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Essential Thrombocythemia
A Review

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IMPORTANCE Essential thrombocythemia, a clonal myeloproliferative neoplasm with excessive platelet production, is associated with an increased risk of thrombosis and bleeding. The annual incidence rate of essential thrombocythemia in the US is 1.5/100 000 persons.

OBSERVATIONS Patients with essential thrombocythemia have a persistent platelet count of 450 × 10^9/L or greater. The differential diagnosis includes myeloproliferative neoplasms (polycythemia vera, primary myelofibrosis, chronic myeloid leukemia); inflammatory conditions such as rheumatoid arthritis and systemic lupus erythematosus; infections; splenectomy; iron deficiency anemia; and solid tumors such as lung cancer. Approximately 90% of individuals with essential thrombocythemia have genetic variants that upregulate the JAK-STAT (signal transducer and activator of transcription 5) signaling pathway, including Janus kinase 2 (*JAK2*, 64%), calreticulin (*CALR*, 23%), and myeloproliferative leukemia virus oncogene (*MPL*, 4%). The median age at diagnosis of essential thrombocythemia is 59 years. The median overall survival exceeds 35 years in those diagnosed at 40 years or younger. Patients with essential thrombocythemia are at increased risk of arterial thrombosis (11%), venous thrombosis (7%), and hemorrhagic complications (8%). Thrombosis risk is increased among those with a history of thrombosis, age older than 60 years, a *JAK2* gene variant, and cardiovascular risk factors (eg, hypertension, diabetes mellitus, hyperlipidemias, tobacco use). Use of aspirin (81-100 mg/d) is suggested for most patients with essential thrombocythemia to lower thrombosis risk. In a retrospective study of 300 affected patients with a low thrombosis risk (younger than 60 years with no prior thrombosis), those not taking aspirin (100 mg/d) had a risk of arterial thrombosis of 9.4/1000 patient-years and a venous thrombosis risk of 8.2/1000 patient years; cardiovascular risk factors were associated with a higher risk of arterial thrombi (incidence rate ratio, 2.5 [95% CI, 1.02-6.1]), and a *JAK2* gene variant was associated with increased risk of venous thrombosis (incidence rate ratio, 4.0 [95% CI, 1.2-12.9]). In a randomized trial of 114 patients at higher risk for thrombosis (age older than 60 years or a prior thrombotic event), cytoreduction with hydroxyurea significantly lowered the risk of arterial or venous thrombotic events compared with no cytoreductive therapy (3.6% vs 24%; $P < .01$). At a median of 8.5 years from diagnosis, approximately 10% of patients with essential thrombocythemia develop myelofibrosis and about 3% develop acute myeloid leukemia.

CONCLUSIONS Essential thrombocythemia is a rare clonal myeloproliferative neoplasm associated with an increased risk of venous and arterial thrombosis, hemorrhage, myelofibrosis, and acute myeloid leukemia. Based on individual risk factors for thrombosis, persons with essential thrombocythemia may be treated with low-dose aspirin, either alone or in combination with a cytoreductive drug such as hydroxyurea.

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Thrombocytosis with a platelet count of 450 × 10^9/L or greater is a major diagnostic criteria of essential thrombocythemia as defined by the International Consensus Classification of Myeloid Neoplasms and Acute Leukemias and the criteria of the World Health Organization.[1,2] In a population-based study of 6281 Swedish patients with myeloproliferative neoplasms, the age-standardized annual incidence of essential thrombocythemia was 1.6 per 100 000 persons[3]; this incidence rate was similar to those reported for US adults (1.55 per 100 000 persons).[4,5]

Most cases of thrombocytosis (85%-90%)[6,7] and extreme thrombocytosis (platelet count ≥1000 × 10^9/L)[8] are secondary to inflammatory states such as rheumatoid arthritis and systemic lupus erythematosus, previous splenectomy, infections such as pneumonia, bacterial sepsis and osteomyelitis, iron deficiency anemia, or solid tumors such as lung cancer (**Table 1** and **Table 2**).[6,8] The most frequent cause of primary thrombocytosis is essential thrombocythemia,[6-8] which in most patients is associated with a *JAK2* gene variant. Other myeloproliferative neoplasms associated with the *JAK2* gene variant include polycythemia vera, primary myelofibrosis (PMF), and unclassifiable myeloproliferative neoplasm in patients who have the variant but do not meet the case definitions for polycythemia vera or PMF.[1] In a retrospective study of 1202 patients with a platelet count of 450 × 10^9/L or greater, 150 patients (12.5%) had primary thrombocytosis, which included essential thrombocythemia (71%), polycythemia vera (17%), PMF (5%), myelodysplastic/myeloproliferative overlap syndromes (3%), chronic myeloid leukemia (2%), and unclassifiable myeloproliferative neoplasm (2%).[6] This review focuses on the epidemiology, clinical presentation, treatment, and prognosis of essential thrombocythemia (**Box**).

Methods

We searched Medline and Embase through the OVID interface from January 1, 1990, through March 25, 2024. The search was restricted to English-language articles. We applied the key word *essential thrombocythemia*; appropriate terms for meta-analyses and clinical queries filters focused on therapy or prognosis, which yielded 946 articles, which were manually reviewed. We included 102 articles, composed of 7 randomized clinical trials[9-15]; 7 nonrandomized prospective clinical trials[16-22]; 43 prospective or retrospective observational studies[6-8,23-62]; 6 meta-analyses and systematic reviews[63-68]; 7 risk modeling and treatment response criteria articles[69-75]; 5 epidemiologic and population-based studies[3-5,76,77]; 7 practice guidelines, position papers, or general reviews[78-84]; 18 scientific and pathophysiology reports[85-102]; and 2 contemporary classification systems.[1,2]

Pathophysiology

Patients with essential thrombocythemia commonly have gain-of-function gene variants of Janus kinase 2 (*JAK2*) (GenBank accession ID, NM_000218.3), located on chromosome 9p24[95]; calreticulin (*CALR*) (GenBank accession ID, NM_004342.3), located on chromosome 19p13.2[96]; and thrombopoietin receptor (myeloproliferative leukemia virus oncogene [*MPL*] [GenBank accession ID, NM_002432.4]), located on chromosome 1p34.[97] *JAK2* gene variants, found in 64% of patients with essential thrombocythemia, result in persistent activation of JAK-STAT (signal transducer and activator of transcription 5), bypassing the need for growth factor ligands, such as erythropoietin and thrombopoietin, which stimulate myeloproliferation and megakaryocyte production. *CALR* gene variants, reported in 23% of patients with essential thrombocythemia, mimic thrombopoietin, binding to its receptor; *MPL* variants, found in 4% of patients with essential thrombocythemia, result in constitutive (ligand-independent) activation of the thrombopoietin receptor.[98] About 10% of persons with essential thrombocythemia do not have these gene variants (termed *triple-negative essential thrombocythemia*), but newer tests with higher sensitivity may sometimes detect novel gene variants in these patients.[99,100] The presence of *JAK2*, *CALR*, or *MPL* gene variants is associated with different clinical presentations (**Table 3**).[69] Other gene variants are associated with decreased survival (eg, *SF3B1*, *SRSF2*, *U2AF1*, *TP53*) and may be present concurrently with *JAK2*, *CALR*, or *MPL* variants.[69]

