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STATE-OF-THE-ART REVIEW

Cardiovascular Disease in Myeloproliferative Neoplasms

JACC: CardioOncology State-of-the-Art Review

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ABSTRACT

Myeloproliferative neoplasms are associated with increased risk for thrombotic complications. These conditions most commonly involve somatic mutations in genes that lead to constitutive activation of the Janus-associated kinase signaling pathway (eg, Janus kinase 2, calreticulin, myeloproliferative leukemia protein). Acquired gain-of-function mutations in these genes, particularly Janus kinase 2, can cause a spectrum of disorders, ranging from clonal hematopoiesis of indeterminate potential, a recently recognized age-related promoter of cardiovascular disease, to frank hematologic malignancy. Beyond thrombosis, patients with myeloproliferative neoplasms can develop other cardiovascular conditions, including heart failure and pulmonary hypertension. The authors review the pathophysiologic mechanisms of cardiovascular complications of myeloproliferative neoplasms, which involve inflammation, prothrombotic and profibrotic factors (including transforming growth factor-beta and lysyl oxidase), and abnormal function of circulating clones of mutated leukocytes and platelets from affected individuals. Anti-inflammatory therapies may provide cardiovascular benefit in patients with myeloproliferative neoplasms, a hypothesis that requires rigorous evaluation in clinical trials. (J Am Coll Cardiol CardioOnc 2022;4:166–182) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Myeloproliferative neoplasms (MPNs) encompass a group of disorders of clonal hematopoiesis and include polycythemia vera, essential thrombocythemia, and primary myelofibrosis. MPNs usually affect older patients, with median ages at diagnosis of 55 years for essential thrombocythemia, 64 years for polycythemia vera, and 63 years for primary myelofibrosis.[1] The long-term prognosis of MPNs is measured in years, with patients with essential thrombocythemia having the best prognosis (median survival 20 years) and those with primary myelofibrosis the worst (median survival 6 years).[1] Patients with MPNs have a predisposition to progress to myelofibrosis or acute leukemia.[2] Moreover, clinicians have long recognized an association between MPNs and increased risk for both thrombotic and hemorrhagic complications. A recent meta-analysis of 13,436 patients with MPNs showed a pooled prevalence of arterial thrombosis of 16.2% and of hemorrhagic complications of 6.2%.[3] Indeed,

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HIGHLIGHTS

- MPNs entail increased thrombotic and cardiovascular risks.
- Among them: atherothrombosis, heart failure, and pulmonary hypertension.
- Genes mutated in MPNs include some seen in CHIP, also raising cardiovascular risk.
- Inflammation likely contributes to increased cardiovascular risk in MPN.
- Anti-inflammatory therapy in selected MPN patients warrants testing.

cardiovascular events often accompany this cluster of hematologic conditions and contribute significantly to morbidity and mortality. Yet the mechanisms that connect MPNs with cardiovascular disease risk and thrombotic diatheses have remained elusive. Recent research has uncovered previously unsuspected pathophysiologic connections between hematologic malignancies in general, and MPNs in particular with cardiovascular complications. These advances not only furnish novel insights into mechanisms but pave the way for further steps forward in risk assessment and management, and highlight the need to develop and test targeted therapies to mitigate the increased cardiovascular disease risk associated with MPNs.

The chronic disorders of clonal hematopoiesis known as MPNs arise from somatic mutations leading to constitutive activation of the Janus-associated kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway, which regulates the production of proinflammatory cytokines.[4,5] Mutations in the Janus kinase 2 (*JAK2*), calreticulin, and myeloproliferative leukemia protein (*MPL*) genes account for the vast majority of driver mutations in MPNs.[6-8] Mutations in the *JAK2* gene, with the $JAK2^{V617F}$ mutation being the most common, are found in 95% of patients with polycythemia vera and in approximately 60% of patients with essential thrombocythemia and primary myelofibrosis.[6,7] Patients with MPNs also harbor other mutations that can be associated with increased inflammation, including in tet methylcytosine dioxygenase 2 (*TET2*), DNA methyltransferase 3 alpha (*DNMT3a*), and additional sex Combs-like 1 (*ASXL1*) genes.[9]

MPNs are situated on the continuum of clonal hematopoietic processes ranging from clonal hematopoiesis of indeterminate potential (CHIP) to more indolent diseases such as essential thrombocythemia and polycythemia vera and more aggressive diseases such as myelofibrosis or post-MPN acute leukemia (Figure 1). CHIP, by definition, does not alter the peripheral blood count and does not involve a hematologic malignancy. The "indeterminate potential" in CHIP reflects uncertainty regarding the risk for developing a hematologic malignancy in those affected by these mutations. Unlike patients with MPNs, patients with CHIP have a normal hemogram. The most commonly mutated genes in CHIP include *TET2*, *DNMT3a*, *JAK2*, and *ASXL1*, which can also lead to MPNs further on this spectrum of disorders. Additionally, mutations in other MPN driver genes, including calreticulin, can cause in CHIP.[10] Individuals with CHIP have a risk for developing hematologic malignancies of 0.5% to 1% annually, so most CHIP carriers will never transition to acute leukemia.[11]

Although people with CHIP may not develop overt MPNs or leukemia, compelling recent evidence links CHIP to atherosclerosis and cardiovascular disease.[12-15] CHIP due to mutations in *JAK2* is associated with the highest risk for myocardial infarction and accounts for up to 19% of all MPN-inducing mutations in patients with myocardial infarction and CHIP.[12] In younger individuals, *JAK2* mutations impart an almost 4-fold increased risk for myocardial infarction. Other studies have shown that patients with heart failure who have CHIP mutations (particularly in *DNMT3a* or *TET2*) have worse outcomes compared with those without CHIP.[16-18] Moreover, patients who have undergone percutaneous aortic valve replacement also fare much more poorly if they carry *DNMT3a* or *TET2* mutations.[19] These recent discoveries suggest elements of shared pathogenesis that connect disorders of clonal hematopoiesis, including MPNs, to atherosclerosis and cardiovascular events. Here we review major cardiovascular complications as they relate to different forms of MPN.

