

## Risk of Thromboembolism in Patients with Immune Thrombocytopenia

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### Abstract

Immune thrombocytopenia (ITP) comprises a heterogeneous group of disorders characterized by autoimmune-mediated platelet destruction and impairment of platelet production. Thromboembolic events have been reported in up to 8% of patients with ITP, suggesting that thromboembolism requires special precaution in this patient group. Thromboembolism can be caused by a disease (i.e. pro-thrombotic disease state) after the introduction of ITP therapies such as corticosteroids, splenectomy, and thrombopoietin receptor agonists, or can occur in association with other diseases. In the care of patients with ITP, it is important to understand the risk of thromboembolism. In this article, we focus on the risk of ITP-related thromboembolism and potential prevention and management options.

**Keywords:** Immune thrombocytopenia; Thromboembolism; Anticoagulation; Platelet

### Introduction

Immune thrombocytopenia (ITP) comprises a heterogeneous group of disorders characterized by autoimmune-mediated platelet destruction and impairment of platelet production [1,2]. Autoimmune-mediated accelerated platelet destruction with subsequent clearance in the reticuloendothelial (RE) system can be reduced by RE phagocytosis-preventing agents, such as intravenous immunoglobulin (IVIG), intravenous anti-D, or corticosteroids, or may be permanently resolved by splenectomy [3,4]. Thrombopoietin receptor (TPO-R) agonists, romiplostim and eltrombopag, stimulate and increase platelet production [3-5]. Rituximab, a chimeric monoclonal antibody against the CD20 antigen, is used in refractory ITP patients and acts through B cell depletion [3,4,6].

In ITP patients, increased risk of comorbidities such as diabetes, renal failure, and vascular events has been reported [7]. Thromboembolism is a potential comorbidity that may require special attention as both management of thromboembolism and

thrombophylaxis in patients with low platelet levels can be challenging [8,9]. To our knowledge, there has been no comprehensive review on the risk of thromboembolism in ITP patients to aid clinicians in the evaluation of therapeutic options.

Therefore, in this article, we focus on the risk and treatment of thromboembolism related to chronic ITP in adults and discuss prevention and management options.

### Thromboembolism in ITP Patients

There have been a number of papers describing rates of thromboembolism in ITP populations (Table 1). Aledort et al. found that 10 (5%) of 186 adult patients with ITP, of which 45% had had a splenectomy and 44% were receiving any ITP treatment, reported having 18 thrombotic/ischemic events [10]. Five events, including 3 for one patient, were arterial, and 13 were venous. Eleven (61.1%) of these events occurred after diagnosis of ITP, while 5 of these patients had had splenectomy. In this study, a number of patients with ITP had comorbid diseases, including thyroid disease (10%), and diabetes (4%), in addition to thrombotic events.

ITP cohort			Comparison cohort		
Patients (n)	Venous events	Arterial events	Subjects (n)	Venous events	Arterial events
186 adults	13	5	-	-	-
391 chronic, adult	10	-	3,128	33	-
1,070 adults	31	44	4,280	82	128
3,131 chronic, adult	21	134	9,392	14	281
379 chronic, adult	-	29	3,790	-	254
525 adults	2	24	-	-	-

986 primary ITP	15	28	-	-	-
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**Table 1:** Frequency of thromboembolic events in patients with immune thrombocytopenia.

Severinsen et al. reported the results of a large-scale epidemiological study using registry data from the Danish National Patient Registry (DNPR) to examine the risk of thromboembolism in 391 patients with adult chronic ITP and no prior diagnosis of venous thromboembolism (VTE) compared with the reference cohort (n=3,128) matched by age, gender, and comorbidity [8]. In the ITP cohort, 10 incident VTEs occurred during 1,879 person-years of follow up [incidence rates (IR)=5.32 (95% confidence interval (CI): 2.86-9.89) per 1,000 person-years], compared with 33 incidents of VTE during 16,196 person-years of follow-up in the reference cohort [IR=2.04 (95% CI: 1.45-2.87) per 1,000 person-years]. This yielded an incidence rate ratio (IRR) of VTE of 2.65 (95% CI: 1.27-5.50) for ITP patients. The IRR was high for both provoked and unprovoked VTE (2.26 and 3.16, respectively). Unprovoked VTE was defined as primary VTE diagnosis in the absence of a prior cancer diagnosis and in the absence of surgery, trauma, pregnancy/delivery, or bone fracture within 90 days prior to VT. This study concluded that chronic ITP patients have a 2-fold higher risk of VTE compared to the general population.

