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Beyond Thrombosis: Pulmonary Hypertension and Heart Failure in Patients With Myeloproliferative Neoplasms

JACC: CardioOncology State-of-the-Art Review

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ABSTRACT

Patients with myeloproliferative neoplasms (MPNs) are at increased risk for cardiovascular disease. Although thrombosis is a well-recognized complication, emerging evidence indicates that nonthrombotic conditions, including heart failure (HF) and pulmonary hypertension (PH), are also prevalent and associated with adverse cardiovascular and hematologic outcomes. Clinical and preclinical data suggest a shared pathophysiology linking MPNs to the development and progression of cardiomyopathy, HF, and both precapillary and postcapillary PH. Recent studies further support a bidirectional relationship, in which HF and PH are associated with hematologic progression and vice versa. Elucidating the mechanisms underlying these interactions may uncover novel therapeutic targets and inform clinical management. Here, the authors review the pathophysiology and impact of HF and PH in patients with MPNs. (JACC CardioOncol. 2025;7:538–553)

Myeloproliferative neoplasms (MPNs) are clonal hematopoietic disorders that include polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF).[1-3] These are chronic conditions typically diagnosed in the fifth or sixth decade of life, with life expectancy measured in years; however, aggressive phenotypes such as MF are associated with significantly reduced survival.[3,4] Patients with MPNs are at risk for hematologic progression to secondary MF or acute leukemia.[4,5] The disease is driven by mutations that constitutively activate the Janus-associated kinase

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HIGHLIGHTS

- PH and HF are complications of MPNs and are associated with adverse outcomes.
- EMH and inflammation may contribute to PH and HF in MPNs.
- Further research is needed to better characterize PH and HF in patients with MPN.

(JAK)/signal transducer and activator of transcription (STAT) signaling pathway, which regulates proinflammatory cytokine production and hematopoietic proliferation.[6] Mutations in JAK2, calreticulin (CALR), and myeloproliferative leukemia protein account for the majority of driver mutations, with JAK2 V617F present in approximately 95% of patients with PV and 60% of those with ET or MF.[7-9] Patients may also harbor nonphenotypic driver mutations that influence the risk for hematologic progression and cardiovascular complications. Frequently implicated genes include *TET2* (Tet methylcystosine dioxygenase 2), *DNMT3A* (DNA methyltransferase 3 alpha), and additional sex combs-like 1, which are also found in clonal hematopoiesis of indeterminate potential (CHIP).[10,11]

Cardiovascular events are common in patients with MPNs and are a major source of morbidity and mortality.[12-14] Although thrombotic complications are well established, emerging evidence indicates that nonthrombotic cardiovascular conditions, including pulmonary hypertension (PH) and heart failure (HF), are also prevalent and contribute significantly to clinical outcomes.[15-17] PH in particular has been linked to worse prognosis in patients with MPNs.[17-20] Despite its relative frequency, the etiology of PH in this population remains poorly understood. Recent studies have begun to elucidate its underlying pathophysiology. Notably, beyond its cardiovascular impact, PH is also associated with increased risk for progression to more aggressive disease phenotypes, including MF and acute leukemia.[17]

HF is also common among patients with MPNs. Prior studies suggest that individuals with MPNs are at increased risk for developing HF compared with the general population.[21] Among patients already at risk, such as those with acute coronary syndrome or arrhythmias, those with MPNs have higher rates of HF hospitalizations.[22-24] Data from mouse models demonstrate that JAK2 and TET2 mutations lead to adverse remodeling and HF phenotypes.[25-29] These findings support a shared pathophysiology linking PH, HF, and MPNs. Understanding these connections may uncover novel diagnostics and therapeutic strategies for 2 seemingly distinct but interconnected disease processes.

EPIDEMIOLOGY AND HEMODYNAMIC CHARACTERIZATION OF PH IN MPNs

PH is characterized by elevated pulmonary artery (PA) pressures and is diagnosed via right heart catheterization (RHC), with a mean PA pressure (mPAP) >20 mm Hg considered diagnostic. Transthoracic echocardiography (TTE) is commonly used for screening and can estimate right ventricular systolic pressure (RVSP) when sufficient tricuspid regurgitation is present. TTE is also useful in identifying abnormalities in right ventricular (RV) size and function, right atrial enlargement, and PA dilation, all of which are associated with PH. Among patients with MPNs, PH appears to be common, although prior studies have used varying diagnostic cutoffs (eg, mPAP for RHC and RVSP for TTE).

Estimates of PH prevalence in MPNs range from 4% to 58% (1% to 78% for ET, 0% to 47% for PV, and 12% to 50% for MF).[17,18,30-42] In a large meta-analysis, the overall prevalence of PH was 33%.[43] Prevalence differed by diagnostic modality: studies using TTE reported a 5-fold higher prevalence compared with those using RHC.[43] The wide availability and noninvasive nature of TTE make it a convenient screening tool for PH, though estimated RVSP by TTE can be inaccurate.[44] Nevertheless, TTE remains the recommended screening tool for PH, whereas RHC is the gold standard for definitive diagnosis.[45] Among TTE-based studies, definitions of PH vary. The most common definition is an estimated RVSP >35 mm Hg (**Table 1**); others include tricuspid regurgitant velocity >2.9 m/s or alternative RVSP thresholds (>40 or >50 mm Hg).

The prevalence of PH in MPNs may vary by MPN phenotype. In a multicenter study of 555 patients with MPN, those with elevated estimated RVSP (≥40 mm Hg) were more