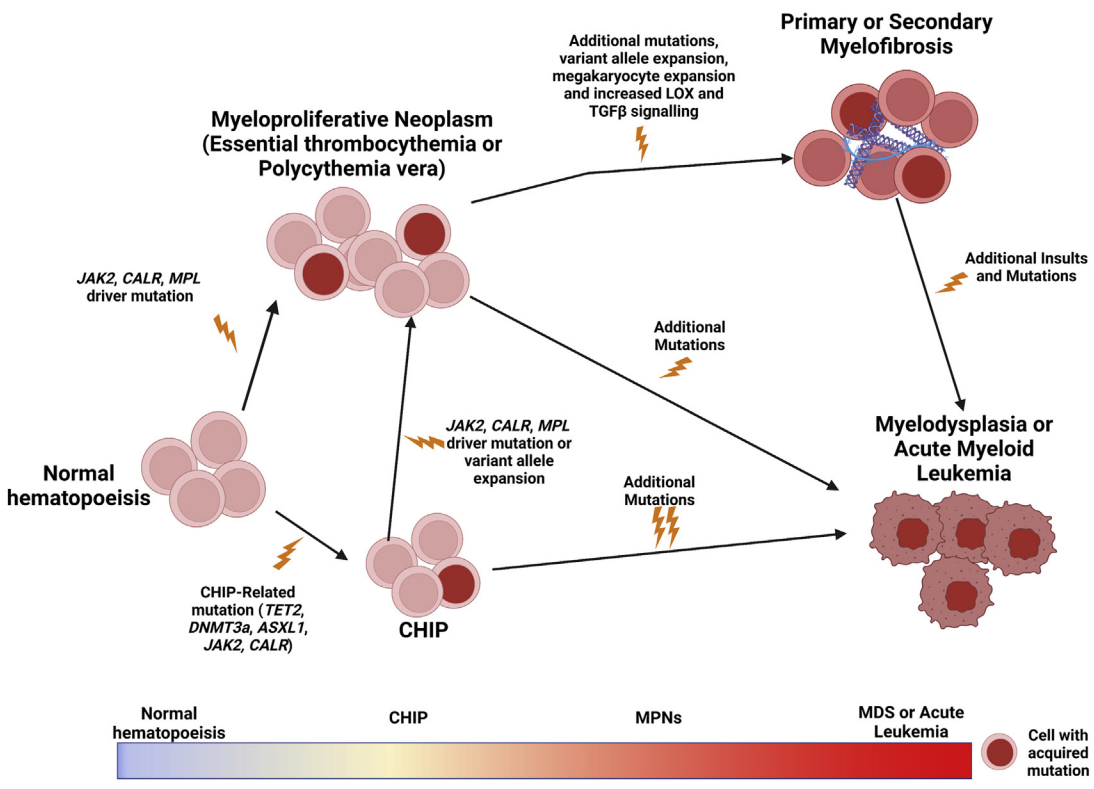
INFLUENCE OF DRIVER MUTATIONS AND CHIP-ASSOCIATED MUTATIONS ON THROMBOSIS IN MPN

A mutation in *JAK2* confers an approximately 2-fold increased risk for arterial thrombotic events compared with non-*JAK2* driver mutations in essential thrombocythemia and primary myelofibrosis.[20-22] Additionally, in polycythemia vera (in which *JAK2* mutation accounts for >95% of driver mutations), increased $JAK2^{V617F}$ burden of mutant leukocytes in peripheral blood (the variant allele frequency) is

ABBREVIATIONS AND ACRONYMS

ASXL1 = additional sex Combs-like 1
CHIP = clonal hematopoiesis of indeterminate potential
DNMT3a = DNA methyltransferase 3 alpha
IL = interleukin
JAK = Janus-associated kinase
JAK2 = Janus kinase 2
LOX = lysyl oxidase
MPL = myeloproliferative leukemia protein
MPN = myeloproliferative neoplasm
STAT = signal transducer and activator of transcription
TET2 = tet methylcytosine dioxygenase 2
TGF = transforming growth factor

FIGURE 1 Spectrum of Disorders of Myelopoiesis



Oversimplified schema of the spectrum of disorders of myelopoiesis. Hematopoietic stem cells can acquire somatic mutations that can lead to myeloproliferative neoplasms (MPNs) directly or through mutations of clonal hematopoiesis of indeterminate potential (CHIP). Although MPN driver mutations can be present in CHIP, variant allele expansion or other genetic insults can result in MPN from CHIP. MPNs can progress to more aggressive disorders including myelodysplastic syndromes and acute leukemia. Additionally, myelofibrosis can be primary (primary myelofibrosis) or secondary (progression from essential thrombocythemia and polycythemia vera). CHIP similarly can lead to myelodysplastic syndrome (MDS) or acute leukemia through additional genetic insults. *ASXL1* = additional sex Combs-like 1; *CALR* = calreticulin; *DNMT3a* = DNA methyltransferase 3 alpha; *JAK2* = Janus kinase 2; LOX = lysyl oxidase; *MPL* = myeloproliferative leukemia protein; *TET2* = tet methylcytosine dioxygenase 2; TGFβ = transforming growth factor-β.

associated with increased venous thrombosis but not arterial thrombosis (Table 1).[23]

Patients with MPNs often harbor nondriver mutations in genes commonly associated with CHIP, including *TET2*, *DNTM3a*, and *ASXL1*. Mutations in CHIP-associated genes may arise before the development of driver mutations (such as of *JAK2* gene) and overt MPN, which is evidence of a CHIP-to-MPN continuum.[24] *TET2* mutations occur in 4% to 15% of patients with polycythemia vera and essential thrombocythemia and in 19% of patients with primary myelofibrosis.[24,25] Mutations in the *ASXL1* gene are relatively scarce in patients with polycythemia vera and essential thrombocythemia (7%-20%) but are found in 19% to 40% of patients with primary myelofibrosis.[26,27] A small minority of patients with MPNs harbor mutations in *DNMT3A*, with a frequency of approximately 9% in patients with polycythemia vera and essential thrombocythemia and in 3% to 15% of patients with primary myelofibrosis.[28,29]

The $JAK2^{V617F}$ mutation is the predominant mutation associated with coincident CHIP and MPNs and also the mutation most strongly associated with cardiovascular disease risk and thrombosis. Additionally, in patients with idiopathic hypereosinophilic syndrome (a heterogeneous disorder characterized by proliferation of potentially neoplastic eosinophils), mutations in CHIP-associated genes indicate an increased risk for thrombotic events.[30] However, cardiovascular implications related to nondriver mutations have not been well characterized in the MPN population. In a small study of 16 patients with polycythemia vera, the presence of *TET2*, *DNMT3A*, or *ASXL1* mutations was associated with increased

TABLE 1 Impact of Driver Mutation and Clonal Hematopoiesis of Indeterminate Potential–Associated Mutations on Thrombosis in Patients With Myeloproliferative Neoplasms

