Young patients (aged 60 years or a history of thrombosis) PV or ET in the form of hydroxyurea as first-line treatment and low-dose aspirin therapy, once or twice daily, in patients aged 60 years with ET or PV and no history of thrombosis are conventionally regarded as having low-risk disease. First-line treatment in low-risk PV is phlebotomy to achieve a hematocrit target of 45% and low-dose aspirin, and first-line treatment in ET is observation alone in the absence of additional risk factors for arterial thrombosis (ie, JAK2 mutation and cardiovascular risk factors) or low-dose aspirin therapy, once or twice daily, in the presence of one or both of these risk factors, respectively. Cytoreductive therapy is indicated in high-risk (patients aged ≥60 years or a history of thrombosis) PV or ET in the form of hydroxyurea as first-line and interferon alfa or busulfan as second-line drugs of choice. We do not use ruxolitinib in patients with PV unless they have severe pruritus or symptomatic splenomegaly that is proved to be refractory to hydroxyurea, interferon alfa, and busulfan.
Essential thrombocythemia (ET) (annual incidence, 0.01-2.61 per 100,000) and polycythemia vera (PV) (annual incidence, 0.21-2.27 per 100,000) are myeloproliferative neoplasms (MPNs) that are characterized primarily by clonal thrombocytosis and erythrocytosis, respectively. Median age at diagnosis is estimated at 71 years for both PV and ET. A female preponderance is noted in ET and a male preponderance in PV. Patients with either ET or PV might also have leukocytosis, splenomegaly, and microvascular symptoms including headaches, visual disturbances (eg, blurry vision), light-headedness, palpitations, atypical chest pain, paresthesias, erythromelalgia (ie, erythema, warmth, and pain in distal extremities), pruritus (usually after bathing), and other constitutional symptoms (eg, fatigue). The clinical course in both ET and PV might be interrupted by thrombohemorrhagic complications and disease transformation to myelofibrosis (MF) or acute myeloid leukemia. A recent Mayo Clinic study found that life expectancy in patients with ET was inferior to that of an age- and sex-matched control population, with estimated median survivals of 20 years for ET and 14 years for PV; in younger patients, the corresponding median survivals were 33 and 24 years. Leukemic or fibrotic transformation rates at 20 years are estimated at 10% to 20% for PV and 5% to 10% for ET.

Patients with PV or ET are characterized by the presence of MPN-specific somatic mutations including Janus kinase 2 (JAK2), calreticulin (CALR), and myeloproliferative leukemia virus oncogene (MPL). These 3 mutations are currently believed to be pathogenetically essential and often occur in a mutually exclusive manner. Polycythemia vera is almost always associated with a JAK2 mutation (98% JAK2V617F and 2% other JAK2 mutations including exon 12 mutations), although rare instances of PV associated with CALR, MPL, or other mutations (eg, LNK [as in links]) have been reported. In general, JAK2 exon 12 mutated PV, compared with JAK2V617F-mutated PV, is more likely to be associated with younger age and predominantly erythroid myelopoiesis.

In ET, the frequencies of JAK2V617F, CALR, and MPL mutations are approximately 60%, 22%, and 3%, respectively. This leaves about 15% of patients with ET that are wild-type for all 3 mutations (ie, are triple-negative). It should be noted that other nonspecific mutations might coexist with the aforementioned MPN-specific mutations, and their incidence and relevance are currently being studied. Similarly, JAK2 mutations have been seen in other myeloid malignant neoplasms, albeit at a much lower frequency; an exception is the myelodysplastic syndrome (MDS)/MPN overlap disease called refractory anemia with ring sideroblasts associated with marked thrombocytosis (RARS-T), in which JAK2V617F mutational frequency has been reported to be as high as 50%. In general, patients who have JAK2 mutations with ET, compared with their counterparts with CALR mutations, are older and have higher hemoglobin levels and leukocyte counts, lower platelet counts, and increased risk of thrombosis. Among patients who have CALR mutations with ET, those with type 2 CALR variant (5-bp TTGTC insertion) express higher platelet counts than those with type 1 variant (a 52-bp deletion).

