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ORIGINAL RESEARCH ARTICLE

# Signal for Thrombosis with Eltrombopag and Romiplostim: A Disproportionality Analysis of Spontaneous Reports Within VigiBase®

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**Abstract**

*Introduction* Eltrombopag and romiplostim are thrombopoietin receptor agonists (TPO-RAs) marketed for immune thrombocytopenia (ITP). Thrombotic events have been reported with both drugs. This study was aimed at assessing whether there is a signal for differential risks of thrombosis between these two TPO-RAs.

*Methods* We carried out a disproportionality analysis in the World Health Organization global individual case safety report (ICSR) database (VigiBase®). We selected all ICSRs with exposure to a TPO-RA between January 2011 and December 2014. We searched for exposures to eltrombopag or romiplostim in thrombosis reports as compared with other ICSRs, and we calculated adjusted reporting odds ratios (aRORs).

*Results* We identified 5850 ICSRs, including 764 cases of thrombosis. In multivariate analyses, there was a signal for an increased risk of thrombosis (venous or arterial; aROR 1.72, 95 % confidence interval [CI] 1.47–2.02), venous thrombosis (aROR 1.88, 95 % CI 1.53–2.31), arterial thrombosis (aROR 1.54, 95 % CI 1.18–2.00), ischaemic stroke (aROR 1.65, 95 % CI 1.13–2.42) and myocardial infarction (aROR 1.50, 95 % CI 1.05–2.13) with eltrombopag as compared with romiplostim. Restriction to ICSRs reported by physicians led to similar results. However, worldwide dispensing data for romiplostim and eltrombopag were not accessible, so the rates of thrombosis with both drugs were not normalized by the daily defined doses and the generalizability of the results is limited.

*Conclusion* This study suggests the presence of a signal for an increased risk of thrombosis with eltrombopag compared with romiplostim. These results must be confirmed and quantified by large aetiological pharmacoepidemiological studies.

**Key Points**

This study suggests the presence of a signal for an increased risk of thrombosis with eltrombopag compared with romiplostim.

This signal of risk concerns both arterial and venous events.

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## 1 Introduction

Eltrombopag and romiplostim are two thrombopoietin receptor agonists (TPO-RAs). They bind to and activate the thrombopoietin receptor on the megakaryocyte membrane, resulting in increased platelet production [1].These drugs are approved worldwide in patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy [2–5]. Recently, eltrombopag has been approved for the treatment of chronic hepatitis C-related thrombocytopenia in adults when thrombocytopenia is interfering with the use of interferon alfa-based therapies [6, 7].

In randomized controlled trials and open-label extension studies, as well as in real-life practice experience, thrombotic events have been reported with both drugs [8–13]. Both arterial and venous thromboses have been described. However, this risk is not well known: the pathophysiology has not been elucidated, although it seems to be a class effect. Thrombocytosis at the time of thrombosis is observed in only one third of cases, suggesting more complex mechanisms [10, 11]. TPO-RA may induce platelet activation [14]. Similarly, observational studies investigating TPO-RA-related thrombosis are lacking. In the largest prospective study, which included 292 patients exposed to romiplostim for up to 5 years, 19 patients (6.5 %) experienced 25 thrombotic events. A risk factor for thrombosis was found in 87 % of the cases, but no common risk factor was identified [11]. In the follow-up of the first patients treated with romiplostim in France ($n = 72$), two arterial thromboses occurred. Once again, no common risk factor was identified [13]. Similarly, 299 patients included in eltrombopag randomized controlled trials were followed in an open-label extension study (median exposure 298.5 days, range 2–1267). Sixteen patients experienced at least one thrombotic event. All had at least one thrombosis risk factor, but no single common factor could be identified [10].

