



## Full Length Article

# Impact of risk factors on the occurrence of arterial thrombosis and venous thromboembolism in adults with primary immune thrombocytopenia – Results from two nationwide cohorts



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## ABSTRACT

**Background:** Previous studies have found that patients with Immune thrombocytopenia (ITP) have an increased risk of arterial thrombosis (AT) and venous thromboembolism (VTE). However, risk factors for thrombosis in adults with primary ITP remain unassessed in large cohorts.

**Aim**

To assess the occurrence and impact of risk factors for AT and VTE in patients with primary ITP in France and Sweden.

**Methods:** Both countries have national health databases, including hospital diagnoses and drug dispensing data. Adults with incident primary ITP identified using algorithms between the years 2009–2015 in France, and 2009–2016 in Sweden were included. Cumulative incidence rates (IR) of AT and VTE were calculated by risk factors and multivariable Cox models were used to estimate associations.

**Results:** The study included 7225 patients from France and 2490 from Sweden. The IR of AT were 15.0 (95% CI: 13.4–16.7) and 14.7 (95% CI: 12.4–17.5) per 1000 person-years, respectively. The incidences of VTE were 6.9 (95% CI: 5.9–8.1) and 6.5 (95% CI: 5.1–8.4), respectively. Increasing age, male sex and a previous AT were associated with AT in both countries and so were exposure to antiplatelet drugs in France and a history of VTE and chronic kidney disease in Sweden. Increasing age and a history of VTE were associated with VTE in both countries, in France also cancer.

**Conclusion:** The IR of AT and VTE were similar in France. Age and male sex remained the most important risk factors for AT, age for VTE.

## 1. Introduction

Immune thrombocytopenia is an autoimmune hematologic disorder characterized by a platelet count below  $100 \times 10^9/L$ , which is classically associated with an increased risk of bleeding [1]. ITP can be either primary, where the underlying cause is unknown, or secondary to an underlying disorder e.g. a systemic auto-immune disease [2]. Some 60–70% of adults with newly diagnosed primary ITP develop a chronic condition of the disease, defined as ITP lasting > 12 months [1,3,4].

Chandan et al. found an increased risk of CVD in patients with ITP compared with the general population [5] and a Danish study reported an increased mortality risk of 50% in patients with ITP due to cardiovascular diseases (CVD) compared with the general population [6]. The mechanisms behind the increased risk of thromboembolic events in patients with ITP is to a large extent unknown but could partly be linked to a pathological complement activation on/by platelets contributing to vascular inflammation and thrombosis [7,8]. An increased risk of thrombosis after splenectomy has also been reported in other

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studies [9]. Boyle et al. reported an increased cumulative incidence of venous thromboembolism (VTE) in patients with ITP after splenectomy [10], and an almost 3-fold increased remaining risk after splenectomy compared with the general population (adjusted for age) was reported by Thomsen et al. [11]. In the Nordic countries, Norgaard et al. reported an increased rate of stroke in Danish patients who had a splenectomy for various indications [12]. The knowledge about the risk for VTE in non-splenectomized patients is limited and the prevalence and impact of baseline risk factors for arterial thrombosis (AT) and VTE in patients with ITP have, to our knowledge, not yet been assessed in large cohorts. Including data from almost 10,000 patients with primary ITP in France and Sweden made it possible to assess incidence rates (IR) of AT and VTE, as well as the prevalence and the impact of baseline risk factors in adults with primary ITP.

## 2. Methods

We included nationwide data from France and Sweden on patients with primary ITP and performed a cohort study to estimate occurrences of AT and VTE. We also undertook an assessment of risk factors.

### 2.1. Data sources

In France, the national health system database *Système National des Données de Santé*, (SNDS) records linkable health information with virtual coverage of the entire French population (66 million inhabitants). It links information from the hospital database (named *Programme de médicalisation des systèmes des informations*), that contains notably inpatient discharge diagnoses in all public and private hospitals in France; and from the inter-scheme consumption (*Données de consommation inter-régimes* - DCIR) data set, that contains all outpatient reimbursed health expenditures, including community dispensing of reimbursed drugs, as well as chronic diseases allowing full reimbursement that are notified by general practitioners. Diagnoses are coded using the International Classification of Diseases, version 10 (ICD-10). An anonymous identifier is derived from the social security number of insured individuals and can be used for linkage between the registers in the database [13,14].

The Swedish National Patient Register (NPR) was founded in 1964, and from 1987 it includes nationwide data for all hospitalizations with recording covering details of hospitalizations such as date and duration of stays, hospital and department names, surgical procedures and discharge diagnoses with a main diagnosis and up to 30 contributory diagnoses (coded with the ICD, 7th–10th versions). The quality of the register is of high standard with almost complete coverage of inpatient care [15]. The coverage on information from outpatient care has increased over the years. The ICD-codes for several diseases have been validated using information from medical charts with a positive predictive value of 85–95% [16]. Information on dispensed drugs can be obtained from the Swedish Prescribed Drug Register (PDR). The register has been available and linkable to other registers in Sweden since July 2005. The PDR contains detailed information on filled prescriptions including product, quantity, dates of prescription and dispensing. The register has complete coverage of all prescribed and dispensed drugs [17,18]. Drugs given in hospital are not covered in the register. The unique personal identification number given to each Swedish resident at birth or immigration is used to link the different registers.

### 2.2. Identification of patients

In France, patients with a diagnosis of ITP from 2009 to 2015 were identified with the ICD-10 code D69.3 (immune thrombocytopenia). Adult patients ( $\geq 18$  years old) with incident primary ITP were identified using an algorithm combining diagnosis codes and drug exposures, which demonstrated high positive predictive values in identifying the date of ITP diagnosis, detailed elsewhere [19]. In Sweden, NPR was

used to identify adult patients with a diagnosis of incident primary ITP from 2009 to 2016 in out- or inpatient care using the ICD-10 code D69.3 (immune thrombocytopenia).

Patients with a D69.3 code at any discharge location were included. Other codes indicating that the thrombocytopenia was due to secondary ITP, such as systemic lupus erythematosus (within the year prior to the diagnosis of ITP or sixth months after), were used to exclude patients who did not have a primary ITP (Supplementary Table 1). We used splenectomy as an exclusion criteria and as a censoring variable because it has been identified as a major risk factor of VTE, both at the time of the surgery, and also after long-term follow up [9–12,20]. Consequently, because we aimed at assessing the impact of baseline risk factors without modification by intervention (demonstrated as linked to thrombosis like splenectomy) we used the surgical procedure code to exclude the follow-up time after splenectomy.

