Received: 27 September 2023 | Revised: 1 December 2023 | Accepted: 4 December 2023

DOI: 10.1111/ejh.14154

European Journal of Haematology WILEY

REVIEW

Risk-based and individualised management of bleeding and thrombotic events in adults with primary immune thrombocytopenia (ITP)

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Funding information
Sobi

Abstract

Although bleeding is one of the main symptoms of primary immune thrombocytopenia (ITP), risk factors for bleeding have yet to be fully established. Low platelet count (PC; <20–30 $\times$ 10^9/L) is generally indicative of increased risk of bleeding. However, PC and bleeding events cannot be fully correlated; many other patient- and disease-related factors are thought to contribute to increased bleeding risk. Furthermore, even though ITP patients have thrombocytopenia and are at increased risk of bleeding, ITP also carries higher risk of thrombotic events. Factors like older age and certain ITP treatments are associated with increased thrombotic risk. Women's health in ITP requires particular attention concerning haemorrhagic and thrombotic complications. Management of bleeding/thrombotic risk, and eventually antithrombotic therapies in ITP patients, should be based on individual risk profiles, using a tailored, patient-centric approach. Currently, evidence-based recommendations and validated tools are lacking to support decision-making and help clinicians weigh risk of bleeding against thrombosis. Moreover, evidence is lacking about optimal PC for achieving haemostasis in invasive procedures settings. Further research is needed to fully define risk factors for each event, enabling development of comprehensive risk stratification approaches. This review discusses risk-based and individualised management of bleeding and thrombosis risk in adults with primary ITP.

KEYWORDS
anticoagulation, bleeding events, immune thrombocytopenia, patient education, platelet count, shared decision-making, thrombotic events

Novelty Statements

What is the new aspect of your work?

The new aspect of this work is a comprehensive overview of risk-based and individualised management of bleeding and thrombosis risk in adults with primary immune thrombocytopenia (ITP).

What is the central finding of your work?

The central finding of this work is the need for further research to fully define risk factors for bleeding and thrombotic events, including the importance of a patient-centric approach to disease management, which will enable the development of comprehensive risk stratification approaches.

What is (or could be) the specific clinical relevance of your work?

The specific clinical relevance of this work is the in-depth summary of the risks and management of bleeding and thrombotic events in adult ITP patients, and overview of validated tools to support decision-making and help.

1 | INTRODUCTION

Primary immune thrombocytopenia (ITP) is an autoimmune disease that is characterised by low platelet counts (PC; <100 × 10^9 platelets/L) and an increased risk of bleeding.[1,2] Though the pathogenesis of ITP has yet to be fully understood, antibody and/or T-cell mediated platelet destruction plays a key role.[2,3] Bleeding manifestations in ITP can range from mild events, such as skin petechiae, to life-threatening events, such as organ bleeding and intracerebral haemorrhage (ICH).[4]

Treatment of ITP predominantly aims to increase the PC to levels adequate to maintain haemostasis and either prevent bleeding events or cease any active bleeding.[2,5,6] According to the main management guidelines, ITP treatments should maintain a PC of >20–30 × 10^9/L in symptomatic patients, as the risk of major bleeding increases beneath this threshold.[5,6] In addition, guidelines recommend that treatment strategies should be individualised to the patients' needs and individual risk profiles.[5,6] The current suggested treatment strategy for ITP patients is initial administration of first-line treatments such as corticosteroids, intravenous immunoglobulin (IVIg) and anti-D immunoglobulins (in countries where approved).[2,5,6] For patients who do not respond to these treatments or relapse, subsequent treatments include immunosuppressive agents such as rituximab (off-label), thrombopoietin receptor agonists (TPO-RAs), the spleen tyrosine kinase (SYK) inhibitor fostamatinib, or splenectomy.[5–7] Initial treatments for life-threatening bleeding include a combination of IV corticosteroids and IVIg and/or platelet transfusions.[6] If response to initial treatment is not observed, administration of TPO-RAs should be considered.[6] Additional further treatments may include IV anti-D, vinca-alkaloids or even emergency splenectomy in rare cases. For details see Table S1.[6,8]

Guidelines also recommend that ITP treatments should have minimal toxicity and optimise, instead of impair, patients' health-related quality of life (HRQoL).[5,6] A shared decision-making approach to treatment is recommended here, whereby a patient and their healthcare professionals (HCPs) work together to make collaborative decisions about care.[5,6,9] Treatments that manage symptoms long-term, with the least amount of impact on daily life, are the most accepted by ITP patients.[10] Treatment strategies for ITP are constantly evolving, and future research and recommendations would benefit from further incorporation of patients' preferences.[5] PC is considered a main predictor of bleeding risk that is generally increased below 20 × 10^9/L.[4,6]

However, PC does not fully correlate with bleeding risk and there are multiple other risk factors thought to play a role.[4,11] Bleeding events can be difficult to predict, and some patients with a low PC, most of the time, display only mild bleeding symptoms.[12] Even though ITP is a bleeding disorder, and despite the presence of thrombocytopenia, patients are also at a higher risk of venous and arterial thrombotic events.[13] This risk of thromboembolism is increased in the presence of certain patient characteristics, such as older age, certain ITP treatments and even aspects of the disease itself.[14–16] Thrombotic events will also require initiation of anticoagulant and/or antiplatelet therapy and this can be challenging in patients with low PC.