Clinical Presentation

More than 50% of patients with essential thrombocythemia are asymptomatic and are diagnosed incidentally based on an abnormal platelet count on a complete blood cell count test. Table 3 outlines presenting clinical and laboratory characteristics of 2000 patients with essential thrombocythemia from the combined Mayo-Florence clinical databases.[23,24] The median age at diagnosis was 59 years (range, 18-94 years).[23,24] Microcirculatory symptoms such as erythromelalgia (pain in distal extremities associated with erythema and warmth), acral paresthesias, burning toes and fingers, blurred vision, or migraine headaches occurred in 29% of patients.[23,24] Signs of essential thrombocythemia at the time of diagnosis included palpable splenomegaly (12%), arterial thrombosis (14%), venous thrombosis (8%), and major hemorrhage (4.5%) (Table 3).[23,24] Median values at essential thrombocythemia diagnosis were platelet count, 738 × 10^9/L (range, 450-3460); hemoglobin level, 14 g/dL (range, 10-17.6); and leukocyte count, 8.5 × 10^9/L (range, 3.2-23).[23,24] Among 1000 Mayo Clinic patients with essential thrombocythemia, 87 (9%) presented with a hemoglobin level of 15.5 g/dL or greater, of whom 69 (79%) had *JAK2* variants.[23]

Patients with myeloproliferative neoplasms such as essential thrombocythemia may present with splanchnic vein thrombosis (portal, mesenteric, splenic, hepatic) or cerebral vein thrombosis.[58,59] In a meta-analysis of 32 observational studies, myeloproliferative neoplasms were diagnosed in 41% of 1062 patients with incident nonmalignant hepatic thrombosis (25% had essential thrombocythemia) and in 32% of 855 patients with nonmalignant, noncirrhotic portal vein thrombosis (26% had essential thrombocythemia).[68] In a retrospective study of 737 patients with essential thrombocythemia (median age, 58 years; range, 18-90 years),[46] a first major venous thrombosis was observed in 131 (18%), of whom 27% had thrombosis prior to the essential thrombocythemia diagnosis, 37% at the time of diagnosis, and 37% during follow-up after diagnosis.[46] Splanchnic venous thrombosis was detected in 5% of patients with essential thrombocythemia (2/38 before or at the time of essential thrombocythemia diagnosis) and 2% had cerebral venous thrombosis (15/16 before or at the time of essential thrombocythemia diagnosis).[46] Patients with splanchnic or cerebral vein thrombosis were younger than those with other venous thrombosis: median age, 40 vs 67 years for splanchnic vein thrombosis ($P < .01$) and 39 vs 67 years for cerebral vein thrombosis ($P = .02$).[46]

Diagnosis

The diagnosis of essential thrombocythemia cannot be made until secondary causes of thrombocytosis, which account for more than 85% of thrombocytosis (platelet count ≥450 × 10^9/L) cases (Table 3), have been excluded. Patients with thrombocytosis should be evaluated for infections, solid tumor malignancy (eg, breast or lung carcinomas; lymphomas), postsplenectomy state or functional asplenia (evidenced by increased nucleated red blood cells, target cells, Howell-Jolly bodies), iron deficiency, and rebound thrombocytosis (eg, recovery from excess alcohol use or chemotherapy). If the initial clinical assessment does not suggest a secondary cause of thrombocytosis, patients should undergo peripheral blood testing for *JAK2*, *CALR*, and *MPL* gene variants.

Formal diagnostic criteria of essential thrombocythemia from the International Consensus Classification of Myeloid Neoplasms and Acute Leukemias and the World Health Organization includes 4 major criteria: (1) thrombocytosis (platelet count ≥450 × 10^9/L), (2) bone marrow examination that shows megakaryocyte proliferation of mature forms, (3) exclusion of other myeloid neoplasms, and (4) a driver variant in *JAK2*, *CALR*, and *MPL*.[1] However, presence of the first 3 major criteria plus no evidence for secondary thrombocytosis is also sufficient to diagnose essential thrombocythemia.[1]

Thrombosis Risk Stratification

Treatment of patients with essential thrombocythemia is guided primarily by thrombosis risk stratification and is intended to lower the incidence of thrombosis. There are currently no therapies for essential thrombocythemia (**Table 4** and **Table 5**) that prevent leukemic or fibrotic transformation or that induce complete molecular, cytogenetic, or morphologic remission or improve survival. The revised International Prognostic Scoring for Essential Thrombocythemia-Thrombosis (IPSET-Thrombosis)[71] is used to assess thrombosis risk and includes 4 risk categories (**Figure 1**): (1) very low risk (age ≤60 years, no thrombosis history, *JAK2* wild type), (2) low risk

Table 1. Distinguishing Features Between Essential Thrombocythemia and Secondary Thrombocytosis

Features	Essential thrombocythemia	Secondary thrombocytosis[a]
Clinical presentation and medical history	Microcirculatory symptoms (≈29%)[b] Overt thrombosis/thrombosis history (≈22%) Splenic discomfort/splenomegaly (≈12%) Superficial thrombophlebitis (<5%) Cerebral vein thrombosis (<2%) Splanchnic vein thrombosis (≈5%)	Systemic symptoms of infection, inflammation, malignancy Incidental trauma or surgery Previous splenectomy History of iron deficiency
Physical examination	Palpable splenomegaly	Absence of splenomegaly
Laboratory parameters	Sustained thrombocytosis on repeated measures Detection of *JAK2*, *CALR*, or *MPL* variant	New-onset thrombocytosis Positive blood culture result Neutrophilia/left shift on blood smear Inflammatory markers (increased CRP level/ESR) Iron deficiency Markers of functional asplenia: Howell-Jolly bodies Nucleated red blood cells

Abbreviations: *CALR*, calreticulin gene; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; *JAK2*, Janus kinase 2 gene; *MPL*, myeloproliferative leukemia virus gene.

[a] Secondary thrombocytosis is not a risk factor for hemorrhage or thrombosis; however, rates of thrombosis are increased with certain underlying conditions (eg, malignancy), especially if additional risk factors are present; management of such cases should be individually tailored according to risk level. There is currently no evidence to recommend systematic treatment of reactive thrombocytosis with aspirin, anticoagulants, platelet-lowering cytoreductive therapy, or plateletpheresis, regardless of platelet count.

[b] Microcirculatory symptoms include erythromelalgia, acral paresthesias, burning toes and fingers, blurred vision, or headaches.

Table 2. Causes, Mechanisms, and Management of Secondary Thrombocytosis in Adults[a]

Cause (percent representation)	Mechanism of thrombocytosis	Management
Infections (17%-43%)	Inflammatory cytokines Nonspecific stimulation Platelet release	Resolution expected with treatment Longer with chronic infection
Inflammatory diseases (4%-12%)	Increased thrombopoietic factors	Directed to underlying conditions
Malignancy (10%) Lung/gastrointestinal/lymphomas	Increased thrombopoietic factors	Treatment of underlying malignancy
Iron deficiency (7%-11%)	Increased proliferation of progenitor cells	Repletion of body iron stores Resolution expected in 1-2 mo
Splenectomy (1%-2%) Peak 1-3 wk	Decreased platelet sequestration Decreased platelet turnover	Thrombocytosis (lifelong) Thrombocytosis might resolve in 1-5 y
Surgery/trauma (22%-32%)	Increased thrombopoietic factors Tissue damage led increase	Resolution expected in days to weeks
Rebound thrombocytosis (7%)	Recovery from cytotoxic chemotherapy Cessation of excessive alcohol use Treatment of vitamin deficiency Treatment of ITP	Resolution expected in 2-4 wk
Drugs (1%-3%) Corticosteroids/epinephrine Vinca alkaloids/gemcitabine Thrombopoietin agonists/ATRA Miconazole/antibiotics Clozapine/LMWH	Variable	Drug dose modification/discontinuation

Abbreviations: ATRA, all-*trans* retinoic acid; ITP, immune thrombocytopenic purpura; LMWH, low-molecular-weight heparin.