ABBREVIATIONS AND ACRONYMS

BM = bone marrow

CALR = calreticulin

CHIP = clonal hematopoiesis of indeterminate potential

CMD = coronary microvascular dysfunction

Cpc-PH = combined precapillary and postcapillary pulmonary hypertension

CTEPH = chronic thromboembolic pulmonary hypertension

CXCL12 = chemokine (C-X-C motif) ligand 12

DNMT3A = DNA methyltransferase 3 alpha

EMH = extramedullary hematopoiesis

EPC = endothelial progenitor cell

ET = essential thrombocythemia

HF = heart failure

HOHF = high-output heart failure

JAK = Janus-associated kinase

LOX = lysyl oxidase

MF = myelofibrosis

mPAP = mean pulmonary artery pressure

MPN = myeloproliferative neoplasm

PA = pulmonary artery

PAH = pulmonary arterial hypertension

PH = pulmonary hypertension

PV = polycythemia vera

PVR = pulmonary vascular resistance

RHC = right heart catheterization

RV = right ventricle/ventricular

RVSP = right ventricular systolic pressure

STAT = signal transducer and activator of transcription

TET2 = Tet methylcystosine dioxygenase 2

TTE = transthoracic echocardiography

VTE = venous thromboembolism

WU = Wood units

TABLE 1 Prevalence of PH in Patients With Myeloproliferative Neoplasms

TTE First Author	Study Type	N	Definition of PH	PH Prevalence, n (%)	ET, n (% of Patients With PH, % Prevalence of PH)	PV, n (% of Patients With PH, % Prevalence of PH)	MF, n (% of Patients With PH, % Prevalence of PH)	RVSP, mm Hg
Khan et al[31]	Retrospective	68	RVSP >35 mm Hg	NA	18 (26, NA)	23 (34, NA)	11 (16, NA)	61 ± 22
Payzin et al[32]	Retrospective	122	RVSP >35 mm Hg	33 (27)	17 (52, 27)	11 (33, 23)	5 (15, 50)	46 (37, 58)
Jindamai et al[33]	Prospective	66	TRV >2.9 m/s	3 (5)	2 (67, 8)	0 (0, 0)	1 (33, 17)	NA
Lee et al[34]	Retrospective	225	TRV >3.4 m/s	34 (15.1)	19 (56, 16)	9 (26, 11)	6 (18, 29)	NA
Kolto et al[111]	Prospective	81	RVSP >40 mm Hg	11 (14)	NA	NA	NA	NA
Lopez-Mattei et al[35]	Retrospective	143	RVSP >35 mm Hg	20 (14)	NA	NA	20 (14)	48 ± 9
Yaylali et al[37]	Retrospective	197	RVSP >40 mm Hg	11 (6)	1 (9, 1)	3 (27, 4)	7 (64, 30)	58 ± 20
Kim et al[18]	Retrospective	301	RVSP >35 mm Hg	135 (45)	26 (19, 44)	29 (21, 47)	29 (21, 51)	48 ± 12
Venton et al[137]	Retrospective	183	RVSP >35 mm Hg	14 (8)	5 (36, 6)	4 (29, 8)	2 (14, 18)	46 (40, 61)
Austin et al[36]	Retrospective	25	RVSP >35 mm Hg	14 (56)	NA	NA	NA	NA
Brabrand et al[30]	Retrospective	158	TRV >2.9 m/s	6 (4)	1 (17, 2)	2 (33, 3)	3 (50, 12)	NA
Mattar et al[38]	Retrospective	60	TRV >2.9 m/s	7 (12)	2 (29 ,11)	2 (29, 7)	3 (43, 23)	NA
Cortelezzi et al[39]	Retrospective	36	RVSP >35 mm Hg	13 (36)	NA	NA	NA	NA
Chebrek et al[138]	Retrospective	103	RVSP >35 mm Hg	8 (8)	1 (12, 4)	0 (0, 0)	3 (37, 20)	40 (36, 50)
Garypidou et al[40]	Retrospective	24	RVSP >35 mm Hg	10 (42)	6 (60, 43)	0 (0, 0)	3 (30, 50)	39 (37, 41)
Gupta et al[41]	Retrospective	25	RVSP >35 mm Hg	1,922 (48)	7 (58, 78)	5 (42, 29)	NA	NA
Altintas et al[42]	Retrospective	46	RVSP >35 mm Hg	22 (48)	NA	NA	NA	47 ± 12
Leiva et al[17]	Retrospective	197	RVSP >50 mm Hg	92 (47)	43 (47, 50)	34 (37, 42)	15 (16, 48)	56 (53, 62)
Leiva et al[110]	Retrospective	555	RVSP >40 mmHg	195 (35.1)	228 (37.4, 32.0)	237 (36.9, 30.4)	90 (25.6, 55.5)	34 (26, 44)

RHC First Author	Study Type	N	Definition of PH	PH Prevalence, n (%)	mPAP, mm Hg	PVR, WU	Cardiac Index, L/min/m^2	Hemodynamic Classification of PH
Dingli et al[48]	Retrospective	5	mPAP >25 mm Hg	NA	42 (36-60)	6.3 (3.7-9.0)	5 (4.1-5.3)	Precapillary: 1 (20) Postcapillary: 1 (20) Cpc-PH: 3 (60)
Guilpain et al[49]	Case series	10	mPAP >25 mm Hg	NA	CTEPH: 51 (34-60) PAH: 53 (36-59)	NA	NA	Precapillary: 10 (100) Postcapillary: 0 Cpc-PH: 0
Brabrand et al[30]	Retrospective	6	mPAP >25 mm Hg	NA	All: 39 (32-41) ET/PV: 34 (28-38) MF: 41 (41-42)	All: 2.9 (1.7-4.7) ET/PV: 1.8 (1.4-2.9) MF: 4.7 (3.0-4.9)	NA	Precapillary: 3 (50) Postcapillary: 2 (33.3) Cpc-PH: 1 (16.7)
Leiva et al[17]	Retrospective	25	mPAP >20 mm Hg	NA	34 (27-37)	3.6 (1.8-4.1)	NA	Precapillary: 12 (48) Postcapillary: 6 (24) Cpc-PH: 7 (28)
Khan et al[31]	Retrospective	68	mPAP >20 mm Hg	60 (88)	All: 37 ± 12 PV: 35.6 ± 12.0 ET: 38.2 ± 8.8 MF: 39.5 ± 11.4	NA	All: 5.2 ± 1.8 PV: 4.6 ± 1.5 ET: 5.1 ± 1.8 MF: 5.4 ± 2.1	Precapillary: 20 (33) Postcapillary: 19 (32) Cpc-PH: 21 (35)
Montani et al[50]	Retrospective	90	mPAP >25 mm Hg	90 (100)	All: 42 (25-61) PV: 44 (26-61) ET: 40 (28-61) MF: 38 (25-53)	All: 6.7 (1.6-15.4) PV: 6.7 (1.6-13.7) ET: 8.1 (3.0-15.4) MF: 4.6 (1.6-10.3)	All: 4.8 (2.7-13.5) PV: 4.9 (3.0-10.1) ET: 4.4 (2.7-7.7) MF: 5.4 (3.0-13.5)	Precapillary: 90 (100) Postcapillary: 0 Cpc-PH: 0

Values are n (%) for categorical variables and median (Q1-Q3) or mean ± SD for categorical variables.

Cpc-PH = combined precapillary and postcapillary pulmonary hypertension; CTEPH = chronic thromboembolic pulmonary hypertension; ET = essential thrombocythemia; MF = myelofibrosis; mPAP = mean pulmonary artery pressure; NA = not available; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; PV = polycythemia vera; PVR = pulmonary vascular resistance; RHC = right heart catheterization; RVSP = right ventricular systolic pressure; TRV = tricuspid regurgitation velocity; TTE = transthoracic echocardiographic; WU = Wood units.

likely to have MF (25.6% vs 11.1%; $P < 0.001$).[46] Similarly, a single-center study of 272 patients with MPNs revealed a higher proportion of MF among those with elevated RVSP (27.5% vs 11.8%; $P = 0.004$).[47] In a cohort of 197 patients with MPNs and cardiovascular disease, patients with MF had a higher incidence of elevated estimated RVSP (≥50 mm Hg) compared with those with ET or PV after competing-risk regression.[17] In a Korean study of 225 patients with MPN who underwent TTE, a greater proportion of MF patients (28.6%) had PH (defined in that study as tricuspid regurgitant velocity > 3.4 m/s) compared with those with ET (15.7%) or PV (10.8%).[34] A meta-analysis further confirmed that

MF was associated with the highest PH prevalence (51.8%), followed by ET (24.3%) and PV (17.0%).[43] Longer MPN disease duration was also linked to increased risk for PH diagnosis.[43,47]

PH is a heterogenous disorder that can be classified by both its hemodynamic profile and its underlying etiology. Hemodynamically, PH is categorized into 3 types: precapillary PH, postcapillary PH, and combined precapillary and postcapillary PH (Cpc-PH). Precapillary PH is defined as mPAP >20 mm Hg, pulmonary capillary wedge pressure ≤15 mm Hg, and pulmonary vascular resistance (PVR) >2.0 WU, reflecting obstruction at the level of the PAs or arterioles, proximal to the alveolar-capillary interface. Isolated postcapillary PH is characterized by elevated pulmonary venous pressures and normal PVR, most often due to left heart disease (including HF and valvular heart disease), and is defined as mPAP >20 mm Hg, pulmonary capillary wedge pressure >15 mm Hg, and PVR ≤2.0 WU. Cpc-PH is defined as mPAP >20 mm Hg, pulmonary capillary wedge pressure >15 mm Hg, and PVR >2 WU. RHC remains the gold standard for hemodynamic characterization and for distinguishing precapillary from postcapillary PH; however, invasive hemodynamic data in patients with MPNs are currently limited.