### 2.3. Risk factors for thrombosis

History of VTE and/or AT was searched for using discharge diagnoses in the register (Supplemental Table 3). Solid tumors, chronic kidney disease (stages 3–5), and liver disease were identified through ICD-10 codes for both in- and out patients. Mild, moderate and severe liver diseases were combined into one variable and considered as a single risk factor for VTE (Supplemental Table 4). Diabetes was identified through relevant ICD-codes or by dispensed antidiabetics. Drugs commonly used in the treatment of CVD, were considered as proxies for CVD. Accordingly, information on antiplatelet, antithrombotic, anti-hypertensive and lipid lowering drugs (AT only) and antiplatelet and antithrombotic drugs (VTE only) were included as time-varying covariates in the multivariable analyses. Only dispensations in the 6 months before the date of ITP diagnosis were considered. (Supplemental Table 4).

### 2.4. Outcome definition

Relevant ICD-10 codes for AT and VTE were searched for in the hospital databases among primary discharge diagnoses. The codes used are indicated in Supplementary Table 3. Only the first event of each type that occurred after the diagnosis of ITP were considered in the analyzes.

### 2.5. Ethical approvals

For the French data, authorizations for use were obtained from the *Institut des Données de Santé* in March 2012 (no. 40) and the *Commission Nationale de l'Informatique et des Libertés* in July 2012 (no. DE-2012-076). In Sweden, the Regional Ethics Committee at Karolinska Institutet and the National Board of Health and Welfare approved the study (Record no 2009/4:10, addendum 2009 1597–31/4 and 2017/53–32).

### 2.6. Statistical methods

The cumulative IR of AT and of VTE were calculated by dividing the number of thrombotic events with person-time in years from the date of diagnosis of ITP to time of censoring due to either an outcome (AT or VTE), splenectomy, death or end of follow up (December 31, 2015 France and December 31, 2016 Sweden). AT and VTE were analyzed separately. The cumulative IRs were first calculated in the overall ITP population in each country, and then by baseline risk factors. For the baseline risk factors: cancer, diabetes, chronic liver disease, kidney disease, exposure to antiplatelet, antithrombotic, antihypertensive or lipid lowering drugs, incidence rate ratios (IRR) were estimated. Patients with the risk factor at baseline were compared with patients who did not have the risk factor. In the sensitivity analysis the baseline risk factors were adjusted for age and sex.

We chose to carry out a cohort study adjusting for age, sex and other

relevant covariates [21]. In our main analysis we performed a time dependent Multivariable Cox counting process to estimate associations between risk factors of AT and VTE, respectively. All variables were adjusted for, including both time-varying covariates and fixed covariates. The follow-up time was from the date of diagnosis of ITP to the time of censoring, defined as above. The following covariates were considered as time-varying covariates: diabetes, renal disease, liver disease, cancer, and treatments associated with cardiovascular disease, such as antiplatelet drugs and antithrombotic drugs. Fixed covariates were age at ITP diagnosis (categorized in four categories: 18–39 years, 40–59, 60–74 and 75 or older), sex and previous AT and VTE events. We used the counting process approach to estimate hazard ratios (HR) and 95% confidence intervals (CI). The counting process approach is an extended version of Cox regression, which requires that data are split into several records (time intervals) for each patient, measuring time to event and taking all covariates into account [22]. The proportional hazard assumption was tested by plotting Kaplan-curves. SAS statistical software™ version 9.4 (SAS Institute, Cary, North Carolina, USA) was used to analyze the data.

### 3. Results

#### 3.1. Patient selection

The number of included adult patients with incident primary ITP in the study period was 7225 from France (2009–2015) and 2490 from Sweden (2009–2016). There were slightly more females in both countries: 4046 (56.0%) in France and 1270 (51.0%) in Sweden. Median age at diagnosis of ITP was 61 years in France with interquartile range (IQR) 39–76 and the corresponding figure in Sweden was 64 years (IQR) 39–77 (Table 1).

#### 3.2. Risk factors

##### 3.2.1. Incidence rates of arterial thrombosis by country, age, sex and type of diagnosis

The IR of AT for all included patients with primary ITP was 15.0 (95% CI 13.4–16.7 per 1000 person-years) in France and 14.7 (95% CI 12.4–17.5 per 1000 person-years) in Sweden (Table 1). In female patients, the IR was 8.4 (95% CI 6.9–10.1 per 1000 person-years) in France and 11.2 (95% CI 8.6–14.6 per 1000 person-years) in Sweden. The IR in male patients was 24.1 (95% CI 21.1–27.6 per 1000 person-years) in France and 19.0 (95% CI 15.2–23.7 per 1000 person-years) in Sweden.

There were 316 events of AT in France and 131 in Sweden, from those 68 (22%) and 40 (31%) were cerebral infarction (I63.0–I63.5,

I63.8, I63.9), 50 (16%) and 55 (42%) were acute myocardial infarction (I21.1, I21.2, I21.4, I21.9), 96 (30%) and 24 (18%) were angina pectoris (I20.0, I20.8, I20.9), 102 (32%) and 12 (9%) were other arterial events (I22.1, I22.9, I24.0, I24.8, I24.9, I74.2 I74.5, I74.8, I51.3, I25.5, I25.6, I65.2, I66.9), respectively. The median age at the time of the event was 73 years (IQR 64–82) in France and 214 (68%) of all patients with AT were male. The corresponding figures in Sweden were 81 years (IQR 73–87) and 77 (59%). In total, 171 (54%) of those with AT in France and 17 (13%) in Sweden had a comorbidity (cancer, diabetes or kidney disease) at the time of the event, 79 (25%) and 8 (6%) received antithrombotic drugs and 133 (42%) and 6 (5%) respectively received antiplatelet drugs. In addition, 76 (24%) in France and 32 (24%) in Sweden had a history of AT.

#### 3.3. Baseline risk factors for arterial thrombosis

IRs increased with age, and in France, those 60 years or older had an IR of 24.9 (95% CI 20.9–29.7 per 1000 person-years). For the Swedish cohort the IR was 16.1 (95% CI 11.8–22.0 per 1000 person-years), Table 2. The most prevalent risk factors of AT other than male sex and increasing age was a history of AT. A history of an AT at baseline yielded an IRR of 4.8 (95% CI 3.8–6.1) in France, and 2.6 (95% CI 1.8–3.8) in Sweden. A history of VTE at baseline yielded an IR three times higher in France IRR = 2.9 (95% CI 1.0–8.0) and four times higher in Sweden IRR = 4.3 (95% CI 1.9–9.5) than those without a history of VTE at baseline.