[a] Sources: Edahiro et al[6]; Rose et al.[7]

Box. Questions Commonly Asked by Generalists About Essential Thrombocythemia

How Is Essential Thrombocythemia Differentiated From Secondary Thrombocytosis?

Most patients (85%-90%) with thrombocytosis have secondary thrombocytosis, caused by inflammatory states such as rheumatoid arthritis and systemic lupus erythematosus; previous splenectomy; infections such as pneumonia, bacterial sepsis, and osteomyelitis; iron deficiency anemia; or solid tumors such as lung cancer. Patients with essential thrombocythemia have a persistent platelet count of 450 × 10^9/L or greater and commonly have *JAK2*, *CALR,* or *MPL* gene variants that are not present in secondary thrombocytosis.

Which Treatments Are Recommended for Patients With Essential Thrombocythemia?

Most patients with essential thrombocythemia should receive low-dose aspirin daily, in the absence of contraindications. Cytoreductive therapy with hydroxyurea, pegylated interferon, or busulfan is advised for patients with essential thrombocytopenia who are at high risk for thrombosis (eg, previous history of thrombosis, older than 60 years, presence of cardiovascular risk factors such as smoking, hypertension, diabetes, and hyperlipidemia). Systemic anticoagulation with warfarin, direct oral anticoagulants, or low-molecular-weight heparin is recommended for patients with essential thrombocytopenia and venous thrombosis.

What Symptoms and Outcomes Are Associated With Essential Thrombocythemia?

Patients with essential thrombocythemia may experience headaches, lightheadedness, acral dysesthesia, and minor mucocutaneous bleeds. Major complications of essential thrombocytopenia include venous and arterial thrombosis, hemorrhage, and development of myelofibrosis and acute myeloid leukemia. Most patients with essential thrombocythemia have a near-normal life expectancy, with median survival exceeding 3 decades in patients younger than 50 years.

CALR indicates calreticulin gene; *JAK2*, Janus kinase 2 gene; *MPL*, myeloproliferative leukemia virus gene.

(age ≤60 years, no thrombosis history, *JAK2* gene variant), (3) intermediate risk (age >60 years, no thrombosis history, *JAK2* wild type), and (4) high risk (thrombosis history or age >60 years with *JAK2* gene variant).[71,73,74] In a study of 1019 patients with essential thrombocythemia, the risk of thrombosis among patients in the very–low-risk category was 1.05% per year and only 0.44% per year among those without cardiovascular risk factors such as hypertension, diabetes, hyperlipidemia, and tobacco use.[71] In contrast, the thrombosis rate among those in the low-risk category was 1.59% per year in the presence of *JAK2* gene variant alone and 2.57% for those with *JAK2* gene variants and cardiovascular risk factors.[71] The thrombosis rates were 1.44% to 1.64% per year in patients in the intermediate-risk category and 2.36% to 4.17% per year in those in the high-risk category.[71]

In a cohort study[23] of 1000 patients from the Mayo Clinic with essential thrombocythemia who were followed up for a median of 8.5 years, postdiagnosis arterial thrombotic events were documented in 13% (n = 137; 1.6/per 100 person-years) and venous thrombosis occurred in 7% (n = 70; 0.8/per 100 person-years).[23] The incidence of arterial thrombosis during follow-up was highest for those with *JAK2* gene variants (n = 617 [14%]), followed by *MPL* (n = 30 [13%]), *CALR* (type 1, n = 149 [11%]; type 2, n = 105 [12%]), and lowest for those with triple-negative status (n = 84 [6%]). In a cohort of 1000 patients from Florence, Italy,[24] the overall arterial thrombosis rate after diagnosis of essential thrombocythemia was 9%, and venous thrombosis occurred in 6%.

Treatment

Formal guidelines for management of patients with essential thrombocythemia include those from the National Comprehensive Cancer Network[78] and the European LeukemiaNet[79] committees (**Table 6**). Patients with essential thrombocythemia should receive treatment for cardiovascular risk factors (eg, hypertension, diabetes, hyperlipidemia, tobacco use) because these conditions substantially increase the risk of thrombosis. Therapy with aspirin or cytoreductive therapies such as hydroxyurea reduce thrombotic complications (**Figure 2**) and alleviate symptoms such as headaches or pain in the hands or feet. However, experts in the treatment of essential thrombocythemia have different opinions regarding the risk-benefit balance for treatment with aspirin or similar antiplatelet agents, primarily due to absence of randomized clinical trials comparing aspirin with placebo and to the inconsistency of studies from observational studies.[66]

Treatment of Patients With Low Risk of Thrombosis

Once-daily aspirin therapy is usually recommended for most patients with essential thrombocythemia to lower the risk of arterial, and possibly venous, thrombosis (Table 6). However, aspirin therapy might not be necessary for patients at very low risk with no cardiovascular risk factors or who are triple-negative (ie, no expression of *JAK2*, *CALR*, or *MPL* variants) (Figure 1).[23,24,60,61]

In a retrospective study of 300 low-risk patients with essential thrombocythemia (younger than age 60 years with no prior thrombosis),[60] 198 received antiplatelet therapy (low-dose aspirin [100 mg/d] in 185 persons), while 102 received observation alone. Overall, there was no difference in total arterial and venous thrombotic events for those taking aspirin (21.2/1000 patient-years vs 17.7 patient-years for observation; $P = .60$). However, not taking aspirin was associated with increased risk of arterial thrombosis among patients with cardiovascular risk factors such as smoking, hypertension, diabetes, and hyperlipidemia (incidence rate ratio, 2.5 [95% CI, 1.02-6.1]; risk without aspirin, 9.4/1000 patient-years). Lack of aspirin use was also associated with a higher risk of venous thrombosis among patients with a *JAK2* gene variant (incidence rate ratio, 4.0 [95% CI, 1.2-12.9]; risk without aspirin, 8.2/1000 patient-years). In a registry study of 1000 patients with essential thrombocythemia, which included individuals younger than 60 years without history of thrombosis, initial aspirin therapy (81 mg/d) was associated with a lower overall risk of arterial thrombosis (0.7 vs 1.7/100 patient-years; $P < .01$).[23] However initial aspirin therapy was not associated with a lower risk of venous thrombosis (0.97/100 patient-years without aspirin vs 0.4/100 patient-years with aspirin; $P = .10$).