Among studies using RHC, the reported prevalence of PH ranged from 47% to 88%, although these estimates may be affected by indication bias, as RHC is typically performed in selected patients.[17,30,31,48-50] In small case series and cohort studies of patients with MPNs and PH, including all hemodynamic phenotypes, the pooled prevalence of precapillary PH was 33.0% (range: 20%-50%), that of isolated postcapillary PH was 37.6% (range: 20%-43%), and that of Cpc-PH was 29.4% (range: 17%-60%).[17,30,31,48] In one study focused primarily on precapillary PH (with Cpc-PH included if the precapillary component was dominant), 90 patients with MPNs were evaluated. Among patients with PH, those with MPNs had a similar median mPAP (42 mm Hg vs 46 mm Hg) but lower median PVR (6.73 WU vs 8.54 WU) and higher median cardiac output (4.8 L/min vs 4.2 L/min)[50] compared with those without MPNs. Among studies reporting hemodynamic data by MPN subtype, mPAP was generally similar across phenotypes, although most showed higher median cardiac output in patients with MF compared with those with PV or ET (**Table 1**).

In one study of patients with MPNs and precapillary PH, the underlying etiology of PH differed between those with MF and those with ET or PV, suggesting distinct phenotypes and pathophysiologic mechanisms.[50] However, substantial heterogeneity exists in the hemodynamic classification of PH across studies. This likely reflects differences in patient selection, diagnostic modality, and inclusion criteria. As such, prospective studies that systematically screen for PH using both TTE and RHC are needed to more accurately define its prevalence, prognostic significance, and hemodynamic characteristics in patients with MPNs.

SUMMARY POINTS.

- PH is common among patients with MPNs, but true prevalence remains unclear because of variability in diagnostic modalities and definitions.
- MF is associated with the highest prevalence of PH, whereas PV is associated with the lowest.
- RHC-based studies suggest a roughly equal distribution of precapillary, postcapillary, and combined (Cpc-PH) phenotypes.

ETIOLOGIES AND PATHOPHYSIOLOGY OF PH IN MPNs

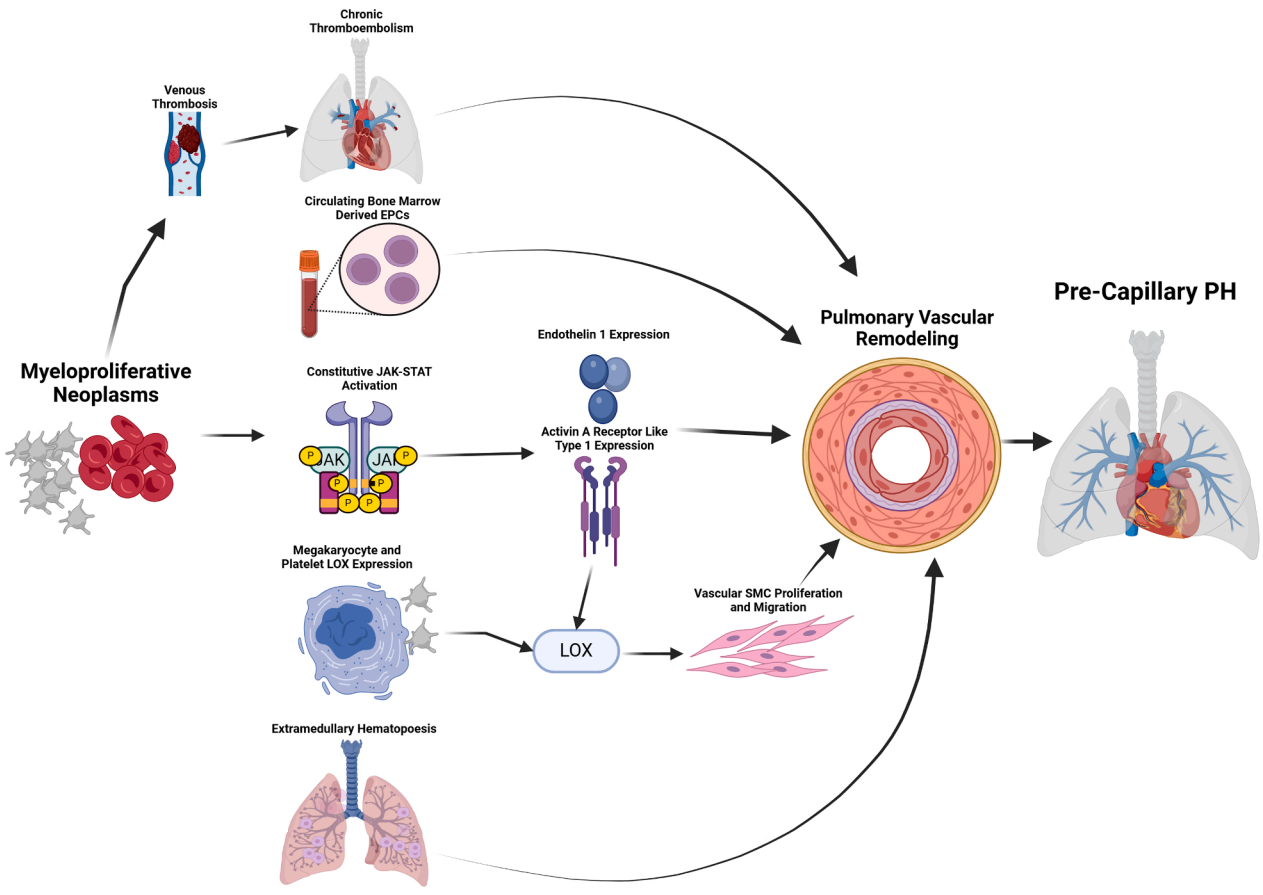
The World Health Organization classifies PH by etiology into 5 groups. Group 1 includes pulmonary arterial hypertension (PAH); group 2, PH due to left heart disease; group 3, PH due to pulmonary disease; group 4, chronic thromboembolic PH (CTEPH); and group 5, PH due to multifactorial mechanisms. The World Health Organization currently categorizes MPN-associated PH as group 5.

However, emerging data suggest that PH in MPNs is heterogenous. In a study of patients with precapillary PH and MPN, those with MF were more likely to have group 5 PH (82% of patients), while CTEPH was the most common etiology in patients with ET or PV (64.5%).[50] This and other studies also report that cardiac output may be higher in patients with MF and PH compared with those with ET or PV.

