Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

**Research Article**

J Exp Clin Med
2025; 42(4): 447-452
**doi:** 10.52142/omujecm.42.4.14

# Evaluation of the incidence of arterial and venous thrombosis and predisposing factors in patients using eltrombopag

**Melda İŞEVİ[1,*], Engin KELKİTLİ[2], Derya Deniz KÜREKÇİ[3], Mehmet TURGUT[2]**

[1]Department of Anesthesiology and Reanimation, Division of Intensive Care, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Türkiye
[2]Department of Internal Medicine, Division of Hematology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Türkiye
[3]Department of Internal Medicine, Hematology Clinic, Samsun Training and Research Hospital, Samsun, Türkiye

**Received:** 08.10.2025 • **Accepted/Published Online:** 30.11.2025 • **Final Version:** 31.12.2025

**Abstract**

Eltrombopag is a small-molecule thrombopoietin receptor agonist that is taken orally and prescribed for the management of conditions such as immune thrombocytopenia (ITP), aplastic anemia (AA), and myelodysplastic syndromes (MDS). By stimulating megakaryocyte differentiation and proliferation, it increases platelet production. Eltrombopag treatment has been linked to an increased likelihood of developing both arterial and venous thrombotic events. The present study sought to determine the frequency of such thrombotic complications among patients diagnosed with ITP, MDS, or AA who were treated with eltrombopag in our institution and to retrospectively assess potential risk factors, aiming to provide additional real-world clinical insights to the existing literature. The medical files of 144 adult individuals diagnosed with immune thrombocytopenia, myelodysplastic syndrome, or aplastic anemia and treated with eltrombopag between 2009 and 2019 were retrospectively reviewed. Demographics, comorbidities, treatment dose and duration, and thromboembolic events were extracted from the hospital database. Statistical analyses were performed to evaluate factors associated with thrombosis. A total of 144 patients were evaluated in the study, comprising 66 men (45.8%) and 78 women (54.2%), with an average age of 54.12 ± 20.08 years. Diagnoses included ITP in 102 patients (70.8%), AA in 31 (21.5%), and MDS in 11 (7.6%). During follow-up, first thromboembolic events occurred in 7 patients (4.9%): 6 venous and 1 arterial. When all vascular complications were taken into account—allowing for more than one episode per individual—a total of 13 thrombotic events were observed. Of these, 7 were venous in origin (including 4 cases of portal vein thrombosis and 3 cases of pulmonary embolism), while 6 were arterial (comprising 5 cerebrovascular events and 1 myocardial infarction). Within this real-life patient population, eltrombopag use corresponded to a 4.9% rate of thromboembolic complications. In our cohort, no statistically significant association between thrombosis and age, diagnosis, comorbidities, eltrombopag dose, or treatment duration could be demonstrated, most likely because of the limited number of thrombotic events.

**Keywords:** eltrombopag, thrombosis, immune thrombocytopenia, aplastic anemia, myelodysplastic syndrome

## 1. Introduction

Eltrombopag is a small-molecule agent that acts as a thrombopoietin receptor stimulator and is administered orally for managing thrombocytopenia in different clinical contexts, such as immune thrombocytopenia (ITP), aplastic anemia (AA), and thrombocytopenia related to hepatitis C infection (1). By binding to the c-Mpl receptor, eltrombopag activates hematopoietic progenitor and megakaryocytic cell lines, leading to enhanced platelet synthesis and a consequent reduction in bleeding tendency. Multiple randomized controlled trials and extended follow-up studies have confirmed the effectiveness and safety profile of eltrombopag, establishing it as a valuable treatment choice, especially for patients unresponsive to conventional first-line therapies (2, 3).

However, with the increasing use of eltrombopag in recent years, clinical concerns have emerged regarding its potential thromboembolic effects. Interestingly, thrombotic events observed in individuals who continue to have low platelet counts indicate that factors other than platelet number may contribute to thrombosis development (4). Reports have documented that patients treated with eltrombopag may experience both arterial events, such as stroke and myocardial infarction, and venous events, including deep vein thrombosis, pulmonary embolism, and portal vein thrombosis (5). Proposed mechanisms include enhanced platelet activation, an increase in procoagulant microparticles, and endothelial dysfunction (6, 7). In addition, the effects of eltrombopag on iron metabolism and mitochondrial function have been suggested to create a proinflammatory or prothrombotic environment (8).