Norgaard et al. analyzed DNPR data to evaluate incidence of arterial thrombosis in patients with chronic ITP. A total of 29 arterial thrombosis events were identified in the chronic ITP cohort (379 patients with no prior history of arterial thrombosis) during a total of 2,551 person-years of follow-up (IR=11.37 per 1,000 person-years) [11]. The comparison cohort (3,790 members of the general population with no prior history of arterial thrombosis) had 254 arterial thrombosis events during 27,902 person-years of follow-up (IR=9.10 per 1,000 person-years). The adjusted IRR of arterial thrombosis was 1.32 (95% CI: 0.88-1.98) for chronic ITP patients compared with the comparison cohort. However, for women with chronic ITP, the IR of arterial thrombosis was 12.37 per 1,000 person-years compared with an IR of 6.48 in the age- and comorbidity-matched women in the comparison cohort, corresponding to an adjusted IRR of 2.27 (95% CI: 1.40-3.69).

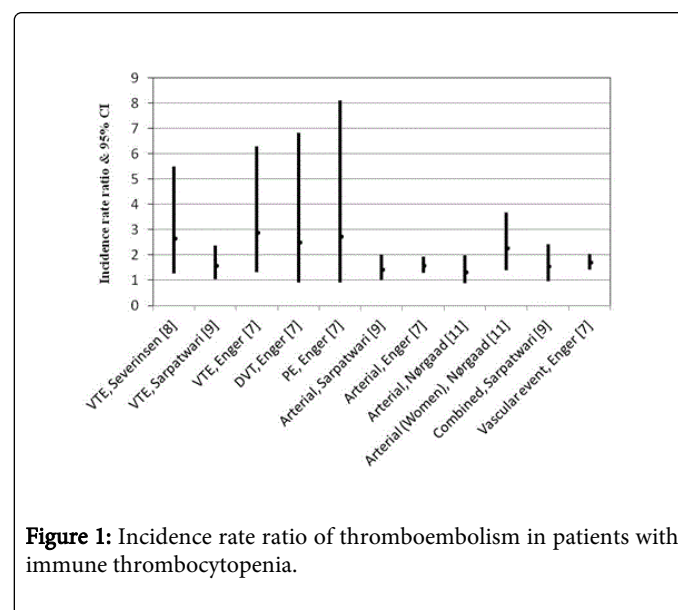
The UK study used the General Practice Research Database (GPRD) of 1,070 adult patients with primary ITP evaluated the prevalence and incidence rate of thromboembolic events (TEEs) compared with 4,280 primary ITP disease-free patients matched by age, gender, primary care practice, and pre-diagnosis observation time [9]. Over a median of 47.6 months of follow-up, the cumulative incidence of venous TEEs (including deep vein thrombosis [DVT], pulmonary embolism [PE], and portal vein thrombosis), arterial TEEs (including ischemic stroke, transient ischemic attack, myocardial infarction [MI], and unstable angina), and combined (arterial or venous) TEEs was 2.9%, 4.1%, and 6.1% in the primary ITP cohort, respectively, and 1.9%, 3.0%, and 4.6% in the primary ITP disease-free cohort, respectively. The IRR of venous, arterial, and combined TEEs was 1.57 (95% CI: 1.04-2.37), 1.43 (95% CI: 1.02-2.02), and 1.55 (95% CI: 0.97-2.43), respectively. Adjusted hazard ratios (HRs) of 1.58 (95% CI: 1.01-2.48), 1.37 (95% CI: 0.94-2.00), and 1.41 (95% CI: 1.04-1.91) were found for venous, arterial, and combined TEEs, respectively. These results suggest that patients with primary ITP are at increased risk for venous TEEs compared with patients without primary ITP.

Enger et al. conducted a retrospective analysis using the database of a large US health insurance plan to compare the prevalence and

incidence rates of comorbidities between the cohort of adult patients with chronic ITP (n=3,131) and an age- and gender-matched reference cohort (n=9,392) [7]. Vascular events (any) occurred 6.9% of patients in the ITP cohort and 4.0% of patients in the comparison cohort. The adjusted IRR of any vascular, venous, and arterial event was 1.70 (95% CI: 1.41-2.05), 2.89 (95% CI: 1.33-6.29), and 1.58 (95% CI: 1.29-1.94), respectively. Among venous events, the adjusted IRR of DVT was 2.5 (95% CI: 0.91-6.84) and the adjusted IRR of PE was 2.72 (95% CI: 0.91-8.10). Among arterial events, the adjusted IRR was 0.80 (95% CI: 0.49-1.30) for MI, 1.83 (95% CI: 1.33-2.51) for unstable angina, 2.05 (95% CI: 1.26-3.36) for ischemic stroke, and 1.69 (95% CI: 1.21-2.35) for transient ischemic attack. These findings suggested that ITP may be associated with an increased frequency of vascular morbidities.