**DIAGNOSIS**

In addition to ET and PV, the World Health Organization (WHO) classification system includes 6 other clinicopathologic entities under the category of MPN and uses bone marrow (BM) morphologic features (now supplanted by genetic studies) to distinguish MPN from MDS and MDS/MPN overlap diseases (Figure 1). A similar process of morphologic diagnosis complemented by mutation analysis was applied to formulate WHO-based diagnostic criteria for ET and PV (Table), which are currently being revised along the lines of a recent proposal submitted by key committee members (Table). However, in routine clinical practice, a more practical approach is desired and discussed subsequently (Figure 2).

**Polycythemia Vera**

Polycythemia vera is often suspected in the presence of real (associated with increased red cell mass) or apparent (not associated with increased red cell mass) increase in hemoglobin/hematocrit values. Other reasons to suspect PV include aquagenic pruritus and large abdominal vein (eg, hepatic or portal vein) thrombosis. In addition to PV, the differential diagnosis of increased hemoglobin/hematocrit values includes
congenital and acquired erythrocytosis (discussed subsequently). The first step in the evaluation of increased hemoglobin/hematocrit values or otherwise suspected PV is screening for JAK2 V617F mutation (Figure 2); this first diagnostic step identifies about 95% of patients with PV because they carry the JAK2 V617F mutation.11 As a first step, we also recommend concomitant measurement of the serum erythropoietin (Epo) level because subnormal values are confirmatory of a PV diagnosis if JAK2 V617F is present but also suggest JAK2 V617F-unmutated PV in the absence of the mutation18 (Figure 2). The latter instance (ie, the combination of subnormal serum Epo level and absence of JAK2 V617F) warrants screening for other JAK2 mutations (eg, JAK2 exon 12 mutation) whose presence supports the diagnosis of PV, and their absence necessitates BM examination to rule out a JAK2-unmutated PV, which might be the case in about 1% of patients11 (Figure 2).

Bone marrow examination is particularly helpful in distinguishing JAK2-mutated ET from “masked” PV.10 A patient with masked PV has PV-consistent BM morphologic features (ie, trilineage hyperplasia with left shift and pleomorphic megakaryocytic hyperplasia with atypical features) but does not meet the hemoglobin threshold level required by the 2008 WHO criteria (>18.5 g/dL in men and >16.5 g/dL in women [to convert hemoglobin values to g/L, multiply by 10.0]).20-22 This particular scenario is one of the rationales for the new proposed revision of the WHO diagnostic criteria for PV, in which BM morphologic features was added as a major diagnostic criterion and the hemoglobin threshold was lowered to 16.5 g/dL for men and 16 g/dL for women12 (Table).
The absence of a JAK2 mutation combined with a normal or increased serum Epo level makes the diagnosis of PV very unlikely and warrants further work-up for congenital or acquired erythrocytosis. In this regard, we highly recommend review of previous records of complete blood cell count to determine if the increase in hemoglobin/hematocrit values is new or chronic/lifelong. The latter suggests congenital erythrocytosis and the former acquired conditions that often result in central or peripheral tissue hypoxia.

When congenital polycythemia is suspected, work-up should include measurement of the oxygen tension at which hemoglobin is 50% saturated (P50) and mutation screening for VHL (von Hippel-Lindau tumor suppressor protein), EPOR (erythropoietin receptor), HIF2α (hypoxia-inducible factor 2α), and PHD2 (prolyl hydroxylase domain—containing

### TABLE. 2008 vs Proposed 2014 World Health Organization Diagnostic Criteria for Polycythemia Vera and Essential Thrombocythemia