While aspirin has not been compared with placebo for prevention of symptoms in patients with essential thrombocythemia, a randomized trial compared 242 patients assigned to aspirin (100 mg/d) once daily (n = 120) vs twice daily (n = 122) for 20 months.[14] Prior to randomization, all patients had been taking once-daily low-dose aspirin and more than half were being treated with a cytoreductive

Table 3. Presenting Characteristics and Events During the Clinical Course of 2000 Patients With Essential Thrombocythemia[a]

Variable	Percent or median (range)	Comments
Characteristics at presentation		
Myeloproliferative neoplasm driver variant		
JAK2	63.8	In ≈10% of patients, none of the 3 variants are detected; such cases are referred to as triple-negative
CALR	22.8	
MPL	3.7	
Age, y	59 (18-94)	Older for *JAK2* (61 y) and *MPL* (64 y) and younger for *CALR* (53 y) and triple-negative (51 y)
Female sex	64	Lower for *CALR* (48%) vs *JAK2* (68%), *MPL* (66%), or triple-negative (75%)
Microcirculatory symptoms/vascular migraine[b]	29.4	Higher for *MPL* (45.2%) vs *CALR* (30.2%), *JAK2* (28.5%), or triple-negative (27.5%)
Palpable splenomegaly	12.4	Lower for *MPL* (6.8%) vs *JAK2* (13.2%), *CALR* (11.5%), or triple-negative (11.3%)
Platelets, $\times 10^9$/L	738 (450-3460)	Higher for *CALR* (897), *MPL* (818), or triple-negative (791) vs *JAK2* (690)
Platelets ≥1000 × 10^9/L	21	Highest for *CALR* (38%), followed by triple-negative (27%), *MPL* (22%), and *JAK2* (14%)
Hemoglobin, g/dL	14 (10-17.6)	Higher for *JAK2* (14.2) vs *CALR* (13.7), *MPL* (13.4), or triple-negative (13.6)
Leukocytes, $\times 10^9$/L	8.5 (3.2-23)	Higher for *JAK2* (8.8) vs *CALR* (8.0), *MPL* (7.4), or triple-negative (7.9)
Leukocytes ≥11 × 10^9/L	19	Higher for *JAK2* (22%) and triple-negative (19.7%) vs *CALR* (11%) or *MPL* (11.3%)
Events at or before diagnosis		
Arterial thrombosis (major)	14	Higher for *JAK2* (16%), *MPL* (12%), and triple-negative (11.9%) vs *CALR* (7.2%)
Venous thrombosis (major)	8.3	Higher for *JAK2* (10%) and *MPL* (11%) vs *CALR* (3%) or triple-negative (7%)
Hemorrhage (major)	4.5	Similar across *JAK2* (4.4%), *CALR* (3.6%), *MPL* (5.4%), and triple-negative (7.3%)
Events after diagnosis		
Arterial thrombosis (major)	11	Lower with triple-negative (4%) vs *JAK2* (12%), *MPL* (13.5%), or *CALR* (10.5%)
Venous thrombosis (major)	7	Lower with triple-negative (2%) vs *JAK2* (8%), *MPL* (5.4%), or *CALR* (6.4%)
Hemorrhage (major)	8.4	Higher for *MPL* (13.5%) vs *JAK2* (8.8%), *CALR* (7.8%), or triple-negative (5.2%)
Myelofibrosis transformation	10	Lower with triple-negative (5.2%) and *JAK2* (7.5%) vs *MPL* (20.3%) or *CALR* (17.1%)
Leukemic transformation	3.4	Lower with triple-negative (0%) vs *MPL* (5.4%), *CALR* (4.4%), or *JAK2* (3.4%)

Abbreviations: *CALR*, calreticulin gene; *JAK2*, Janus kinase 2 gene; *MPL*, myeloproliferative leukemia virus gene.

[a] Sources: Gangat et al[23]; Loscocco et al.[24] Median follow-up, 8.2 (range, 0.02-52.7) years.

[b] Microcirculatory symptoms include erythromelalgia, acral paresthesias, burning toes and fingers, blurred vision, or headaches.

medication, including hydroxyurea or anagrelide. Compared with patients assigned to once-daily aspirin, those randomized to twice-daily aspirin experienced less severe pain in their hands (19% vs 25%; $P < .01$) and feet (20% vs 27%; $P < .01$) and were more likely to have no symptoms associated with essential thrombocythemia (17.3% vs 14.3%; $P = .05$). The number of major thrombotic events were too low to allow valid statistical comparisons between the once-daily (3 events) and twice-daily (one event) aspirin treatment groups. Importantly, major bleeding and gastrointestinal symptoms were not significantly different between the treatment groups (Table 4 and Table 5). Twice-daily aspirin dosing may be considered in certain patients at high risk of thrombosis or in the presence of essential thrombocythemia symptoms such as acral paresthesias, burning sensation in the toes and fingers, blurred vision, or headaches despite once-daily aspirin treatment (Figure 1).

The overall risk of bleeding in patients with essential thrombocythemia at low risk for thrombosis who are treated with low-dose aspirin therapy may be similar to that in those not treated with aspirin. In an observational study of 433 patients with essential thrombocythemia who were younger than age 60 years and had no prior thrombosis, the overall rate of major bleeding was similar for those taking low-dose aspirin (81-100 mg/d) vs not taking aspirin (incidence rate, 9.9 per 1000 person-years for those taking low-dose aspirin and 4.6 events per 1000 person-years for those taking no aspirin; $P = .20$).[61] Frequency of bleeding events in patients with a *JAK2* gene variant was not modified by treatment with low-dose aspirin. However, among individuals with *CALR* gene variants, those who received aspirin had more bleeding events than those not treated with aspirin (12.9 bleeding events per 1000 person-years for those receiving aspirin vs 1.8 per 1000 patient years for those not receiving aspirin; $P = .03$).[61]

For patients in any thrombotic risk category who have essential thrombocythemia symptoms despite aspirin treatment, hydroxyurea or other cytoreductive agent such as pegylated interferon may be added and the dose adjusted to achieve the target platelet count at which symptoms are relieved (Table 6). In patients

Table 4. Conventional Drugs Used in Treatment of Essential Thrombocythemia

Drug[a]	Mechanism	Dose	Hematologic toxicity	Nonhematologic toxicity[b]	Monitoring
Aspirin	Cyclooxygenase inhibitor	81 mg orally, 1-2 times daily		Gastrointestinal ulcer (up to 50% prolonged use) Gastrointestinal hemorrhage (<10%) Tinnitus (<10%) Bronchospasm (infrequent) Angioedema (infrequent) Congestive heart failure (rare)	
Hydroxyurea	Ribonucleotide reductase inhibitor	Initial: 500 mg orally, twice daily	ANC <1000 (hold)	Xeroderma (10%-30%) Skin ulcer (5%-10%) Nail discoloration (10%-30%) Fever (rare) Pneumonitis (rare)	CBC every 1-2 wk for first mo
Pegylated interferon alfa	Not fully understood (antiproliferative activity against megakaryocytes)	Initial: Pegylated interferon alfa-2a (45 µg subcutaneously weekly) Ropeginterferon alfa-2b (100 µg subcutaneously every 2 wk)	ANC <1000 (hold)	Influenza-like illness (15%-90%) Fatigue (10%-30%) Loss of appetite (15%-30%) Alopecia (15%-30%) Fever (30%-50%) Arthralgia (20%-30%) Elevated liver enzyme levels Depression (15%-20%)	CBC every 1-2 wk for first mo LFT/TSH every 3 mo
Anagrelide	Platelet maturation inhibitor	0.5-1 mg orally, 4 times daily	Platelets <100 × 10^9/L (hold)	Edema (15%-30%) Palpitations (10%-20%) Diarrhea (10%-30%) Headache (20%-50%)	CBC every 1-2 wk for first mo
Oral busulfan	Alkylating agent	2-4 mg orally, daily	ANC<1500 (hold) Platelets <200 × 10^9/L (hold)	Pulmonary fibrosis (rare) Hyperpigmentation (infrequent)	CBC every 1-2 wk

Abbreviations: ANC, absolute neutrophil count; CBC, complete blood cell count; LFT, liver function test; TSH, thyrotopin.