Zhou et al. retrospectively reviewed 525 elderly ITP patients (age ≥60 years) diagnosed at a single center in China [12]. During 27 months (range 1-253 months) of the median duration of follow-up, 26 patients (5%) developed thrombosis including cerebral thrombosis (N=20), peripheral arterial thrombosis (N=2), DVT (N=2), MI (N=1), and concurrent cerebral thrombosis/peripheral arterial thrombosis (N=1). In this study, 10 patients developed thrombosis during treatment of ITP.

Ruggeri et al. analyzed 986 primary patients with ITP [13]. In this study, venous VTE occurred in 15 patients and arterial events occurred in 28 patients during a 3,888 person-years of follow up. The observed cumulative incidence of venous and arterial thrombotic events at 5 years was 1.4% (95% CI: 0.8-2.5) and 3.2% (95% CI: 2.0-5.0), respectively. On multivariate Cox regression analysis, age above 60 years (HR 5.8, 95% CI: 1.6-21.1), 3 or more arterial risk factors for thrombosis at diagnosis (HR 13.7, 95% CI: 4.5-41.1), splenectomy (HR 3.5, 95% CI: 1.6-7.6), and steroids at any time from diagnosis (HR 3.3, 95% CI: 1.0-11.0) were clearly associated with an increased risk of a thromboembolism (Figure 1).



**Figure 1:** Incidence rate ratio of thromboembolism in patients with immune thrombocytopenia.

Incidence rate ratio and 95% CI of thromboembolism in patients with immune thrombocytopenia are shown [7-9,11].

VTE: Venous Thromboembolism; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism.

These data suggest that there may be an increased risk of venous and arterial thrombosis in patients with ITP compared to the general population

### Risk of Thromboembolism In ITP Patients

Despite thrombocytopenia, venous and arterial thrombosis cases have been reported in ITP patients [7-12]. In these patients, thrombocytopenia itself may not be predictive, as other factors beyond platelet count may be involved. TEE in ITP may be due to the disease itself, ITP treatments, or other diseases and comorbidities [14].

### ITP itself may induce thromboembolism

Elevated pro-inflammatory cytokines such as interleukin 6 and interleukin 21, increased level of anti-inflammatory cytokines, such as interleukin 10, and Th17 cells/regulatory T cell imbalance in ITP patients suggest that ITP may be an inflammatory disease [15-21]. If this is true, inflammatory activity in ITP patients may interfere with various stages of hemostasis through coagulation, inducing thrombosis [22,23], although conflicting results have been reported [24].

Microparticles (MPs) are small vesicles that result from blebbing of the cellular membrane during activation or apoptosis processes. They are commonly described as heterogeneous vesicles with a diameter of 100-1,000 nm and generally express antigens representative of their parent cells. The most prominent property of cell-derived MPs is their procoagulant potential, mainly based on phosphatidylserine exposure and tissue factor expression. This characteristic explains why MPs were ascribed critical roles in coagulation activation, arterial and venous thrombosis, and cardiovascular disease. MPs also modulate other functions such as inflammation, angiogenesis, or immune response [25,26].

Monocyte MPs are an important sources of circulating tissue factor for arterial thrombus formation [25,27]. Endothelial MPs may also play an important role in arterial thrombosis by accumulating at the site of thrombus formation through CD36 [25]. In VTE, MPs released from endothelial cells and their interactions with leukocytes are likely to play a central role on thrombogenesis [28].

An increase in MPs was found in 21% of ITP patients and some also had a significant increase in platelet-associated IgM levels [29]. Sewify et al. reported significantly increased levels of red cell and platelet MPs in 29 patients with chronic ITP (8 of them had splenectomy) [30]. These patients also had significantly higher levels of factors VIII, IX, and XI than controls. The higher levels of MPs in ITP patients may point toward a prothrombotic tendency. Increased levels of platelet MPs in ITP patients may be associated with ischemic small vessel disease [31].

Cultured human endothelial cells synthesize a plasma membrane protein complex immunologically related to the platelet glycoprotein IIb/IIIa complex [32,33]. In ITP patients, endothelial damage induced by autoantibodies directed against antigens presented on both platelet and endothelial cells may be another mechanism that could affect the development of TEEs [34].