Beyond hemodynamic status, recent data indicate that the development of PH in MPNs is not only associated with adverse cardiovascular outcomes but may also precede hematologic progression to secondary MF or acute leukemia.[17]

A multicenter study of 555 patients with MPN and at least 1 transthoracic echocardiography examination after diagnosis demonstrated an association between PH and hematologic progression. Left heart disease—defined in the study as diastolic dysfunction (H2FPEF score >5), left atrial enlargement, reduced left ventricular ejection fraction, or at least moderate mitral or aortic valve regurgitation or stenosis—was present in 65% of patients at the time of PH diagnosis, suggesting that group 2 PH is common in this population. However, both the absence of left heart

FIGURE 1 Pathophysiology of Precapillary Pulmonary Hypertension in MPNs



Precapillary pulmonary hypertension (PH) in myeloproliferative neoplasms (MPNs) is multifactorial. Patients with MPNs are at increased risk for venous thromboembolism and chronic thromboembolic PH. Additionally, contributors may include bone marrow–derived endothelial progenitor cells (EPCs), activation of the JAK (Janus-associated kinase)/STAT (signal transducer and activator of transcription) signaling pathway, increased lysyl oxidase (LOX) expression by megakaryocytes and platelets, and extramedullary hematopoiesis. Additional details regarding the pathophysiology can be found in the corresponding text. SMC = smooth muscle cell.

disease on TTE at the time of PH diagnosis and elevated cardiac output were independently associated with an increased risk for hematologic progression, regardless of anemia status.

PATHOPHYSIOLOGY OF POSTCAPILLARY PH IN MPNs. Patients with MPNs are at increased risk for cardiovascular diseases, including HF and coronary artery disease, which may in turn predispose them to the development of group 2 PH (postcapillary PH). The most common driver mutation in MPNs, JAK2 V617F, has been associated with an increased risk for HF in both murine models and clinical observational studies.[29,51-53] Additionally, non-phenotypic driver mutations frequently seen in MPNs and CHIP, such as TET2, additional sex combs-like 1, and DNMT3A, have also been associated with HF risk and may contribute to the development of postcapillary PH.[25-27,52-57]

PATHOPHYSIOLOGY OF PRECAPILLARY PH IN MPNs. The pathophysiology of the precapillary component of PH in patients with MPNs is less well understood and likely multifactorial (**Figure 1**). Patients with MPNs are at increased risk for venous thromboembolism (VTE), which in turn raises the risk for CTEPH.[58,59] In one study of patients with ET or PV, who are at higher risk for VTE than those with MF, CTEPH was identified as the most common etiology of precapillary PH.[50]

Although the prevalence of MPNs among patients with CTEPH is not well defined, one study of 40 patients with CTEPH showed that 3 had JAK2 mutations and were subsequently diagnosed with MPNs.[60]

Additionally, patients with MPNs may also undergo splenectomy when symptoms from splenomegaly are refractory to medical therapy. Splenectomy has been associated with increased VTE risk, and one study identified it as a risk factor for both CTEPH and PAH.[61]

Another potential link between MPNs and precapillary PH involves interactions between the bone marrow (BM) and adverse pulmonary arteriolar remodeling. Increased $CD34^+/CD133^+$ circulating BM-derived endothelial progenitor cells (EPCs) have been observed in both patients with MF and those with PAH, compared with healthy control subjects.[62-68] Additionally, mice transplanted with $CD34^+/CD133^+$ EPCs from patients with PAH developed features of PAH, including angioproliferative remodeling and RV failure.[63,68]

In a separate study of patients with PAH without known MPN diagnoses, BM biopsy revealed greater than normal BM fibrosis and increased numbers of hematopoietic progenitors, despite the absence of hematologic disease.[64] In addition to elevated circulating EPCs, both PH and MPNs have been associated with increased expression of chemokine (C-X-C motif) ligand 12 (CXCL12), a key homing chemokine. Plexiform lesions in patients with PAH and endothelial cells with the JAK2 V617F mutation show abundant CXCL12 expression.[69,70] In MF, elevated CXCL12 expression may also contribute to clonal cell expansion.[71]

Whether increased expression of CXCL12 and other homing chemokines occurs in the pulmonary endothelium of patients with MPN, and whether this contributes to PH development, remains unknown. These data suggest that increased levels of circulating $CD34^+/CD133^+$ EPCs may represent a mechanistic link between MPNs, particularly MF, and the development of precapillary PH. Prospective studies are needed to understand the temporal relationship between EPC levels and PH onset in MPNs, with the goal of improving risk stratification, monitoring hematologic progression, and identifying novel therapeutic targets.

Mutations associated with MPNs may predispose individuals to the development of precapillary PH. In a chronic hypoxia-induced mouse model of PAH, mice with the JAK2 V617F mutation exhibited accelerated pulmonary vascular remodeling compared with wild-type controls.[72] This effect may be mediated by increased perivascular neutrophilic infiltration. JAK2-mutated mice also demonstrated elevated expression of activin A receptor-like type 1, a receptor implicated in PAH pathogenesis through enhanced STAT3 signaling.[73] Sotatercept, a novel antiproliferative therapy for PAH, exerts its effect by binding activins and growth differentiation factors that signal through this pathway.[74] Sotatercept has also been evaluated in a recent phase 2 trial in patients with MF and anemia, showing some evidence of efficacy.[75]

CALR mutations are the second most common driver mutations in MPNs. One preclinical study suggested that CALR mutations may also predispose to PAH.[76] In that study, wild-type mice underwent BM transplantation with either CALR-mutated or wild-type cells. Mice receiving CALR-mutated BM exhibited greater STAT3 activation, increased pulmonary vascular remodeling, and elevated PA pressures in a chronic hypoxia model of PAH.[76] Expression of endothelin-1, a protein implicated in PAH and targeted by several PAH-directed therapies, was also increased in mice transplanted with CALR-mutated cells.[77]

In a study of patients with MPN who underwent TTE, those with ET and PH had higher rates of the JAK2 V617F mutation (79.8% vs 64.3%) and lower rates of CALR mutation (7.1% vs 28.6%) compared with patients without PH.[34] This may reflect a more proliferative phenotype in JAK2 V617F–mutated ET vs CALR-mutated ET, increased thrombotic risk associated with JAK2 mutations, or a combination of these and other factors yet to be elucidated.[78]

Other mutations implicated in the development of PAH include CHIP-associated mutations, including TET2 and DNMT3A.[79,80] TET2-mutated mice developed PAH and adverse pulmonary vascular remodeling, which was ameliorated by targeting interleukin-1β, a cytokine elevated in the setting of TET2 mutation.[79] Notably, both TET2 and DNMT3A are epigenetic regulators, suggesting that epigenetic mechanisms may contribute to the progression of both PAH and MPNs and warrant further investigation.

Among patients with MF, extramedullary hematopoiesis (EMH) is hallmark of advanced disease and a driver of symptoms. EMH most commonly leads to splenomegaly, which can be detected on physical examination or imaging and results from progressive BM failure.[81] Although rare, pulmonary EMH has been described in the literature and may contribute to PH development in patients with MF.[82-88] The prevalence of pulmonary EMH in MPNs remains unknown; however, case reports and series describing PH improvement after low-dose pulmonary radiation therapy or treatment with ruxolitinib suggest that EMH may be a contributing factor in a subset of patients.[84,86,88] Prospective studies with systemic screening for pulmonary EMH are needed to better

define its prevalence and potential role in PH pathogenesis among patients with MPNs.