Whether there are differential risks of thrombosis between the two TPO-RAs is unknown. This can be suspected because (1) the two drugs have different structures and therefore different sites of action: romiplostim is a fragment crystallizable (Fc)–peptide fusion protein binding to the extracellular TPO receptor domain, while eltrombopag is a small non-peptide molecule that binds to a transmembrane site of the TPO receptor [1]; consequently, the intracellular signaling pathways activated by TPO-RAs are not strictly similar [15]; (2) in clinical practice, a patient who stops a given TPO-RA because of inefficacy, an adverse drug reaction (ADR) or important platelet fluctuations can be efficiently rechallenged with the other TPO-RA [16, 17]; and (3) a disproportionality study carried out in the French pharmacovigilance database between 2009 and 2013 suggested the presence of a signal for differential ADR patterns between the two drugs [18]. Indeed, there were signals for an increased risk of haematological ADRs and a decreased risk of gastrointestinal ADRs with romiplostim as compared with eltrombopag; the age- and gender-adjusted reporting odds ratios (aRORs) were 14.36 (95 % confidence interval [CI] 1.73–119.08; $P = 0.01$) and 0.03 (95 % CI 0.00–0.31; $P = 0.003$), respectively. However, that study was underpowered to assess differential risks of thrombosis, as only 12 venous and eight arterial thromboses occurred. When dispensing data obtained from the French national health insurance database were analysed, the rates of reported thromboses per million defined daily doses dispensed were 18.82 with romiplostim and 22.80 with eltrombopag ($P = 0.5$). They were 12.94 and 17.10, respectively, for venous thrombosis ($P = 0.5$) [18].

The aim of our study was to identify a signal for differential risks of thrombosis (overall, venous or arterial), arterial thrombosis, venous thrombosis, ischaemic stroke and myocardial infarction between eltrombopag and romiplostim.

## 2 Methods

We carried out a disproportionality analysis (case/non-case design) in the World Health Organization (WHO) global individual case safety report (ICSR) database (VigiBase®).

### 2.1 Data Source: The WHO Global Individual Case Safety Report Database

The WHO Programme for International Drug Monitoring collects ADR reports worldwide to identify the earliest possible safety signals. It was established in 1968 and has over 120 member countries around the world [19]. ICSRs are sent from each national centre for pharmacovigilance to the WHO Collaborating Centre for International Drug Monitoring, which enters and maintains the reports in VigiBase® [19, 20].

In most countries, the ICSRs can be reported by health professionals and patients. Each report includes the patient's demographics, the reporter's qualification, the seriousness of the ADR, the drugs used at the time of the ADR, a causality assessment for each of these drugs and additional information relevant to the case. ADRs are coded according to the Medical Dictionary for Regulatory Activities (MedDRA) [21]. MedDRA is a classification system of ADR terms, based on a five-level hierarchy (from less to more accurate: System Organ Class [SOC], High Level Group Term [HLGT], High Level Term [HLT],

Preferred Term [PT] and Lowest Level Term [LLT]). Standardized MedDRA Queries (SMQs) are groupings of MedDRA terms, ordinarily at the PT level, which are related to a defined medical condition or area of interest [22]. They have been developed to identify a given condition in databases using MedDRA coding (e.g. a given ADR in pharmacovigilance databases).

### 2.2 Study Population

In VigiBase®, we selected all ICSRs with exposure to at least one TPO-RA between 1 January 2011 and 31 December 2014. The beginning of the study period in 2011 was justified by the availability of both TPO-RAs in the most represented countries/regions in VigiBase® (the USA, the European Union, Canada and Japan).

We excluded all reports with exposures to both TPO-RAs, those with undetailed ADRs and those where the ADR was coded as 'idiopathic thrombocytopenic purpura' because of a probable miscoding, confusing the indication and the ADR (see Fig. 1).

