Thromboembolic events among adult patients with primary immune thrombocytopenia in the United Kingdom General Practice Research Database

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Funding: this work was sponsored by GlaxoSmithKline.

Acknowledgments: the authors would like to thank Nydjie Payas for assistance in formatting the manuscript, Dr. George Quartey for helping to test the proportional hazards assumption, and the Medicines and Healthcare products Regulatory Agency for providing access to the General Practice Research Database. A. Sarpatwari is a PhD candidate at the University of Cambridge, and this work is submitted in partial fulfilment of the requirement for the PhD.

Manuscript received on October 12, 2009. Revised version arrived on January 6, 2010. Manuscript accepted on January 7, 2010.

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ABSTRACT

Background

The risk of thromboembolic events in adults with primary immune thrombocytopenia has been little investigated despite findings of increased susceptibility in other thrombocytopenic autoimmune conditions. The objective of this study was to evaluate the risk of thromboembolic events among adult patients with and without primary immune thrombocytopenia in the UK General Practice Research Database.

Design and Methods

Using the General Practice Research Database, 1,070 adults (≥18 years) with coded records for primary immune thrombocytopenia first referenced between January 1st 1992 and November 30th 2007, and having at least one year pre-diagnosis and three months post-diagnosis medical history were matched (1:4 ratio) with 4,280 primary immune thrombocytopenia disease free patients by age, gender, primary care practice, and pre-diagnosis observation time. The baseline prevalence and incidence rate of thromboembolic events were quantified, with comparative risk modelled by Cox's proportional hazards regression.

Results

Over a median 47.6 months of follow-up (range: 3.0-192.5 months), adjusted hazard ratios of 1.58 (95% CI, 1.01-2.48), 1.37 (95% CI, 0.94-2.00), and 1.41 (95% CI, 1.04-1.91) were found for venous, arterial, and combined (arterial and venous) thromboembolic events, respectively, when comparing the primary immune thrombocytopenia cohort with the primary immune thrombocytopenia disease free cohort. Further event categorization revealed an elevated incidence rate for each occurring venous thromboembolic subtype among the adult patients with primary immune thrombocytopenia.

Conclusions

Patients with primary immune thrombocytopenia are at increased risk for venous thromboembolic events compared with patients without primary immune thrombocytopenia.

Key words: primary immune thrombocytopenia, General Practice Research Database, thromboembolic events.

Citation: Sarpatwari A, Bennett D, Logie JW, Shukla A, Beach KJ, Newland AC, Sanderson S, and Provan D. Thromboembolic events among adult patients with primary immune thrombocytopenia in the United Kingdom General Practice Research Database. Haematologica 2010;95:1167-1175. doi:10.3324/haematol.2009.018390

Introduction

Primary immune thrombocytopenia (ITP) is an autoimmune disorder characterized by decreased platelet count (<150×10^9/L) resulting from autoantibody-mediated, peripheral platelet destruction and suboptimal platelet production.[1-5] It is a condition of imprecise etiology and, as such, can only be diagnosed by a thorough, exclusionary evaluation.[6] Among children, primary immune thrombocytopenia is commonly acute (< 6 months) in duration, whereas in adults (18 ≥ years) it is usually chronic, increasing susceptibility to major bleeding events and more commonly to bruising and petechiae.[7]

Literature on the descriptive epidemiology of primary immune thrombocytopenia is limited; a systematic review on autoimmune diseases conducted by Jacobsen *et al.* in 1997 found no population-based studies on primary immune thrombocytopenia in the medical literature.[8] Four such studies have since been conducted and published; two in the United Kingdom (UK),[9-10] one in the United States,[11] and one in Denmark;[12] revealing an annual incidence of 1.6 to 3.2 cases per 100,000 adults. The investigations document an increased incidence of primary immune thrombocytopenia among the elderly and a moderate female preponderance noted to dissipate with age.[9-10,12]

Although heterogeneous, the phenotype of primary immune thrombocytopenia in adults is generally mild, with approximately one-fourth of patients presenting asymptomatically.[9,12] Retrospective cohort studies with long-term follow-up, moreover, illustrate only a moderate risk of major bleeding events, occurring primarily among patients with platelet counts below 10×10^9/L. Portielje *et al.*, for example, reported no bleeding complications in individuals with moderate thrombocytopenia (> 30×10^9/L) when assessing 152 consecutive adult patients with primary immune thrombocytopenia over a median 10.5 year period.[13] Further data collected by Neylon *et al.* over a 5-year median follow-up of 245 adults with primary immune thrombocytopenia, revealed a 1.6% cumulative incidence of fatal hemorrhage.[9]