First Author, Ref. #	MPNs Studied	N	Cardiovascular Outcomes	Effect of *JAK2* Mutation on Thrombosis	Effect of CHIP Mutation on Thrombosis	Comments
Carobbio et al[21]	ET	891	Arterial thrombosis	HR: 2.57 (95% CI: 1.27-5.19) vs no *JAK2* mutation	NA	
Tefferi et al[32]	ET and PV	316	Any thrombosis	For ET: RR: 4.8 (95% CI: 1.6-14.2) *JAK2* vs *CALR*	For ET: *TET2* mutation associated with increased risk for thrombosis (RR: 3.4; 95% CI: 1.4-8.4)	No association between adverse mutations (including *TET2*, *ASXL1*) with thrombosis in patients with PV
Guglielmelli et al[23]	PV	576	Arterial and venous thrombosis	$JAK2^{V617F}$ VAF >50% Arterial thrombosis: HR: 0.9 (95% CI: 0.5-1.6) Venous: HR: 3.8 (95% CI: 1.7-8.6)	NA	
Segura-Diaz et al[31]	PV	16	Any thrombosis	NA	≥1 mutation in *TET2*, *DNMT3A*, or *ASXL1* was associated with increased risk for thrombosis (OR: 4.68; 95% CI: 1.49-14.64)	
Cerquozzi et al[20]	PV	587	Arterial thrombosis	NA	No difference between *TET2* (14% with arterial thrombosis vs 20% without; $P = 0.40$) or *ASXL1* (12% vs 10%; $P = 0.80$)	
Rumi et al[22]	PMF	617	Any thrombosis	SHR: 2.19 (95% CI: 1.15-4.18) vs *CALR* mutation	NA	No difference in leukemia-free survival between *JAK2* and *CALR* mutations Worse overall survival with *JAK2* compared with *CALR* (HR: 2.3; $P < 0.001$)
Barbui et al[41]	PMF	707	Any thrombosis	HR: 1.92 (95% CI: 1.10-3.34) vs no *JAK2* mutation	NA	

ASXL1 = additional sex Combs-like 1;*CALR* = calreticulin; CHIP = clonal hematopoiesis of indeterminate potential; *DNMT3a* = DNA methyltransferase 3 alpha; ET = essential thrombocythemia; *JAK2* = Janus kinase 2; MPN = myeloproliferative neoplasm; NA = not applicable; PMF = primary myelofibrosis; PV = polycythemia vera; RR = relative risk; SHR = subdistribution HR; *TET2* = tet methylcytosine dioxygenase 2; VAF = variant allele fraction.

risk for thrombotic events.[31] Another study of 183 patients with essential thrombocythemia and 133 patients with polycythemia vera showed an increased risk for thrombosis in patients with essential thrombocythemia who had *TET2* mutations.[32] A larger single-center study of 587 patients with polycythemia vera, however, did not affirm an association with *TET2* or *ASXL1* mutation and arterial thrombosis.[20] Interestingly, in patients with essential thrombocythemia, *ASXL1* mutations were associated with a decreased risk for thrombosis, while $JAK2^{V617F}$ was associated with increased thrombosis.[27] Yet in patients with primary myelofibrosis and essential thrombocytosis, mutations in *ASXL1* were associated with worse survival and increased risk for leukemic transformation.[33,34] The presence of CHIP-associated mutations in patients with MPN is likely associated with worse outcomes; however, their impact on cardiovascular events and outcomes requires further thorough investigation.

SUMMARY POINTS.

- The majority of patients with MPNs have driver mutations in *JAK2* and have increased thrombotic risk compared with non-*JAK2* driver mutations (calreticulin and *MPL*).
- Patients with MPNs commonly harbor mutated genes associated with CHIP, including *TET2*, *DNMT3A*, and *ASXL1*.
- The impact of various CHIP-associated genes on thrombotic risk requires further investigation.

CARDIOVASCULAR COMPLICATIONS IN MPNs

ARTERIAL THROMBOSIS. Thrombosis, including arterial and venous thromboembolism, causes much morbidity and mortality in patients with MPNs.[35] Thrombosis can occur in any vascular bed, venous as well as arterial, and either polycythemia vera or essential thrombocythemia may initially present as an acute coronary syndrome.[36-39] Although malignant transformation causes most deaths in those with MPNs, acute coronary syndrome and other cardiovascular events remain a major challenge in these patients.[38,40,41] A meta-analysis involving more than 13,000 patients with MPNs evaluated arterial thrombotic events (stroke, transient ischemic attack, coronary heart disease, and peripheral artery disease). Stroke and transient ischemic attack led incident arterial thrombotic events in patients with MPNs.[3] Although this meta-analysis showed a rate of 16.2% of arterial thrombotic events in patients with MPNs,

TABLE 2 World Health Organization 2016 Criteria for Myeloproliferative Neoplasms and Risk for Arterial Thrombosis

MPNs	Hemogram Abnormalities	Genetics in Major Criteria	Minor Criteria	Arterial Thrombosis Risk	References
PV	Men: hemoglobin >16.5 g/dL or hematocrit >49%; women: hemoglobin >16.0 g/dL or hematocrit >48% or increased red cell mass (major criteria)	*JAK2* or *JAK2* exon 12 mutation	Subnormal serum erythropoietin level	16.5%-28.6%	3,23,74
ET	Platelet count ≥450,000/μL (major criterion)	*JAK2*, *CALR*, or *MPL* mutation	Presence of a clonal marker or no of evidence for reactive thrombocytosis	12%-20.7%	3,21
PMF	Leukocytosis ≥11,000/μL (minor criterion) Anemia not attributed to another comorbidity Leukoerythroblastosis	*JAK2*, *CALR*, or *MPL* mutation or another clonal marker	Palpable splenomegaly Elevated serum lactate dehydrogenase level	7.2%-11.6%	3,41,43

MPL = myeloproliferative leukemia protein; other abbreviations as in Table 1.

the rates of arterial thrombosis events vary considerably among other studies, likely because of differences in length of follow-up, case definition, adjudication, and other factors (Table 2).[3,21,40-44]