This review will discuss the risks of both bleeding and thrombotic events in adult ITP patients, as well as the aspects of ITP that specifically impact on women's health and quality of life, which are of particular concern due to haemorrhagic and thrombotic complications. Ensuring that patients are informed and aware of the lifestyle risks, disease history, signs and symptoms of either event should also form a key part of disease management.[16]

2 | BLEEDING IN ADULT PATIENTS WITH ITP

2.1 | Frequency of bleeding events in ITP

Experiencing a bleeding event has been linked to poor outcomes and increased mortality in ITP patients. In a study of 3584 patients across Denmark, Sweden and Norway from 2009 to 2015, 536 (15%) patients experienced bleeding that required hospital contact.[17] For these patients, the risk of mortality increased by 4.9 fold at 1 year and 3.4 fold at 5 years versus those who did not experience a bleeding event.[17] The risk of bleeding increased over time, from 7.5% to 17.2% at 1 and 5 years, respectively.[17] Major bleeding events, which include severe organ bleeding and gastrointestinal (GI) bleeding,[4] have estimated frequencies between 10% and 20%.[4,18] A systematic review identified 51 prospective studies of

ITP patients reporting on incidence of ICH; in these, only 1.0% of overall ITP patients developed ICH.[12] Although most ITP patients only experience minor bleeding, the fear of more serious bleeds can negatively impact patients' quality of life.[10] Experiencing a major bleeding is associated with poor prognosis, increased risk of mortality and can have substantial negative impacts on a patient's QoL.[17,19] Despite this impact on patients' lives and outcomes, there remain many gaps in our understanding of what increases the risk of a bleeding event.

2.2 | Bleeding risk factors in ITP

2.2.1 | Platelet count

As discussed previously, PC is considered one of the major risk factors of bleeding (Table 1). A low PC is indicative of a higher risk of bleeding: the risk of bleeding events generally appears to increase when PC is $<20 \times 10^9$/L, with a 4.5-fold increased rate observed with PCs $<25 \times 10^9$/L compared to the normal range.[11,17] However, risk of bleeding cannot be fully correlated with PC and appears to vary depending on the type of bleeding event. Indeed, there is some indication that occurrence of mild bleeding events, such as mucosal, oral and skin bleeding, can be correlated with PC, but not that of major bleeding events, such as organ bleeding.[4,11] However, this is not consistently observed. A study of a large dataset (>19 000 patients) of newly diagnosed ITP patients in Japan showed a substantial increase in mucosal and organ bleeding, associated with a threshold of PC $10–15 \times 10^9$/L, but no association with PC above this.[4] The same study also identified a low PC of $<10 \times 10^9$/L (odds ratio [OR]: 2.96 [95% Confidence interval [CI]: 2.11–4.15]; $p < .001$) as a risk factor for ICH.[4] Thus, bleeding and PC thresholds at time of diagnosis do not necessarily reflect the risk of bleeding during the later course of disease.

TABLE 1 Risk factors for bleeding and signs for the development of severe bleeding in ITP patients.

Suggested predictors of severe bleeding	• Severe thrombocytopenia (PC <10–20 × 10^9/L)[4,12] • Any previous haemorrhagic events[12,77] • Older age (>60 years)[4,20,21,77] • Chronic ITP (for ICH)[12]
General risk factors of bleeding events[11]	• Exposure to anticoagulants • Exposure to anticoagulants[22] and antiplatelet agents including NSAIDs • Presence of comorbidities
Signs preceding the development of ICH[19]	• Mucocutaneous bleeding • Gross haematuria

Abbreviations: ICH, intracranial haemorrhage; ITP, immune thrombocytopenia; NSAIDs, non-steroidal anti-inflammatory drugs; PC, platelet count.

2.2.2 | Age

Older age (≥60 years) has been consistently identified as a risk factor for bleeding[4] and similar to PC, there is some indication that risk might differ depending on type of bleeding event. Risk of skin/mucosal bleeding events has been shown to modestly correlate with age,[11] whereas a much greater risk of organ bleeding with increased age was shown.[4] Older age is a strong predictor for major bleeding events,[20] with severe haemorrhagic events such as GI and central nervous system (CNS) bleeding observed with greater frequency in elderly patients with ITP.[21] Analyses from several registries have identified older age (≥60–65) as a predictor of experiencing haemorrhages at diagnosis and during follow-up and for ICH.[4,20,21] Analyses from the CARMEN-France registry reported a similar frequency of any bleeding and mucosal bleeding events for very elderly ITP patients (≥80 years) and those aged 65–79 years, but a higher frequency of severe bleeding in the very elderly group, despite similar median PCs at ITP diagnosis. Due to the low number of events, this result did not reach statistical significance but seems to delineate a trend for increased severe bleeding in very elderly patients.[22]