### 2.3 Disproportionality Analysis

Case/non-case design studies have been widely used in pharmacovigilance databases for safety problem detection [23]. This design allows estimation of the disproportionality between the frequency of exposure to a drug of interest in patients who experience an ADR of interest (the cases here being thrombosis reports) and exposure to the same drug in other ADR reports that occur during the same study period (the non-cases here being reports of all ADRs other than thrombosis). The strength of the association between the drug and the ADR of interest is estimated by calculating the reporting odds ratio (ROR) and its 95 % CI. The ROR is the odds of exposure to the drug among the cases, divided by the odds of exposure to the drug among the non-cases. Of note, this method reveals a safety signal

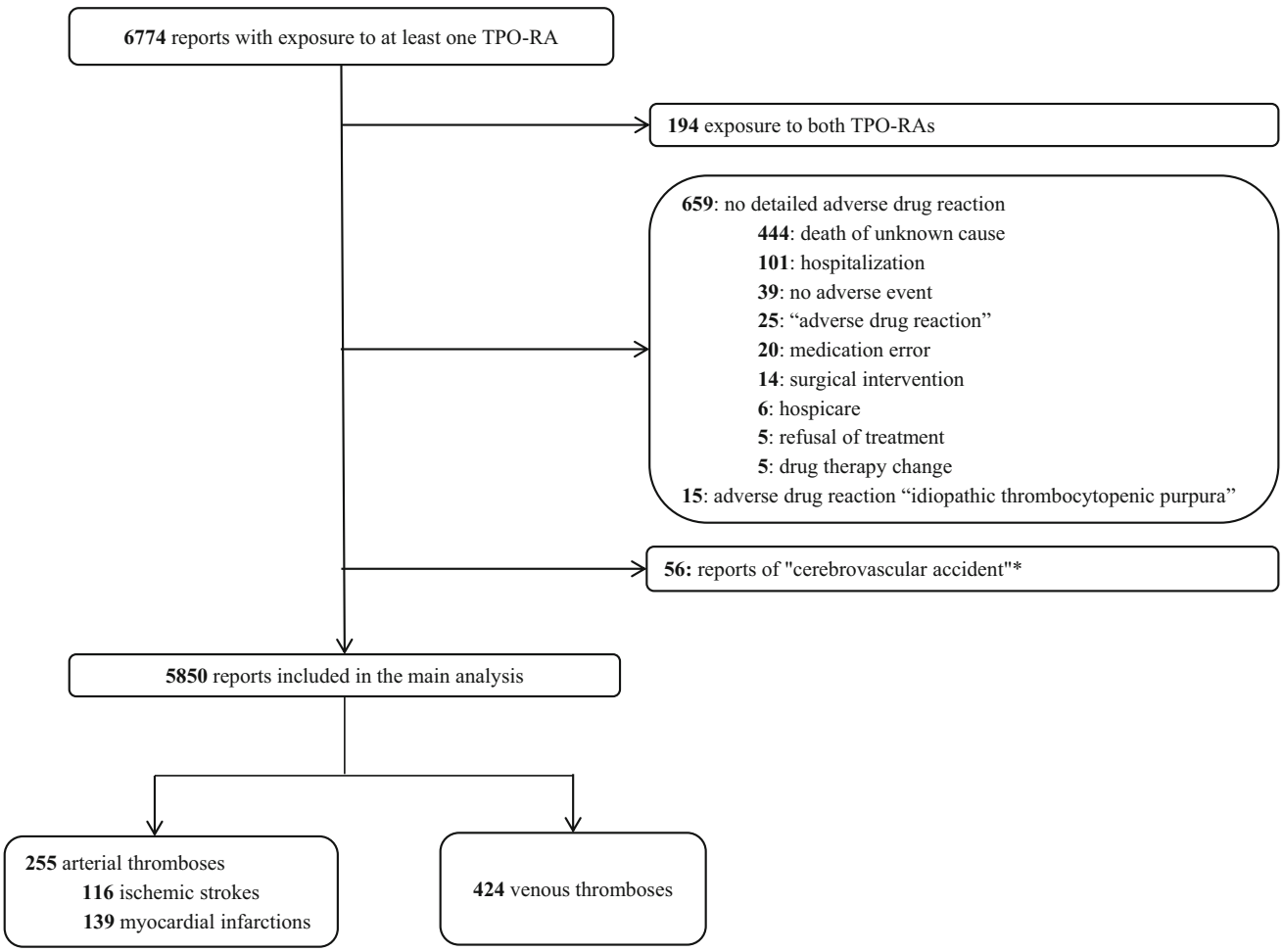


**Fig. 1** Flowchart illustrating the process of selection of the study population. *These reports were included in the second sensitivity analysis as cases of thrombosis, arterial thrombosis and ischaemic stroke. *TPO-RA* thrombopoietin receptor agonist

but does not quantify the risk for a given patient exposed to the drug [23].