<table>
<thead>
<tr>
<th>2008 WHO diagnostic criteria for PV (diagnosis requires meeting either both major criteria and 1 minor criterion or the first major criterion and 2 minor criteria)</th>
<th>2014 Proposed changes for PV (diagnosis requires meeting all 3 major criteria or the first 2 major criteria and 1 minor criterion)</th>
<th>2008 WHO diagnostic criteria for ET (diagnosis requires meeting all 4 major criteria or the first 3 major criteria and 1 minor criterion)</th>
<th>2014 Proposed changes for ET (diagnosis requires meeting all 4 major criteria or the first 3 major criteria and 1 minor criterion)</th>
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</thead>
<tbody>
<tr>
<td>Major criteria</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1. Hemoglobin &gt;18.5 g/dL (men)</td>
<td>Hemoglobin &gt;16.5 g/dL (men)</td>
<td>Platelet count ≥450 × 10^9/L</td>
<td>Platelet count ≥450 × 10^9/L</td>
</tr>
<tr>
<td>or &gt;16.5 g/dL (women)</td>
<td>or &gt;16 g/dL (women)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or hemoglobin/hematocrit &gt;99th percentile of reference range for age, sex, or altitude of residence</td>
<td>or Hematocrit &gt;49% (men) &gt;48% (women)</td>
<td></td>
<td></td>
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<tr>
<td>or red cell mass &gt;25% above mean normal predicted</td>
<td></td>
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<tr>
<td>or hemoglobin &gt;17 g/dL (men), &gt;15 g/dL (women) if associated with a sustained increase of ≥2 g/dL from baseline that cannot be attributed to correction of iron deficiency</td>
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<tr>
<td>2. Presence of JAK2V617F or JAK2 exon 12 mutation</td>
<td>Bone marrow trilineage myeloproliferation with pleomorphic megakaryocytes</td>
<td>Megakaryocyte proliferation with large and mature morphologic features</td>
<td>Megakaryocyte proliferation with large and mature morphologic features</td>
</tr>
<tr>
<td>or JAK2 exon 12 mutation</td>
<td>Presence of JAK2 mutation</td>
<td>Not meeting WHO criteria for CML, PV, PMF, MDS, or other myeloid neoplasm</td>
<td>Not meeting WHO criteria for CML, PV, PMF, MDS, or other myeloid neoplasm</td>
</tr>
<tr>
<td>3. NA</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4. NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Bone marrow trilineage myeloproliferation</td>
<td>Subnormal serum erythropoietin level</td>
<td>NA</td>
<td>Presence of a clonal marker or absence of evidence for reactive thrombocytosis</td>
</tr>
<tr>
<td>2. Subnormal serum erythropoietin level</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>3. Endogenous erythroid colony growth</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

*CML = chronic myelogenous leukemia; ET = essential thrombocythemia; MDS = myelodysplastic syndrome; NA = not applicable; PMF = primary myelofibrosis; PV = polycythemia vera.

SI conversion factor: To convert hemoglobin values to g/L, multiply by 10.0.
Subnormal P50 suggests high oxygen affinity hemoglobinopathy (usually autosomal dominant), 2,3-diphosphoglycerate deficiency (usually autosomal recessive), or methemoglobinemia (autosomal recessive and dominant forms often associated with cyanosis). These mutations are rare, and most cases with a working diagnosis of congenital polycythemia end up being negative for both P50 and these germline mutations.

The differential diagnosis of acquired erythrocytosis that is not PV includes hypoxia-driven and hypoxia-independent processes. Included in the former are high-altitude habitat, hypoxic lung disease, right-to-left cardiopulmonary shunts, tobacco abuse, carbon monoxide poisoning, sleep apnea, and renal artery stenosis. Hypoxia-independent causes of acquired erythrocytosis include drugs (eg, erythropoiesis-stimulating agents, testosterone preparations), Epo-producing tumors (eg, renal cell carcinoma, hepatocellular carcinoma, cerebellar hemangioblastoma, meningioma, pheochromocytoma, uterine leiomyoma, parathyroid adenoma), renal cysts, and renal transplant. In general, the serum Epo level is normal or slightly elevated in hypoxia-driven erythrocytosis and markedly increased in the presence of Epo-producing tumors, which should be evaluated with the appropriate imaging studies.