Those with a baseline risk factor such as any comorbidity or a drug for CVD had a higher IR of AT compared with not having the comorbidity or the CVD drug e.g. the cumulative incidence was higher in patients with diabetes at baseline compared to not having diabetes. The IR was 29.2 (95% CI 23.3–36.6 per 1000 person-years) for those with diabetes, and 13.0 (95% CI 11.4–14.7 per 1000 person-years) for those without diabetes in France. In Sweden, the IR was 36.7 (95% CI 26.2–51.4 per 1000 person-years) for those with diabetes and 12.2 (95% CI 10.0–14.9 per 1000 person-years) for those without diabetes. Patients who filled a prescription for drugs used for cardiovascular conditions, such as antiplatelet drugs had around four fold higher rates IRR = 4.4 (95% CI 3.5–5.5) in France and twofold in Sweden 2.2 (95% CI 1.3–3.8) compared with patients who did not (Table 2).

##### 3.3.1. Incidence rates of venous thromboembolism by country, age, sex and type of diagnoses

The IR of VTE was 6.9 (95% CI 5.9–8.1 per 1000 person-years) in France and 6.5 (95% CI 5.1–8.4 per 1000 person-years) in Sweden. The IR of VTE was similar in men and women in both countries (Table 1).

There were 148 events of VTE in France and 59 in Sweden, from

**Table 1**  
Characteristics of patients with primary immune thrombocytopenia (ITP) in Sweden and France.

	Sweden			France		
	Total	Male	Female	Total	Male	Female
Patients with primary ITP in study period N (%)	2490	1220 (49)	1270 (51)	7225	3199 (44)	4046 (56)
Age at ITP diagnosis						
Median	64	66	60	61	65	57
(IQR)	(39–77)	(49–78)	(34–76)	(39–76)	(47–78)	(35–75)
Mean	59	62	56	58	61	55
(SD)	(22)	(20)	(22)	(23)	(20)	(22)
Number of events						
Arterial <sup>a</sup>	131	77 (59)	54 (41)	316	214 (68)	102(32)
Venous <sup>b</sup>	59	30 (51)	29 (49)	148	65 (44)	83 (56)
Rate of AT	14.7	19.0	11.2	15.0	24.1	8.4
95% CI per 1000	(12.4–17.5)	(15.2–23.7)	(8.6–14.6)	(13.4–16.7)	(21.1–27.6)	(6.9–10.1)
Rate of VT	6.5	7.1	6.0	6.9	7.1	6.8
95% CI per 1000 patient-years	(5.1–8.4)	4.9–10.1	4.2–8.7	(5.9–8.1)	(5.6–9.1)	(5.5–8.4)

<sup>a</sup> I740 I741 I742 I743 I744 I745 I748 I749 I20 I21 I22 I24 I255 I256 I513 I630 I631 I632 I634 I635 I638 I639 I65 I66

<sup>b</sup> I800 I801 I802 I803 I808 I809 I81 I821 I822 I823 I828 I829 I260 I269 I636 I676 O22.

**Table 2**  
Arterial event rates, baseline variables.

		Sweden Censored on splenectomy, arterial event, death					France Censored on splenectomy, arterial event, death				
		Person-time (years)	Number of events	Rate	CI <sup>0</sup> low	CI high	Person-time (years)	Number of events	Rate	CI low	CI high
All		8898.9	131	14.7	12.4	17.5	21,083.1	316	15.0	13.4	16.7
Sex	Male	4064.4	77	19.0	15.2	23.7	8874.5	214	24.1	21.1	27.6
	Female	4737.7	54	11.2	8.6	14.6	12,208.6	102	8.4	6.9	10.1
Age group (years)	18–39	2649.8	2	0.8	0.2	3.0	5719.8	5	0.9	0.4	2.1
	40–59	1881.5	7	3.7	1.8	7.8	4775.9	42	8.8	6.5	11.9
	60–74	2422.4	39	16.1	11.81	22.0	5018.0	125	24.9	20.9	29.7
	≤75	1945.3	83	42.7	34.4	52.9	5569.4	144	25.9	22.0	30.4
Diabetes <sup>1</sup>	No	7972.9	97	12.2	10.0	14.9	18,483.3	240	13.0	11.4	14.7
	Yes	926.0	34	36.7	26.2	51.4	2599.8	76	29.2	23.3	36.6
Cardiovascular disease <sup>2</sup>	No	8874.2	128	14.4	12.1	17.2	19,426.2	221	11.4	10.0	13.0
	Yes	24.7	3	121.3	39.1	376.0	1656.9	95	57.3	46.9	70.1
Kidney disease <sup>3</sup>	No	8845.2	127	14.4	12.1	17.1	20,478.3	294	14.4	12.8	16.1
	Yes	53.7	4	74.5	28.0	198.5	604.7	22	36.4	24.0	55.3
Liver disease <sup>4</sup>	No	8821.5	127	14.4	12.1	17.1	20,374.9	306	15.0	13.4	16.8
	Yes	77.4	4	51.7	19.4	137.7	708.1	10	14.1	7.6	26.2
Cancer <sup>5</sup>	No	8332.0	119	14.3	11.9	17.1	19,534.0	282	14.4	12.8	16.2
	Yes	567.0	12	21.1	12.0	37.3	1549.1	34	21.9	15.7	30.7
History of AT <sup>6</sup>	No	8489.5	99	11.7	9.6	14.2	20,009.8	240	12.0	10.6	13.6
	Yes	409.2	32	78.2	55.3	110.6	1073.3	76	70.8	56.6	88.7
History of VTE <sup>7</sup>	No	8823.3	126	14.3	12.0	17.0	21,012.6	313	14.9	13.3	16.6
	Yes	75.6	5	66.1	27.5	158.9	70.4	3	42.6	13.7	132.1
<b>Co-medications</b>											
Antithrombotics <sup>8</sup>	No	8297.9	109	13.1	10.9	15.9	18,996.6	242	12.7	11.2	14.4
	Yes	601.0	22	36.6	24.1	55.6	2086.4	74	35.5	28.2	44.5
Antiplatelets <sup>9</sup>	No	8632.5	117	13.6	11.3	16.3	18,295.0	189	10.3	9.0	11.9
	Yes	266.4	14	52.6	31.1	88.7	2788.1	127	45.6	38.3	54.2
Antihypertensives <sup>10</sup>	No	6484.1	42	6.5	4.8	8.8	13,633.0	112	8.2	6.8	9.9
	Yes	2414.8	89	36.9	29.9	45.4	7450.1	204	27.4	23.9	31.4
Lipid lowering <sup>11</sup>	No	7327.0	76	10.4	8.3	13.0	16,709.3	178	10.7	9.2	12.3
	Yes	1571.9	55	35.0	26.9	45.6	4373.8	138	31.6	26.7	37.3

<sup>0</sup>CI = Confidence Interval. <sup>1</sup>E119 E10 E103-E105 E107 E112 E113-E117 E122 E123 E124 E125 E127 E132- E135 E137 E142-E145 E147 A10BA0 <sup>2</sup>I110 I130 I132 I50. <sup>3</sup>N183- N185

<sup>4</sup>B18 I850 I859 I864 I982 K700-K703 K704 K709 K711 K713 K715 K717 K721 K729 K73 K74 K760 K762-K764 K765 K766 K767 K768 K769 Z944.