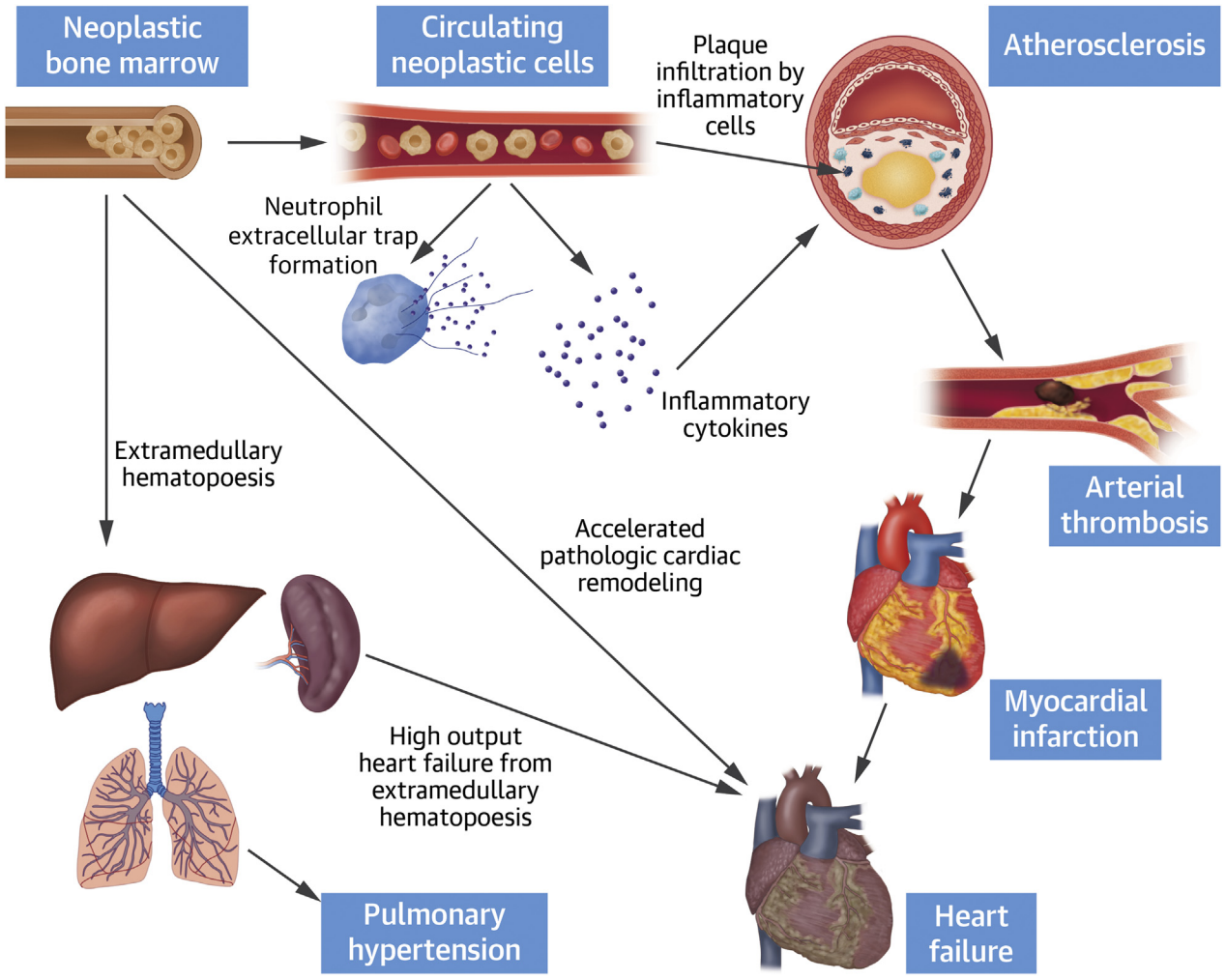
HEART FAILURE. Heart failure may also associate with MPNs. The activation of the JAK-STAT pathway is associated with cardiac fibrosis and cardiac remodeling in mice with hypertensive heart disease induced by angiotensin II infusion.[45,46] In experimental heart failure in mice, transgenic myeloid expression of $JAK2^{V617F}$ accelerated adverse cardiac remodeling and enhanced the inflammatory response to myocardial infarction.[47] One large Medicaid database study showed a >2-fold increased risk for heart failure in patients with MPNs compared with those without MPNs (incidence of 9.27 vs 3.70 per 1,000 person-years).[44] The exact etiology of heart failure in these patients remains ill defined. High-output heart failure may contribute to heart failure in some patients with MPNs; one study showed that 8% of high-output heart failure etiologies resulted from MPNs, and this may be related to increased metabolism by malignant cells, extramedullary hematopoiesis, or anemia.[48]

PULMONARY HYPERTENSION. Pulmonary hypertension can also complicate MPN, although the prevalence of this condition in this patient population remains poorly defined.[49] The World Health Organization classifies MPN-associated pulmonary hypertension in group 5. Two recent studies estimated a 3% to 7% prevalence of pulmonary hypertension in patients with MPNs.[50,51] Pulmonary hypertension can also link with increased risk for cardiovascular mortality in patients with MPNs.[52] Patients with MPNs can also develop right ventricular dysfunction.[53] Increased circulating myeloid and proangiogenic progenitor cells may contribute to the mechanisms of this increased risk for pulmonary hypertension in patients with MPNs.[54] Patients with primary pulmonary arterial hypertension also have increased numbers of circulating bone marrow–derived proangiogenic progenitor cells and exhibit myeloproliferative-like changes in their bone marrow, including reticulin fibrosis (early collagen fibrosis), suggesting a possible common pathophysiology.[55,56] Other potential etiologies of pulmonary hypertension in patients with MPNs include pulmonary extramedullary hematopoiesis and pulmonary veno-occlusive disease.[51,57,58] Additionally, patients with MPNs have a heightened risk for pulmonary embolism and recurrent venous thromboembolism; thus, chronic thromboembolic pulmonary hypertension likely contributes to the prevalence of pulmonary hypertension in this patient population.[59,60]

ATHEROSCLEROSIS. Experimental studies in mice have begun to unravel the pathophysiologic mechanisms that underlie increased cardiovascular disease risk in clonal hematopoietic processes, including MPNs. Low-density lipoprotein receptor–deficient mice transplanted with bone marrow from donors with $Jak2^{V617F}$ mutations have accelerated atherosclerosis and larger plaques with increased necrotic cores.[61] This mutation activates the interferon-inducible absent in melanoma 2 (AIM 2) inflammasome and interleukin (IL)-1 beta signaling, while inhibitors of IL-1 can limit necrotic core expansion and fibrous cap thinning in experimental atheroma in mice with clonal hematopoiesis.[62]

The majority of patients with polycythemia vera bear the $Jak2^{V617F}$ mutation. $Jak2^{V617F}$-mutated macrophages have impaired ability to engulf dead cells (defective efferocytosis), contributing to enlarged necrotic cores. In contrast, $Jak2^{V617F}$

CENTRAL ILLUSTRATION **Pathophysiology of Cardiovascular Disease in Myeloproliferative Neoplasms**



Leiva O, et al. J Am Coll Cardiol CardioOnc. 2022;4(2):166–182.

Arrows indicate relationships. Circulating myeloid neoplastic cells contribute to atherosclerosis and thrombosis via production of inflammatory cytokines, neutrophil extracellular trap formation, and plaque infiltration. Heart failure in myeloproliferative neoplasm mediated by arterial thrombosis (myocardial infarction) and accelerated pathologic remodeling. Extramedullary hematopoiesis can lead to high-output heart failure and pulmonary hypertension.

macrophages show increased erythrophagocytosis compared with wild-type *Jak2* macrophages. The breakdown of hemoglobin releases iron that can augment local oxidative stress through the Fenton reaction.[63,64] *Jak2* hyperactivation can also interfere with cholesterol efflux in macrophages, thus fostering foam cell accumulation in plaques in atherosclerotic mice, through a pathway that involves the liver X receptor.[65] Atherosclerosis-prone mice transplanted with bone marrow from mice with loss of function in *Tet2*, another gene commonly mutated in CHIP and MPNs, also have augmented lesion formation and markers of inflammation.[12,66]

One study compared the progression of carotid artery stiffness in patients with *JAK2*-mutated essential thrombocythemia and healthy control subjects. Patients with *JAK2*-mutated essential thrombocythemia had faster progression of carotid artery stiffness, a noninvasive index of atherosclerosis, compared with healthy control subjects.[67] Peripheral

artery disease may also be associated with MPN, although this relationship requires further study.[68] Consistent with the evolving theme that distinct gene mutations on the spectrum of CHIP to MPN and leukemia have differing pathophysiologic mechanisms, mutations in the DNA damage repair genes tumor protein p53 and protein phosphatase, Mg^{2+}/Mn^{2+} dependent 1D are associated particularly with peripheral artery disease in humans.[69]

SUMMARY POINTS.