### Association between ITP treatment and thromboembolism

**Corticosteroids:** Oral corticosteroid use is associated with greater risk of VTE [35-37]. Low-dose glucocorticoids (prednisolone daily dose equivalent <5 mg) carried a twofold increased risk of PE (odds ratio (OR), 1.8; 95% CI, 1.3-2.4), whereas a high dose of glucocorticoids (prednisolone >30 mg) was associated with a 10-fold increased risk (OR, 9.6; 95% CI, 4.2-20.5) [37].

Girolami et al. critically analyzed reported cases of thrombosis in ITP patients [38] and suggested that prednisone therapy may represent a prothrombotic condition either, alone or in association with other risk factors such as diabetes, hypertension, and old age. Twenty-nine patients were reported to have had either arterial (20 cases) or venous (9 cases) thrombosis while platelet count was below  $50 \times 10^3/\mu\text{L}$ . The most frequent clinical manifestation was a MI. Thrombosis occurred in the majority of patients (19 of the 29 patients) during prednisone therapy.

**High-dose intravenous immunoglobulin (IVIG):** Venous and arterial thrombosis following administration of IVIG has been reported in patients with various disorders including ITP [39,40]. Incidence rates of post IVIG thrombosis ranged from 0.6 to 3% per patient, and from 0.15 to 1.2% per treatment course [39]. Arterial thrombosis was four times more common than venous thrombosis. Arterial thrombosis occurred early after IVIG administration (49% within 4 hours, 77% within 24 hours) and was associated with advanced age and atherosclerotic vascular disease, while venous thrombosis occurred later (54% more than 24 hours after IVIG administration) and was associated with factors contributing to venous stasis (obesity and immobility) [39].

Three basic mechanisms have been cited as contributors to the potential generation of TEEs after IVIG administration [41]:

(1) Increased blood viscosity. Plasma viscosity increased from a mean of 1.26 centipoise (cp) to 1.54 cp (22% increase) in 4 ITP patients receiving 24-54 g/day of IVIG. This increase remained for 4 to 5 days after the end of treatment [42].

(2) Platelet activation induced by IVIG, Woodruff et al. demonstrated enhanced ATP release and platelet aggregation in vitro after IVIG exposure [43].

(3) Arterial vasospasm [44].

In patients presenting with predictive factors of TEEs, IVIG may be prescribed after careful consideration of potential risks and benefits.

**Splenectomy:** Splenectomy is a standard therapy in the treatment of patients who show a resistance to corticosteroids but has well-documented complications both in the peri- and post-operative periods.

Vianelli et al. retrospectively analyzed the data of 233 splenectomized ITP patients with a minimum follow-up of 10 years [45]. Eighteen patients (8%) developed 26 thrombotic events, after a median of 36 months (range, 0 - 363 months) following splenectomy.

Boyle et al. evaluated the cumulative incidence of VTE in adult ITP patients who underwent splenectomy (n=1,762) compared with ITP patients who did not undergo splenectomy (n=8,214) [46]. The cumulative incidence of abdominal VTE was 1.6% compared to 1% in patients who did not undergo splenectomy. The cumulative incidence of DVT and PE after splenectomy was 4.3% and 1.7% in patients who did not undergo splenectomy. There was an increased risk of

abdominal VTE early (<90 days; HR 5.4, CI: 2.3-12.5), but not late (≥90 days; HR 1.5, CI: 0.9-2.6) after splenectomy. There was increased risk of DVT and PE both early (HR 5.2, CI: 3.2-8.5) and late (HR 2.7, CI: 1.9-3.8) after splenectomy. This study showed that ITP patients are at increased risk for abdominal VTE, DVT, and PE following splenectomy.

In addition, the DNPR data showed that the risk of VTE in splenectomized ITP patients during the follow-up periods of >365 days remained 2.7-fold (95% CI: 1.1-6.3) and 2.6-fold (95% CI: 0.9-7.1) higher compared with that in their age-matched population and appendectomized comparisons, respectively [47].

Fontana et al. investigated levels of cell-derived MPs derived from platelets, leukocytes, red cells, and endothelial cells, coagulation parameters, and activities of factor VIII, IX, and XI in 23 splenectomized ITP patients and 53 non-splenectomized ITP patients [48]. Levels of all cell-derived MPs were higher in splenectomized ITP

patients than those in non-splenectomized ITP patients, but only red cell MPs and leukocyte MPs reached statistical significance. The activated partial thromboplastin time was significantly shorter in splenectomized ITP patients.

These data suggest that ITP patients who have undergone splenectomy are at an increased risk of TEEs and should be carefully monitored.