**Essential Thrombocythemia**

Thrombocytosis is commonly encountered in routine clinical practice and represents a reactive process in most cases; causes of reactive thrombocytosis (RT) include infections, tissue damage, malignant neoplasms, chronic inflammation, hemolysis, drugs, iron deficiency anemia, and splenectomy. Acquired nonreactive thrombocytosis often indicates an underlying myeloid malignant disorder, including ET. Congenital thrombocytosis is very rare and has been associated with activating mutations of either thrombopoietin (Tpo) or its receptor (Mpl).
Because RT is by far the most frequent cause of thrombocytosis encountered in routine clinical practice, it is important to use clinical judgment before embarking on mutation analysis as a first step of evaluation. Clonal markers used for an otherwise unexplained and persistent thrombocytosis include JAK2V617F (present in about 60% of patients with ET, primary myelofibrosis [PMF], or RARS-T and 95% of patients with PV), CALR mutations (present in about 20%-25% of patients with ET or PMF), MPL mutations (present in 3%-7% of patients with ET or PMF), BCR-ABL1 (breakpoint cluster region protein—Abelson murine leukemia viral oncogene homolog 1) (present in 100% of patients with chronic myeloid leukemia), and SF3BI (splicing factor 3B subunit 1) mutations (present in approximately 80% of patients with RARS-T). Obviously, one should not investigate all of these mutations concurrently. We recommend starting with screening for JAK2V617F and BCR-ABL1, and if results of these screens are negative, test for CALR and then MPL screening if CALR results are negative (Figure 2).

We also recommend BM examination for the evaluation of unexplained thrombocytosis because the absence of mutations does not rule out the possibility of ET (approximately 15% of patients might be wild-type for JAK2, CALR, and MPL—so-called triple-negative cases), and the presence of JAK2, CALR, or MPL cannot by itself distinguish between ET and PMF. Bone marrow in patients with ET or related MPN often exhibits hypercellularity and megakaryocyte cluster formation, both of which are absent in RT. Also, the megakaryocyte proliferation in ET is associated with large and mature morphologic features with loose cluster formation, whereas in PMF, it is associated with aberrant
nuclear-cytoplasmic ratio and hyperchromatic and irregularly folded nuclei, dense clustering, granulocyte proliferation, and decreased erythropoiesis. Furthermore, reticulin and/or collagen fibrosis might not be easily apparent in prefibrotic PMF.31

PROGNOSIS

Survival

A recent Mayo Clinic-Italian study of 1581 patients included 826 Mayo Clinic patients, 292 with ET and 267 with PV.4 Of the Mayo Clinic patients, 58% were followed up until death, with median follow-up time for living patients of 17.3 years for ET and 11.8 years for PV. Median survival was significantly better in ET than in PV, with 19.8 years for ET and 13.5 years for PV (hazard ratio, 1.8; 95% CI, 1.4-2.2). The corresponding median survivals for patients younger than age 60 years were 32.7 years for ET and 23.8 years for PV. Life expectancy in patients with ET was inferior to that of the age- and sex-matched US population (P<.001).4 The survival advantage of ET over PV was not affected by age, sex, or mutational status (ie, JAK2 vs CALR vs MPL mutated vs triple-negative).

Leukemic, Fibrotic, and Polycythemic Transformation

In the aforementioned Mayo Clinic-Italian study,4 in the Mayo patient cohort, leukemic transformation was reported in 18 of the 267 patients with PV (6.7%) and in 12 of the 292 patients with ET (4.1%), and fibrotic transformation was reported in 34 patients with PV (12.7%) and 29 patients with ET (9.9%). In the Italian patient cohort of 594 patients (310 with PV and 284 with ET), 91 fibrotic transformations were reported, including 65 in patients with PV (21.0%) and 26 in patients with ET (9.2%) (P<.01). On the other hand, conversion of ET to PV was infrequent in both the Mayo Clinic (N=9; 3%) and Italian (N=2; 1%) cohorts.