- Patients with MPNs have a heightened risk for cardiovascular complications, including arterial thrombosis, heart failure, pulmonary hypertension, and accelerated atherosclerosis, depending on the form of MPN and the driver mutation associated with it.
- Increased heart failure risk in patients with MPNs may involve accelerated adverse cardiac remodeling and inflammation.
- Pulmonary hypertension can occur in patients with MPNs, especially those with primary myelofibrosis, and likely has a multifactorial etiology.
- Patients with *JAK2*^{V617F}-induced MPNs have accelerated atherosclerosis contributed by inflammation and/or defective macrophage lipid efflux and efferocytosis.

MECHANISMS OF CARDIOVASCULAR COMPLICATIONS IN MPNs

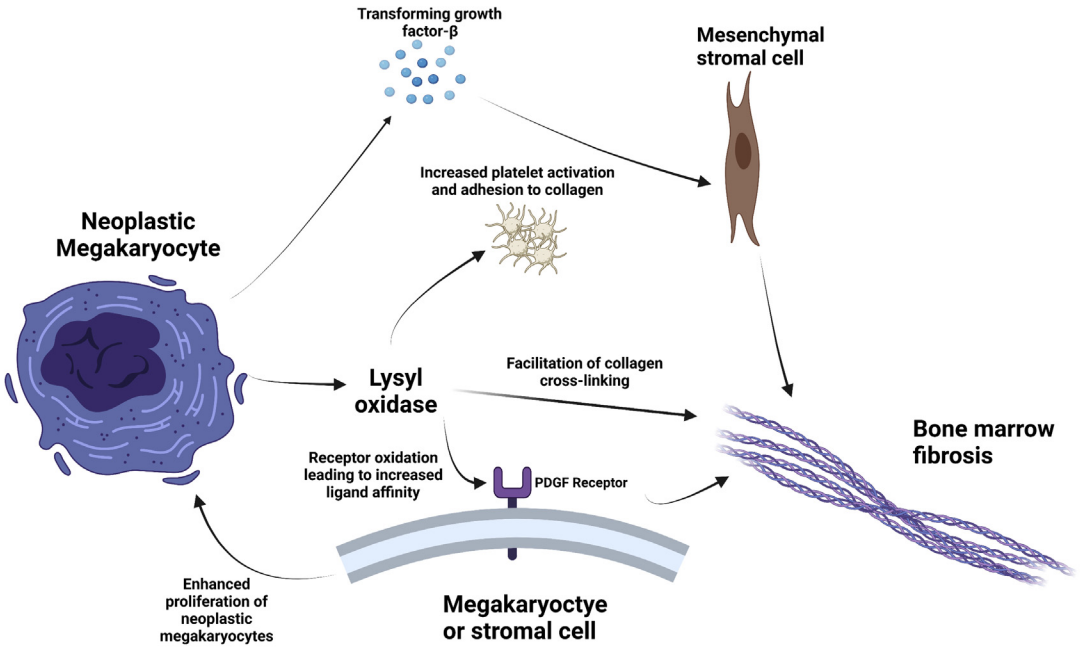
INFLAMMATION. Multiple mechanisms likely enhance thrombosis and atherogenesis in MPN, but many may converge on inflammatory pathways (**Central Illustration**).[70,71] Constitutive JAK/STAT signaling at the center of MPN pathogenesis promotes expression of inflammatory cytokines. Increased serum C-reactive protein concentration in patients with essential thrombocythemia and polycythemia vera reflects this inflammatory state and correlates with *JAK2*^{V617F} allele burden, as well as decreased leukemia-free survival in primary myelofibrosis.[72,73] Increased neutrophil-to-lymphocyte ratio, a measure of systemic inflammation, is associated with increased thrombotic risk in patients with polycythemia vera.[74] In addition, patients with MPNs have elevated serum levels of inflammatory cytokines,[75] such as IL-6, and tumor necrosis factor-alpha in bone marrow niche cells, including stromal cells, and in osteoblasts.[76] Plasma levels of IL-1, IL-2, IL-6, IL-8, IL-12, IL-18, tumor necrosis factor-alpha, platelet-derived growth factor, and vascular endothelial growth factor levels increase in patients with MPNs. A number of these mediators may promote atherogenesis.[61,77-82]

Reactive oxygen species are proinflammatory and contribute to chronic inflammatory states.[83] Patients with MPNs have indications of increased oxidative stress and reactive oxygen species production,[84-86] dependent on mutational status. Patients with primary myelofibrosis and *JAK2*^{V617F} mutations had higher production of proinflammatory reactive oxygen species compared with patients with calreticulin mutations.[87] The role of increased reactive oxygen species and oxidative stress has undergone extensive study in atherosclerosis as well.[88] Local increases in iron from heme catabolism can also promote oxidative stress in plaques.[61,64] Increased oxidative stress is associated with more severe coronary artery disease and worse outcomes in myocardial infarction.[89,90] Additionally, oxidation of low-density lipoprotein by monocyte-derived reactive oxygen species may contribute to foam cell formation in atherosclerotic plaque.[91]

Elevations in plasma C-reactive protein or IL-6 predict cardiovascular events independently of standard cardiovascular disease risk markers.[92-95] In the CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study), IL-1β inhibition by a monoclonal antibody decreased cardiovascular events in chronic coronary artery disease patients with prior myocardial infarction and above-median C-reactive protein. This study provided the first evidence that targeting inflammation could improve cardiovascular outcomes and validated the role of inflammation in human atherosclerosis.[96] Colchicine has also shown promise as an effective anti-inflammatory agent in preventing recurrent cardiovascular events.[97,98] In addition to involvement in cardiovascular disease, investigators have long implicated inflammation in the progression of malignancies. The 2 biggest causes of mortality in developed countries, thus, share inflammation as a common mechanism.[99-101]

TRANSFORMING GROWTH FACTOR. In addition to inflammatory cytokines, the mechanisms that promote atherothrombosis in MPN likely involve other soluble factors, including vascular endothelial growth factor, platelet-derived growth factor, and transforming growth factor (TGF)-β.[4,77] MPN has been associated with increased expression and serum levels of TGF-β.[102,103] Although older studies suggested that TGF-β may limit atherogenesis, newer evidence suggests a more complex picture and indicates that TGF-β may actually promote atherogenesis.[104-106] One small study noted increased TGF-β expression in platelets of patients with acute