The identification of thrombosis cases was based on the following SMQs: 'arterial embolic and thrombotic events', 'venous embolic and thrombotic events' and 'embolic and thrombotic events of unspecified vessel (mixed arterial and venous)'. Cases of ischaemic stroke and myocardial infarction were selected by using the SMQs 'ischaemic cerebrovascular conditions' and 'myocardial infarction', respectively. All selected cases of thrombosis were independently reviewed by two investigators (TTLN and GM). Discrepancies were solved by consensus. A third evaluator (MLM) intervened in cases of persistent disagreement. In addition, reports of 'cerebrovascular accident' were excluded from the main analysis because of the imprecise mechanism (whether it corresponded to ischemia or bleeding).

### 2.4 Missing Data

Missing data were observed for three covariables (age, gender and TPO-RA indication). For age, we attributed to missing values the mean age of the corresponding group (cases versus non-cases). For gender and the indication, we randomly attributed a value to reports with missing values, in accordance with the pattern of the variable in the reports with no missing values in the corresponding group (cases versus non-cases). We also performed sensitivity analyses restricted to ADR reports with no missing values.

### 2.5 Statistical Analysis

Exposure to eltrombopag (versus romiplostim) was searched for in cases and non-cases in order to calculate RORs. We performed univariate and then multivariate logistic regression analyses, adjusted for thrombotic risk factors available in the ICSRs. Variables associated with the outcome at the threshold of 20 % in the univariate models were included in the multivariate model to estimate the aRORs. The adjustment variables were the indication for the TPO-RA, age, gender, duration of exposure to the TPO-RA and concomitant exposure to prothrombotic drugs. In fact, thrombotic events are not uncommon in ITP patients [24, 25]. On the other hand, TPO-RAs are also used off-label for thrombocytopenia occurring in the context of various malignancies where the baseline risk of thrombosis is major [26]. For these reasons, we categorized the indications into three classes: ITP, cancer and other indications that are not associated with a baseline risk of thrombosis. The prothrombotic drugs most frequently used in ITP patients were considered separately. These were corticosteroids, danazol, intravenous immunoglobulin (IVIg), oral contraceptives and rituximab (whose safety in real-life practice in ITP patients has not been well assessed). Other prothrombotic drugs (see Table S1 in the Electronic Supplementary Material) were grouped into a single variable. The analyses were also adjusted for antiplatelet drug exposure (Anatomical, Therapeutic and Chemical [ATC] classification code B01AC), anticoagulant drug exposure (ATC codes B01AA, B01AB, B01AE, B01AF, B01AX) and statin exposure (ATC code C10AA).

We first performed a sensitivity analysis restricted to ICSRs reported by physicians because the diagnoses of ADRs were probably more adequate in comparison with the reports submitted by non-health professionals. Other sensitivity analyses were conducted: including reports of 'cerebrovascular accidents' as cases of thrombosis, arterial thrombosis and ischaemic stroke; excluding reports of portal vein thrombosis because of a possible channelling bias (in cases of liver cirrhosis); including in the model the duration of TPO-RA exposure (thus, considering only ICSRs with no missing value for this variable); and restricting the analyses to ICSRs without any concomitant exposure to a prothrombotic drug other than TPO-RA, and to ICSRs without any concomitant drug exposure.

All calculations were performed using SAS 9.3™ statistical software (SAS Institute, Cary, NC, USA).