<sup>5</sup>C00-C26 C30-C34 C37-41 C43 C45-C58 C60-C76 C81-C85 C88 C90-C97.

<sup>6</sup>I740 I741 I742 I743 I744 I745 I748 I749 I20 I21 I22 I24 I255 I256 I513 I630 I631 I632 I634 I635 I638 I639 I65 I66.

<sup>7</sup>B01A0 B01A1 B01A2 B01A3 B01A4 B01A5 B01A6 B01A7 B01A8 B01A9 B01AA B01AB B01AC B01AD B01AE B01AF B01AG B01AH B01AI B01AJ B01AK B01AL B01AM B01AN B01AO B01AP B01AQ B01AR B01AS B01AT B01AU B01AV B01AW B01AX B01AY B01AZ B01BA B01BB B01BC B01BD B01BE B01BF B01BG B01BH B01BI B01BJ B01BK B01BL B01BM B01BN B01BO B01BP B01BQ B01BR B01BS B01BT B01BU B01BV B01BW B01BX B01BY B01BZ B01CA B01CB B01CC B01CD B01CE B01CF B01CG B01CH B01CI B01CJ B01CK B01CL B01CM B01CN B01CO B01CP B01CQ B01CR B01CS B01CT B01CU B01CV B01CW B01CX B01CY B01CZ B01DA B01DB B01DC B01DD B01DE B01DF B01DG B01DH B01DI B01DJ B01DK B01DL B01DM B01DN B01DO B01DP B01DQ B01DR B01DS B01DT B01DU B01DV B01DW B01DX B01DY B01DZ B01EA B01EB B01EC B01ED B01EE B01EF B01EG B01EH B01EI B01EJ B01EK B01EL B01EM B01EN B01EO B01EP B01EQ B01ER B01ES B01ET B01EU B01EV B01EW B01EX B01EY B01EZ B01FA B01FB B01FC B01FD B01FE B01FF B01FG B01FH B01FI B01FJ B01FK B01FL B01FM B01FN B01FO B01FP B01FQ B01FR B01FS B01FT B01FU B01FV B01FW B01FX B01FY B01FZ B01GA B01GB B01GC B01GD B01GE B01GF B01GG B01GH B01GI B01GJ B01GK B01GL B01GM B01GN B01GO B01GP B01GQ B01GR B01GS B01GT B01GU B01GV B01GW B01GX B01GY B01GZ B01HA B01HB B01HC B01HD B01HE B01HF B01HG B01HH B01HI B01HJ B01HK B01HL B01HM B01HN B01HO B01HP B01HQ B01HR B01HS B01HT B01HU B01HV B01HW B01HX B01HY B01HZ B01IA B01IB B01IC B01ID B01IE B01IF B01IG B01IH B01IJ B01IK B01IL B01IM B01IN B01IO B01IP B01IQ B01IR B01IS B01IT B01IU B01IV B01IW B01IX B01IY B01IZ B01JA B01JB B01JC B01JD B01JE B01JF B01JG B01JH B01JI B01JJ B01JK B01JL B01JM B01JN B01JO B01JP B01JQ B01JR B01JS B01JT B01JU B01JV B01JW B01JX B01JY B01JZ B01KA B01KB B01KC B01KD B01KE B01KF B01KG B01KH B01KI B01KJ B01KK B01KL B01KM B01KN B01KO B01KP B01KQ B01KR B01KS B01KT B01KU B01KV B01KW B01KX B01KY B01KZ B01LA B01LB B01LC B01LD B01LE B01LF B01LG B01LH B01LI B01LJ B01LK B01LL B01LM B01LN B01LO B01LP B01LQ B01LR B01LS B01LT B01LU B01LV B01LW B01LX B01LY B01LZ B01MA B01MB B01MC B01MD B01ME B01MF B01MG B01MH B01MI B01MJ B01MK B01ML B01MN B01MO B01MP B01MQ B01MR B01MS B01MT B01MU B01MV B01MW B01MX B01MY B01MZ B01NA B01NB B01NC B01ND B01NE B01NF B01NG B01NH B01NI B01NJ B01NK B01NL B01NM B01NO B01NP B01NQ B01NR B01NS B01NT B01NU B01NV B01NW B01NX B01NY B01NZ B01OA B01OB B01OC B01OD B01OE B01OF B01OG B01OH B01OI B01OJ B01OK B01OL B01OM B01ON B01OO B01OP B01OQ B01OR B01OS B01OT B01OU B01OV B01OW B01OX B01OY B01OZ B01PA B01PB B01PC B01PD B01PE B01PF B01PG B01PH B01PI B01PJ B01PK B01PL B01PM B01PN B01PO B01PP B01PQ B01PR B01PS B01PT B01PU B01PV B01PW B01PX B01PY B01PZ B01QA B01QB B01QC B01QD B01QE B01QF B01QG B01QH B01QI B01QJ B01QK B01QL B01QM B01QN B01QO B01QP B01QQ B01QR B01QS B01QT B01QU B01QV B01QW B01QX B01QY B01QZ B01RA B01RB B01RC B01RD B01RE B01RF B01RG B01RH B01RI B01RJ B01RK B01RL B01RM B01RN B01RO B01RP B01RQ B01RR B01RS B01RT B01RU B01RV B01RW B01RX B01RY B01RZ B01SA B01SB B01SC B01SD B01SE B01SF B01SG B01SH B01SI B01SJ B01SK B01SL B01SM B01SN B01SO B01SP B01SQ B01SR B01SS B01ST B01SU B01SV B01SW B01SX B01SY B01SZ B01TA B01TB B01TC B01TD B01TE B01TF B01TG B01TH B01TI B01TJ B01TK B01TL B01TM B01TN B01TO B01TP B01TQ B01TR B01TS B01TT B01TU B01TV B01TW B01TX B01TY B01TZ B01UA B01UB B01UC B01UD B01UE B01UF B01UG B01UH B01UI B01UJ B01UK B01UL B01UM B01UN B01UO B01UP B01UQ B01UR B01US B01UT B01UU B01UV B01UW B01UX B01UY B01UZ B01VA B01VB B01VC B01VD B01VE B01VF B01VG B01VH B01VI B01VJ B01VK B01VL B01VM B01VN B01VO B01VP B01VQ B01VR B01VS B01VT B01VU B01VV B01VW B01VX B01VY B01VZ B01WA B01WB B01WC B01WD B01WE B01WF B01WG B01WH B01WI B01WJ B01WK B01WL B01WM B01WN B01WO B01WP B01WQ B01WR B01WS B01WT B01WU B01WV B01WW B01WX B01WY B01WZ B01XA B01XB B01XC B01XD B01XE B01XF B01XG B01XH B01XI B01XJ B01XK B01XL B01XM B01XN B01XO B01XP B01XQ B01XR B01XS B01XT B01XU B01XV B01XW B01XX B01XY B01XZ B01YA B01YB B01YC B01YD B01YE B01YF B01YG B01YH B01YI B01YJ B01YK B01YL B01YM B01YN B01YO B01YP B01YQ B01YR B01YS B01YT B01YU B01YV B01YW B01YX B01YY B01YZ B01ZA B01ZB B01ZC B01ZD B01ZE B01ZF B01ZG B01ZH B01ZI B01ZJ B01ZK B01ZL B01ZM B01ZN B01ZO B01ZP B01ZQ B01ZR B01ZS B01ZT B01ZU B01ZV B01ZW B01ZX B01ZY B01ZZ

