BMS-Celgene M.M. has received consultancy fees from Gilead srl. E.B. has been a speaker for Novartis, Alexion and Incyte. A.M. has taken part in an advisory board for Amgen. D.R. has been advisor for Blueprint Medicines and has received travel grants from Novartis. The authors report no other conflicts of interest in this work.

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