[a] Supporting evidence for drugs listed in this table is reported in Table 5.

[b] Adverse effects frequencies obtained from Micromedex.

with essential thrombocythemia at low risk of thrombosis, the presence of extreme thrombocytosis, defined as platelet count greater than 1000 × 10^9/L, is not associated with an increased risk of thrombosis and does not require use of cytoreductive therapy.[44,46]

Treatment of Patients at Intermediate or High Risk of Thrombosis

The revised IPSET-Thrombosis stratification system categorizes individuals with a prior thrombosis or older than 60 years with the *JAK2* variant as at high risk for subsequent thrombosis[71]; these patients may benefit from cytoreductive therapy to lower risk of thrombosis.[71] In a randomized trial, 114 patients with high-risk essential thrombocythemia (46% with thrombosis history and 85% older than 60 years), with platelet count of less than 1500 × 10^9/L, were assigned to receive hydroxyurea (n = 56) or no cytoreductive therapy (n = 58) and followed up for 27 months.[15] The dose of hydroxyurea was adjusted to keep the platelet count less than 600 × 10^9/L. Additional treatment was equally distributed between the 2 treatment groups and included aspirin (300 mg/d [44%]) or ticlopidine (500 mg/d [25%]), based on the presence of thrombosis history or microcirculatory symptoms such as acral paresthesias, burning sensation in the toes and fingers, blurred vision, or headaches. In this study, 16 patients (14%) experienced thrombotic complications, including superficial thrombophlebitis, and the rate was significantly higher in the group not receiving cytoreductive therapy (24% vs 3.6%; $P < .01$). Thus, hydroxyurea therapy is often suggested for secondary prevention of recurrent thrombosis in patients with essential thrombocythemia (Figure 1). In contrast, patients older than 60 years with intermediate thrombosis risk may not benefit from cytoreductive therapy, especially in the absence of cardiovascular risk factors (Figure 1).[71,72]

Similarly, the therapeutic value of hydroxyurea appears to be limited in patients with low-risk essential thrombocythemia without extreme thrombocytosis.[44] In a randomized clinical trial (382 patients aged 40-59 years) that compared hydroxyurea plus aspirin vs aspirin alone in patients without a history of thrombi or extreme thrombocytosis (platelet count ≥1500 × 10^9/L), at a median follow-up of 73 months, there was no significant difference between the 2 groups in the composite incidence of arterial or venous thrombi, serious hemorrhage, or death from vascular causes (11 events in each group).[12]

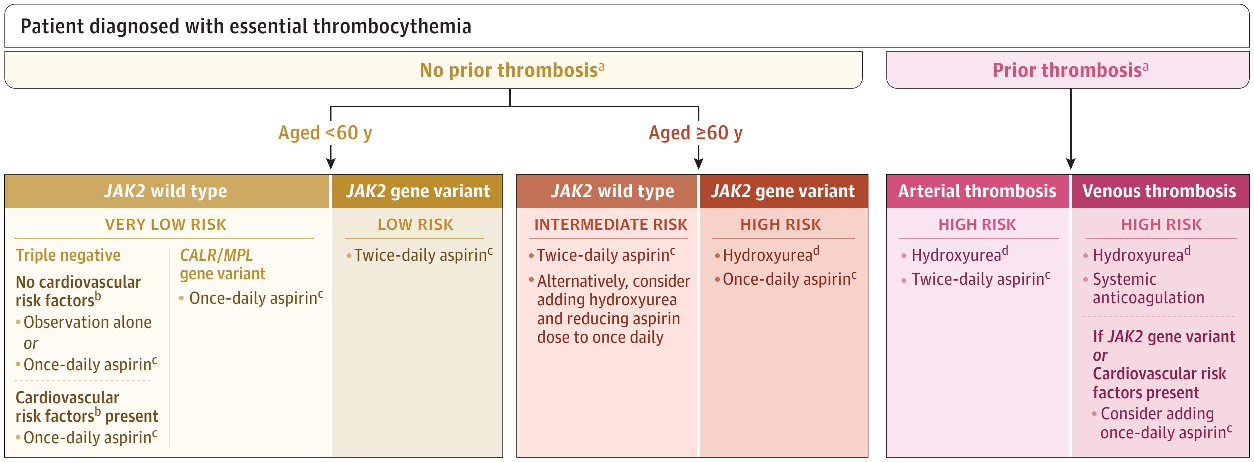
Hydroxyurea may cause adverse effects (Table 4 and Table 5), including painful mucocutaneous ulcers (5%-10%), nail discolorations (10%-30%), gastrointestinal symptoms such as nausea or upper abdominal pain (5%-10%), extreme fatigue (5%-10%), recurrent skin lesions (10%-30%), nonmelanoma skin cancers (<5%), myelosuppression including anemia (50%-70%), and allergic reactions (<5%). Second-line cytoreductive medications for patients with essential thrombocythemia are pegylated interferon alfa[9,17,18,22,65] and busulfan[37-40] (Table 4 and Table 5). For patients who cannot take twice-daily aspirin and do not tolerate or are

Table 5. Supporting Evidence for Conventional Drugs Used in Treatment of Essential Thrombocythemia

Supporting studies	Study design	Dose	Platelet count	Thrombosis/bleeding	Disease transformation
Aspirin					
Rocca et al[14] 2024	Randomized phase 2 trial of 2 aspirin regimens (N = 242)	100 mg once daily vs 100 mg twice daily		Twice daily vs once daily: Thrombosis: 0.8% vs 2.5% Nonmajor bleeding: 6.6% vs 1.7%	
Alvarez-Larran et al,[61] 2016	Retrospective Antiplatelet monotherapy vs observation in low-risk essential thrombocythemia (N = 433)	81-100 mg		Antiplatelet vs observation: 10.7 vs 12.1 per 1000 person-years *CALR* mutated: 9.7 vs 6.9 per 1000 person-years *JAK2* mutated: 11.6 vs 21.1 per 1000 person-years	
Alvarez-Larran et al,[60] 2010	Retrospective Antiplatelet monotherapy vs observation in low-risk essential thrombocythemia (N = 300)	Aspirin (100 mg) Dipyridamole (150 mg) Triflusal (600 mg) Ticlopidine (250 mg)		Antiplatelet vs observation: 21.2 vs 17.7 per 1000 person-years	
Hydroxyurea					
Cortelazzo et al,[15] 1995	Randomized Hydroxyurea vs no chemotherapy in high-risk essential thrombocythemia (N = 114)	Initial: 15 mg/kg Maintenance based on platelet count <600 × 10^9/L and white blood cell count >4 × 10^9/L	Hydroxyurea vs control: median, 809 × 10^9/L (range, 533-1165) vs 747 × 10^9/L (range, 620-1240)	Hydroxyurea vs control: 4% vs 24%	
Godfrey et al,[12] 2018	Randomized Hydroxyurea + aspirin vs aspirin alone in non-high-risk patients 40-59 y (N = 382)	Hydroxyurea (0.5-2 g) orally, daily Aspirin (75-100 mg) daily		Hydroxyurea + aspirin vs aspirin alone: 6% vs 6%	Hydroxyurea + aspirin vs aspirin alone: Myelofibrosis: 3% vs 3% AML: 1.6% vs 1.1%
Pegylated interferon alfa					
Mascarenhas et al,[9] 2022	Randomized Interferon vs hydroxyurea in newly diagnosed high-risk essential thrombocythemia (N = 81)	Interferon (45-180 µg) subcutaneously, weekly Hydroxyurea (500 mg) orally, wice daily	≤400 × 10^9/L at 12 mo: 44% vs 45%	Interferon vs hydroxyurea: 2% vs 2%	Interferon vs hydroxyurea: 0% vs 2%
Anagrelide					
Harrison et al,[10] 2005	Randomized Anagrelide vs hydroxyurea + low-dose aspirin in high-risk essential thrombocythemia (N = 809)	Anagrelide (0.5 mg) orally, twice daily Hydroxyurea (500 mg-1 g) orally, daily	≤400 × 10^9/L; similar at 9 mo	Anagrelide vs hydroxyurea: Arterial thrombosis: 9% vs 4% Venous thrombosis: 0.7% vs 3%	Anagrelide vs hydroxyurea: Myelofibrosis: 4% vs 1% AML: 1% vs 1%
Gisslinger et al,[11] 2013	Randomized Anagrelide vs hydroxyurea in newly-diagnosed essential thrombocythemia (N = 259)	Anagrelide (0.5 mg) orally, twice daily Hydroxyurea (1500 mg) orally, daily	Platelet control similar	Anagrelide vs hydroxyurea: Arterial thrombosis: 6% vs 6% Venous thrombosis: 1.6% vs 4.5%	Anagrelide vs hydroxyurea: Myelofibrosis: 1.6% vs 0.8% AML: 0% vs 0%
Busulphan					
Renso et al,[37] 2018	Retrospective elderly patients resistant/intolerant to hydroxyurea (N = 26)	4-6 mg orally, weekly	≤400 × 10^9/L in 92%	Arterial thrombosis: 23% Venous thrombosis: 8%	AML: 7.7%
Begna et al,[39] 2016	Retrospective (N = 37)		Median, 303 × 10^9/L (range, 124-833)		AML: 3%