## 3 Results

### 3.1 Selection of the Population

During the study period, 4,412,877 ICSRs were registered in VigiBase®, of which 6774 involved exposure to at least one TPO-RA. The selection process is illustrated in Fig. 1. Finally, 5850 ICSRs were included in the main analysis. In addition, 56 reports of 'cerebrovascular accident' were included in the second sensitivity analysis. The ICSRs stemmed mainly from North America (88.7 %), followed by European countries (9.5 %) and Asia (4.7 %).

Among the 5850 ICSRs, there were 764 thromboses. Among them, 255 were arterial thromboses (116 ischaemic strokes and 139 myocardial infarctions), 424 were venous thromboses and 98 were not specified. The 424 venous thromboses included 191 pulmonary embolisms (45.1 %), 51 portal vein thromboses (12.0 %) and 30 cerebral venous thromboses (7.1 %).

### 3.2 Characteristics of the Population

There was no major difference with regard to the characteristics of patients exposed to romiplostim versus patients exposed to eltrombopag. However, the reporter was more frequently a patient for eltrombopag ICSRs (see Table S2 in the Electronic Supplementary Material).

A comparison of cases of thrombosis and other ADR reports' characteristics is shown in Table S3 in the Electronic Supplementary Material (a description of the patients' characteristics for each subgroup of thromboses is detailed in Table S4 in the Electronic Supplementary Material). The main TPO-RA indication was ITP in both cases and non-cases. The reporter was a physician in 73.3 % of cases and in 60.3 % of non-cases. Conversely, the reporter was a patient in 9.2 % of cases and in 19.1 % of non-cases. Other characteristics were similar between the two groups. Exposure to eltrombopag was found in 42.0 % of cases, as compared with 29.0 % of non-cases.

The median time from the first TPO-RA exposure to thrombosis occurrence was 76.6 days (range 3–597); data were available in 28.6 % of cases. The median times were 77.6 days (range 3–597) for venous events and 76.2 days (range 3–478) for arterial events. The median daily dosages (available for 61.7 % of romiplostim cases and 51 % of eltrombopag cases) were 34.4 mg (range 12.5–100.0) for eltrombopag and 3 μg/kg (range 1–15) for romiplostim. The platelet count at the time of the event was described in 38 arterial thromboses and 68 venous thromboses. Thrombocytosis was found in 44.7 % and 50.0 %, respectively. The mortality rates were 31.1 % after arterial thrombosis and 11.7 % after venous thrombosis.

Among the non-cases, haematological ADRs were more frequently reported with romiplostim than with eltrombopag ($P < 0.001$). The frequency of non-serious gastrointestinal ADRs reported by patients was higher with eltrombopag than with romiplostim (84.0 versus 16.0 % of non-cases reported by patients, respectively; $P = 0.007$).

### 3.3 Disproportionality Analysis

The univariate models are presented in Table S5 in the Electronic Supplementary Material. The results of the multivariate model are presented in Table 1. In the multivariate model, there were signals for increased risks of overall thrombosis (aROR 1.72, 95 % CI 1.47–2.02), venous thrombosis (aROR 1.88, 95 % CI 1.53–2.31), arterial thrombosis (aROR 1.54, 95 % CI 1.18–2.00), ischaemic stroke (aROR 1.65, 95 % CI 1.13–2.42) and myocardial infarction (aROR 1.50, 95 % CI 1.05–2.13) with eltrombopag as compared with romiplostim. Age was independently associated with the risk of thrombosis. Female gender was associated with venous thrombosis (ROR 1.47, 95 % CI 1.20–1.81). In contrast, it was negatively associated with myocardial infarction (ROR 0.51, 95 % CI 0.36–0.74). Exposure to oral contraceptives was also associated with venous thrombosis (ROR 5.83, 95 % CI 2.99–11.36). Exposure to IVIg was associated with myocardial infarction (ROR 1.86, 95 % CI 1.20–2.90). Exposure to corticosteroids was associated with venous thrombosis and with ischaemic stroke. Exposures to antiplatelet drugs, anticoagulant drugs and statins were associated with arterial thrombosis. Exposure to anticoagulant drugs was associated with venous thrombosis and ischaemic stroke.