**Thrombopoietin-receptor agonists:** TPO-R agonists are a recent addition to the treatment of chronic ITP [49]. They promote megakaryocyte differentiation, proliferation, and platelet production [50]. In these patients with ITP treated with TPO-R agonists, a significant number of TEEs has been reported (0 to 6.7%) [51-63] (Table 2). Arterial and/or venous TEEs occurred in these patients. In 8 randomized controlled trials, TEEs occurred in 0% to 6.7% of eltrombopag- or romiplostim-treated patients and 0% to 25% of patients in the placebo/standard of care group [51-54,57,58,60-62].

TPO-R agonists	Trial	Report	Year	TPO-R agonists cohort (n)	Number of pts with TEE (%)	Control cohort (n)	Number of pts with TEE (%)
Eltrombopag	NCT00102739, Phase II	Bussel	2007	88	1 (1.1)	29	0
Eltrombopag	NCT00102739, Phase III	Bussel	2009	73	0	37	0
Eltrombopag	NCT00370331, Phase III (RAISE)	Cheng	2011	135	3 (2.2)	62	0
Eltrombopag	NCT00540432, Phase II/III	Tomiyama	2012	15	1 (6.7)	8	0
Eltrombopag	NCT00424177, Phase II (REPEAT)	Bussel	2013	66	0	-	-
Eltrombopag	NCT00351468, Phase III (EXTEND)	Seleh	2013	299	16 (5.4)	-	-
Romiplostim	NCT00111475, Phase II	Bussel	2006	17	0	4	1 (25)
Romiplostim	NCT00102323, Phase II	Kuter	2008	84	2 (2.4)	41	1 (2.4)
	NCT00102336, Phase III (EXTENSION)	Bussel	2009	101	4 (4.0)	-	-
	NCT00116688	Gernsheimer	2010				
Romiplostim	NCT00415532, Phase III	Kuter	2010	154	6 (3.9)	75	2 (2.7)
Romiplostim	NCT00603642, Phase III	Shirasugi	2011	22	0	12	0
Romiplostim	NCT00116688	Kuter	2013	291	19 (6.5)	-	-
Romiplostim	NCT01013181	Khellaf	2014	72	2 (2.8)	-	-
Romiplostim	13 trials	Rodeghiero	2013	653	39 (5.9)	138	5 (3.6)

**Table 2:** Thromboembolic events in patients with immune thrombocytopenia treated with thrombopoietin receptor agonists.

Rodeghiero et al. analyzed pooled data of 13 clinical trials treated with romiplostim in 653 patients with ITP for up to 5 years [64]. TEEs occurred in 39 (5.9%) patients in romiplostim group and 5 (3.6%) patients in the placebo/standard of care group (7.5 versus 5.5 events per 100 person-years, respectively). While TEEs continued to occur over time, there was no apparent tendency for the risk of such event to increase over time and no difference in overall cumulative risk between the two treatment groups.

Catalá-López et al. conducted a meta-analysis of 8 randomized controlled trials of TPO-R agonists (n=1,180 patients) to identify possible risk factors for thromboembolism [65]. The estimated frequency of TEEs was 3.1% (95% CI, 1.8-4.4%) for TPO-R agonists compared with 1.7% (95% CI, 0.3-3.1%) for controls. Patients receiving TPO-R agonists versus controls showed an absolute risk increase of 1.8% (95% CI, -0.1-3.6%) and a 49.3% risk increase of thromboembolism [meta-relative risk (RR)=1.5; 95% CI, 0.7-3.3]. They concluded that TPO-R agonists show a numerically but non-



statistically significant trend to increase the occurrence of thromboembolisms compared to controls.

In epidemiological studies, TEEs have been reported in 5 to 6.9% of ITP patients who would not have been treated with TPO-R agonists [7,10], suggesting a baseline/background incidence of TEEs in ITP patients.

Moullis et al. conducted disproportionality analysis using the French Pharmacovigilance Database [66]. They compared adverse drug reaction patterns of romiplostim and eltrombopag.

Results of the disproportionality analysis showed no signal for an excess risk of thrombosis with romiplostim versus eltrombopag (Reporting OR: 1.45; 95% CI, 0.48-4.45).

It has also been reported that high platelet counts per se are not the main determinant of TEEs in ITP patients treated with TPO-R agonists [55,63].