Megakaryocytes are a key cell type in the development of MPNs.[89-95] In MF, they play a central role in driving BM fibrosis and EMH. A potential mechanistic link between MPNs and PH involves pulmonary megakaryocytes. Emerging evidence suggests that megakaryocytes reside in the lungs and may contribute to immune surveillance and platelet formation.[96,97]

In a study analyzing lung biopsy samples from transplant donors and recipients, megakaryocytes in healthy donor lungs were located primarily in the interalveolar septa, supporting their role in immune regulation and surveillance.[98] In contrast, biopsy samples from lung recipients with PAH showed significantly greater numbers of megakaryocytes compared with recipients without PAH. Intracapillary megakaryocytes were also more frequently observed in patients with PAH.[98]

Although pulmonary megakaryocytes have been rarely reported in patients with MPNs, the presence of EMH in this population raises the possibility that they may contribute to PH pathogenesis. Further preclinical and clinical studies are needed to explore this hypothesis.[99-101]

Megakaryocytes and platelets in patients with MPNs, especially MF, have been shown to up-regulate lysyl oxidase (LOX), an enzyme involved in cross-linking collagen fibrils. Recent studies in MPN mouse models suggest that LOX contributes to MF progression by accelerating megakaryocyte proliferation through oxidation of platelet-derived growth factor receptors.[90,92,102,103]

LOX may also facilitate platelet adhesion to collagen, potentially contributing to thrombosis in MPNs. In mouse models, LOX inhibition ameliorated BM fibrosis, and clinical trials are under way to assess the efficacy of LOX inhibitors in MF.[102,104] Beyond BM, LOX has been shown to oxidize cell membrane proteins, enhance vascular smooth muscle cell chemotaxis, and promote proliferation.[105] These findings suggest a possible role for LOX in PH pathogenesis. Supporting this, LOX expression is elevated in the lungs of patients with idiopathic PAH and is localized predominantly to PA smooth muscle cells and adventitial fibroblasts.[106]

Endothelin-1 has been shown to up-regulate LOX expression in PA smooth muscle cells.[107] In chronic hypoxia mouse models of PAH, LOX inhibition reduced RVSP and vascular remodeling.[106] A related enzyme, LOX-like 2, is also expressed in PAH and, when inhibited, similarly improved pulmonary arteriolar remodeling in preclinical models.[106,108] Whether LOX contributes to the pathogenesis of PH in MPN—and whether its inhibition can prevent or ameliorate PH in this context, particularly in MF—remains unknown and represents an important area for future investigation.

SUMMARY POINTS.

- Patients with MPN are at increased risk for both precapillary and postcapillary PH.
- Because of the elevated thrombotic risk in MPNs, CTEPH is a key etiology of precapillary PH in this population.
- Both MPNs and PAH are associated with increased circulating BM-derived EPCs; mouse models receiving BM transplants from patients with PAH exhibit features of PAH, suggesting a BM-mediated mechanism.
- Activation of the JAK/STAT pathway in MPNs may promote pro-proliferative signaling that contributes to precapillary PH development.
- Pulmonary megakaryocytes and EMH may represent an additional mechanistic link between precapillary PH and MPN disease progression

PROGNOSTIC IMPLICATIONS OF PH IN MPNs

Patients with PH are at increased risk for RV failure and cardiovascular death. Accordingly, several studies have demonstrated an association between PH and reduced overall survival in patients with MPNs.[17,18] Greater PH severity and the presence of RV dysfunction have both been linked to higher mortality risk in this population.[18]

However, cardiovascular disease may not be the sole driver of poor outcomes. Progression to secondary MF or acute leukemia remains a major source of morbidity and mortality in MPNs. Notably, the development of PH has been associated with an increased risk for secondary MF or acute leukemia.[17] In a single-center study of patients with MPNs and cardiovascular disease, PH, defined as RVSP >50 mm Hg on TTE or mPAP >20 mm Hg on RHC, was present in 47% of patients and was associated with a 2-fold higher risk for hematologic progression to secondary MF or acute leukemia in patients with MPN.[17] In a separate single-center study of 133 patients with PV, PH (defined as tricuspid regurgitant velocity >2.8 m/s) was observed in 25% of patients and was associated with both an increased risk for hematologic progression and worse overall survival.[109]

In a multicenter study of 555 patients with MPN who underwent TTE after diagnosis, PH (defined as RVSP >40 mm Hg) was present in 35.1% at the time of

the first examination and in 47.9% of patients at any time after MPN diagnosis.[110] PH was associated with an increased risk for hematologic progression overall, as well as a higher risk for secondary MF in patients with ET or PV. Additionally, patients with PH had a higher risk for major adverse cardiovascular events, including thrombosis, HF hospitalization, and cardiovascular death. Left heart disease was present in 65% of patients with PH.[110]

Interestingly, the absence of left heart disease was associated with a significantly higher risk for hematologic progression among all patients with MPN. It was also linked to an increased risk for secondary MF progression among patients with ET or PV, as well as higher rates of acute leukemia progression among patients with MF. Additional risk factors for hematologic progression among patients with PH included anemia (hemoglobin <9 mg/dL), elevated estimated cardiac output (>7 L/min), the presence of non-phenotypic driver mutations, and driver mutation variant allele fraction > 50%.[110]

These findings underscore the heterogeneity of PH in MPNs. A substantial proportion of patients had features suggestive of postcapillary PH. However, patients with a lower pretest probability of postcapillary PH—defined by the absence of left ventricular hypertrophy or left atrial enlargement, H2FPEF score > 5, left ventricular ejection fraction < 50%, and absence of significant valvular disease—were at increased risk for hematologic progression. This supports a potential shared pathophysiology between precapillary PH and MPN progression, as well as the existence of distinct phenotypes within the MPN population. Elevated cardiac output may reflect a higher cardiac output state driven by EMH, anemia, or increased catabolism, common complications of MF. Further research is needed to explore these hypotheses and to evaluate the value of routine PH screening in patients with MPN.

SUMMARY.

- PH in MPN has been associated with an increased risk for disease to secondary MF or acute leukemia, particularly in patients without left heart disease.
- Elevated cardiac output on TTE was also linked to increased risk for MPN progression, independent of anemia; this may reflect a high-output state driven by EMH or increased neoplastic cell proliferation contributing to PH.
- Whether PH serves as a marker or a risk factor for disease progression remains to be determined.

PROPOSED SCREENING AND TREATMENT STRATEGIES FOR MPN-ASSOCIATED PH

PH appears to be common among patients with MPNs, with all hemodynamic classifications reported. Current MPN and PH guidelines do not provide specific recommendations for PH screening in this population. However, given its prevalence and association with adverse hematologic and cardiovascular outcomes, screening may be warranted in high-risk or symptomatic patients. TTE is recommended as the initial screening test, with RHC required for definitive diagnosis and hemodynamic assessment. Cardiac biomarkers such as N-terminal pro-B-type natriuretic peptide may aid in guiding the decision to screen.[111,112] Cardiopulmonary exercise testing may also aid in identifying PH.[112] Given the association between more proliferative phenotypes (eg, MF, splenomegaly, JAK2 mutation) and PH, screening should be considered in patients with suspected disease progression or long-standing MPNs.

Postcapillary PH in MPNs should be treated according to current guidelines, with treatment directed at underlying left heart disease and HF. Given the increased risk for VTE in MPNs, patients with precapillary PH should be evaluated for CTEPH and managed per established guidelines, which may include pulmonary endarterectomy, balloon pulmonary angioplasty, and pulmonary vasodilators such as riociguat.[45] Data on CTEPH treatment outcomes in MPNs are limited. In a small single-center study comparing patients who underwent pulmonary endarterectomy with (n = 29) vs without (n = 646) MPNs, those with MPNs had higher rates of infectious complications, need for extracorporeal membrane oxygenation, and death (31.0% vs 6.0%; $P < 0.0001$).[113] Whether less invasive approaches, such as percutaneous balloon pulmonary angioplasty or medical therapy alone, result in better outcomes for patients with MPN remains unknown.