*Correspondence: drmeldaisevi@gmail.com

Although the incidence of thromboembolic events associated with eltrombopag has generally been reported as less than 5% in clinical trials, these studies were conducted in selected patient populations under close monitoring (2). Evidence from real-world observations suggests that thrombotic risk tends to increase in older individuals, in patients with coexisting cardiovascular conditions, and with prolonged use of eltrombopag (9, 10). Therefore, assessing the risk of thrombosis in patients receiving prolonged eltrombopag therapy, such as those with chronic ITP or relapsing AA, is crucial for clinical follow-up and treatment planning.

However, there is a scarcity of retrospective research evaluating the long-term frequency of thrombotic events and the related risk determinants in individuals receiving eltrombopag therapy. Most available literature consists of case reports, small cohort analyses, or pharmacovigilance data. Moreover, many of these studies have not performed subgroup analyses according to patient risk profiles, limiting their contribution to clinical decision-making.

The objective of this study was to assess the occurrence of arterial and venous thrombotic events and to identify related clinical risk factors among patients treated with eltrombopag over a 10-year period in a tertiary university center. The findings are expected to contribute to the better identification of high-risk groups and to the individualization of treatment strategies.

## 2. Materials and Methods

This single-center retrospective study was carried out in the Hematology Department of a tertiary university hospital. Ethical approval was obtained from the Institutional Review Board (Date: February 28, 2020; Approval No: 2020/94). The research was performed in full compliance with the ethical standards outlined in the Declaration of Helsinki (2013 update).

The study enrolled 144 adult patients (≥18 years) who had been diagnosed with immune thrombocytopenia, myelodysplastic syndrome, or aplastic anemia and had received eltrombopag therapy for at least one month between 2009 and 2019.

Exclusion criteria were as follows:

- Insufficient medical records or follow-up data,
- Conditions leading to immobility after starting eltrombopag (e.g., surgery, lower extremity fractures, hemorrhagic stroke),
- Diagnosis of malignancy (excluding MDS, which was one of the predefined study groups). Solid organ malignancies and other hematologic neoplasms such as acute leukemia, lymphoma, or myeloproliferative neoplasms were excluded.

Information on demographic and clinical characteristics—such as age, sex, underlying indication for eltrombopag use, accompanying diseases, concurrent medications, initial platelet levels, prescribed dose, and duration of therapy—was collected from patient records. Thromboembolic events occurring during or after treatment were evaluated, and events were classified as arterial or venous with their associated clinical outcomes.

Concurrent medications were reviewed specifically for agents with potential effects on thrombotic risk, including antiplatelet drugs (aspirin, clopidogrel) and anticoagulants (warfarin and direct oral anticoagulants). Patients receiving therapeutic anticoagulation for pre-existing thrombotic disorders prior to eltrombopag initiation were excluded from the analysis, whereas those using low-dose aspirin for cardiovascular prophylaxis were included.

### 2.1. Statistical Analysis

All statistical evaluations were conducted using IBM SPSS Statistics software (version 22.0, Chicago, IL, USA). Continuous data are presented as mean ± standard deviation for normally distributed variables or as median values with range (minimum–maximum) for non-normally distributed variables. Categorical parameters were summarized as counts and percentages**.**

The Shapiro–Wilk test was used to assess the normality of data distribution. Differences between groups were analyzed with one-way ANOVA for normally distributed variables, followed by Bonferroni or Tamhane's T2 post-hoc tests when appropriate. For non-normally distributed variables, comparisons were performed using the Kruskal–Wallis test with subsequent pairwise analyses. Chi-square or Fisher's exact tests were applied to compare categorical data.

To identify independent predictors of thrombosis, logistic regression analysis was performed. A p-value $< 0.05$ was regarded as statistically significant.

## 3. Results

The study population consisted of 144 individuals who received eltrombopag therapy. Among them, 66 (45.8%) were men and 78 (54.2%) were women, with an average age of 54.1 ± 20.1 years. Regarding underlying diagnoses, 102 patients (70.8%) were classified as having immune thrombocytopenia (ITP), 31 (21.5%) were diagnosed with aplastic anemia, and 11 (7.6%) with myelodysplastic syndrome (MDS) (Table 1).

The median eltrombopag dose administered was 50 mg (range, 25–150 mg), and no statistically significant variation was detected among the diagnostic groups ($p = 0.310$). The median duration of therapy was 12 months (range, 1–96 months), showing a significant difference across diagnoses ($p = 0.038$); patients with immune thrombocytopenia had notably longer treatment durations compared to those with myelodysplastic syndrome. The median baseline platelet count was 15,000/μL (range, 1,000–624,000), and no statistically significant variation was observed among the different diagnostic categories ($p = 0.210$) (Tables 2 and 3).