<sup>10</sup>C02 C03 C07 C08C C08GA C09A C09B C09C C09D <sup>11</sup>C10AA C10B.

those 80 (54%) and 37 (63%) had pulmonary embolism (I26.9, I26.0), 55 (37%) and 14 (24%) had phlebitis and thrombophlebitis (I80.0-I80.3, I80.8, I80.9), 13 (9%) and 8 (13%) had other venous embolism and thrombosis (I82.2, I82.8, I82.9), portal venous thrombosis (I81, I81.9) or other cerebral venous thrombosis (I63.9 and I67.6), respectively. The median age at the time of the event was 72 (IQR 56–81) in France and 65 (44%) of all patients with VTE were male. The corresponding figures in Sweden were 78 years (IQR 69–83) and 30 (54%). In total 43 (29%) of those with VTE in France and 8 (14%) in Sweden had a comorbidity at baseline (cancer, diabetes, liver or kidney disease), 51 (34%) and 8 (14%) had a co-medication with antiplatelet or antithrombotic drugs. In addition, 2 (1%) in France and 8 (26%) in Sweden had a history of VTE.

### 3.4. Baseline risk factors for venous thromboembolism

The most prevalent risk factors were increasing age, a history of VTE, and cancer. In both countries the cumulative incidence was two-fold higher IR = 12.1(95% CI 7.7–19.0) in France, 12.3 (95% 5.9–25.7 CI in Sweden) in the presence of cancer at baseline compared with absence of cancer, for which the IRs were 6.5 (95% CI 5.5–7.7) and 6.1 (95% CI 4.7–8.0) respectively. All investigated baseline risk factors and drugs used as a proxy for CVD increased the risk of VTE when studied separately (Table 3.)

### 3.5. Sensitivity analysis

Stratifying by age and sex the estimates were imprecise, but indicated that higher age contributed to a higher IR. Male patients 60 years or older had a more than twofold higher IR for AT than females of the same age (Supplemental Table 1). For VTE, the IR for females and males 75 years or older were similar. There were no recordings of certain comorbidities and CVD drugs in the lowest age group, e.g. cancer and kidney diseases (Supplemental Table 2).

### 3.6. Cox multivariable analyses

In the multivariable Cox models, risk factors associated with an increased risk of AT were: age, in age-group 60–74 years, with an HR of 19.7 (95% CI 7.5–51.3) in France, and 23.4 (95% CI 5.5–101.2) in Sweden; a history of AT, in France the HR was 2.5 (95% CI 1.8–3.5) and in Sweden it was 3.1 (95% CI (2.0–5.0)). In France, exposure to antiplatelet drugs showed an increased risk, with an HR of 1.6 (95% CI 1.2–2.1) and in Sweden, a history of VTE showed an increased risk, with an HR of 2.6 (95% CI 1.1–6.5). In Sweden, chronic kidney disease was also shown to increase the risk of AT, with an HR of 2.6 (95% CI 1.2–6.0), Table 4.

For VTE, the risk factors were being above 60 years of age, in France the HR was 2.2 (95% CI 1.2–3.8) and in Sweden it was 5.6 (95% CI 1.6–19.8). In France, cancer was shown to increase the risk, with an HR