While efforts to understand disease progression in adult patients with primary immune thrombocytopenia have naturally centered on site-specific hemorrhagic risk, further investigation into thromboembolic susceptibility is warranted. Elevated rates of both types of thromboembolic events have been well documented in a series of autoimmune diseases, including thrombocytopenic conditions like thrombotic thrombocytopenic purpura (TTP)[14] and systemic lupus erythematosus (SLE).[15] A retrospective study conducted by Aledort *et al.* suggests that a heightened risk may be present in primary immune thrombocytopenia. Among a multi-center cohort of 186 adults, a total of 18 thromboembolic events were recorded in 10 patients, of which 11 thromboembolic events (61.1%) occurred following the diagnosis of primary immune thrombocytopenia.[16] More recently, using administrative claims from a large health plan affiliated with the company i3 Drug Safety in the United States, Bennett *et al.* reported a 6.9% cumulative incidence of thromboembolic events among adult patients with chronic, primary immune thrombocytopenia over a median 15-month follow-up period.[17]

Knowledge of an association between primary immune thrombocytopenia in adults and thromboembolic events, were it to exist, would likely influence long-term management paradigms. The objective of this study was to evaluate the risk of thromboembolic events among adult patients with and without primary immune thrombocytopenia in the UK General Practice Research Database (GPRD), described below.

Design and Methods

The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) of the General Practice Research Database for the UK Medicines and Healthcare Products Regulatory Agency (MHRA). The study was a retrospective cohort study.

Data from the General Practice Research Database are drawn from the computer systems of a representative sample of general practices throughout the UK[18] and currently include information regarding diagnoses, prescriptions, referrals, outcomes and laboratory results, together with basic demographic information for approximately 6.4 million patients from over 480 centers. The database is population-based and representative of the age, sex and geographical regions of the UK.[18] Inclusion is based on registration with a contributing general practice, rather than consultations, and there is no requirement that patients be actively receiving treatment. Data are stored using Oxford Medical Information System (OXMIS) or Read codes for diseases that are cross-referenced to the International Classification of Diseases (ICD-9);[19] with OXMIS usage primarily restricted to the period prior to the introduction of Read codes in 1997. The quality of entered data is continuously monitored by the Medicines and Healthcare products Regulatory Agency, with practices failing to adhere to established standards excluded from participation. General Practice Research Database coding has been subject to a number of validation studies, which have found it an accurate identification tool for a wide spectrum of conditions and diseases.[10,20-21]

Data were collected for adult patients (age ≥18 years) with OXMIS or Read codes for primary immune thrombocytopenia first referenced between January 1st 1992 and November 30th 2007 in the General Practice Research Database. Utilized codes (Read: 288599, D313000, D313012, 42P2.11 and OXMIS: 2871C) were determined by the study team, which included a physician with extensive experience managing adult patients with primary immune thrombocytopenia in the UK National Health Service (NHS), and have recently been validated for diagnosis of cases of primary immune thrombocytopenia in a study by Schoonen *et al.* as having a high positive predictive value.[10] Inclusion within the primary immune thrombocytopenia cohort was restricted to code-identified patients with at least one year pre-diagnosis and three months post-diagnosis medical history. These criteria were applied to ensure sufficient information was available to determine a patient's baseline medical status and provide a minimum period of post immune thrombocytopenia follow-up. To define thrombocytopenia, a commonly utilized threshold of less than 150×10^9/L was selected a priori during protocol development in 2007, prior to publication of new consensus terminology recommendations published by Rodeghiero *et al.*[22] in 2009.

For comparative purposes, a non-case cohort was assembled and consisted of primary immune thrombocytopenia disease free adult patients from the General Practice Research Database matched at a ratio of 1:4 by age (five-year bands), gender, primary care practice, and pre-index observation time (one, two, three and four years). Date of entry into the primary immune thrombocytopenia cohort (index date) was defined as the date of diagnosis, and index dates for the primary immune thrombocytopenia dis-

ease free cohort were taken from their matched counterparts.

The outcome of interest was thromboembolic events, grouped as venous, arterial, and combined (venous or arterial) thromboembolic events. Events were identified using OXMIS/Read codes and sub-grouped by deep vein thrombosis (DVT), pulmonary embolism (PE), portal vein thrombosis (PVT), other venous thromboembolic events, myocardial infarction (MI), unstable angina (UA), ischemic stroke (IS), transient ischemic attack (TIA), other arterial thromboembolic events, and unclassifiable thromboembolic events.