During follow-up, thrombosis developed in 7 patients (4.9%), representing the first thromboembolic event in each

case (Table 4). Of these first events, 6 were venous and 1 was arterial (Table 5). When all vascular events were considered (allowing for multiple events per patient), a total of 13 events were recorded: 7 venous and 6 arterial (Table 6). No thromboembolic events were observed in the MDS group.

**Table 1.** Demographic and clinical characteristics of the study population

| Variable | n (%) / Mean ± SD |
|---|---|
| Age (years) | 54.12±20.08 |
| Sex | Male: 66 (45.8%) |
| | Female: 78 (54.2%) |
| Diagnosis | ITP[a]: 102 (70.8%) |
| | Aplastic anemia: 31 (21.5%) |
| | MDS[b]: 11 (7.6%) |
| Treatments | IVIG[c] + Methylprednisolone: 73 (50.7%) |
| | Methylprednisolone: 22 (15.3%) |
| | Splenectomy: 8 (5.6%) |
| | Cyclosporine: 24 (16.7%) |
| Comorbidities | Hypertension: 58 (40.3%) |
| | Diabetes Mellitus: 25 (17.4%) |
| | Cardiovascular diseases: 9 (6.3%) |
| | Other[d]: 11 (7.6%) |
| | No comorbidity: 66 (45.8%) |

[a]**ITP:** Immune Thrombocytopenia, [b]**MDS:** Myelodysplastic Syndrome, [c]**IVIG:** Intravenous Immunoglobulin, [d]**Other:** Hypothyroidism, Parkinson's disease, Familial Mediterranean Fever, Gout, Rheumatoid Arthritis, Vitiligo, Chronic Obstructive Pulmonary Disease.

Low-dose aspirin was the only antithrombotic agent used concurrently in the cohort; no patients were on therapeutic anticoagulation before starting eltrombopag.

Univariate logistic regression revealed no variables that were significantly associated with the occurrence of thrombosis. Patient age, sex, history of hypertension and diabetes, presence of cardiac comorbidity, eltrombopag dose and duration, and ANA positivity were not statistically associated with the development of thrombosis (all $p > 0.05$), which is most likely related to the limited number of thromboembolic events in the cohort (Table 7). This absence of statistically significant associations is likely related to the low number of thromboembolic events in the cohort.

## 4. Discussion

Eltrombopag, acting through thrombopoietin receptor activation, represents an established and effective therapeutic approach for patients with ITP, aplastic anemia, and MDS. Despite its platelet-stimulating benefits, concerns remain regarding a possible elevation in thromboembolic risk. In the present study, we assessed the frequency of these events among individuals treated with eltrombopag and contextualized our results within the framework of previously published data.

**Table 2.** Distribution of demographic data according to diagnosis

| Variable | Aplastic Anemia (n=31) | ITP[a] (n=102) | MDS[b] (n=11) | p-value |
|---|---|---|---|---|
| Age (years) | 53.19±19.80 | 53.16±20.05 | 65.14±19.18 | 0.141[c] |
| Sex | | | | |
| Male | 17 (54.8%) | 41 (40.2%) | 8 (72.7%) | 0.063[d] |
| Female | 14 (45.2%) | 61 (59.8%) | 3 (27.3%) | |

**Table 3.** Duration and dose of eltrombopag treatment according to diagnosis

| Variable | All Patients (n=144) | Aplastic Anemia (n=31) | ITP[a] (n=102) | MDS[b] (n=11) | p-value |
|---|---|---|---|---|---|
| Eltrombopag Dose (mg) | 50 (25–150) | 50 (25–150) | 50 (50–150) | 50 (25–75) | 0.310[c] |
| Duration of eltrombopag use (months) | 12 (1-96) | 12 (1-48) | 13.5 (1-96) | 3 (1-55) | 0.038[d] |
| Baseline Platelet Count (/μL) | 15000 (1000-624000) | 19000 (1000-624000) | 13000 (1000-116000) | 20000 (4000-50000) | 0.210 |

[a]**ITP:** Immune Thrombocytopenia, [b]**MDS:** Myelodysplastic Syndrome, [c]**:** Kruskal–Wallis test, [d]**:** Aplastic anemia vs. MDS p=0.061, MDS vs. ITP p=0.011, Aplastic anemia vs. ITP p=0.467. Data are presented as median (min–max).