For patients with MPN and precapillary PH without CTEPH, the role of vasodilatory testing is unclear and likely limited. In a study of 90 patients with MPNs and precapillary PH, 63 underwent pulmonary vasodilatory testing, and none demonstrated an acute response.[50] Data on the role of pulmonary vasodilators for MPN-associated group 5 PH remain limited. Current PH guidelines recommend treatment of the underlying disease. Nonetheless, in the same cohort of 90 patients with precapillary MPN-associated PH confirmed on RHC, 40% of patients

with group 5 PH were managed with pulmonary vasodilators, including endothelin receptor antagonists and phosphodiesterase 5 inhibitors.[45,50,114] In a separate study of 15 patients with MF, treatment with the JAK2 inhibitor ruxolitinib was associated with reduced RVSP on TTE, increased nitric oxide levels, and reduced N-terminal pro-B-type natriuretic peptide levels.[115] Additionally, a study of 490 patients with MPNs showed an association between ruxolitinib therapy and reduced risk for HF.[116] Further studies are needed to elucidate the potential role of JAK2 inhibition in MPN-associated PH.

Data on the impact of other cytoreductive therapies such as hydroxyurea or interferon alfa on PH outcomes are scarce. Both agents are used to treat patients with ET and PV; although clinical outcomes are similar, interferon alfa more effectively reduces JAK2 mutant allele burden compared with hydroxyurea.[117] However, interferon alfa has been associated with PH development, although its role in MPN-associated PH remains unclear.[118,119] Hydroxyurea is the most commonly used cytoreductive agent in MPN and is also used to treat sickle-cell disease, another hematologic condition associated with PH. In sickle-cell disease, hydroxyurea has been associated with improved PH through nitric oxide replacement, though the mechanisms in MPNs likely differ.[120] Therefore, it is unclear whether hydroxyurea therapy affects PH risk in MPNs, and further study is needed. A proposed screening and treatment algorithm for PH in MPN is shown in **Figure 2**.

SUMMARY POINTS.

- PH in MPNs is heterogenous, and treatment strategies specific to this population remain largely unstudied.
- PH screening should be considered in patients with MF, long-standing MPNs, signs of disease progression, or splenomegaly.
- JAK2 inhibition may improve hemodynamic status and clinical outcomes in MPN-associated PH, but further investigation is needed.

EPIDEMIOLOGY, RISK FACTORS, AND PATHOPHYSIOLOGY OF HF IN MPNs

Patients with MPNs are at increased risk for developing HF, although data on its prevalence are limited and suggest that it may be higher than in the general populations.[21] One study of 490 patients with MPNs and no prior HF showed that 17.6% were later hospitalized for HF.[116] Patients with coexisting cardiovascular disease, including those hospitalized for acute coronary syndrome or atrial fibrillation, may be at particularly elevated risk.[22,23] Whether HF incidence varies by MPN subtype remains unclear; however, data suggest that patients with MF may be especially vulnerable and experience worse HF-specific outcomes. In a study of patients with MPNs hospitalized for HF and acute coronary syndrome, those with MF had higher rates of in-hospital death and 90-day HF and cardiovascular readmissions.[15,22]

Data on the prevalence of specific HF phenotypes in patients with MPNs are limited. In one study of patients hospitalized for HF, those with MPNs were less likely to have HF with reduced ejection fraction compared with those without MPNs.[15] High-output HF (HOHF) has been classically associated with MPNs, although its prevalence in this population is not well characterized. In a study of 120 patients, 8% were diagnosed with HOHF attributed to MPNs.[121] Larger studies are needed to gain a deeper understanding of the overall prevalence and distribution of HF phenotypes in patients with MPN.

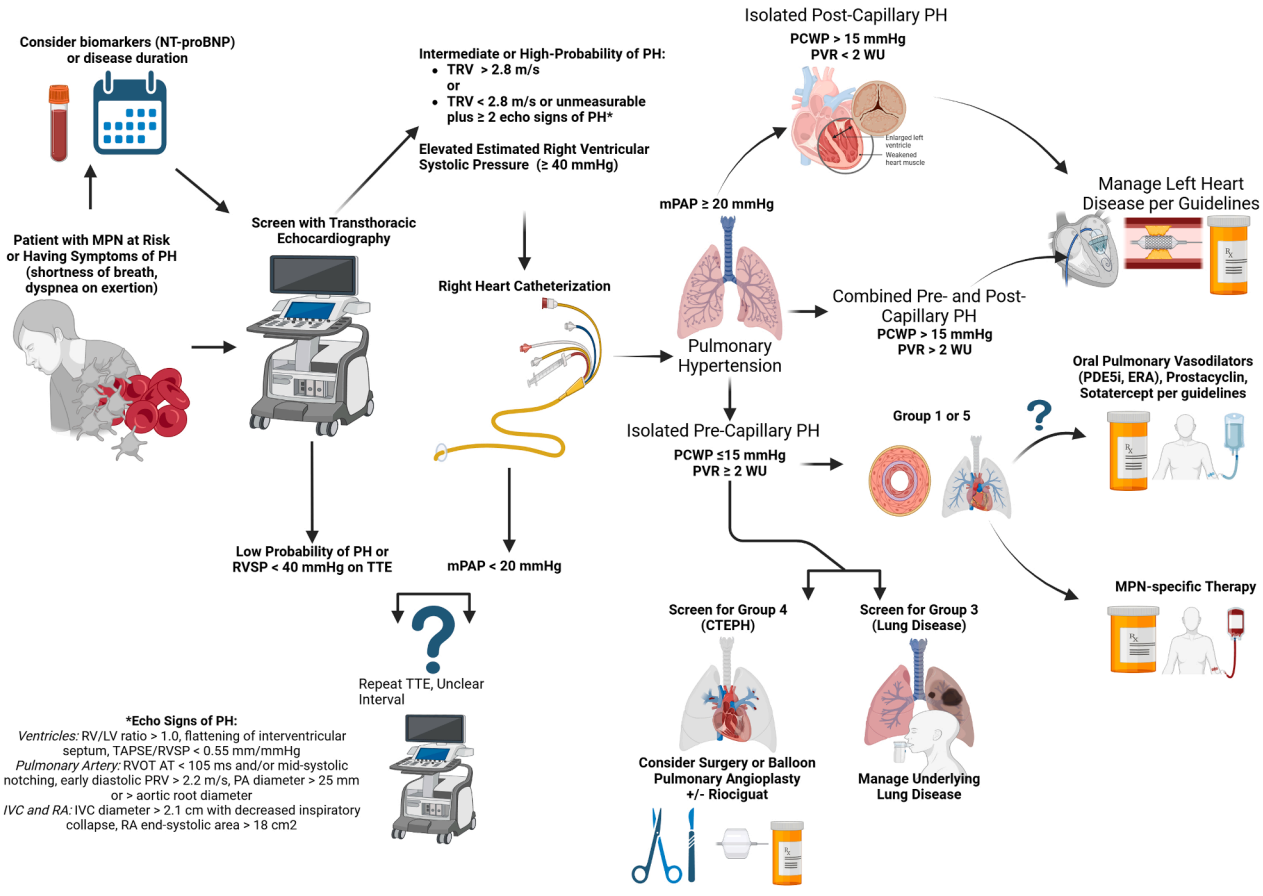
The etiology and pathophysiology of HF in MPNs are not well characterized and appear to be multifactorial. In one study of patients hospitalized for HF, those with MPNs had lower rates of coronary artery disease and diabetes compared with patients without MPNs,[15] suggesting that HF in MPN may develop independently of traditional cardiovascular risk factors. Disease-specific mechanisms, such as JAK/STAT pathway activation, may contribute to HF pathogenesis. Preclinical data support this hypothesis: in a murine model of angiotensin II-induced hypertensive cardiac remodeling, elevated expression of pyruvate kinase isozyme type M2, which phosphorylates and activates STAT proteins in the JAK2/STAT3 pathway, was observed. Inhibition of pyruvate kinase isozyme type M2 attenuated cardiomyocyte hypotrophy and fibrosis in this model.[122]