Abbreviations: AML, acute myeloid leukemia; *CALR*, calreticulin gene; *JAK2*, Janus kinase 2 gene.

Figure 1. Current Treatment Algorithm in Essential Thrombocythemia



JAK2 indicates Janus kinase 2 gene.

[a]Major thrombosis history not including superficial thrombophlebitis.

[b]Cardiovascular risk factors: diabetes, hypertension, tobacco use, hyperlipidemia.

[c]Use of aspirin in patients with extreme thrombocytosis requires careful monitoring for bleeding and clinically relevant acquired von Willebrand syndrome. These patients are advised not to use if von Willebrand factor activity is less than 20% to 30%; screening is advised for patients with platelet count greater than 1000 × 10^9/L or excessive mucocutaneous bleeding.

[d]Second-line drugs of choice in hydroxyurea-intolerant patients or those with refractory disease include pegylated interferon alfa and busulfan.

Table 6. Management Guidelines for Essential Thrombocythemia

Risk stratification	Very low risk	Low risk	Intermediate risk	High risk
IPSET-T[73]	Age ≤60 y *JAK2* wild type No thrombosis history	Age ≤60 y *JAK2* mutated No thrombosis history	Age >60 y *JAK2* wild-type No thrombosis history	Thrombosis history or Age ≥60 y *JAK2* variant
NCCN[78]	Aspirin (81-100 mg/d)[a] for patients with microvascular disturbances (otherwise, observation) Manage cardiovascular risk factors Indications for cytoreductive therapy: new thrombosis or bleeding, acquired von Willebrand syndrome, progressive thrombocytosis/leukocytosis, splenomegaly, disease-related symptoms (eg, pruritus, night sweats), or vasomotor/microvascular symptoms unresponsive to aspirin[b]	Aspirin (81-100 mg/d)[a] Manage cardiovascular risk factors Indications for cytoreductive therapy: new thrombosis or bleeding, acquired von Willebrand syndrome, progressive thrombocytosis/leukocytosis, splenomegaly, disease-related symptoms (eg, pruritus, night sweats), or vasomotor/microvascular symptoms unresponsive to aspirin[b]	Aspirin (81-100 mg/d)[a] Manage cardiovascular risk factors Indications for cytoreductive therapy: new thrombosis or bleeding, acquired von Willebrand syndrome, progressive thrombocytosis/leukocytosis, splenomegaly, disease-related symptoms (eg, pruritus, night sweats), or vasomotor/microvascular symptoms unresponsive to aspirin[b]	Aspirin (81-100 mg/d)[a] Manage cardiovascular risk factors Cytoreductive therapy (indications: new thrombosis or bleeding, acquired von Willebrand syndrome, progressive thrombocytosis/leukocytosis, splenomegaly, disease-related symptoms (eg, pruritus, night sweats), or vasomotor/microvascular symptoms unresponsive to aspirin)[b]
ELN[79]	NA	Low-dose aspirin Start cytoreductive therapy once age is ≥60 y, occurrence of major hemorrhagic event, platelet count >1500 × 10^9/L, progressive splenomegaly, or uncontrolled disease-related symptoms[c]	Low-dose aspirin Start cytoreductive therapy once age is ≥60 y, occurrence of major hemorrhagic event, platelet count >1500 × 10^9/L, progressive splenomegaly, or uncontrolled disease-related symptoms[c]	Low-dose aspirin Cytoreductive therapy[c]

Abbreviations: ELN, European LeukemiaNet; IPSET-T, International Prognostic Score of Thrombosis in World Health Organization–Essential Thrombocytopenia; *JAK2*, Janus kinase 2 gene; NA, not applicable; NCCN, National Comprehensive Cancer Network.