**Table 4.** Distribution of thrombosis incidence according to diagnosis

| | All Patients | Aplastic Anemia | ITP[a] | MDS[b] | p-value[c] |
|---|---|---|---|---|---|
| **Thrombosis** | 7 (4.9%) | 2 (1.38%) | 5 (3.52%) | 0 (0.0%) | 0.694 |
| **Venous thrombosis** | 6 (4.2%) | 1 (0.69%) | 5 (3.52%) | 0 (0.0%) | 0.710 |
| **Arterial thrombosis** | 1 (0.7%) | 1 (0.69%) | 0 (0.0%) | 0 (0.0%) | 0.292 |

[a]**ITP:** Immune Thrombocytopenia, [b]**MDS:** Myelodysplastic Syndrome, [c]**:** Kruskal–Wallis test

**Table 5.** Baseline characteristics of patients who experienced thromboembolic events (n=7)

| Patient no | Sex | Age | Comorbidity | Diagnosis | Duration of use (months) | Dose (mg) | Thrombosis type | Mortality |
|---|---|---|---|---|---|---|---|---|
| **1** | Female | 51 | Hypothyroidism | ITP[a] | 2 | 75 | Venous | No |
| **2** | Male | 64 | HT[b] | ITP | 4 | 75 | Venous | No |
| **3** | Female | 62 | None | ITP | 84 | 75 | Venous | No |
| **4** | Male | 70 | HT | ITP | 6 | 75 | Venous | No |
| **5** | Female | 65 | HT, DM[c] | AA[d] | 24 | 75 | Venous | No |
| **6** | Male | 32 | None | ITP | 12 | 50 | Venous | No |
| **7** | Female | 66 | DM | AA | 1 | 75 | Arterial | No |

[a]**ITP:** Immune thrombocytopenia, [b]**HT:** Hypertension, [c]**DM:** Diabetes mellitus, [d]**AA:** Aplastic anemia.

**Table 6.** Mortality and specific vascular events according to diagnosis

| | All patients | Aplastic Anemia | ITP[a] | MDS[b] | p-value[c] |
|---|---|---|---|---|---|
| **Mortality** | 25 (17.4%) | 7 (22.6%) | 14 (13.7%) | 4 (36.4%) | 0.117 |
| **MI[d]** | 1 (0.7%) | 1 (3.2%) | 0 | 0 | 0.292 |
| **Stroke** | 5 (3.5%) | 2 (6.5%) | 3 (2.9%) | 0 | 0.553 |
| **PVT[e]** | 4 (2.8%) | 0 | 4 (3.9%) | 0 | 0.690 |
| **PE[f]** | 3 (2.1%) | 0 | 3 (2.9%) | 0 | 0.532 |
| **DVT[g]** | 0 | 0 | 0 | 0 | - |

[a]**ITP:** Immune thrombocytopenia, [b]**MDS:** Myelodysplastic syndrome, [c]**:** p-values were calculated using the Chi-square or Fisher's exact test, [d]**MI:** Myocardial infarction, [e]**PVT:** Portal vein thrombosis, [f]**PE:** Pulmonary embolism, [g]**DVT:** Deep vein thrombosis. Values are expressed as n (%).

**Table 7.** Univariate analysis of risk factors associated with thrombosis

| Variable | OR[a] | 95% CI[b] | | p-value |
|---|---|---|---|---|
| | | Lower | Upper | |
| Age | 1.01 | 0.97 | 1.05 | 0.548 |
| Sex | 1.13 | 0.24 | 5.26 | 0.871 |
| Cardiac disease[c] | 0 | 0 | 0 | 0.999 |
| HT[d] | 1.64 | 0.35 | 7.64 | 0.529 |
| DM[e] | 1.98 | 0.36 | 10.85 | 0.430 |
| Duration of Eltrombopag use | 1.00 | 0.97 | 1.04 | 0.748 |
| Eltrombopag dose (mg) | 1.02 | 0.99 | 1.05 | 0.120 |
| ANA[f] positivity | 0.89 | 0.16 | 4.79 | 0.893 |

[a]OR: Odds ratio, [b]CI: Confidence interval, [c]Cardiac disease: Not estimable due to zero events in the group, [d]HT: Hypertension, [e]DM: Diabetes mellitus, [f]ANA: Antinuclear antibody.

In a phase 3 randomized trial conducted by Cheng et al., eltrombopag successfully sustained platelet levels within the desired therapeutic range throughout six months of treatment in patients with chronic ITP, leading to reduced bleeding episodes and enhanced quality of life. Nevertheless, approximately 2% of the participants experienced thromboembolic complications, highlighting the importance of evaluating each patient's individual risk profile before initiating therapy (11).

Likewise, the EXTEND trial, which investigated the prolonged safety and therapeutic effectiveness of eltrombopag, documented thromboembolic complications in up to 6% of participants (12). Meta-analyses also support this risk; in a systematic review by Catalá-López et al., the incidence of thromboembolism was 3.1% among patients treated with eltrombopag compared with 1.7% in the control group (13). More recent meta-analytic data focusing on ITP patients treated with thrombopoietic agents have similarly reported a modestly increased thrombotic risk, particularly in elderly individuals, patients with prior thrombosis, and those with prolonged exposure to TPO-RAs (14).