When we restricted the analysis to ICSRs reported by physicians, all aROR measures were slightly increased

**Table 1** Results of the main disproportionality analysis (multivariate model)[a]

| Variable | Multivariate analysis | |
|---|---|---|
| | ROR (95 % CI) | *P* value |
| Thrombosis ($n = 764$) | | |
| Eltrombopag versus romiplostim | 1.72 (1.47–2.02) | <0.001 |
| Age: 1 year of increase | 1.01 (1.00–1.01) | 0.02 |
| Exposure to oral contraceptives | 4.11 (2.15–7.83) | <0.001 |
| Exposure to antiplatelet drugs | 2.92 (1.94–4.40) | <0.001 |
| Exposure to anticoagulant drugs | 3.79 (2.56–5.61) | <0.001 |
| Exposure to statins | 1.89 (1.21–2.96) | 0.005 |
| Exposure to corticosteroids | 1.41 (1.19–1.68) | <0.001 |
| Arterial thrombosis ($n = 255$) | | |
| Eltrombopag versus romiplostim | 1.54 (1.18–2.00) | 0.001 |
| Age: 1 year of increase | 1.02 (1.01–1.03) | <0.001 |
| Female gender | 0.77 (0.60–0.99) | 0.05 |
| Exposure to antiplatelet drugs | 6.37 (4.00–10.15) | <0.001 |
| Exposure to anticoagulant drugs | 2.01 (1.09–3.71) | 0.03 |
| Exposure to statins | 2.06 (1.13–3.75) | 0.02 |
| Venous thrombosis ($n = 424$) | | |
| Eltrombopag versus romiplostim | 1.88 (1.53–2.31) | <0.001 |
| Age: 1 year of increase | 1.00 (1.00–1.01) | 0.19 |
| Female gender | 1.47 (1.20–1.81) | <0.001 |
| Exposure to oral contraceptives | 5.83 (2.99–11.36) | <0.001 |
| Exposure to anticoagulant drugs | 4.95 (3.21–7.64) | <0.001 |
| Exposure to statins | 1.96 (1.13–3.40) | 0.02 |
| Exposure to corticosteroids | 1.40 (1.12–1.75) | 0.003 |
| Ischaemic stroke ($n = 116$) | | |
| Eltrombopag versus romiplostim | 1.65 (1.13–2.42) | 0.01 |
| Age: 1 year of increase | 1.02 (1.00–1.03) | 0.01 |
| Exposure to antiplatelet drugs | 7.64 (4.30–13.54) | <0.001 |
| Exposure to anticoagulant drugs | 2.44 (1.13–5.24) | 0.02 |
| Exposure to corticosteroids | 1.55 (1.04–2.31) | 0.03 |
| Myocardial infarction ($n = 139$) | | |
| Eltrombopag versus romiplostim | 1.50 (1.05–2.13) | 0.03 |
| Age: 1 year of increase | 1.03 (1.01–1.04) | <0.001 |
| Female gender | 0.51 (0.36–0.74) | <0.001 |
| Exposure to IVIg | 1.86 (1.20–2.90) | 0.006 |
| Exposure to antiplatelet drugs | 5.41 (3.01–9.72) | 0.001 |

*CI* confidence interval, *IVIg* intravenous immunoglobulin, *ROR* reporting odds ratio

[a] Adjusted for indication; age; gender; and exposure to danazol, intravenous polyvalent immunoglobulin, oral contraceptives, rituximab, other prothrombotic drugs, antiplatelet drugs, anticoagulant drugs, statins and corticosteroids

(Table 2). Inclusion of the 56 reports of 'cerebrovascular accident' did not influence the results; nor did restriction to ICSRs without any missing values (data not shown).