Another preclinical study using a murine model of angiotensin II-induced hypertensive cardiac remodeling revealed elevated expression of erythropoietin-producing hepatoma interactor B2, a profibrotic mediator in cardiac fibroblasts driven by STAT3 activation.[123] In a separate myocardial infarction model using left anterior descending coronary artery ligation, mice transduced with the JAK2 V617F mutation exhibited increased myocardial inflammation and accelerated HF compared with controls.[51]

These studies collectively support a key role for JAK/STAT signaling in the development of HF in MPNs. Additionally, nonphenotypic driver mutations, such as those in TET2 and DNMT3A, are common in MPNs and have been associated with increased HF risk in both clinical and preclinical studies.[51,54,124]

In patients with MPNs and HOHF, a hypermetabolic state, EMH, and reduced systemic vascular

FIGURE 2 **Proposed Screening Algorithm for PH in Patients With MPNs**



Patients with MPNs and high clinical suspicion of PH should undergo screening with transthoracic echocardiography (TTE). Findings suggestive of PH should prompt RHC for definitive diagnosis of PH and hemodynamic assessment. PH management should follow established guidelines, with consideration of MPN-specific therapies when appropriate. The role of prospective screening for PH in MPNs warrants further investigation. Additional details regarding the pathophysiology can be found in the corresponding text. AT = acceleration time; CTEPH = chronic thromboembolic pulmonary hypertension; ERA = endothelin receptor antagonist; IVC = inferior vena cava; LV = left ventricle/ventricular; mPAP = mean pulmonary artery pressure; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PA = pulmonary artery; PCWP = pulmonary capillary wedge pressure; PDE5i = phosphodiesterase 5 inhibitor; PRV = pulmonic regurgitation velocity; PVR = pulmonary vascular resistance; RA = right atrial/atrium; RHC = right heart catheterization; RV = right ventricle/ventricular; RVOT = right ventricular outflow tract; RVSP = right ventricular systolic pressure; TAPSE = tricuspid annular plane systolic excursion; TRV = tricuspid regurgitant velocity; WU = Wood units; other abbreviations as in **Figure 1**.

resistance, driven by elevated cytokines, can lead to an imbalance between myocardial oxygen supply and tissue demand. These factors likely contribute to the development of HOHF.[121,125] In particular, patients with MF often present with splenomegaly due to EMH and anemia, which may help explain their higher risk for HF compared with those with ET or PV. Further studies, especially those building on preclinical models, are needed to clarify the pathophysiology of HF in MPNs by HF phenotype. This understanding will be essential for developing targeted and effective therapies for affected patients.

SUMMARY POINTS.

- HF may be more prevalent in patients with MPNs compared with the general population.
- Traditional cardiovascular risk factors are less common in MPNs, suggesting a distinct HF phenotype in this population.
- Activation of the JAK/STAT pathway has been implicated in HF pathogenesis in preclinical models.
- Further research is needed to characterize and HF phenotypes and underlying mechanisms in patients with MPN

PROGNOSTIC IMPLICATIONS OF HF IN MPNs

HF in the general population is associated with significant morbidity and mortality.[126] Patients with MPNs who develop HF may face even worse outcomes. In a cohort of 490 patients with MPNs, those with at least 1 HF hospitalization had a higher risk for all-cause mortality.[116] Another study showed that among patients hospitalized for HF, those with MPNs had increased rates of in-hospital death and 90-day cardiovascular readmissions compared with those without MPNs.[15] Future research is needed to clarify both short-term and long-term outcomes in this population, including differences by HF phenotype and treatment strategy.

SUMMARY POINTS.

- Patients with MPNs who develop HF have an elevated risk for mortality.
- Among patients hospitalized for HF, those with MPNs experience higher rates of cardiovascular readmissions.

MANAGEMENT OF HF IN PATIENTS WITH MPNs

Optimal HF management in patients with MPNs has not been well studied. Current National Comprehensive Cancer Network guidelines recommend addressing cardiovascular risk factors in MPNs but do not specifically discuss HF or PH management.[2] Limited data suggest a potential role for JAK inhibitors. One case study described clinical improvement in HOHF following ruxolitinib therapy in a patient with PV, secondary MF, and HOHF.[125] In a retrospective study of 490 patients with MPNs and no prior HF, ruxolitinib use was associated with a reduced risk for HF hospitalization.[116] The effect of therapies targeting shared pathophysiological pathways, such as JAK/STAT signaling and nonphenotypic driver mutation, on HF outcomes remains an important area for future investigation.

Society guidelines for HF management identify patients with cancer as a high-risk group with unique considerations related to HF incidence, risk factors, clinical care needs, and outcomes.[127] These guidelines focus primarily on cancer therapy–related cardiomyopathy and recommend multidisciplinary discussions about continuation, interruption, or discontinuation of cancer therapy in patients with HF. However, in MPNs, HF may arise from shared pathophysiologic mechanisms rather than cardiotoxic effects of treatment.[128] In the absence of MPN-specific HF management guidelines, clinicians should follow standard guideline-directed medical therapy.[129] Attention to polypharmacy is essential, given the advanced median age and high burden of comorbidities in this population. Notably, recent data suggest that most drug-drug interactions in patients with MPNs do not involve cytoreductive or cardiovascular medications.[130]

Emerging evidence suggests that certain HF therapies may have additional effects in patients with MPNs. In a retrospective multicenter study of 647 patients with PV receiving antihypertensive medications, those treated with angiotensin-converting enzyme inhibitors were less likely to require cytoreductive chemotherapy.[131] In murine models of MF, captopril reduced spleen size and BM fibrosis.[132] Sodium-glucose cotransporter-2 inhibitors, another component of HF guideline-directed medical therapy, have been shown to increase hematocrit across all MPN phenotypes. In a single-center study of 28 patients with MPNs (11 with ET, 9 with PV, and 8 with MF), all patients experienced hematocrit elevation after sodium-glucose cotransporter-2 inhibitor initiation.[133,134] One patient with PV developed a thrombotic event attributed to elevated hematocrit. Given the prevalence of anemia in MF, hematocrit elevation may offer benefit in some cases but pose thrombotic risk in others. Clinicians should monitor hematocrit levels closely when prescribing sodium-glucose cotransporter-2 inhibitors, particularly in patients with PV.[133,134] Further studies are needed to clarify the risks and benefits of sodium-glucose cotransporter-2 inhibitors in this population.