According to the recommendations of the American Society of Hematology for the management of immune thrombocytopenia, thrombopoietin receptor agonists—including eltrombopag—should be prescribed cautiously because of their potential association with thrombotic risk (15, 16). Similarly, the international consensus report prepared by Rodeghiero et al. advises that thromboembolic risk should always be assessed before initiating therapy (17).

In this context, the 4.9% thromboembolism rate observed in our study is consistent with rates reported in the literature. Notably, venous thromboses predominated, a finding that also parallels previous reports (18, 19). This pattern is in line with contemporary pharmacovigilance analyses and mixed trial/real-world safety datasets, which have identified thromboembolism—more often of venous origin—as an infrequent but clinically relevant adverse event associated with eltrombopag and other TPO-RAs, thereby warranting careful monitoring during treatment (20, 21).

In addition, no thromboembolic events were observed among patients with MDS in our study. This finding is consistent with previous observations in the MDS population, where more conservative approaches to eltrombopag dose and treatment duration are generally applied, despite this

population being older with more comorbidities (22, 23). Conversely, a French multicentre real-life cohort of patients with MDS or CMML reported thrombotic complications in approximately 10% of eltrombopag-treated patients, almost all of whom had a history of prior arterial or venous thrombosis (24). These discrepancies underscore the influence of baseline thrombotic risk profile and treatment selection on observed event rates.

However, certain studies have found no evidence of thromboembolic events. For instance, in the short-term trial conducted by Bussel and colleagues, the incidence of thrombosis did not differ significantly between the eltrombopag and placebo groups, and no thrombotic episodes were detected (1). Likewise, the research conducted by Ecsedi and colleagues involving patients with aplastic anemia reported no occurrences of thrombotic complications (25). Such variations may stem from differences in study population size, length of follow-up, coexisting risk factors, and treatment dosage protocols.

The literature also suggests that eltrombopag may create a prothrombotic environment beyond simply increasing platelet counts by enhancing platelet activation and adhesion. This may lead to clinically significant thrombosis, particularly in conditions such as ITP where young, reactive platelets predominate (26, 27). However, it should be emphasized that patients who develop thromboembolism often have additional underlying risk factors (e.g., smoking, hypertension, malignancy) (11, 12).

For this reason, our study excluded individuals with major confounding risk factors such as active malignancy or prolonged immobility, which may help to better delineate the risk attributable to the therapy itself. Even so, the small number of participants and the retrospective nature of the study limit the extent to which these results can be generalized. The low number of thromboembolic events in our cohort substantially limits the statistical power of the analyses. Therefore, the absence of significant associations between clinical variables and thrombosis should be interpreted as an inability to demonstrate a relationship rather than evidence of no true association. Larger, adequately powered studies are required to clarify these potential risk factors.

In our cohort, however, we were not able to demonstrate a statistically significant association between thrombosis and age, underlying diagnosis (ITP, AA, MDS), comorbidities, or eltrombopag dose and treatment duration. This lack of statistically significant predictors is likely attributable to the low number of thromboembolic events rather than the absence of a true effect, and thus our findings should be interpreted with caution.

Our findings underscore the need for continued pharmacovigilance in patients receiving eltrombopag, particularly in long-term therapy. Establishing standardized protocols for baseline cardiovascular assessment and periodic monitoring of coagulation parameters could enhance patient safety. Integrating clinical decision support systems into electronic medical records may also help clinicians identify high-risk individuals and tailor treatment duration and dosing more precisely.

In conclusion, our results support that the risk of thromboembolism should not be overlooked during eltrombopag therapy. A careful evaluation of individual risk factors is essential before initiating treatment, and patients should be closely monitored throughout its course. Prospective, large-scale, and well-standardized studies with respect to risk factors are warranted to address the existing knowledge gaps in this area.

**Conflict of interest**

The authors declared no conflict of interest.

**Funding**

No funding was used for the study.

**Acknowledgments**

This study was presented as a poster at the European Hematology-Oncology Congress (EHOC 2021) (Poster Code: PP-57).

**Authors' contributions**

Concept: M.İ., E.K., M.T., Design: M.İ., E.K., M.T., Data Collection or Processing: D.D.K., E.K., Analysis or Interpretation: M.İ., D.D.K., Literature Search: M.İ., D.D.K., Writing: M.İ.

**Ethical Statement**

Ethical approval was obtained from the Institutional Review Board (Date: February 28, 2020; Approval No: 2020/94).

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