2.2.3 | Other risk factors for bleeding in ITP

Other factors beyond PC and age that may influence the risk of bleeds include presence of comorbidities and exposure to drugs (Table 1).[4,6,11] Analyses from the CARMEN registry showed that patients with ≥1 comorbidity (as defined by the Charlson Comorbidity Index) have an almost two-fold increased risk compared to patients with no comorbidities (OR: 1.99 [95% CI: 0.60–6.56]).[11] Polypharmacy also increases risk, in particular patients treated with nonsteroidal anti-inflammatory drugs and anticoagulants are at a higher risk of experiencing severe bleeds.[11] Treatment with anticoagulants has been reported as one of the most important risk factors for experiencing severe bleeding (OR: 4.30 [95% CI: 1.31–14.14]).[11] Presence of haematuria has been identified by one study as a risk factor for ICH [OR: 1.56; 95% CI: 1.04–2.35]; $p = .033$).[4]

Corticosteroid use has been linked to an increased risk of GI bleeding in a systematic review of patients hospitalised for multiple medical conditions.[23] Alcohol intake may also increase risk of bleeding due to its negative effect on platelet function, accelerating the degradation and apoptosis of platelets.[24] Physicians and patients should have awareness of commonly used drugs and herbal agents, such as selective serotonin reuptake inhibitors (SSRIs) and ginkgo biloba, that are known to interfere with platelet activity.[25,26] Little evidence specific to ITP patients currently exists exploring the effect of SSRIs on bleeding. Data from the CARMEN registry reported 7% of patients using SSRIs, and associated the use with an increased risk of bleeding events.[11] With the growing use of SSRIs in general over recent decades, further investigation of their effects on bleeding in ITP patients may be beneficial.

Occupation and lifestyle may also substantially impact the bleeding risk in individuals with ITP. Certain occupations, such as those

involving heavy machinery operation or contact sports, or lifestyles that involve activities with a high risk of injury, like hiking or motorcycling, may expose individuals to a higher risk of physical trauma, increasing the likelihood of bleeding episodes.

Biomarkers beyond PC that could predict the bleeding risk in ITP have also been investigated, such as antiplatelet autoantibodies. In one retrospective study, patients who tested positive for antiplatelet autoantibodies at disease onset had a greater bleeding score and a higher rate of chronic ITP than those who tested negative.[27] The utility of these biomarkers in clinical practice remains uncertain at the present time.

As bleeding events can cause many complications for patients, the ability to stratify patients according to their bleeding risk and identify the most high-risk patients would help manage the disease and limit negative impacts on patients' QoL.[28] However, as a fully defined, comprehensive overview of risk factors for bleeding is still lacking, and developing such risk stratification approaches presents a challenge.[28] Risk stratification should capture the multifactorial nature of bleeding manifestations, including a patient's baseline characteristics, PC, and bleeding score. The need to incorporate a patient's personal and familial history, occupation, and lifestyle to further personalise risk stratification has also been highlighted, with patients who have experienced severe bleeding events themselves or within their family may be at greater risk than those who have only experienced minor bleeds.[10]

2.3 | Scores and tools for bleeding assessment

Despite being a hallmark symptom of ITP, there is currently no universally accepted definition of or criteria for a major bleed, with considerable heterogeneity observed across studies,[12] and no standardised management strategies have been established. The International Society of Thrombosis and Hemostasis Scientific Standardization Committee (ISTH SSC) has recently issued a definition for a critical ITP bleed, as either (1) a bleed in a critical anatomical site including intracranial, intraspinal, intraocular, retroperitoneal, pericardial, or intramuscular with compartment syndrome; or (2) an ongoing bleed that results in haemodynamic instability or respiratory compromise.[29] A small number of tools exist to help describe major bleeding events, including the WHO Scale, the ITP bleeding scale and the ITP-specific bleeding assessment tool (Table 2). However, no standardised score has been put into routine practice in the clinic. The growing field of personalised medicine could also be utilised to predict the risk of major bleeds in ITP patients, through the design of machine-learning based clinical prediction models. One such model demonstrating good predictive efficacy uses nine common predictors of bleeding: initial PC, current age, age at ITP onset, infection status, ITP type, occurrence of skin and mucosal bleeding, low PC ($<20 \times 10^9$ L), presence of uncontrolled diabetes and presence of cardiovascular disease.[30]

TABLE 2 Bleeding and thrombotic risk scores.

Tool	Description	Specific to ITP
Bleeding risk scores		
WHO scale[78,79]	• Grades bleeding in patients with chemotherapy-induced thrombocytopenias (0–4 based on severity of bleeding)	No
ITP Bleeding Scale (IBLS)[18,80]	• Assigns a bleeding severity score from 0 (no bleeding) to 2 (marked bleeding) at nine anatomical sites by history (skin, oral, epistaxis, gastrointestinal, urinary, gynaecologic, pulmonary, intracranial and subconjunctival) as well as two anatomical sites by physical examination (skin and oral)	Yes
ITP-specific bleeding assessment tool (ITP-BAT)[78]	• Groups symptoms into the following domains: skin, visible mucosae and organs and then applies a grade for severity (0–5, with 5 indicating fatal) • Bleeding reported by the patient without medical documentation is graded 1 • Within each domain, the same grade is assigned to bleeding manifestations of similar clinical impact. The 'worst bleeding manifestation since the last visit' is graded and the highest grade within each domain is recorded	Yes
ITP bleeding score proposed by Khellaf et al.[81]	• Scores patients based on presence and severity of bleeding at cutaneous, mucosal, gastrointestinal, urinary, genitourinary and CNS sites and includes age as a factor • Bleeding severity is graded on a numerical scale based on physical examination • When the bleeding score was ≤ or = 8, the patients were treated with steroids alone. For scores >8, patients received IVIg (1–2 g/kg) in combination with oral steroids	Yes
Thrombotic Risk Scores		
Thrombosis and thrombocytopenia risk assessment score (TH2)[61]	• Comprises two thrombotic risk factors (high thrombotic risk and recent ITP treatment with known thrombotic risk) given a score of +1 and two bleeding risk factors (platelet count $<20 \times 10^9$/L and a major bleed at presentation) given a score of −1 • An overall score that is nil or positive indicates the patient is at an increased risk of thrombosis • An overall score that is negative indicates the patient is at increased risk of bleeding	Yes