Risk Factors for Survival, Leukemic Transformation, and Fibrotic Progression

Essential thrombocythemia and PV have similar risk factors for shortened survival: advanced age, leukocytosis, and a history of thrombosis.5,32,33 In addition, abnormal karyotype has been associated with worse survival in PV, independent of the aforementioned risk factors.3 In one PV study, age greater than 70 years, leukocyte count less than $13 \times 10^9/L$, and absence of thrombosis were associated with a 10-year relative survival of 84% vs 59% in the presence of 1 and 26% in the presence of 2 or more of these risk factors.33 In ET, age less than 60 years, normal hemoglobin level, and leukocyte count less than $15 \times 10^9/L$ were associated with a median survival of more than 20 years vs 9 years in the presence of 2 or more of these risk factors.34 Risk factors for leukemic transformation in PV include advanced age, leukocytosis, and abnormal karyotype,3 and risk factors for fibrotic transformation include JAK2V617F allele burden of more than 50%.35 In a combined study population of patients with ET and prefibrotic PMF, survival was significantly shorter in the presence of prefibrotic PMF morphologic features, advanced age; history of thrombosis; leukocytosis; and anemia.6 In the same study, leukaemia-free survival was also adversely affected by prefibrotic PMF morphologic features and history of thrombosis but also by extreme thrombocytosis.6 Similarly, prefibrotic PMF morphologic features, advanced age, anemia, and absence of JAK2 mutation were associated with increased risk of fibrotic progression.6

Risk Factors for Thrombosis

Recent studies have underscored the difference in prevalence and risk factor profile of arterial vs venous thrombosis in PV and ET. It is now well established that the strongest risk factor for arterial and venous thrombosis is a history of these events. Additional risk factors for arterial thrombosis in PV include a history of hypertension and for venous thrombosis, older age.36 Additional risk factors for arterial thrombosis in ET include age greater than 60 years, presence of cardiovascular (CV) risk factors, leukocytosis, and presence of JAK2V617F and for venous thrombosis, male sex.37 It is important to note that it is the absence of JAK2V617F and not necessarily the presence of CALR mutation or triple-negative mutational status that is associated with lower risk of thrombosis compared with JAK2-mutated cases.38

TREATMENT

Current drug therapy for PV or ET is not curative, and it has not prolonged survival or prevented disease transformation to AML or post-PV or post-ET MF.39 In other words,
drug therapy has limited value in modifying the natural history of the disease in either PV or ET, and patients should be fully informed of this fact and clearly understand the goal of drug treatment, which is either to prevent thrombosis in high-risk patients or to alleviate symptoms, if present. On the other hand, median survival in PV before the era of phlebotomy was reportedly less than 2 years, and the current figure of approximately 14 years is clearly an improvement. Therefore, phlebotomy is currently considered the cornerstone of treatment in PV, and its value was further confirmed in a recent randomized trial in which the hematocrit target of 45% was superior to that of 45% to 50% in preventing recurrent thrombosis. In other words, phlebotomy in PV improves both overall and thrombosis-free survival.

Drug therapy in the form of either antiplatelet (eg, aspirin) or cytoreductive (eg, hydroxyurea) agents is used in PV or ET for the purposes of thrombosis prophylaxis and alleviation of symptoms such as headaches, light-headedness, atypical chest pain, palpatitations, acral paresthesias, erythromelalgia, pruritus, and symptomatic splenomegaly. Controlled studies have found significant reduction of thrombosis risk with once-daily low-dose aspirin in PV, cytoreductive therapy with chlorambucil or radiophosphorus in PV, and hydroxyurea therapy in high-risk ET. However, the use of chlorambucil and radiophosphorus was complicated by shortened survival because of the increased leukemogenicity of these drugs. Papobroman, another myelosuppressive drug used in Europe, was also recently implicated as being leukemogenic in PV, while the use of yet another drug, anagrelide, in high-risk ET was associated with increased risk of post-ET MF. Therefore, although the antithrombotic value of cytoreductive therapy in high-risk PV and ET is well recognized, the only drug with adequate evidence of efficacy and safety in this regard is hydroxyurea, which is currently our first-line drug of choice in high-risk PV or ET.