Psaila et al. examined in vivo effects of eltrombopag on platelet function in 20 ITP patients [67]. They concluded that although thrombocytopenic ITP patients have a higher level of baseline platelet activation than controls, eltrombopag does not result in additional platelet activation or hyper reactivity in patients with chronic ITP, irrespective of whether the patients were responders or nonresponders to eltrombopag. Eltrombopag-induced platelet function was similar to those from control ITP patients without discernible increased hyper-reactivity [68]. In addition, therapy with TPO-R agonists did not alter plasma- and MP-associated procoagulant state of ITP patients who responded to TPO-R agonist [69] and did not activate the coagulation-fibrinolytic pathway, due to the lack of increase in D-dimer levels following therapy with TPO-R agonists [70].

However, further analysis of clinical and safety data is required to clarify pathophysiology of TEE in ITP patients treated with TPO-R agonists.

### **Comorbidities of ITP as a possible risk factor for thromboembolism**

**Antiphospholipid antibodies (aPL) and thromboembolism in ITP patients:** A study that summarized data from 9 published series reported that 25-75% (mean 43%) of ITP patients were positive for aPL [71]. aPL includes anticardiolipin antibodies (aCL), anti- $\beta$ 2-glycoprotein 1 antibodies, and lupus anticoagulant (LA). In addition, thrombocytopenia was noted in 22% to 42% of patients with antiphospholipid syndrome (APS) [72]. A prospective cohort study showed that a significant proportion of ITP patients with aPL developed APS [73]. They also concluded that the persistent presence of aPL is an important risk factor for the development of APS.

The pathogenesis of aPL-mediated thrombosis likely involves several pathogenic mechanisms such as the activation of endothelial cells, monocytes, and/or platelets and the effects of thrombogenic MPs derived from these cells; the inhibition of the activity of natural antithrombotic proteins such as protein C, tissue factor pathway inhibitor, and annexin A5; the activation of the complement system; and the impairment of fibrinolysis [74,75]. aPL form a complex with the corresponding antigen, leading to the cell perturbation, activation of cell signaling pathways, the transcription of procoagulant substances, adhesion molecules and subsequently thrombus formation [76]. Nomura et al. reported that aCL activates platelets in patients

with ITP and causes the generation of MPs rich in  $\beta$ 2-glycoprotein I and P-selectin [77].

These data suggested that aCL may interact with activated platelets and platelet-derived MPs in the presence of  $\beta$ 2-glycoprotein I and prothrombin to lessen the inhibitory effect of this glycoprotein and cause an increase in procoagulant activity.

In patients with ITP, the presence of unidentified aPL might increase the risk of TEEs. Occurrence of thrombosis has been reported in 0% to 71% (mean 21%) of ITP patients with aPL [71]. These results suggest that aPL itself may not be sufficient to trigger TEEs. In addition, various distinctions such as quality of antibodies, levels of aPL, study population, and follow-up duration may reflect mechanisms responsible for frequency of TEEs in these patients with aPL. Kim et al. reported that cumulative IRR of aPL-positive to aPL-negative ITP patients for thromboembolism was 3.15 (95% CI, 2.1-8.17) after adjusting for age, hypertension, diabetes, dyslipidemia, smoking, pregnancy/puerperium, and SLE [78].

In the other study, thrombosis in patients with ITP was associated with LA [HR, 9.9; 95% CI, 2.3-43.4] and high IgG-aCL level [HR, 7.5; 95% CI, 1.8-31.5] [79]. It has also been reported that the positivity rate for LA was significantly higher in those patients with ITP who developed APS [ $\chi^2$ : P=.0036; RR, 7.15 (95% CI, 1.7-47)] [73]. However, Bidot et al. suggested that aPL are prevalent in ITP but their profiles differ from APS [80]. In APS, antibodies were predominantly against  $\beta$ 2GP1 and 80% of patients had positive LA, while in ITP, aPL reacted most often with the phospholipids without LA.

ITP patients may be associated with one or more risk factors at the diagnosis or during ITP.

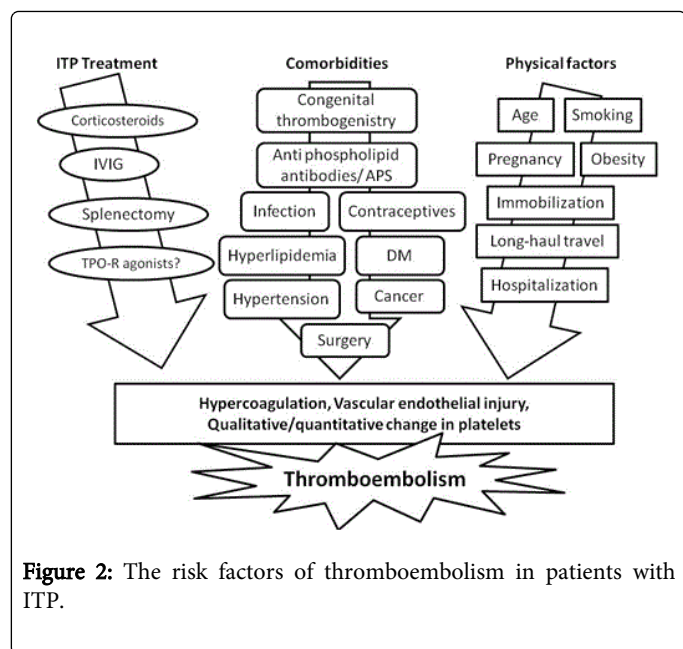
Strong genetic risk factors for venous thrombosis that lead to a hypercoagulable state include deficiencies in antithrombin, protein C, and protein S.