Abbreviation: ITP, immune thrombocytopenia.

2.4 | Platelet thresholds for invasive procedures

The ability to accurately stratify patients according to bleeding risk would also be beneficial for situations such as invasive procedures and perioperative care. Currently, the difficulty of correlating PC with risk of bleeding leads to uncertainties prior to surgery as there is currently no clear definition of a 'safe' PC at which a procedure can be undertaken.[31] The International Consensus Report (ICR) currently recommends a PC of ≥30 × 10^9L for procedures such as simple dental extractions, increasing to ≥50 × 10^9L for minor surgeries and ≥ 80 × 10^9 L for major surgeries.[6] ITP patients can also be given platelet transfusions as part of preoperative care to minimise bleeding risks. However, there are no standardised thresholds for this to be undertaken, with current recommendations based on scarce evidence or expert reviews.[31]

2.5 | Management of bleeding in the emergency setting

In the case of emergency and life-threatening bleedings in ITP, treatments should aim to rapidly elevate PC to an adequate level to achieve haemostasis.[6,32,33] In an analysis of patients presenting at emergency departments for bleeding events, approximately 10% of major bleeding events resulted in death and almost all resulted in hospitalisation (median length of stay was 5 days).[19] In addition, 28% of patients with major bleeding events went on to experience recurrent major bleeds.[19] Emergency physicians should be prepared to treat bleeding ITP patients when a haematologist is not available for consultation. The Khellaf score (Table 1) could be useful in such scenarios, as it provides guidance on the need for use of IVIg based on bleeding score.[30]

3 | THROMBOEMBOLIC EVENTS IN ITP

ITP also carries an increased risk of experiencing a thromboembolic events (TEE), with TEEs reported in up to 8% of patients.[34] A review of several population-based studies investigating thrombotic risk in ITP patients showed that risk of venous thromboembolism (VTE) is two times higher compared to population-based controls.[35] An increased, but not statistically significant, risk for arterial thromboembolism (ATE) was also suggested.[35] A meta-analysis of three large population-based studies from Denmark, United Kingdom and United States also supports this finding, with ITP patients shown to be at 1.5× and 1.9× greater risk of ATE and VTE, respectively, than the general population.[36] A study of 7225 patients from France and 2490 from Sweden reported a cumulative incidence of arterial thrombosis of 15.0 (95% CI: 13.4–16.7) and 14.7 (95% CI: 12.4–17.5) per 1000 person-years, respectively.[37] The incidences of VTE were 6.9 (95% CI: 5.9–8.1) and 6.5 (95% CI: 5.1–8.4), respectively. Risk factors associated with ATE for both cohorts were increasing age, male sex and a previous ATE, as well as exposure to antiplatelet drugs in the French cohort, and a history of VTE and chronic kidney disease in the Swedish cohort. Risk factors associated with VTE for both groups were increasing age and a history of VTE, as well as presence of cancer in the French cohort.[37]

3.1 | Risk factors of TEEs in adult patients with ITP

Comorbidities, ITP treatments and aspects of ITP itself have been shown to play a role in this increased TTE risk (Table 2). Evidence of dysregulated pro-/anti-inflammatory cytokines in ITP have suggested that ITP is an inflammatory disease and this increased inflammatory activity can lead to induced thrombosis.[34] Other factors of ITP itself with a potential prothrombotic role include a large proportion of young activated platelets and the presence of procoagulant, proinflammatory microparticles.[13] Both are elevated in patients with ITP, but definitive evidence linking them to increased thrombosis is lacking.[13]

3.1.1 | Patient characteristics

Similar to risk of bleeding, increased age and presence of comorbidities are also associated with increased thrombotic risk in ITP. One analysis suggested that the risk of VTE and ATE occurring in ITP patients was not increased above what would be expected in a normal population.[14] Instead, they highlighted that older age (>60), steroid use, splenectomy and a combination of ≥3 of any vascular risk factors (including diabetes mellitus, hypercholesterolemia, arterial hypertension, smoking, atrial fibrillation, valvular disease and coronary disease) were independent predictors of both venous and arterial thrombotic events.[14] Obesity, a postoperative state, male sex and cancer have been identified as additional risk factors for occurrence of TEEs.[13,38–40] However, prospective studies analysing TEE risk in ITP patients have not been conducted.