**Table 3**  
Venous event rates, baseline variables.

	Sweden Censored of splenectomy, venous event, death					France Censored of splenectomy, venous event, death				
	Person-time (years)	Number of events	Rate	CI <sup>3</sup> low	CI high	Person-time (years)	Number of events	Rate	CI low	CI high
All	9057	59	6.5	5.1	8.4	21,379.6	148	6.9	5.9	8.1
Sex										
Male	4243.2	30	7.1	4.9	10.1	9160.0	65	7.1	5.6	9.1
Female	4814.5	29	6.0	4.2	8.7	12,219.6	83	6.8	5.5	8.4
Age group (years)										
18–39	2649.8	3	1.1	0.4	3.5	5682.3	18	3.2	2.0	5.0
40–59	1891.8	6	3.2	1.4	7.1	4816.4	25	5.2	3.5	7.7
60–74	2496.5	16	6.4	3.9	10.5	5208.1	37	7.1	5.2	9.8
≤75	2019.6	34	16.8	12.0	23.6	5672.7	68	12.0	9.5	15.2
Diabetes <sup>1</sup>										
No	8076.9	47	5.8	4.4	7.7	18,664.2	128	6.9	5.8	8.2
Yes	980.9	12	12.2	7.0	21.5	2715.4	20	7.4	4.8	11.4
Cardiovascular disease <sup>2</sup>										
No	9031.4	59	6.5	5.1	8.4	19,563.9	125	6.4	5.4	7.6
Yes	26.3	0	–	–	–	1815.6	23	12.7	8.4	19.1
Kidney disease <sup>3</sup>										
No	900.8	58	6.4	5.0	8.3	20,478.3	294	14.4	12.8	16.1
Yes	57.0	1	17.5	2.5	124.5	604.7	22	36.4	24.0	55.3
Liver disease <sup>4</sup>										
No	8979.4	59	6.4	4.9	8.2	20,662.0	141	6.8	5.8	8.1
Yes	78.3	2	25.5	6.4	102.1	717.5	7	9.8	4.7	20.5
Cancer <sup>5</sup>										
No	8486.9	52	6.1	4.7	8.0	19,807.3	129	6.5	5.5	7.7
Yes	570.9	7	12.3	5.9	25.7	1572.3	19	12.1	7.7	19.0
History of VT <sup>6</sup>										
No	8990.7	51	5.7	4.3	7.5	20,166.4	137	6.8	5.8	8.0
Yes	67.1	8	119.3	59.6	238.5	1213.2	11	9.1	5.0	16.4
History of AT <sup>7</sup>										
No	8587.1	55	6.4	4.9	8.3	20,166.4	137	6.8	5.8	8.0
Yes	470.6	4	8.5	3.2	22.7	1213.2	11	9.1	5.02	16.4
<b>Co-medications</b>										
Antithrombotics <sup>8</sup>										
No	8439.1	47	5.6	4.2	7.4	19,231.5	115	6.0	5.0	7.2
Yes	618.7	12	19.4	10.0	34.2	2148.1	33	15.4	10.9	21.6
Antiplatelets <sup>9</sup>										
No	8780.9	54	6.2	4.7	8.0	18,359.6	122	6.6	5.6	7.9
Yes	276.8	5	18.1	7.5	43.4	3020.0	26	8.6	5.9	12.6
Antihypertensives <sup>10</sup>										
No	6529.9	38	5.8	4.2	8.0	13,680.4	77	5.6	4.5	7.0
Yes	2527.8	21	8.3	5.4	12.7	7699.1	71	9.2	7.3	11.6
Lipid lowering <sup>11</sup>										
No	7407.0	45	6.1	4.5	8.1	16,809.7	101	6.0	4.9	7.3
Yes	1650.8	14	8.5	5.0	14.3	4569.9	47	10.3	7.7	13.7

<sup>0</sup>CI = Confidence Interval <sup>1</sup>E119 E10 E103-E105 E107 E112 E113-E117 E122 E123 E124 E125 E127 E132- E135 E137 E142-E145 E147 A10BA0 <sup>2</sup>I110 I130 I132 I50. <sup>3</sup>N183- N185.

<sup>4</sup>B18 I850 I859 I864 I982 K700-K703 K704 K709 K711 K713 K715 K717 K721 K729 K73 K74 K760 K762-K764 K765 K766 K767 K768 K769 Z944.

<sup>5</sup>C00-C26 C30-C34 C37-41 C43 C45-C58 C60-C76 C81-C85 C88 C90-C97

<sup>6</sup>I740 I741 I742 I743 I744 I745 I748 I749 I20 I21 I22 I24 I255 I256 I513 I630 I631 I632 I634 I635 I638 I639 I65 I66

<sup>7</sup>I800I801 I802 I803 I808 I809 I81 I821 I822 I823 I828 I829 I260 I269 I636 I676 O22

<sup>8</sup>B01AA B01AB B01AE B01AF B01AX

<sup>9</sup>B01AA B01AB B01AE B01AF B01AX

<sup>10</sup>B01AC.

<sup>11</sup>C02 C03 C07 C08C C08GA C09A C09B C09C C09D <sup>11</sup>C10AA C10B.

of 1.8 (95% CI 1.2–2.7). In Sweden a history of VTE increased the risk, with an HR of 13.5 (95% CI 5.5–33.4), [Table 5](#).

## 4. Discussion

### 4.1. Incidence rates of thrombosis in ITP patients

We observed similar IRs of AT and VTE in France and Sweden in adult patients with primary ITP. The IR of AT was higher than the IR of VTE. The IR of both AT and VTE in our study are consistent with findings reported from other countries. The rates of both AT and VTE are higher than those reported for the general population. A Scandinavian study reported an IR of 16.0 for AT patients with chronic ITP and an IR of 8.8 for the general population [23]. A meta-analysis of observational studies from both Europe and the US (all stages of ITP were included) reported the IR of AT to be in the range of 10.0–28.0 in patients with ITP and 7.0–18.0 in populations without ITP. For VTE the meta-analysis reported an IR of 4.0–7.0 in patients with ITP, and 1.0–4.0 in populations without ITP [24]. The Scandinavian study reported the IR for VTE in chronic ITP to be 9.0 [23] and for the general population without ITP to be 2.8. In a study from the USA the HR of a VTE event was 7.7 per 1000 person-years relative to an HR of 1.9 per 1000 person-years for those without ITP [25].

The clinical relevance of our findings, in the light of these other studies, is the increased risk of AT and VTE in patients with ITP, the similar rates in France and Sweden strengthen this finding. Treating patients with ITP can be complex since they have both a risk of bleeding and of thrombosis, this is especially important in patients with anticoagulation, and in an elderly population it is extremely relevant.

### 4.2. Comorbidities and medications for cardiovascular disease at baseline

We confirmed that having a cardiovascular disease, when diagnosed with ITP, is associated with an increased risk of both arterial and venous thrombosis and that an increased risk of AT was associated with high age, male sex and a previous AT in both countries. Among French patients with ITP, the exposure to antiplatelet drugs, a proxy for baseline CVD, was also associated with AT occurrence. In addition, among the Swedish patients with an ITP diagnosis, a previous venous thrombosis and chronic kidney disease diagnosis increased the risk. Increasing age was associated with VTE in both countries, as well as cancer in France. Cancer is a heterogeneous disease and the slightly higher risk in France may be linked to the fact that some cancers vary in incidence from country to country [26]. It could also be due to the larger population in France, relative to Sweden, meaning there is additional power to detect an association. Using the multivariable model

**Table 4**  
Hazard ratio with confidence interval (CI) for the association between potential risk factors and arterial thrombosis.