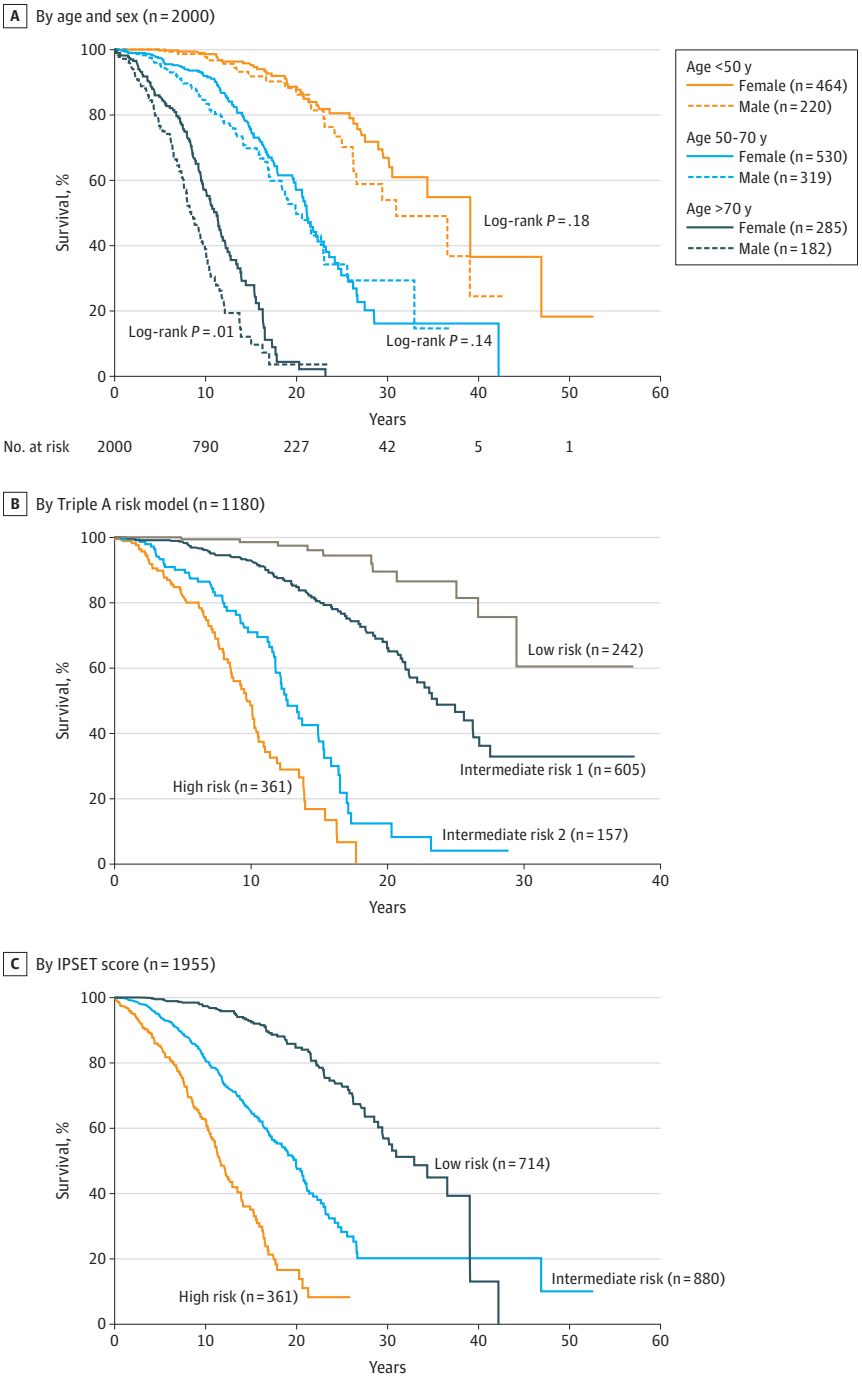
[a] Aspirin should be used with caution in patients with acquired von Willebrand syndrome. Higher-dose aspirin may be appropriate in selected patients. The risks and benefits of higher-dose aspirin (>100 mg) must be weighed based on the presence of vasomotor symptoms vs the risk of bleeding. Twice-daily aspirin may be considered for patients with refractory symptoms.

[b] Hydroxyurea is the preferred first-line cytoreductive therapy; other options include peginterferon alfa-2a or anagrelide. Peginterferon alfa-2a can be considered for patients in need of cytoreductive therapy who are younger or pregnant or who defer hydroxyurea.

[c] Hydroxyurea or recombinant interferon alfa recommended for first-line; anagrelide recommended as alternative cytoreductive option.

resistant to cytoreductive therapy, some experts may recommend systemic anticoagulation for venous thromboembolism prophylaxis with vitamin K antagonists or direct-acting anticoagulants (DOACs). However, there are currently no clinical trial data about use of oral anticoagulants in these patients. Table 6 provides additional information about treatment guidelines published by the

Figure 2. Overall Survival Data Among 2000 Patients With Essential Thrombocythemia Who Were Assembled From the Mayo Clinic, US (n = 1000), and the University of Florence, Italy (n = 1000)



A, Median survival was 39 years for younger than 50 years/female, 31 years for younger than 50 years/male, 21 years for age 50 to 70 years/female, 20 years for age 5- to 70 years male, 11.2 years for older than 70 years/female, and 8.4 years for older than 70 years/male. B, The Triple A risk model assigns 4 points for age older than 70 years; 2 points for age 50 to 70 years; 1 point for absolute neutrophil count 8×10^9/L or greater; and 1 point for absolute lymphocyte count less than 1.7×10^9/L. Median survival was not reached for low risk (0-1 points) and was 23.6 years for intermediate risk 1 (2-3 points), 12.8 years for intermediate risk 2 (4 points), and 9.7 years for high risk (5-6 points). C, The International Prognostic Score for Essential Thrombocythemia (IPSET) assigns 2 points for age 60 years or older; 1 point for white blood cell count greater than 11×10^9/L, and 1 point for previous thrombosis. Median survival was 33 years for low risk (0 points), 20 years for intermediate risk (1-2 points), and 11.6 years for high risk (3-4 points). Data sources: Gangat et al,[23] 2024; Loscocco et al,[24] 2024; Tefferi et al,[75] 2023; Passamonti et al,[70] 2012.

European LeukemiaNet[79] and National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology.[78]

Treatment of Patients With Thrombosis

Patients with essential thrombocythemia who develop venous thrombosis are typically treated similarly to individuals with venous thrombosis without essential thrombocythemia.[80] Once diagnosis of deep vein thrombosis/pulmonary embolism is confirmed, systemic anticoagulation should be instituted with DOACs or low-molecular-weight heparin (LMWH).[81] For arterial thrombosis, antiplatelet medications, such as aspirin, are recommended for those without contraindications such as frequent mucocutaneous bleeding and gastric ulcers. Evidence for use of dual antiplatelet therapy with aspirin and another antiplatelet agent (such as clopidogrel, dipyridamole) for secondary prevention of recurrent stroke or transient ischemic attack in persons with essential thrombocythemia,

is currently not available.[67] Although no prospective clinical trials have been published assessing the overall benefit of systemic anticoagulation or cytoreduction in patients with thrombosis, most patients with essential thrombocythemia who have splanchnic or cerebral venous thrombosis are treated with LMWH for 1 to 3 months, followed by long-term anticoagulation with vitamin K antagonists or DOACs for an indefinite period unless they develop a condition or comorbidity that modifies the risk-benefit balance.[46]

Acquired von Willebrand Syndrome

Persons with essential thrombocythemia may develop acquired von Willebrand syndrome (AvWS) as a result of accelerated von Willebrand factor (VWF) degradation, likely mediated by increased in vivo platelet activation.[101,102] In a study of 170 patients with essential thrombocythemia, 34 (20%) had laboratory findings consistent with AvWS (eg, abnormal VWF multimer pattern, reduced ratio of VWF ristocetin cofactor to VWF antigen, reduced VWF ristocetin cofactor activity).[98] In this study, mean platelet count was 701 × 10^9/L in patients with AvWS vs 472 × 10^9/L in those without AvWS (P < .01).[62] Screening for AvWS is generally not advised for patients with essential thrombocythemia, except for those with extreme thrombocytosis (platelet count ≥1000 × 10^9/L), which develops in 16% to 26% of patients[23,24] and is associated with increased susceptibility to bleeding.[82,101] For patients with essential thrombocythemia who have markedly reduced VWF activity without evidence of bleeding, some experts suggest either avoiding or postponing treatment with aspirin until the VWF abnormality is corrected by cytoreductive therapy.[82,83]

Pregnancy and Hormone-Related Risk of Thrombosis and Hemorrhage

Pregnancy outcomes in patients with essential thrombocythemia are primarily reported from retrospective studies. Among 598 patients from 4 observational studies,[50-52,54] live birth rates ranged from 68% to 75%, fetal loss from 25% to 32%, first-trimester fetal loss from 16% to 26%, and maternal complications, including hemorrhage and preeclampsia, from 8% to 13%. For comparison, population-based estimates of miscarriage rates among clinically recognized pregnancies range from 10% to 20%.[77] In a cohort of 200 pregnancies involving 100 women with essential thrombocythemia, the incidence of fetal loss was significantly lower among 135 patients who were receiving aspirin before conception and continued during pregnancy (antepartum), compared with those (n = 65) who did not receive aspirin during pregnancy (16% vs 45%; P < .01).[54] The Mayo Clinic study also reported an association between *CALR* gene variant and maternal major hemorrhage (13% in those with *CALR* variant vs 4% in those without *CALR* variant; P = .05).[54] The potential benefit of treatment with low-dose aspirin to prevent first-trimester pregnancy loss requires prospective clinical studies. Use of hydroxyurea (pregnancy risk category D) or anagrelide (pregnancy risk category C) is not recommended during pregnancy and lactation.