Antiphospholipid syndrome may be another causative factor for increased thrombotic risk.[34] ITP patients frequently present with antiphospholipid antibodies (aPLs), with reports of aPLs occurring in 25% to as high as 75% of ITP patients.[34] Presence of aPLs is not thought to impact on ITP severity; however, some studies have suggested an association between aPLs and increased thrombotic risk. A meta-analysis of 10 studies (total 1574 patients) supports this, associating the risk of ATE and VTE with the presence of the aPLs lupus anticoagulant (OR: 6.11 [95% CI: 3.40–10.99]) and anticardiolipin (OR: 2.14 [95% CI: 1.11–4.12]).[41]

3.1.2 | ITP treatments

Both first- and second-line ITP treatments and interventions can further exacerbate the risk of a TEE[13,34,40] (Table 3). IVIg treatment may contribute to thrombosis by increasing blood viscosity and platelet activation.[34] An analysis of 65 reported cases estimated an incidence

TABLE 3 Risk factors for thrombotic events in ITP patients.

ITP disease	• Elevated level of immature circulating platelets[13] • Dysregulated proinflammatory cytokines[13] • Proinflammatory/procoagulant microparticles[13]
Patient characteristics and comorbidities	• Congenital thrombogenicity, infection, cancer and surgery[34] • ≥3 cardiovascular risk factors such as diabetes mellitus, hyperlipidaemia and hypertension, smoking, alcohol use and obesity[14,34] • Age > 60 years[34,82] • Pregnancy and hormonal contraceptives[34] • Immobilisation, hospitalisation and long-haul travel[34] • Lupus anticoagulant, antiphospholipid syndrome[34] • History of venous or arterial thrombosis[82]
ITP treatment	• Splenectomy[34,82] • Corticosteroids[34,82] • IVIg[34,82] • TPO-RA[82]

Abbreviations: ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin; TPO-RA, thrombopoietin-receptor agonist.

rate of 0.15%–1.2% per treatment course of IVIg and a mortality rate of 20%, with ATE events four times more common than VTE.[42] However, the majority of the patients that experienced a TEE in this analysis were not patients with ITP, fewer than 20% of patients had received IVIg for ITP.[42] The consensus opinion is that IVIg treatment has a low risk for causing thrombosis in patients with ITP (<1% of patients).[13]

Administration of corticosteroids may also lead to an increased risk of thrombosis. Thrombotic factors are upregulated in response to corticosteroid exposure in in vitro and animal studies[13] and general population-based studies have shown a greater risk of TEEs with oral corticosteroid use.[34] Evidence for this in ITP patients is limited but some studies indicate an increased risk of TEE occurring with prednisone use[14,43] and a higher risk of hospitalisation for VTE.[40]

Thrombotic risk related to TPO-RA use in patients with ITP is still debated. As TPO-RAs stimulate platelet production and increase PC, they may increase the risk of TEEs,[13] with reports of up to 10% of ITP patients experiencing TEEs following TPO-RA treatment.[34,44] In a pooled analysis of data from 13 clinical trials with romiplostim, TEE event rates per 100 person years were 7.5 versus 5.5 for romiplostim versus placebo-treated patients, respectively. However, there was no increased risk over time or no difference in cumulative risk between the two treatment groups.[45] Further analysis of longer term data reported an incidence rate for all TEE events of 4.2 per 100 person years and incidence of thrombosis did not seem to be related to the dose received, the duration of treatment or PC.[35] A study analysing 292 adult ITP patients treated with romiplostim for up to 5 years showed that TEEs per patient-week (0.08/100 patient-weeks) was comparable to that seen in earlier studies with romiplostim (0.09–0.15/100 patient-weeks).[46] Roumier et al. raised the potential thrombotic risk associated with high-dose romiplostim as rescue therapy for ITP patients with severe bleeding and suggested to restrict the use of this strategy to life-threatening bleeds, while awaiting more robust safety data.[47] The open-label EXTEND study evaluating long-term safety and efficacy of eltrombopag in 302 adult ITP patients revealed a TEE rate of 6%, which did not increase with treatment duration greater than 1 year.[48]

Differing patient characteristics may also influence risk of TEE with TPO-RA treatment. An analysis from a French cohort emphasised that although a higher risk of hospitalisations for VTE and ATE was observed with TPO-RA administration, other individual risk factors are relevant, including older age, male sex, a history of cardiovascular disease, splenectomy and exposure to IVIg.[40] For patients with conditions such as systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS), the use of TPO-RAs should be carefully discussed case by case and used with caution, as evidence from SLE indicates a possible increase in the risk of TEE in APS-positive SLE patients treated with TPO-RAs.[49] Recent meta-analyses support a lack of increased risk of TEEs with TPO-RAs, suggesting that although more TEEs were reported in TPO-RA treated ITP patients compared to those not receiving TPO-RAs, the difference in risk was not statistically significant.[50,51] Meta-analyses comparing effects of several treatments including the TPO-RAs eltrombopag, romiplostim or avatrombopag also found no significant differences in the rate of TEEs for any treatment versus placebo[50,52,53] (or between the treatments in the case of Deng et al.[54]). It should be noted, however, that most of these meta-analyses report overall risk for TPO-RAs as a drug class and not by individual drugs.