Acquired risk factors for venous thrombosis include age, surgery, obesity, cancer, pregnancy, hormone-based contraceptives, hormone replacement, antiphospholipid syndrome, acute infection, immobilization, paralysis, long-haul travel, smoking, hospitalization, reduced fibrinolysis, and acquired thrombophilia (increased levels of procoagulant factors and/or decreased levels of anticoagulant factors) [81].

Risk factors for arterial thrombosis include lifestyle diseases such as diabetes mellitus, hypertension, and hyperlipidemia.

However, some risk factors for atherothrombosis such as age, obesity, infections, diabetes, and the metabolic syndrome may also have a role in VTE, while for other risk factors such as smoking, hypertension, and hyperlipidemia, the association is less evident. Hypercoagulability is likely to be the pathogenic mechanism linking venous and arterial disease [82].

We summarized the risk factors of thromboembolism in ITP patients in Figure 2.



**Figure 2:** The risk factors of thromboembolism in patients with ITP.

ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; TPO-R, thrombopoietin receptor; APS, antiphospholipid syndrome; DM, diabetes mellitus.

### Management of thromboembolism in ITP patients

**Prevention of thromboembolism:** Prophylactic anticoagulation is usually offered to immobilized medical patients or to postoperative surgical patients. These patients may have an increased risk of thromboembolism (e.g. total hip or knee replacement). This risk however has to be weighed against the risk of bleeding in a patient who is thrombocytopenic [83].

In patients with ITP, international consensus reports recommend that ITP patients who underwent splenectomy should receive appropriate postoperative thromboprophylaxis [3]. However, prophylactic anticoagulation with low doses of low-molecular weight heparins (LMWH) perioperatively has not eliminated the appearance of portal vein thrombosis [84]. The Intercontinental Cooperative ITP Study Group (ICIS) expert group recommended that prophylactic dose LMWH should be administered as usual in ITP patients with high-risk surgery such as orthopedic or cancer surgery, if platelet counts are above 30,000/ $\mu\text{L}$  [85]. On the other hand, there have been conflicting reports regarding thromboprophylaxis of aspirin in aPL-positive patients [86-88].

Hereng et al. reported that aPL-positive patients with autoimmune thrombocytopenia developed significantly fewer TEEs while taking aspirin ( $P=0.01$ ) [86], while aPL-positive individuals did not benefit from aspirin for primary thrombosis prophylaxis [87,88].

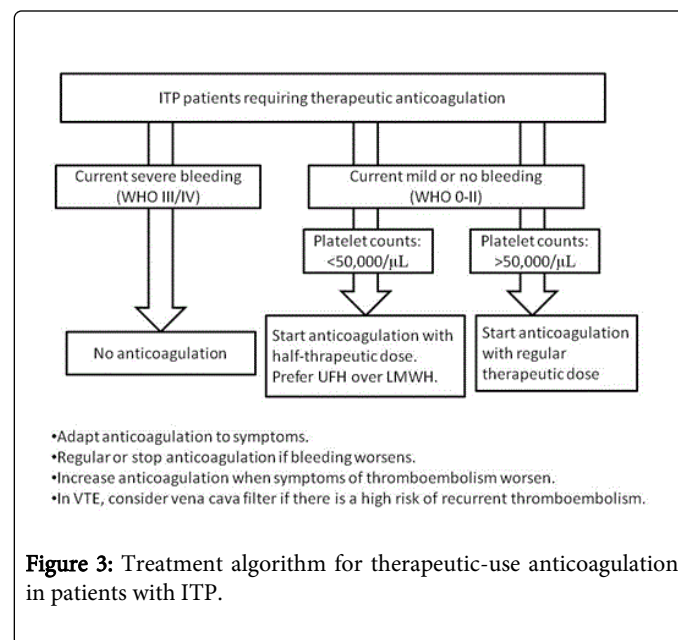
### Treatment of thromboembolism

For the treatment of thrombosis in patients with ITP, ICIS expert group recommend that treatment of thrombosis should be started with unfractionated heparin (UFH) at half-therapeutic dose while increasing the platelet count in patients with low platelet counts [85]. If the patient tolerates half-therapeutic UFH for a few days, the dose should be increased to the therapeutic level, and later UFH should be

replaced by LMWH or warfarin. With a platelet count of  $>30,000/\mu\text{L}$ , LMWH should be started with half-therapeutic dose. If platelet count is  $>50,000/\mu\text{L}$ , full dose of LMWH should be given.