FIGURE 2 **Fibrogenic Mediators Promote Bone Marrow Fibrosis in Myeloproliferative Neoplasms**



Arrows indicate relationships. Neoplastic megakaryocytes in myeloproliferative neoplasms secrete transforming growth factor-β and lysyl oxidase, which promote bone marrow fibrosis. Lysyl oxidase oxidizes platelet-derived growth factor (PDGF) receptors on the surface of stromal cells and megakaryocytes, which enhances ligand affinity to receptors and promotes proliferation of neoplastic megakaryocytes. Lysyl oxidase also exerts effects on platelets and increases platelet activation and adhesion to collagen.

coronary syndrome compared with patients with stable coronary artery disease, though lower platelet TGF-β levels were associated with increased mortality.[107] In another study, augmented activation of endothelial TGF-β signaling correlated with the extent of left main coronary atherosclerosis in patients with coronary artery disease.[106] In patients on peritoneal dialysis, serum TGF-β1 levels were associated with increased common carotid artery intima-media thickness.[108] TGF-β contributes to endothelial/epithelial-mesenchymal transition, a process known to contribute to oncogenesis. Endothelial/epithelial-mesenchymal transition can not only participate in atherogenesis but could promote fibrosis in the bone marrow niche.[109] Although increased TGF-β is associated with MPNs and may contribute to atherosclerosis, the direct role of TGF-β in MPN-associated atherosclerosis and cardiovascular disease remains unproved and furnishes a fertile field for future investigation.

LYSYL OXIDASE: A COMMON MECHANISM IN MPN AND CARDIOVASCULAR CONDITIONS. Lysyl oxidase (LOX), a secreted enzyme that facilitates cross-link formation during the maturation of collagen or elastin fibrils,[110] was first described as elevated in MPN, using a mouse model of the disease.[111] Following this study, it was also reported as elevated in sera of patients with MPNs.[112] LOX level may rise in MPNs, at least in part, because of increased serum and bone marrow megakaryocyte TGF-β concentrations and signaling, as the latter is a known stimulator of LOX expression.[4,112,113] LOX not only facilitates collagen crosslinking, but recent results implicate this enzyme in the progression of MPNs (especially primary myelofibrosis) and in the development of thrombosis. Elevated LOX was found to augment platelet adhesion to collagen and platelet activation[4,114] (**Figure 2**). LOX could also contribute to the pathogenesis and progression of cardiovascular disease by oxidizing platelet-derived growth factor receptors, causing an increased affinity for platelet-derived growth factor, decreasing the turnover of components of the platelet-derived growth factor receptor signal transduction pathway and amplifying its mitogenic and fibrogenic signals, as well as by increasing extracellular matrix stiffness.[111,115,116] Inhibition of LOX can reduce the fibrotic burden in primary myelofibrosis and improve the heightened thrombogenic potential in mice with experimental MPNs and arterial thrombosis.[111,114,117] Furthermore,

LOX may participate in atherogenesis through its effects on vascular smooth muscle proliferation and migration.[118,119] Endothelial LOX diminishes with elevated low-density lipoprotein levels in early atherosclerotic disease and increases in late atherosclerotic disease.[120,121] The fibrous cap of atherosclerotic lesions harbors high levels of LOX, where this enzyme may promote plaque stability.[122]

Through its effects on vascular smooth muscle migration and proliferation, however, LOX may also contribute to restenosis after arterial interventions.[123,124] Inhibition of LOX activity predisposes to arterial aneurysm formation (lathyrism). LOX may also aggravate adverse left ventricular remodeling after myocardial infarction. In mice with experimental myocardial infarction, increased expression of LOX in the myocardium was associated with heightened cardiac fibrosis and expansion of the infarct zone, effects attenuated by pharmacologic inhibition of LOX.[125-127] The role of LOX in restenosis, post-myocardial infarction adverse cardiac remodeling, and platelet activation could explain how the elevated LOX levels in MPN predispose these patients to increased complications after myocardial infarction and primary percutaneous coronary intervention, as suggested by a small case series in patients with essential thrombocythemia that showed increased complication rates in this context.[128]

BLOOD CELLS AND THROMBOSIS. Unlike CHIP, patients with MPNs have abnormal hemograms disclosing features that can contribute to thrombosis and cardiovascular disease risk in addition to the risk imparted by genetic mutations. Neutrophils, defenders against pathogenic invaders, may have altered function in MPNs and may also contribute to complications of atherosclerosis and cardiovascular disease. Indeed, leukocytosis is associated with increased risk for arterial thrombosis in patients with MPNs.[20,21,129,130] Neutrophils from patients with unstable angina exhibit more ready activation, as evidenced by higher blood levels of myeloperoxidase.[131] Neutrophils can undergo a specialized form of cell death and extrude DNA that forms neutrophil extracellular traps, structures initially implicated in trapping bacterial pathogens.[132] Beyond a putative antimicrobial action, neutrophil extracellular trap formation also appears to promote thrombosis and activate endothelial cells, enhancing atherosclerotic plaque formation and thrombotic complications.[133-136] Although one study did not show increased ex vivo production of neutrophil extracellular traps in patients with MPNs, the neutrophils of patients with MPNs show increased reactivity and produce higher basal levels of reactive oxygen species, potential contributors to neutrophil extracellular trap production.[137-140] Neutrophils in *Jak2*^{V617F} mice have increased rolling and adhesion, as well as augmented atherosclerotic plaque infiltration.[61] These cells also exhibit greater tendency to form neutrophil extracellular traps and display aggravated experimental venous thrombosis.[140] This increased neutrophil activation provides yet another link between MPNs and atherothrombosis.

Platelets participate prominently in the formation of thrombi. Antiplatelet therapy is a cornerstone in the management and secondary prevention of cardiovascular disease. Thrombocytosis often accompanies MPNs and can occur in all 3 disorders (polycythemia vera, essential thrombocythemia, and prefibrotic primary myelofibrosis).[141] In addition to elevated numbers, platelets exhibit altered functions in MPNs, which contributes to both thrombotic and hemorrhagic complications associated with these disorders.[70] Patients with myelofibrosis and essential thrombocythemia can have increased platelet activation, which likely contributes to thrombogenesis.[113,142,143] Additionally, patients with essential thrombocythemia may have decreased sensitivity to the antiplatelet effect of aspirin via decreased thromboxane A_2 production inhibition.[144,145] Platelets from primary myelofibrosis patients have increased adhesion to collagen compared with healthy control subjects, another property attributed to increased LOX activity.[113]