Although these studies indicate that any increased risk of TEEs is non-significant and related to specific patient characteristics, there is a need to be observant and collect more long-term data. Individual patient risk profiles should therefore be assessed when considering use of TPO-RAs, and the lowest dose that allows maintenance of a safe PC (≥50 × 10^9/L) should be used.[6,35] For patients at high risk of thrombosis receiving a TPO-RA, anticoagulation or antiplatelet therapy could also be considered, once PC has reached 50 × 10^9/L.[55]

Splenectomy has also been as associated with increased risk of thrombotic events.[34] A retrospective Danish population-based analysis identified an increased risk of VTE (2.7-fold) in splenectomised ITP patients versus age-matched controls from the general population.[56] A French long-term cohort study of primary ITP patients showed that those who were splenectomised experienced more VTE than those who were not (n = 13 vs. 2, p = .005). In this study, splenectomy was an independent risk factor of VTE (Hazard ratio [HR] = 4.006, p = .032 [95% CI: 1.1–14.2]).[57]

A more recent analysis of 14 studies with long-term follow-up indicated an overall increased risk of VTE over time in ITP patients

who received splenectomy versus those who did not.[58] The study from Italian centres also highlighted splenectomy as a risk factor (HR [95%CI] for all events vs. no splenectomy: 3.5 [1.6–7.6]).[14] Patients undergoing splenectomy should therefore be carefully monitored post-procedure for possible TEEs.

Similar to risk factors for bleeding events, key gaps remain in our understanding of thrombotic risk factors in ITP. Further evidence is needed on the potential impact of obesity and the use of hormonal therapy such as contraception and ovarian stimulation, antiphospholipid antibodies and presence of other risk factors. Discussions of patients' familial history to identify any presence of underlying thrombophilia will be important to help establish the risk of patients experiencing a TEE. For patients undergoing surgery, stratification according to risk of TEE and implementation of prophylactic measures according to risk severity could be valuable in preventing TEEs following procedures. The benefits of this have been discussed for general surgical patients[59] and further exploration is warranted for ITP patients.

3.2 | Anticoagulation and antiplatelet therapy in ITP

Therapeutic anticoagulation is a suggested treatment for VTE and antiplatelet therapy for ATE in ITP patients.[13] As the incidence of ITP increases with age, patients can often present at diagnosis with other cardiac and vascular comorbidities that require anticoagulation and antiplatelet therapy.[16] However, antithrombotic therapy is not discussed in depth in recent guidelines[6] and no definitive guidance exists for the management of thrombosis in ITP patients. There is a need for evidence-based guidance to help clinicians balance the risk of thrombosis versus the risk of bleeding.[60]

Anticoagulation and antiplatelet treatment should be individualised to minimise bleeding and thrombosis as well as to control cardiovascular risk factors.[16,34] The Thrombosis and Thrombocytopenia risk assessment score (TH2) can provide an indication of a patients' thrombotic risk and guide subsequent decisions regarding anticoagulation treatment (Table 2).[61] The TH2 score was retrospectively applied to data from a cohort of 13 ITP patients who received anticoagulation and was able to successfully identify all seven patients who went on to experience a thrombotic event. TH2 scores were shown to change quickly, over a matter of days, suggesting that patients should have frequent risk assessments when undergoing ITP treatment.[61] Further validation of the TH2 score in larger datasets would be valuable to increase its use as a tool in guiding treatment decisions.

Currently there are no defined acceptable PC thresholds for antiplatelet/anticoagulant therapy. The 2019 ASH guidelines and ICR identified an unmet need in the boundaries of bleeding risk in ITP patients treated with antiplatelet therapies.[5] A selection of ITP specialists and general haematologists were surveyed to gain insights on this topic, with clinical scenarios including aspirin treatment for stable coronary artery disease, dual antiplatelet therapy for coronary stent placement and anticoagulation for atrial fibrillation or VTE.[60] Although the suggested PCs varied widely (from ≥10 × 10^9/L to ≥100 × 10^9/L), the general consensus was a PC ≥50 × 10^9/L for patients without a history of bleeding,[60] aligned with the recommendations by the ICR for anticoagulation therapy.[6] When patients had a history of bleeding, many physicians recommended a higher threshold.[60] Recent recommendations from an expert group suggest adapting treatment strategies for anticoagulation therapy and antiplatelet therapy based on PC as well as the individual thrombotic, bleeding and cardiovascular risks of the patient. In cases of PC <25 × 10^9/L, it was suggested that both anticoagulation and antiplatelet therapy should be stopped.[16] In 2023, analyses from the CARMEN registry reported on 143 patients exposed to an antiplatelet drug at time of ITP diagnosis and the frequencies of bleeding in this population. The bleeding frequency with PC < 20 × 10^9/L was significantly associated with bleeding in ITP patients treated with aspirin alone, similarly to most ITP patients not exposed to aspirin.[62]

4 | ITP AND WOMEN'S HEALTH

There are several aspects of ITP that specifically impact on women's health and QoL, including pregnancy, childbirth, postpartum state, menstrual bleeding and birth control (contraception).[6,63,64] Thrombocytopenia occurs in approximately 7%–10% of pregnancies and approximately 1%–4% of these cases are due to ITP.[63] ITP can develop at any time during pregnancy in patients who were previously unaffected and patients with pre-existing ITP can experience worsening of their disease.[64]