Sensitivity analysis excluding portal vein thrombosis led to similar results (see Table S6 in the Electronic Supplementary Material). Inclusion of the duration of TPO-RA exposure in the multivariate model did not change the findings. Indeed, this variable could be withdrawn from all of the models because it was not associated with the outcome (see Table S7 in the Electronic Supplementary Material). Lastly, restriction of the analyses to ICSRs without any concomitant exposure to a prothrombotic drug other than TPO-RA, and restriction to ICSRs without any concomitant drug exposure also led to signals for an increased risk of thrombosis with eltrombopag (see Table S8 in the Electronic Supplementary Material).

**Table 2** Results of the sensitivity analysis, restricted to cases and non-cases reported by physicians (multivariate model)[a]

| Variable | Multivariate analysis | |
|---|---|---|
| | ROR (95 % CI) | *P* value |
| Thrombosis ($n = 560$) | | |
| Eltrombopag versus romiplostim | 2.92 (2.40–3.56) | <0.001 |
| Age: 1 year of increase | 1.01 (1.00–1.02) | 0.003 |
| Exposure to oral contraceptives | 4.05 (1.80–9.12) | 0.001 |
| Exposure to antiplatelet drugs | 3.15 (1.68–5.32) | <0.001 |
| Exposure to anticoagulant drugs | 3.18 (1.88–5.38) | <0.001 |
| Arterial thrombosis ($n = 188$) | | |
| Eltrombopag versus romiplostim | 2.37 (1.73–3.24) | <0.001 |
| Age: 1 year of increase | 1.03 (1.02–1.04) | <0.001 |
| Exposure to antiplatelet drugs | 6.15 (3.44–10.98) | <0.001 |
| Venous thrombosis ($n = 308$) | | |
| Eltrombopag versus romiplostim | 3.01 (2.35–3.86) | <0.001 |
| Age: 1 year of increase | 1.01 (1.00–1.01) | 0.18 |
| Female gender | 1.53 (1.19–1.95) | 0.001 |
| Exposure to oral contraceptives | 5.72 (2.45–13.35) | <0.001 |
| Exposure to anticoagulant drugs | 4.07 (2.31–7.17) | <0.001 |
| Ischaemic stroke ($n = 86$) | | |
| Eltrombopag versus romiplostim | 2.81 (1.80–4.38) | <0.001 |
| Age: 1 year of increase | 1.03 (1.01–1.05) | <0.001 |
| Exposure to antiplatelet drugs | 6.63 (3.24–13.57) | <0.001 |
| Myocardial infarction ($n = 103$) | | |
| Eltrombopag versus romiplostim | 1.84 (1.20–2.81) | 0.005 |
| Age: 1 year of increase | 1.02 (1.01–1.04) | 0.007 |
| Female gender | 0.54 (0.36–0.82) | 0.004 |
| Exposure to antiplatelet drugs | 3.44 (1.54–7.71) | 0.003 |
| Exposure to statins | 2.49 (1.01–6.14) | 0.05 |

*CI* confidence interval, *ROR* reporting odds ratio

[a] Adjusted for indication; age; gender; and exposure to danazol, intravenous polyvalent immunoglobulin, oral contraceptives, rituximab, other prothrombotic drugs, antiplatelet drugs, anticoagulant drugs, statins and corticosteroids

## 4 Discussion

This study was aimed at identifying a signal for differential risks of thrombosis with eltrombopag and romiplostim. It found a signal for an increased risk of thrombosis with eltrombopag as compared with romiplostim.

In open-label extension studies, thrombotic events occurred in 5 % of patients treated with eltrombopag and 6.5 % of patients treated with romiplostim [10, 11]. Of note, crude comparisons of these rates cannot be drawn from these studies, which included different populations with different durations of exposure and were underpowered to detect small differences in risk. Thrombocytosis was found in only one third of cases of patients who experienced thrombotic events [10, 11], in comparison with 37.5 % of arterial thromboses and 48.4 % of venous thromboses in our study. In these studies, no specific risk factors were identified. Our results suggest that age, gender and—for some events—exposure to prothrombotic drugs are independent risk factors for thrombosis in the population of patients exposed to TPO-RAs. Of note, exposure to IVIg was associated with myocardial infarction, which has also been suggested previously [27]. Interstingly, most of the events occurred with a TPO-RA daily dosage in accordance with drug labelling.