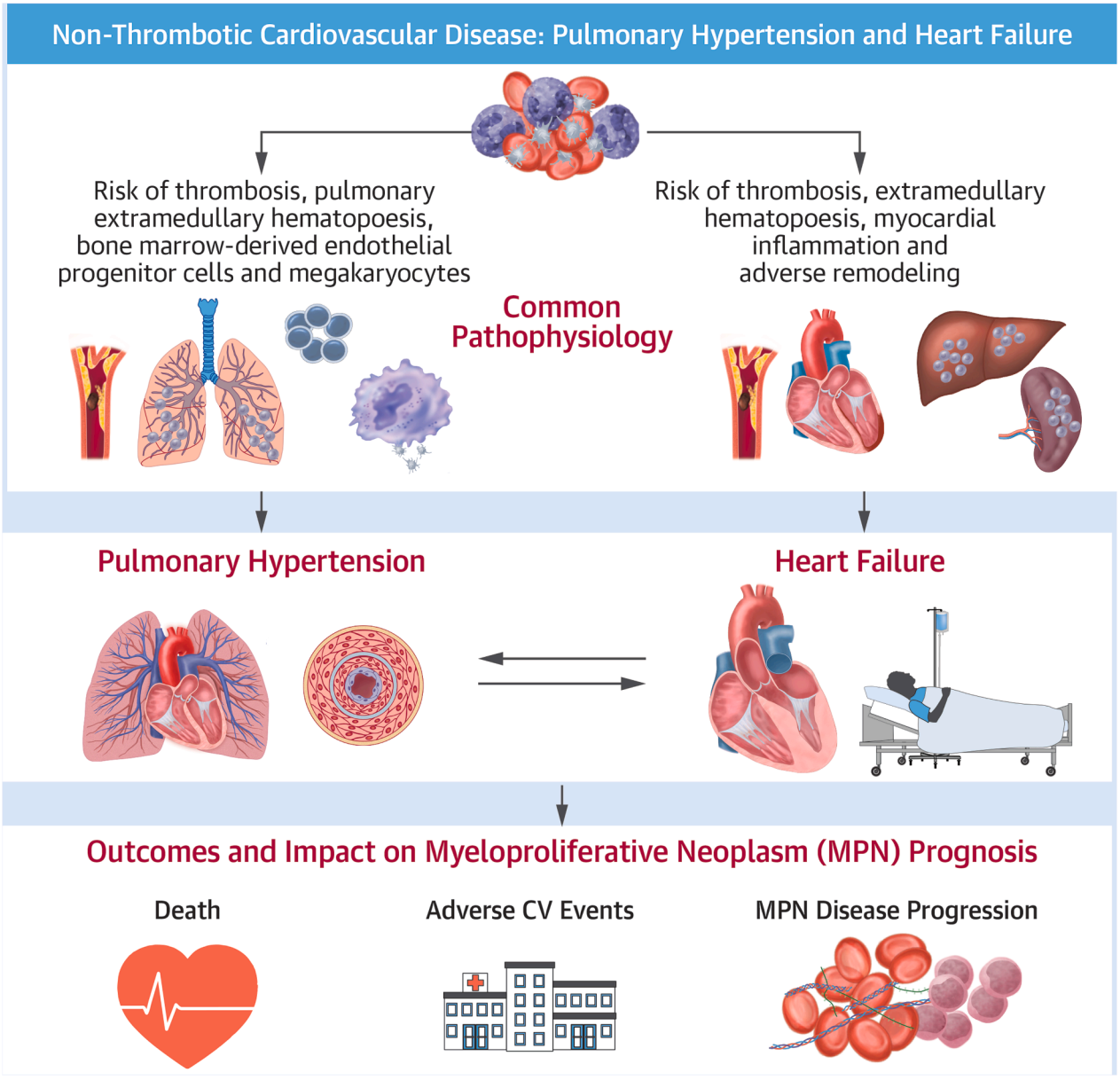
SUMMARY POINTS.

- Current guidelines do not specifically address HF management in patients with MPNs; therefore, treatment should follow established HF guidelines.
- In patients with MPN and no prior HF hospitalization, JAK2 inhibition was associated with a reduced risk for incident HF, though further studies are needed to confirm this association.

FUTURE DIRECTIONS AND RESEARCH GAPS IN PH AND HF AMONG PATIENTS WITH MPNs

Significant gaps remain in our current understanding of PH and HF in patients with MPNs, despite mounting evidence that these overlooked cardiovascular complications are both common and clinically significant. The true prevalence of PH and HF in this population is unclear, largely because of reliance on retrospective studies that are suspectable to bias and confounding, particularly referral bias.

CENTRAL ILLUSTRATION **The Association Between MPNs and Pulmonary Hypertension and Heart Failure**



Leiva O, et al. JACC CardioOncol. 2025;7(5):538-553.

Patients with myeloproliferative neoplasms (MPNs) are at increased risk for both thrombotic and nonthrombotic cardiovascular disease. Nonthrombotic cardiovascular diseases, particularly pulmonary hypertension and heart failure, are increasingly recognized and may carry a poor prognosis. Shared pathophysiologic mechanisms, including activation of the JAK (Janus-associated kinase)/STAT (signal transducer and activator of transcription) signaling pathway, may underlie these associations. Further research into the interplay among bone marrow, pulmonary vasculature, and cardiac function may lead to novel therapeutic strategies for both MPNs and cardiovascular disease. Additional details regarding the pathophysiology can be found in the corresponding text. CV = cardiovascular.

Prospective studies with systematic screening, using TTE or cardiac biomarkers, are needed to define the burden of disease more accurately. HOHF driven by EMH and rapid cell turnover, along with precapillary PH from various mechanisms, are potential contributors to HF in MPNs. However, more research is needed to characterize cardiovascular phenotypes in this population. Although patients with MPNs are at

increased risk for thrombosis and accelerated atherosclerosis, existing evidence suggests that these are not the predominant drivers of HF in this setting.

Another potential but unexplored contributor to HF in MPN is coronary microvascular dysfunction (CMD).[135] In a study comparing patients with ET or PV to age- and sex-matched control subjects without known coronary artery disease, coronary flow reserve, a surrogate for CMD, was investigated using transthoracic Doppler echocardiography.[136] Patients with ET had lower coronary flow reserve than control subjects, suggesting a higher prevalence of CMD.[136] However, the role of CMD in the development of HF among patients with MPN has not yet been studied. Additional gaps include the lack of studies evaluating advanced cardiac imaging modalities, such as cardiac magnetic resonance imaging and positron emission tomography, which may allow the noninvasive assessment of CMD in this population.

SUMMARY POINT.

- Prospective studies are needed to accurately define the incidence, risk factors, and pathophysiologic mechanisms of PH and HF in patients with MPN.

CONCLUSIONS

Patients with MPNs are at increased risk for cardiovascular disease. Although thrombotic complications have been extensively studied, emerging evidence suggests that nonthrombotic cardiovascular conditions, including HF and PH, are also prevalent and clinically significant. Emerging data suggest that both PH and progressive HF may be associated with hematologic progression in MPNs, highlighting potential shared pathophysiology, such as chronic inflammation and JAK/STAT pathway activation. Further research into the mechanism linking MPNs with PH and HF may uncover novel therapeutic targets (**Central Illustration**). In addition, studies are needed to assess the utility of screening tools, such as TTE, for the early detection of PH and HF in this high-risk population.

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