A stable PC of 20–30 × 10^9/L is considered to be safe for the majority of pregnancies, with maintaining a PC of ≥50 × 10^9/L preferred late in the third trimester for delivery.[6] If PC stays within these ranges, ITP can be managed by observation alone, provided the patient does not have any bleeding manifestations or planned procedures.[6] Treatment of ITP during pregnancy is challenging, especially with regards to the side effects, the contraindications and the uncertainties about some ITP therapies. Whilst TPO-RAs are currently not recommended in pregnancy, as their safety is not fully established, recent evidence of off-label use supports their efficacy and safety during pregnancy, though the optimal timing for initiation remains to be determined.[65] Results from 15 pregnant women with ITP treated with either eltrombopag ($n = 8$) or romiplostim ($n = 7$) with a median TPO-RA exposure of 4.4 weeks showed a response rate of 77%. Neither thromboembolic events among mothers nor TPO-RA-related foetal or neonatal complications were observed, apart from one case of neonatal thrombocytosis.[65] Similarly, pregnancy, birth outcomes and adverse events data from 186 patients exposed to romiplostim during pregnancy collected in the Pregnancy Surveillance Program (PSP), did not reveal any specific safety concerns for mothers, foetuses or infants.[66] A Chinese-based study of pregnant ITP patients treated with recombinant human thrombopoietin (rhTPO) again showed similar promising results. The majority of patients responded, rhTPO treatment was well-tolerated and no TEEs or safety concerns were detected.[67] A recent prospective study in pregnant/non-pregnant

matched cohorts showed that ITP treatments administered during pregnancy were almost exclusively corticosteroids and IVIg, with only one patient receiving romiplostim.[68] This supports the idea that in most cases, ITP can be managed using steroids and IVIg during pregnancy and that TPO-RAs should only be dedicated to complex cases and in late pregnancy.

For delivery, a PC of ≥50 × 10^9/L is generally recommended, although a minimum PC has not been defined.[6] Patients with thrombocytopenia are often refused neuraxial anaesthesia during delivery, due to a potential risk of spinal epidural haematomas. However, evidence suggests that this risk may not be as great as initially perceived. The risk of experiencing an epidural haematoma was retrospectively assessed in a combined dataset of 1524 thrombocytopenic patients who gave birth. For patients with a PC 70–100 × 10^9/L, estimated risk of experiencing an epidural haematoma was 0%–0.2%.[69] A recent consensus statement from a multi-disciplinary panel also concluded that in the case of a PC ≥70 × 10^9/L, the risk of spinal epidural haematoma following a neuraxial procedure is likely to be low.[70] Patients with PC <50 × 10^9/L are likely to have an increased risk and neuraxial procedures should be avoided, although the analysis highlighted that recommendations for patients with PC <70 × 10^9/L are based on limited data. Risk factors to consider include the presence of high-risk comorbidities or any indications of an increased risk of bleeding (history of bleeding, presence of bruising or abnormal coagulation testing).[6,70]

Patients with ITP do not need to be advised against becoming pregnant and women of child-bearing age at diagnosis can be reassured of the rarity of bleeding complications during pregnancy and postpartum.[71] However, there are certain characteristics that might make pregnancy more difficult for an ITP patient, including a history of recent bleeding, a low PC (<20 × 10^9/L), and poor response to treatment.[6] Counselling from a multi-disciplinary team for patients intending to become pregnant is therefore advisable to discuss disease course and treatment options.

For ITP patients not wishing to become pregnant, hormonal contraception needs to be carefully discussed. Hormonal therapies are generally known to carry a risk of thrombosis and reports indicate a 2–9-fold increased risk of a thrombotic event in women taking combined oral contraceptives versus those who do not.[72] This increased risk is associated with oestrogen-containing compounds, with evidence for progestin-only formulations, including oral progesterone, intrauterine device and subdermal implants, demonstrating no increased risk of thrombosis (OR: 1.03 [95% CI: 0.76–1.39]).[72] When considering hormonal contraception for ITP patients, clinicians need to make a balanced decision between hormonal therapy and the risk of thrombotic events, taking into account the dose, administration and type of hormone, as well as any personal and familial history of thrombosis or presence of other prothrombotic risk factors (e.g., age, BMI or presence of thrombophilia).[72] Similarly, hormone-replacement therapy is associated with an increased risk of thrombosis and this risk is further elevated with increased age and BMI.[72]

Heavy menstrual bleeding, or menorrhagia, is another concern for female patients with ITP. Menorrhagia can be defined as a loss of >80 mL per cycle[73]; however, this can be difficult to measure in daily life and estimates are often based on the use of self-reporting tools. A systematic review identified eight studies that reported on prevalence of menorrhagia, ranging from 6% to 55% at ITP diagnosis and 17% to 79% during the disease.[60] The impact of menorrhagia on patients' QoL was assessed using data from seven studies and indicated that menorrhagia had a negative influence on a patients' QoL, particularly