A recent study in mice bearing the *Jak2*^{V617F} mutation in bone marrow megakaryocytes and platelets showed that the mutated platelets had a significantly reduced number of dense granules, which could explain an observed diminished second wave of activation. Compared with matched controls, the mutated mice formed small thrombi upon vascular injury (potentially occlusive of small veins) and prolonged bleeding time, observations that may help understand the mechanisms of the hemorrhagic events associated with MPN.[146] In accordance, studies involving human MPN cohorts identified dense granule storage defects. In one study of 9 patients with myeloproliferative disorders of myelofibrosis, platelets were found to have significant storage pool depletion (measured by adenosine diphosphate/adenosine triphosphate ratio and ^{14}C-serotonin platelet disappearance patterns).[147] Another study reported a defect in mepacrine uptake in platelet-dense granules in 71% of the subjects with polycythemia vera and in 48% of those with essential thrombocythemia, suggesting deficiency in platelet-dense granules.[148]

In addition to leukocytes and platelets, alterations in erythrocyte form and function may also contribute

to increased atherosclerosis and thrombosis.[149] Patients with CHIP, and particularly those with *JAK2* mutations, have increased erythrocyte anisocytosis.[11] Studies involving small cohorts revealed an association between increased erythrocyte anisocytosis and thrombosis in patients with essential thrombocythemia and polycythemia vera and increased death in primary myelofibrosis.[150,151] In patients without CHIP or MPNs, anisocytosis was also associated with increased cardiovascular disease risk.[152,153] Additionally, erythrocytosis by itself may increase cardiovascular disease risk, independent of erythrocyte function. In patients with polycythemia vera, hematocrits of >45% was associated with increased risk for cardiovascular events and death.[154] Tradition ascribed this risk to hyperviscosity, but erythrocytosis may serve as a biomarker of the complex of biological abnormalities associated with MPN. One study demonstrated that erythrocyte-derived microvesicles can facilitate arterial vasospasm by disturbing the endothelial nitric oxide pathway in a *Jak2*-mutated mouse model.[155] Erythrocytosis also heightens risk in cardiovascular disease in patients without MPNs.[156] Additionally, either anemia or erythrocytosis can worsen outcomes after acute ischemic strokes.[157]

RENIN-ANGIOTENSIN SYSTEM ALTERATIONS IN MPNs AND ATHEROSCLEROSIS. A dysregulated renin-angiotensin system causes deleterious effects on the cardiovascular system.[80] Increased renin-angiotensin system activation in the bone marrow of patients may result from overactivity of the JAK/STAT signaling pathway in MPNs.[158] Additionally, the use of angiotensin-converting enzyme inhibitors in patients with polycythemia vera improved hematocrit levels and reduced the need for cytoreductive drugs.[159] Similarly, mice with experimental myelofibrosis treated with captopril (an angiotensin-converting enzyme inhibitor) have reduced splenomegaly and bone marrow fibrosis.[160] Whether systemic renin-angiotensin system activation contributes to atherogenesis in patients with MPNs remains speculative and merits further investigation.

SUMMARY POINTS.

- Increased inflammation is associated with MPNs and may contribute to increased cardiovascular disease risk in these patients.
- Patients with MPNs have increased TGF-β and LOX expression, which play a role in bone marrow fibrosis, atherogenesis, and thrombosis.
- Patients with MPNs have altered numbers and functions of blood cells, including red cells, leukocytes, and platelets, which contribute to the risk for cardiovascular events, especially thrombosis and bleeding.
- The renin-angiotensin system may also participate in a common pathophysiologic pathway in MPN and cardiovascular disease, though further studies are needed to elucidate its role in cardiovascular disease in patients with MPNs.

CLINICAL IMPLICATIONS AND CHALLENGES IN MANAGING CARDIOVASCULAR DISEASE AND RISK FACTORS IN PATIENTS WITH MPNs. Preventing thrombotic events should be a priority to reduce morbidity and mortality in MPN.[161] Aspirin is commonly used in patients with polycythemia vera and essential thrombocythemia, and to some extent in those with primary myelofibrosis, and can reduce the risk for thrombosis.[162-164] Small studies, however, have suggested incomplete inhibition by aspirin of production of the prothrombotic thromboxane A_2 in patients with essential thrombocythemia, though twice-daily dosing of aspirin may suffice to overcome this resistance.[144,145,165] Therapy with other antiplatelet agents, including $P2Y_{12}$ inhibitors, has not undergone rigorous study in the MPN population. Cytoreduction can also reduce the risk for thrombosis in patients with MPN.[166] In polycythemia vera, phlebotomy to control hematocrit levels to <45% limits thrombosis and reduces the incidence of cardiovascular events.[154] In a study of patients with hypertension enrolled in the ECLAP (European Collaboration on Low-Dose Aspirin in Polycythemia Vera) trial, treatment with angiotensin-converting enzyme inhibitors (a mainstay in cardiovascular management) in patients with polycythemia vera led to improved hematologic parameters, but its effect on cardiovascular events in this population remains uncertain.[159]

In addition to thrombotic complications, patients with MPNs have increased risk for hemorrhage, which complicates the use of anticoagulation and antiplatelet therapy in primary and secondary prevention of coronary artery disease in these patients.[3] In one meta-analysis, the pooled prevalence of hemorrhagic complications at MPN diagnosis was 6.2%, with primary myelofibrosis having the highest prevalence (8.9% vs 7.3% and 6.9% for essential thrombocythemia and polycythemia vera, respectively).[3] Common sites of bleeding included mucocutaneous (2.8%), gastrointestinal (2.1%), and epistaxis (1.0%).[3] Multiple factors contribute to increased bleeding in MPN, among them acquired von Willebrand factor deficiency in patients with MPNs, particularly those with extreme thrombocytosis.[167] Despite this finding, however, one study showed similar rates of major

bleeding after stroke in patients with polycythemia vera treated with anticoagulation or antiplatelet agents and in the general population.[168] Likewise, antithrombotic therapy for venous thromboembolism in patients with MPNs appears safe, though patients with MPNs may have higher risk for thrombosis after discontinuation of vitamin K antagonists.[169]

A systematic review and meta-analysis of studies evaluating anticoagulant and/or antiplatelet therapy, with and without cytoreduction, in patients with MPNs and venous thromboembolism, showed that the use of direct oral anticoagulant agents with cytoreduction was associated with lower recurrent venous thromboembolism compared with the use of vitamin K antagonists with cytoreduction (7.9% vs 17.6%).[170] In a single-center study, patients with MPNs treated with direct oral anticoagulant agents had a high 1-year risk for bleeding, with 12.3% of patients developing bleeding.[171] In a study of 1,602 patients with polycythemia vera, however, the concurrent use of aspirin and anticoagulation was associated with a more than 5-fold increased risk for hemorrhage compared with aspirin alone.[172] Therefore, the management of patients with MPNs who have indications for both antiplatelet and anticoagulation therapy requires considerable care. In addition to venous thromboembolism, atrial fibrillation is another common indication for anticoagulation in patients with MPNs. However, traditional risk scores used to evaluate risk for hemorrhage vs benefit of thrombosis prevention do not include MPN status and may not accurately predict bleeding or thrombosis in patients with MPN.[173] Therefore, further investigation of balancing thrombotic with bleeding risk and the development of risk stratification scores is warranted.