Variables	Sweden				France			
	Person-time years	Events	Univariate 95% CI	Multivariable 95% CI	Person-time years	Events	Univariate 95% CI	Multivariable 95% CI
<b>Overall</b>	30,452	131	NA	NA	21,083	316	NA	NA
Male	14,648	77	Reference	Reference	8875	214	Reference	Reference
Female	15,472	53	0.6 (0.4–0.8)	0.7 (0.5–1.0)	12,209	102	0.35 (0.28–0.45)	0.5 (0.4–0.7)
<b>Age at diagnosis of ITP</b>								
18–39	7014	2	Reference	Reference	5720	5	Reference	Reference
40–59	6375	7	5.8 (1.2–28.5)	6.2 (1.3–30.6)	4776	42	9.9 (3.9–25.0)	8.4 (3.2–22.2)
60–74	9595	39	25.1 (6.0–105.0)	23.4 (5.5–101.2)	5018	125	27.8 (11.4–67.8)	19.7 (7.5–51.3)
≥75	7468	83	75.4 (18.1–314.4)	67.2 (15.7–287.8)	5569	144	28.5 (11.7–69.5)	18.6 (7.1–48.7)
Diabetes <sup>1</sup>	1090	6	1.6 (0.7–3.7)	1.0 (0.4–2.2)	3323	88	2.3 (1.8–2.9)	1.3 (1.0–1.7)
Kidney disease <sup>2</sup>	652	7	3.9 (1.8–8.4)	2.6 (1.2–6.0)	1776	39	2.3 (1.6–3.1)	1.2 (0.9–1.7)
Cancer <sup>3</sup>	2014	4	0.6 (0.2–1.6)	0.3 (0.1–0.8)	2916	44	1.3 (0.9–1.8)	0.8 (0.5–1.0)
History of AT <sup>4</sup>	1563	32	7.1 (4.7–10.7)	3.1 (2.0–5.0)	1073	76	5.6 (4.3–7.3)	2.5 (1.8–3.5)
History of VTE <sup>5</sup>	301	5	4.9 (2.1–11.7)	2.6 (1.1–6.5)	70	3	2.9 (0.9–8.9)	1.8 (0.5–6.4)
Antithrombotics <sup>6</sup>	3118	8	0.6 (0.3–1.2)	0.5 (0.2–0.9)	4855	79	0.7 (0.5–1.1)	0.9 (0.6–1.1)
Antiplatelets <sup>7</sup>	1420	6	1.0 (0.5–2.3)	1.4 (0.6–3.2)	3773	133	2.5 (1.8–3.5)	1.6 (1.2–2.1)
Antihypertensive <sup>8</sup>	2899	8	0.7 (0.3–1.4)	0.7 (0.4–1.4)	10,328	215	1.3 (0.9–1.9)	0.9 (0.7–1.1)
Lipid lowering <sup>9</sup>	1301	3	0.5 (0.2–1.7)	0.4 (0.1–1.4)	5155	137	1.7(1.3–2.4)	1.0 (0.7–1.3)

<sup>1</sup>E119 E10 E103-E105 E107 E112 E113-E117 E122 E123 E124 E125 E127 E132- E135 E137 E142-E145 E147 A10BA02.

<sup>2</sup>N183- N185.

<sup>3</sup>C00-C26 C30-C34 C37–41 C43 C45-C58 C60-C76 C81-C85 C88 C90-C97.

<sup>4</sup>I740 I741 I742 I743 I744 I745 I748 I749 I20 I21 I22 I24 I255 I256 I513 I630 I631 I632 I634 I635 I638 I639 I65 I66.

<sup>5</sup>I800 I801 I802 I803 I808 I809 I81 I821 1822 1823 1828 1829 I260 1269 I636 I676 O22.

<sup>6</sup>B01AA B01AB B01AE B01AF B01AX.

<sup>7</sup>B01AC.

<sup>8</sup>C02 C03 C07 C08C C08GA C09A C09B C09C C09D.

<sup>9</sup>C10AA C10B.

**Table 5**  
Hazard ratio with confidence interval (CI) for the association between potential risk factors and venous thromboembolism.

Variables	Sweden				France			
	Person-time years	Events	Univariate 95% CI	Multivariable 95% CI	Person-time years	Events	Univariate 95% CI	Multivariable 95% CI
<b>Overall</b>	31,613	59	NA	NA	21,380	148	NA	NA
Male	15,510	30	Reference	Reference	9160	65	Reference	Reference
Female	16,103	29	0.8 (0.5–1.4)	0.9 (0.5–1.6)	12,220	83	1.0 (0.7–1.4)	1.2 (0.9–1.7)
<b>Age at diagnosis of ITP</b>								
18–39	7024	3	Reference	Reference	5682	18	Reference	Reference
40–59	6437	6	2.8 (0.7–11.4)	2.5 (0.6–10.4)	4816	25	1.6 (0.9–2.9)	1.9 (1.1–3.4)
60–74	10,029	16	5.7 (1.6–19.7)	5.6 (1.6–19.8)	5208	37	2.2 (1.2–3.8)	2.3 (1.3–4.0)
≥75	8124	34	16.1 (4.9–52.7)	15.0 (4.2–54.0)	5673	68	3.6 (2.1–6.1)	3.5 (2.1–6.0)
Diabetes <sup>1</sup>	1168	2	1.2 (0.3–4.8)	0.8 (0.2–3.2)	3485	25	1.3 (0.9–2.0)	1.0 (0.7–1.5)
Kidney disease <sup>2</sup>	793	–	–	–	1859	15	1.9 (1.2–3.2)	1.5 (0.9–2.5)
Liver Disease <sup>3</sup>	874	3	2.1 (0.7–6.4)	2.3 (0.7–7.3)	1412	11	1.5 (0.8–2.7)	1.3 (0.7–2.4)
Cancer <sup>4</sup>	2014	3	1.0 (0.3–3.1)	0.6 (0.2–2.0)	2989	27	2.2 (1.5–3.2)	1.8 (1.2–2.7)
History of AT <sup>5</sup>	1921	4	1.4 (0.5–3.9)	0.9 (0.3–2.4)	1213	11	1.3 (0.7–2.4)	0.9 (0.5–1.7)
History of VT <sup>6</sup>	236	8	21.1 (9.5–46.7)	13.5 (5.5–33.4)	70	2	4.3 (1.1–17.3)	3.5 (0.8–14.2)
Antithrombotics <sup>7</sup>	3292	7	1.2 (0.6–2.6)	1.6 (0.6–4.56)	4795	27	0.5 (0.2–0.9)	0.6 (0.4–1.0)
Antiplatelets <sup>8</sup>	1798	2	0.6 (0.2–2.6)	0.3 (0.1–2.0)	4318	32	0.7 (0.4–1.2)	1.0 (0.7–1.4)

<sup>1</sup>E119 E10 E103-E105 E107 E112 E113-E117 E122 E123 E124 E125 E127 E132- E135 E137 E142-E145 E147 A10BA02.

<sup>2</sup>N183–N185.

<sup>3</sup>B18 I850 I859 I864 I982 K700-K703 K704 K709 K711 K713 K715 K717 K721 K729 K73 K74 K760 K762-K764 K765 K766 K767 K768 K769 Z944.