Data about estrogen-based hormone treatment are derived from a retrospective observational study of 305 women with essential thrombocythemia followed up for a median of 133 months.[55] In this study, rates of thrombosis were similar among those taking vs not taking oral estrogen–based hormone treatment at time of essential thrombocythemia diagnosis (19% vs 25%; P = .28); postdiagnosis thrombosis rates were also similar among patients who continued hormonal therapy (31%) vs discontinued hormonal therapy (29%).[55]

Perioperative Care

A multidisciplinary approach, involving hematology and surgery, should be used for perioperative care of patients with essential thrombocythemia to evaluate the thrombosis and bleeding risk of a planned surgical procedure. Some experts recommend a target preprocedure platelet count less than 450 × 10^9/L in high-risk patients and a target of less than 600 × 10^9/L in low-risk patients to lower the risk of thrombosis and bleeding; attainment of target platelet count in low-risk patients may require a short course of treatment with hydroxyurea. Current evidence is lacking about the perioperative use of aspirin or anticoagulant therapy in patients with essential thrombocythemia. Thus, experts recommend following existing guidelines for individuals without essential thrombocythemia regarding continuing or stopping aspirin prior to surgery and restarting after surgery.[42]

A recent retrospective review evaluated outcomes among 66 patients with essential thrombocythemia who underwent 121 elective or urgent surgical procedures.[57] At the time of surgery, median platelet count was 365 × 10^9/L (IQR, 27-1039), and ongoing treatments prior to surgery included antiplatelet agents (84%); cytoreductive therapy with hydroxyurea, busulfan, or anagrelide (87%); and systemic anticoagulation (10%). Preoperatively, antiplatelet agents were discontinued in 40% of patients, cytoreductive therapy was discontinued in 11%, and systemic anticoagulation was discontinued in 31%.[57] Postoperative prophylactic anticoagulation was documented after 13 procedures with LMWH used in the majority of cases, followed by unfractionated heparin and, infrequently, DOACs. None of the 66 patients had perioperative bleeding, and 90-day postoperative risks were 1% for arterial thrombosis, 1% for venous thrombosis, 4% for hemorrhage, and 2% for death. The strongest risk factors for 90-day hemorrhagic events were *CALR* vs *JAK2* gene variants (hazard ratio [HR], 19 [95% CI, 2.1-180]; P < .01) and urgent vs elective surgery (HR, 17.5 [95% CI, 1.8-172]; P < .01). Independent risk factors for a composite end point of perioperative complications (thrombosis, bleeding, and death) included urgent procedures (HR, 11.6 [95% CI, 2.9-46.3]; P < .01), major surgical procedures (HR, 4.8 [95% CI, 1.3-17.9]; P < .01), platelet count greater than 450 × 10^9/L (P = .02), and perioperative discontinuation of aspirin (HR, 4.1 [95% CI, 1.1-15.3]; P = .02).[57] These study findings suggest that it may be reasonable to continue cytoreductive and aspirin therapy during most surgery for patients with essential thrombocythemia, unless they are undergoing a high bleeding risk procedure.

Prognosis

The median overall survival from the time of diagnosis of essential thrombocythemia for individuals younger than 50 years is 39 years for women and 31 years for men; for individuals diagnosed at age 50 to 70 years, median survival is 21 years for women and 20 years for men; and for those older than 70 years, median survival is 11.2 years for women and 8.4 years for men (Figure 2).[23,24] In 2 large series of patients with essential thrombocythemia from the Mayo Clinic and University of Florence, Italy, causes of death included cardiovascular disease (25% and 23%, respectively), progression to

acute myeloid leukemia or myelofibrosis (23% and 27%), infection (12% and 5%), bleeding (10% and 3%), malignancies other than essential thrombocythemia (5% and 12%), and other causes (24% and 35%).[75]

The original International Prognostic Score for Essential Thrombocythemia (IPSET) model for overall survival considers 3 risk factors including age 60 years or older, leukocyte count 11 × 10^9/L or greater, and prior thrombosis.[70] The Triple A (AAA) predictive model includes age, absolute neutrophil count, and absolute lymphocyte count (Figure 2).[75] A third survival model incorporates gene variants and is referred to as the Mutation-Enhanced International Prognostic System for Essential Thrombocythemia (MIPSS-ET); this model considers 4 variables: age older than 60 years, male sex, leukocyte count 11 × 10(9)/L or greater, and adverse genetic variants that occur in 10% of persons (*SF3B1*, *SRSF2*, *U2AF1*, *TP53*).[69]

Figure 2 illustrates application of the IPSET[70] and AAA[75] survival models in a database of 2000 patients combined from the Mayo Clinic (followed up from 1967-2023) and the University of Florence, Italy (followed up from 1980-2023).[23,24] Because of the long survival of patients considered low risk under the AAA model (0-1 points) (Figure 2), the median survival time has not been reached.[23,24] Based on the AAA model,[75] median survival was 23.6 years for intermediate-1-risk patients (2-3 points), 12.8 years for intermediate-2-risk patients (4 points), and 9.7 years for high-risk patients (5-6 points).[23,24] Based on the IPSET model,[70] median survival was 33 years for low-risk patients, 20 years for intermediate-risk patients (1-2 points) (Figure 2), and 11.6 years for high-risk patients (3-4 points).[23,24] In the MIPSS-ET model,[69] patients with adverse gene variants had significantly shorter survival compared with those without these gene variants (median, 11.7 vs 23.7 years; $P < .01$). Risk factors for leukemic transformation, according to a recent Mayo Clinic study,[23] included extreme thrombocytosis (platelet count ≥1000 × 10^9/L) and presence of cytogenetic abnormalities (eg, loss of the long arm of chromosome 20; extra chromosomes 8 or 9); the 20-year risk was 3% in the absence of both risk factors but increased to 13% in the presence of at least 1 of these 2 risk factors.[23] The study also identified *MPL* variant and neutrophilia (absolute neutrophil count ≥8 × 10^9) as risk factors for disease transformation into myelofibrosis; the 20-year risk was 12% in the absence of both risk factors but was 49% in the presence of both risk factors.[23]

Limitations

The current review has several limitations. First, the quality of included literature was not formally evaluated. Second, relevant articles may have been missed. Third, the strength of treatment recommendations is limited by the paucity of randomized clinical trials. Most management recommendations were based on observations from heterogenous retrospective studies.

Conclusions

Essential thrombocythemia is a rare clonal myeloproliferative neoplasm associated with an increased risk of venous and arterial thrombosis, hemorrhage, myelofibrosis, and acute myeloid leukemia. Based on individual risk factors for thrombosis, persons with essential thrombocythemia may be treated with low-dose aspirin, either alone or in combination with a cytoreductive drug such as hydroxyurea.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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