In hydroxyurea-refractory cases, data from uncontrolled studies support the use of interferon alfa or busulfan as second-line drugs of choice. There is adequate long-term safety information on these drugs, which have both been reported to significantly reduce JAK2 or CALR mutant allele burden, although the effect of such biologic activity on risk of thrombosis or survival is unknown. Ruxolitinib (a JAK inhibitor) was recently approved for use in hydroxyurea-intolerant/resistant PV based on its ability to alleviate constitutional symptoms and reduce spleen size, but the drug lacked disease-modifying activity. Furthermore, there is currently a lack of long-term safety information on ruxolitinib use in PV, and the drug has been found to cause immune suppression and increase the risk of opportunistic infections in patients with MF. Therefore, we usually do not use ruxolitinib in PV unless we are confronted with hydroxyurea-refractory symptomatic splenomegaly or intractable pruritus.

Considering the fact that “high risk for thrombosis” is the main indication of cytoreductive therapy in both PV and ET, it is important to accurately delineate high-risk disease and limit chemotherapy exposure to such patients. Over the years, a history of thrombosis and advanced age (≥60 years) have been identified as the most important risk factors for thrombosis in both PV and ET, and their absence or presence has been used to stratify patients into low-risk and high-risk disease categories, respectively. More recent studies have confirmed the independent prognostic value of thrombosis history and age of 60 years or older in predicting all thrombotic events as well as arterial and venous thrombosis considered separately.

In addition to thrombosis history and advanced age, recent studies have also disclosed the additional prognostic value of JAK2 mutations and CV risk factors for arterial thrombosis. Mutational status is particularly relevant in ET, in which the presence of JAK2V617F was associated with a higher risk of thrombosis than CALR mutations or triple-negative mutational status. The independent association between JAK2V617F or CV risk factors and thrombosis was also highlighted in another large multicenter study. We have recently highlighted this new development and have revised current risk stratification in ET and PV (Figure 3). Accordingly, patients who are traditionally considered at low risk (ie, age <60 years and no history of thrombosis) can now be further subcategorized as having “very low-risk” and “low-risk” disease depending on the absence or presence of JAK2V617F or CV risk factors, respectively (Figure 3). Our revised treatment algorithm
takes these new developments into account and provides an expertise-based recommendation list that is directed at minimizing recurrent thrombotic events and unnecessary drug exposure (Figure 3).

In patients with venous thrombosis, systemic anticoagulation is recommended in addition to cytoreductive treatment, and its duration depends on whether the underlying MPN was well controlled at the time of the thrombotic event. If venous thrombosis occurred in the context of well-controlled disease, we recommend systemic anticoagulation indefinitely. If, on the other hand, the event occurred in a patient whose disease was not optimally managed at the time of the venous event, as evidenced by hematocrit levels above 45% or platelet counts greater than 450 × 10^9/L, then it is reasonable to consider limiting the duration of systemic anticoagulation to 6 months, as long as other treatment measures to adequately control the disease have been instituted.

**DISCUSSION**

Mutation screening has now become an integral part of the diagnostic process in PV and ET. In certain cases, the detection of a relatively specific mutation with an overt clinical picture might make BM examination unnecessary. Examples include a man with a hemoglobin level higher than 18.5 g/dL (higher than 16.5 g/dL in women), a JAK2 mutation, and no evidence on peripheral blood morphologic examination for an alternative diagnosis such as myelofibrosis. Similarly, BM examination might not be critical in elderly patients for accurately distinguishing WHO-deﬁned ET from prefibrotic myelofibrosis because it may not greatly affect specific therapy. However, in all other instances we strongly recommend BM examination for accurate diagnosis, disease prognostication, and appropriate therapy.