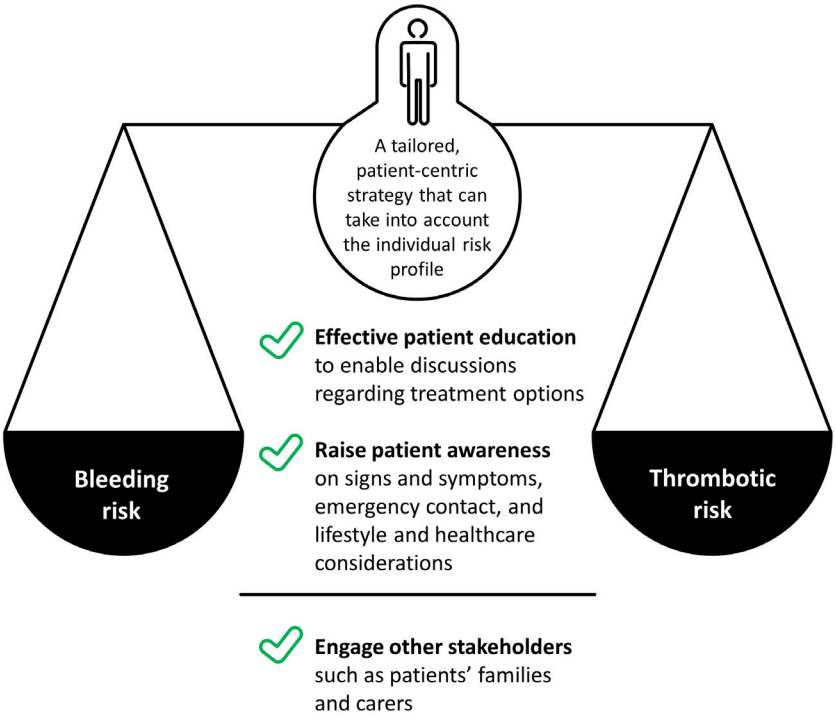

FIGURE 1 Key aspects of patient education in bleeding and thrombotic risk.[9,16,83]

patients with a low PC.[74] In the iWISH study on patient perception, menorrhagia was rated as one of the most severe symptoms of ITP by 83% of surveyed patients who experienced it at diagnosis and by 62% who experienced it at throughout the disease.[75] In practice, menorrhagia is managed on an individual basis, notably by elevating PC and therapeutic interventions such as administration of tranexamic acid, and use of hormonal contraception.[73] Further research and increased awareness of menstrual issues in women with ITP is needed.

5 | PATIENT EDUCATION AND PERSONALISED TREATMENT PERTAINING TO SPECIAL SITUATIONS IN ITP

Due to the inherent challenge of balancing bleeding and thrombotic risk, management of patients with ITP is patient-centric and tailored to take into account individual risk profiles[28,40] (Figure 1). The hallmark of a patient-centric approach is enabling discussions regarding treatment options with patients and this starts with effective patient education.[16,76] Making patients aware of certain lifestyle and healthcare considerations might also help their experience with ITP.[9] Educated patients will have an improved understanding of the need to take medication and a reduced perception of harm from treatment.[76] Patients who are informed about ITP and the risks of bleeds and thromboses can more effectively collaborate with clinicians to make decisions about their treatments and care. Current guidelines emphasise the importance of shared decision-making and encourage future trials and studies to incorporate this into their study outcomes.[5,6]

6 | CONCLUSIONS AND EXPERT OPINION

ITP carries a risk of bleeding and thrombotic events. Further research is needed to increase awareness and develop evidence-based, standardised guidelines, and valid tools to help physicians in decision-making and balancing the risk of bleeding against thrombosis in patients with ITP. Profiling a patient's individual risk, using a tailored, patient-centric approach is essential. Comprehensive patient education should also form part of patient management to ensure patients are aware of symptoms of bleeding and thrombosis, and that they feel empowered to discuss their own treatment and care with their HCPs. Women with ITP might warrant specific attention to their bleeding and thrombotic risks.

AUTHOR CONTRIBUTIONS

All authors contributed to the conceptualisation, writing, reviewing and editing of the manuscript. All authors have read and agreed to the published version of the manuscript.

ACKNOWLEDGEMENTS

Medical writing support was provided by Laura Corbett, nspm ltd (Meggen, Switzerland) and was funded by Sobi.

CONFLICT OF INTEREST STATEMENT

Catherine Lambert has participated on advisory boards for Sobi, Sanofi, CSL, Roche and Amgen and has received lecture honoraria from Bayer, Sobi, Sanofi, Roche and Amgen. Hillary Maitland has participated on speaker boards for Sobi and Sanofi. Waleed Ghanima reports fees for participation in Advisory board from Amgen, Novartis, Pfizer, Principia Biopharma Inc—a Sanofi Company, Sanofi, SOBI, Grifols, UCB, Argenx, Cellphire, Alpine, Kedrion, HiBio. Lecture honoraria from Amgen, Novartis, Pfizer, Bristol Myers Squibb, SOBI, Grifols, Sanofi and Bayer. Research grants from Bayer, BMS/Pfizer and UCB.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Lambert C, Maitland H, Ghanima W. Risk-based and individualised management of bleeding and thrombotic events in adults with primary immune thrombocytopenia (ITP). *Eur J Haematol*. 2024;112(4):504-515. doi:10.1111/ejh.14154