<sup>4</sup>C00-C26 C30-C34 C37–41 C43 C45-C58 C60-C76 C81-C85 C88 C90-C97.

<sup>5</sup>I740 I741 I742 I743 I744 I745 I748 I749 I20 I21 I22 I24 I255 I256 I513 I630 I631 I632 I634 I635 I638 I639 I65 I66.

<sup>6</sup>I800 I801 I802 I803 I808 I809 I81 I821 1822 1823 1828 1829 I260 1269 I636 I676 O22.

<sup>7</sup>B01AA B01AB B01AE B01AF B01AX.

<sup>8</sup>B01AC.

where confounders can be simultaneously adjusted for, even though some residual confounding might remain, we confirmed that increasing age and a history of VTE are two important risk factors of VTE. The incidence of ITP increases with age, the median age at diagnosis is 61 years (IQR 39–76) in France and 64 years (IQR 39–77) in Sweden.

**4.3. In comparison to other studies**

Other studies which have investigated CVD in patients with ITP have produced similar results to those found in this study. Chandan et al. found an IRR of 1.4 (95% CI 1.23–1.55) of CVD in patients with incident ITP compared to a comparison cohort without ITP for

conditions such as hypertension, diabetes, use of lipid lowering drugs and antiplatelet drugs [5]. Moulis et al. previously reported data from the clinical CARMEN registry where they found that CVDs are frequent in patients with ITP at the time of ITP diagnosis; 75.3% had at least one CVD risk factor and among them 13.9% had diabetes, 18% had antiplatelet drugs and 39.2% had antihypertensive drugs [27]. Enger et al. found an increased IRR of diabetes and CVD (IRR = 1.7), and kidney failure (IRR = 2.0) in patients with persistent or chronic ITP compared to a comparison cohort without ITP from a US claims database [28]. A multicenter study from the Netherlands also reported an increased risk of AT and VTE in patients with kidney disease [29]. The association between cancer and VTE found in our study is in line with the results of other studies [30–32]. The risk of a recurrent VTE is well documented [33,34] and an increased risk was found in both the French and the Swedish cohorts, with the strongest association found in the latter. There is a known risk of recurrent arterial events after a first arterial thrombosis. In our study, patients with a history of an arterial thrombosis did have an increased risk of recurrent arterial thrombosis. A history of a venous thrombosis also increases the risk of an arterial event [35,36]. VTE and AT shared common risk factors such as high age and diabetes [37–39].

The findings of this study and previously published studies on risk of thrombosis in ITP patients suggest that the patients have increased risk of both bleeding and thromboembolic events. Although the mechanisms behind the risk of thromboembolic events in patients with ITP are to a large extent unknown, it is clear that a low platelet count does not protect against thrombosis [6,40]. In a recent study, Balitsky et al. proposed a “Thrombosis and Thrombocytopenia risk assessment score” to summarize the net risk of thrombosis and bleeding in patients with ITP, which can help clinicians with decision making when the patients have indication for treatment with anticoagulation. The study highlighted the importance of comorbidities, when considering risk of bleeding and thrombosis, in line with the findings of our study [40].

#### 4.4. What this study adds and future studies needed

With data from two national databases we reported IRs for both AT and VTE which were higher in patients with ITP compared with IRs for the general populations. The results from this study confirms certain risk factors of thrombosis, including increasing age and male sex for AT. This has applications especially when treating the elderly and in patients with many comorbidities.

#### 4.5. Strengths

Since the SNDS and the Swedish Health Registers have national coverage, the risk of selection bias should be a minor issue. Hospital visits and prescribed drugs dispensed from pharmacies are obliged to be registered in Sweden, and in France the reimbursement system covers the entire French population. To our knowledge this is the largest ITP study population analyzed using the same methods on harmonized data sets, including 7225 incident patients with ITP from France and 2490 from Sweden. With such a large dataset we were able to use multivariable models to adjust for important covariates yielding less biased estimates.

There is also good consistency between data from France and Sweden. Both databases contain ICD-10 codes to detect hospital diagnoses and ATC-codes for drugs, and cover the same type of hospital visits and dispensed drugs. The quality of the data is good in both countries: in the French database the codes for ITP have been validated with the most recently reported PPV being 96% [41] [19], The outcomes are also validated separately with medical chart review, with a PPV of 83–99% [42,43]. In Sweden there is an overall PPV of 85–95% for myocardial infarction and stroke where the codes have been validated separately with medical chart review [16]. Including data from separate countries increases the external validity of the study, and the

detailed information about patient characteristics to analyze the impact of various risk factors is beneficial. There are consistent results between the two countries and the results are also consistent with clinical data.

#### 4.6. Limitations

There were some unmeasured confounders and potential risk factors, which we were not able to measure in this study. Examples are information about known platelet counts, genetic risk factors for AT and VTE, and immobilization (a risk factor for VTE), smoking, and BMI (risk factors for both VTE and AT). Moreover, we adjusted for anti-hypertensive drugs, lipid lowering drugs and other drugs related to cardiovascular disease. Lack of laboratory data at the time of the event is also an important limitation. However, the focus of this study was to investigate the impact of baseline risk factors in a cohort of ITP patients. Primary ITP is a diagnosis of exclusion and some patients may be misdiagnosed, for example with myelodysplastic syndrome. However, in both France and Sweden, the diagnosis is given after an extensive list of exclusion criteria to rule out other causes of the thrombocytopenia and validation studies showed that a high proportion of records were the correct diagnosis [16,19]. > 30% of the patients do not require any treatment for their ITP [44]. According to a validation study from France > 95% of the patients with incident ITP had a hospital code of D69.3 at diagnosis [19] [45].

#### 5. Conclusion

For patients with primary ITP, the IR of AT and of VTE were of similar magnitude in France and in Sweden, and for both AT and VTE the risk was almost two times higher relative to a comparison population of similar age. As in the general population, the rate of AT was higher than that of VTE. Using multivariable methods to adjust for several risk factors simultaneously, age and male sex remained as the most important risk factors for AT and age for VTE. When treating patients with ITP, the occurrence of risk factors associated with the disease and with thrombosis, should be acknowledged.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.thromres.2019.04.016>.

#### Statement of conflict of interest

Charlotta Ekstrand, Shahram Bahmanyar, Helle Kieler and Marie Linder are employed at the Centre for Pharmacoepidemiology, which receive grants from several entities (pharmaceutical companies, regulatory authorities and contract research organizations) for performance of drug safety and drug utilization studies. None of them were involved in this study at any stage of the process.

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