Tran et al. reported that 7 patients with portal splenic vein thrombosis (PSVT) following laparoscopic splenectomy were treated with subcutaneous LMWH followed by warfarin, which was adjusted to achieve an internal normalized ratio [INR] between 2.0 and 3.0. These patients, including 3 patients with ITP, showed improvement or complete resolution on follow-up [89]. Ikeda et al. used low-intensity warfarin, designed to maintain the INR between 1.5 to 2.0 for a median period of about 3 months in 12 patients with PSVT (4 of whom had ITP) after laparoscopic splenectomy. Follow-up studies demonstrated complete resolution of PSVT in 9 of 12 patients and improvement in the other 3 patients. [90].

Matzdorff et al. proposed the treatment algorithm for therapeutic-use anticoagulation in ITP patients with severe thrombocytopenia: (1) Corticosteroid and IVIG should be administered to raise platelet counts rapidly to a safe level (i.e.,  $>30,000-50,000/\mu\text{L}$ ); (2) TPO-R agonists should be given to maintain platelet counts within a safe range when corticosteroids are tapered and the effects of IVIG begin to wear off; (3) In patients with life-threatening bleeding or bleeding requiring blood transfusion (WHO grade III/IV), anticoagulation should not be given regardless of the platelet count. Vena cava filter should be considered in DVT patients; (4) In all other patients with ITP (no bleeding, petechiae, hematomas, or stable hemoglobin (WHO grade 0-II)), anticoagulation should be started at standard doses with a platelet count of  $\geq 50,000/\mu\text{L}$ , or at half-standard doses with a platelet count of  $<50,000/\mu\text{L}$  increased to full doses if platelet counts rise to  $\geq 50,000/\mu\text{L}$  [83]. Patients with ITP with WHO grade 0-II and a platelet count of  $<50,000/\mu\text{L}$  should be started with UFH instead of LMWH. UFH has a shorter half-life, and it can be discontinued and monitored (Figure 3).



**Figure 3:** Treatment algorithm for therapeutic-use anticoagulation in patients with ITP.

ITP, immune thrombocytopenia; UFH, unfractionated heparin; LMWH, low-molecular weight heparins; VTE, venous thromboembolism.

## Management of thromboembolism in ITP patients with coronary artery disease

In patients with ITP with coronary artery disease, the risk of MI usually outweighs the risk of mild bleeding. In patients with a platelet count above 30,000/ $\mu$ L, aspirin or thienopyridines are recommended, as is the case in non-thrombocytopenic patients. In -patients with ITP with atrial fibrillation, initial anticoagulation with LMWH is preferred, and subsequent continuation of anticoagulation only, if no bleeding occurs. Initial target international normalized ratio (INR) should be in the lower range (e.g., 1.5–2.0) and increased to the regular level (INR 2.0-2.5), only if this has been shown to be safe [85].

The management for anticoagulation is often difficult due to low platelet counts. Successful concomitant use of TPO-R agonists and anticoagulation has been reported in patients with ITP with low platelet counts and severe cardiac comorbidities [91,92].

In ITP patients with acute coronary syndromes, Neskovic et al. recommended percutaneous coronary intervention (PCI) by using bare-metal stent placement [93]. Coated coronary stents should not be used because they require more intensive anticoagulation [85]. UFH (70-100 IU/kg) or fondaparinux (2.5 mg) + half dose UFH during PCI and acetylsalicylic acid (ASA) (300 mg) plus clopidogrel (300-600 mg) after stent placement is recommended [93].

## Conclusion

TEEs have been reported in up to 8% of ITP patients. ITP patients are at increased risk for TEEs compared with the general population. In addition, ITP treatment and the presence of aPL might be associated with a greater risk of TEEs. Anticoagulation therapy of TEEs in patients with ITP should be considered based on platelet counts and bleeding status. In the care and treatment of ITP patients, it is important to understand risk of thromboembolism. Treatment should be always personalized to the individual to minimize bleeding and risk of thromboembolism.

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