Our new and revised treatment algorithm (Figure 3) is based on the fact that current therapy to prevent thrombosis is inadequate and new information on the significant influence of mutational status and CV risk factors on the risk of recurrent thrombosis. We consider phlebotomy and aspirin therapy as the 2 most important treatment modalities based on results from both controlled and uncontrolled studies. In addition, preliminary clinical observations and controlled laboratory studies have recently disclosed the value of twice-daily, as opposed to once-daily, aspirin therapy and aspirin’s potential value in the prevention of recurrent venous thrombosis. Accordingly, phlebotomy is mandated in all patients with PV who have a hematocrit target of 45%. As far as drug therapy is concerned, “very low-risk” patients with ET might not need any treatment, including aspirin therapy (Figure 3). In contrast, “low-risk” patients with ET or PV require either once-daily or twice-daily aspirin (81-mg dose), depending on the respective presence of either 1 or 2 or more of the newly described risk factors for arterial thrombosis (ie, JAK2V617F, CV risk factors, and age ≥60 years; Figure 3).

In high-risk disease, cytoreductive therapy is universally applied in patients with a history of either arterial or venous thrombosis (Figure 3); hydroxyurea is our first-line drug of choice in this regard. We also use once-daily aspirin in addition to cytoreductive therapy in most instances, with the exception of patients who are receiving systemic anticoagulants and do not have any risk factors for arterial thrombosis except advanced age (Figure 3). In addition, twice-daily aspirin might be necessary in high-risk patients with a history of arterial thrombosis and an additional risk factor for arterial thrombosis (Figure 3).

Other aspects of management in PV and ET include acquired von Willebrand syndrome, which might accompany extreme thrombocytopenia and thus require laboratory screening for ristocetin cofactor activity; aspirin should be avoided in the presence of less than 20% activity. Treatment for PV-associated pruritus includes antihistamines, selective serotonin reuptake inhibitors, JAK inhibitors, interferon alfa, and narrow-band ultraviolet B phototherapy. Management during pregnancy includes aspirin therapy for low-risk and interferon alfa for high-risk patients.

**CONCLUSION**

Despite a number of seminal discoveries regarding mutations in ET and PV, their molecular pathogenesis remains obscure and incompletely understood. Better information in this regard is essential for the development of drugs that have the ability to modify disease natural history. Current drug therapy is employed for prevention of thrombosis and in this regard
aspirin and cyto-reductive drugs are used for low and high risk disease, respectively. Prospective studies are needed to clarify the role of twice-daily aspirin therapy and whether or not cyto-reductive therapy is indeed essential for older ET patients that are JAK2-ummutated and with no history of thrombosis. The introduction of next-generation sequencing technology into clinical practice has the potential to refine current prognostic models in both PV and ET.

Abbreviations and Acronyms: BM = bone marrow; CALR = calreticulin; CV = cardiovascular; Epo = erythropoietin; ET = essential thrombocythemia; JAK2 = Janus kinase 2; MDS = myelodysplastic syndrome; MF = myelofibrosis; MPL = myeloproliferative leukemia virus oncogene; MPN = myeloproliferative neoplasm; PSO = oxygen tension at which hemoglobin is 50% saturated; PMF = primary myelofibrosis; PV = polycythemia vera; RARS-T = refractory anemia with ring sideroblasts associated with marked thrombocytosis; RT = reactive thrombocytosis; WHO = World Health Organization

Correspondence: Address to Ayalew Tefferi, MD, Division of Hematology, Department of Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (tefferi.ayalew@mayo.edu). Individual reprints of this article and a bound reprint of the entire Symposium on Neoplastic Hematology and Medical Oncology will be available for purchase from our website www.mayoclinicproceedings.org.

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REFERENCES