Aside from thrombotic and hemorrhagic complications, patients with MPNs can progress to acute myeloid leukemia. Primary myelofibrosis having the highest risk for leukemic transformation.[2] Progression to secondary myelofibrosis occurred in 12.7% of patients with polycythemia vera and 9.9% of those with essential thrombocythemia.[1] Patients with primary myelofibrosis have a 10% to 20% risk for leukemic transformation at 10 years after diagnosis compared with 2.3% in those with polycythemia vera and 1% to 10% in those with essential thrombocythemia.[2] Thus, management of thrombotic complications in patients with MPNs who experienced progression of their disease and have competing risks, including bleeding and noncardiovascular death, requires risk/benefit calculations.

SUMMARY POINTS.

- In addition to cardiovascular disease, patients with MPNs often have competing risks, including bleeding and hematologic progression to secondary myelofibrosis or acute leukemia, which may complicate cardiovascular disease management.
- Cytoreduction is an important therapy used in patients with MPNs to reduce thrombotic risk.
- Bleeding can complicate anticoagulation and antiplatelet use in patients with MPNs, with the risk being highest among patients on both antiplatelet (eg, aspirin) therapy and anticoagulation.
- Direct oral anticoagulant agents may more effectively prevent recurrent venous thromboembolism compared with vitamin K antagonists in patients with MPNs, but more investigation is needed.

POTENTIAL NOVEL CARDIOVASCULAR THERAPEUTIC TARGETS IN PATIENTS WITH MPNs

Precision medicine promises to tailor medical therapy to individual patients and their personal risk profiles. In MPNs, inflammation likely contributes to both pathogenesis and complications. Similarly, inflammation is a hallmark in atherosclerosis and cardiovascular disease. CANTOS allocated IL-1β antagonism to patients with previous myocardial infarction who had persistently elevated C-reactive protein (>2 mg/L) despite standard-of-care therapy.[96] Although IL-1β inhibition has not been explored in the context of MPNs, exploratory analyses from CANTOS showed reduced deaths due to malignancy.[174] The reduced incident and fatal lung cancer accounted for most of this substantial drop in cancer. As noted earlier, IL-1 neutralization in hypercholesterolemic mice with myeloid *Jak2*^{V617F} mutations reduces features in atheroma that are associated with propensity to provoke thrombotic events in humans.[62] An exploratory analysis of CANTOS showed that those participants with CHIP due to *TET2* mutations trended toward greater benefit with canakinumab treatment. This analysis had insufficient power to assess the effect of IL-1β neutralization in those participants with *JAK2* mutations.[175] Anti-inflammatory therapies thus merit further exploration in the treatment of MPN and cancer in general.[71,174,176]

Currently, inhibition of the JAK/STAT pathway with ruxolitinib is the only U.S. Food and Drug Administration approved tailored therapy available to patients with MPNs. Ruxolitinib, a JAK1 and JAK2 inhibitor, was originally approved for primary

myelofibrosis and now for high-risk polycythemia vera, and showed modest improvement in survival in patients with primary myelofibrosis.[177,178] In essential thrombocythemia, ruxolitinib has not shown benefit compared with the best available therapy and thus is not used in these patients.[179] Although the trials involving ruxolitinib in polycythemia vera were not powered for prevention of thrombosis, thrombosis tended to be decreased in the ruxolitinib arms (0.9% vs 5.4%).[180] A meta-analysis of 3 large trials comparing ruxolitinib with standard of care (COMFORT, COMFORT-2, and RESPONSE) showed that treatment of patients with polycythemia vera or myelofibrosis with ruxolitinib reduced arterial or venous thrombotic events (risk ratio: 0.46; 95% CI: 0.23-0.88).[181] Thus, JAK inhibition may decrease markers of thrombosis in patients with MPNs, as potentially suggested through the assessment of the effects of ruxolitinib. Yet the effects of other JAK inhibitors on thrombosis and cardiovascular disease require more investigation, as illustrated by a recent Food and Drug Administration notice regarding tofacitinib, a JAK inhibitor that preferentially inhibits JAK1 and 3, citing increased risk for thrombosis in patients with rheumatoid arthritis or inflammatory bowel disease.[182] A recent trial showed signals for cardiovascular hazard, cancers, and infections in patients with rheumatoid arthritis treated with tofacitinib compared with tumor necrosis factor inhibitors during a mean exposure of about 40 months.[183] These concerning data should spur the development and evaluation of safety and efficacy of more selective JAK inhibitors.

In addition, LOX inhibition has shown promise in ameliorating fibrosis in animal studies of primary myelofibrosis.[111,117] Given the possible participation of LOX in platelet activation and adhesion, targeting this enzyme deserves further investigation in patients with MPNs.[114] In particular, LOX inhibition merits consideration in the post-percutaneous coronary intervention and myocardial infarction settings, as LOX may play a larger role in restenosis and cardiovascular remodeling than in atherogenesis itself, although studies would have to monitor the development of arterial aneurysms.

SUMMARY POINTS.

- Ruxolitinib, a JAK1 and JAK2 inhibitor, may reduce the risk for thrombosis in patients with MPNs, although the use of JAK inhibitors warrants caution given the reports of other JAK inhibitors (eg, tofacitinib) augmenting cardiovascular disease risk in other patient populations.
- Anti-inflammatory therapy may be beneficial in patients with MPNs to reduce cardiovascular disease risk, though this remains an area of further investigation.
- LOX inhibition may be a novel therapeutic option in MPNs, and its effect on cardiovascular and thrombotic risk remains to be explored in human studies.

CONCLUSIONS

Increasing evidence has demonstrated common pathophysiologic mechanisms that underlie 2 seemingly disparate diseases, cardiovascular conditions and diseases caused by somatic mutations in bone marrow stem cells that fall on the spectrum of clonal hematopoiesis and that often develop with aging. This discovery has dramatically altered the way both conditions are viewed and will surely alter treatment strategies. These new convergences create ample opportunity for further research and investigation and promise to alter radically the way clinicians treat patients with MPNs. Cardiovascular disease in the setting of MPNs, although largely underappreciated, offers manifold opportunities for future investigation. Recent and ongoing research in inflammation, clonal hematopoiesis, and MPN will likely expand mechanistic understanding of the disease and yield novel treatments for this cluster of conditions that intersect cardiovascular medicine, hematology-oncology, and aging. Ultimately, the application of these new insights should lead to improved outcomes in this vulnerable population.

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company developing therapeutic human antibodies; and has a financial interest in TenSixteen Bio, a company targeting somatic mosaicism and CHIP to discover and develop novel therapeutics to treat age-related diseases. Dr Libby's interests were reviewed and are managed by Brigham and Women's Hospital and Mass General Brigham in accordance with their conflict-of-interest policies. Dr Leiva has reported that he has no relationships relevant to the contents of this paper to disclose.

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