In the sensitivity analysis restricted to ICSRs reported by physicians, we found increased ROR values. This may have been due to the fact that serious ADRs are mainly reported by physicians, while patients tend to report non-serious ADRs [28–30]. Indeed, we found a high rate of non-serious gastrointestinal ADRs with exposure to eltrombopag reported by patients. A signal for an increased risk of gastrointestinal disorders with eltrombopag (versus romiplostim) was supported by a disproportionality analysis in the French pharmacovigilance database [18]. In addition, eltrombopag is an oral agent given daily; in contrast, romiplostim is administered as a weekly subcutaneous injection. This difference may, in part, explain patients' penchant for reporting such non-serious ADRs.

VigiBase®, the world's largest pharmacovigilance data resource [20], provides sufficient statistical power for a disproportionality analysis to highlight signals. To date, this series of thromboses that occurred on TPO-RA is the most important to ever be investigated. The sensitivity analyses demonstrated high stability of the results. Lastly, as discussed above, there are pharmacodynamic and clinical data to explain a potential difference in the effects of the two TPO-RAs [15, 16], supporting the findings of this disproportionality analysis.

Some limitations should also be discussed. First, the quality and completeness of the data in the WHO global ICSR database are not always guaranteed, and we had to deal with missing data. Second, we could not adjust for some thrombotic risk factors not recorded in VigiBase®, such as smoking, dyslipidaemia, comorbidities and heredity. However, these factors do not influence a priori the exposure to eltrombopag versus romiplostim. Similarly, we could not deal with dose modifications over time, which may have differed between the two TPO-RAs, as well as food interactions that would influence eltrombopag bioavailability. The link of exposures to statins, antiplatelet and anticoagulant drugs with thrombosis in our study could have been explained by a channelling bias. In fact, exposures to these drugs may reflect a high risk of thrombosis and can be considered in our models as a proxy for unmeasured cardiovascular risk factors. Third, underreporting is a major limitation of spontaneous reporting systems. The seriousness of ADRs may affect their reporting. In fact, the cases of thrombosis reported in our series may have been the most serious cases, as evidenced by the mortality observed after thrombotic events. Nevertheless, we were interested in the same type of serious ADR (thrombosis), since the two TPO-RAs were both available to prescribers. Underreporting is usually similar for drugs sharing the same indication, country and period of marketing [31]. Moreover, risks of thrombosis have been described with both drugs in clinical trials. As a result, notoriety bias was unlikely, as was bias due to variations in ADR reports over time [32–34]. Altogether, there was no strong reason for differential underreporting between eltrombopag and romiplostim that could have heavily biased our results. We carried out multiple analyses, increasing the risk of significant results by chance. Another important limitation was that we could not confirm these results by comparing the rates of thrombosis reports according to romiplostim and eltrombopag dispensing data. Indeed, unlike the study conducted in France [18], we could not obtain worldwide dispensing data. Lastly, but most importantly, one should keep in mind that disproportionality analysis is designed to reveal a safety signal and does not quantify the risk for a given patient. It is intrinsically sensitive to detect a potential association between a given drug and a given ADR. Therefore, this signal must be confirmed and quantified by large aetiological pharmacoepidemiological studies.

## 5 Conclusion

Overall, our study suggests the presence of a signal for an increased risk of thrombosis with eltrombopag compared with romiplostim. This finding deserves to be confirmed by aetiological studies.

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**Compliance with Ethical Standards**

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***Conflict of interest*** Thi-Thanh Loan Nguyen, Aurore Palmaro, François Montastruc, Maryse Lapeyre-Mestre and Guillaume Moulis have no conflicts of interest that are directly relevant to the content of this study.

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