Primary immune thrombocytopenia status comprised the principal exposure in the study. Additional covariates included immune thrombocytopenia treatment (oral corticosteroid usage, intravenous immunoglobulin [IVIg] treatment, and splenectomy status), age (grouped as 18-39, 40-49, 50-59, 60-69, 70-79, 80-89 and ≥90 years), gender, and baseline co-morbid status (hypertension, diabetes, chronic renal failure, and prior thromboembolic events).

Follow-up time for each patient extended from the date of cohort entry until censoring, disenrollment from the database (by the patient or contributing primary care practice), death, or end of the study period (December 31st 2007). Censoring took place at the time of first event occurrence (i.e. patients with a prior history of arterial but not venous thromboembolic events were excluded from arterial thromboembolic events and combined thromboembolic events rate analyses, although they were considered in analyses of venous events alone). Thus, only true incidences of thromboembolic events were assessed.

Statistical analyses

Incidence and Cox's survival analyses were based upon the follow-up time detailed above. For analyses of prevalence and cumulative incidence, thromboembolic events were counted over discrete, post-index intervals of 1-90 days, 91-180 days, 181-360 days, 361 days to 2.5 years, and greater than 2.5 years. Incidence rates for venous, arterial, and combined events were reported within these intervals, with cumulative incidence estimates compiled over post-index periods of 180 days, 360 days, and 2.5 years.

Following inspection of logarithmic graphs of cumulative survival to verify the assumption of proportional hazards between the cohorts, unadjusted and adjusted (covariates: immune thrombocytopenia treatment and co-morbid conditions) hazard ratios

Table 1. Baseline characteristics of the primary ITP and primary ITP-disease free cohorts.

Description	Primary ITP cohort	Primary ITP-disease free cohort	*P* value Unmatched variables
All patients	1,070 (100%)	4,280 (100%)	
Gender and age (years)			
Female	620 (57.9%)	2,480 (57.9%)	
18-39	179 (16.7%)	716 (16.7%)	
40-49	73 (6.8%)	292 (6.8%)	
50-59	97 (9.1%)	388 (9.1%)	
60-69	93 (8.7%)	372 (8.7%)	
70-79	101 (9.2%)	404 (9.2%)	
80-89	70 (6.5%)	280 (6.5%)	
≥90	7 (0.7%)	28 (0.7%)	
Male	450 (42.1%)	1,800 (42.1%)	
18-39	81 (7.6%)	324 (7.6%)	
40-49	58 (5.4%)	232 (5.4%)	
50-59	68 (6.4%)	272 (6.4%)	
60-69	72 (6.7%)	288 (6.7%)	
70-79	120 (11.2%)	480 (11.2%)	
80-89	45 (4.2%)	180 (4.2%)	
≥90 yrs	6 (0.6%)	24 (0.6%)	
Co-morbid conditions			
Hypertension	297 (27.8%)	1,110 (25.9%)	0.226
Diabetes	100 (9.3%)	231 (5.4%)	< 0.001
Chronic renal failure	30 (2.8%)	56 (1.3%)	< 0.001
Platelet count (x10^9/L)			
< 50	173 (16.2%)	1 (0.0%)	
50-75	136 (12.7%)	0 (0%)	< 0.001
75-150	246 (23.0%)	34 (0.8%)	
No data available	376 (35.1%)	3,152 (73.6%)	
ITP-specific treatment			
Pre-Index, past year oral corticosteroid use	200 (18.7%)	180 (4.2%)	< 0.001
Pre-Index, past year IVIg use	0 (0%)	1 (~0.0%)	0.617
Pre-Index, splenectomy	25 (2.3%)	3 (0.1%)	< 0.001
Thromboembolic event (TE) history			
Venous TE	64 (6.0%)	198 (4.6%)	0.066
Arterial TE	105 (9.8%)	280 (6.5%)	< 0.001
Combined (Venous & Arterial) TE	165 (15.4%)	453 (10.6%)	< 0.001

(HRs) of venous, arterial, and combined thromboembolic events were modelled with SAS 9.1.3 (Cary, North Carolina) using Cox's regression.

To explore the relationship between the severity of thrombocytopenia and thromboembolic events, subgroup analyses were planned of the incidence rate ratio of thromboembolic events among primary immune thrombocytopenia cohort patients with baseline platelet counts of: 1) less than 50×10^9/L; 2) 50-75×10^9/L; and 3) 75-150×10^9/L relative to the primary immune thrombocytopenia disease free cohort.

Results

Baseline characteristics of the primary immune thrombocytopenia and primary immune thrombocytopenia disease free cohorts are illustrated in Table 1. Briefly, 1,070 and 4,280 adult patients with and without primary immune thrombocytopenia were identified, respectively, and followed for a median of 47.6 months (range: 3.0-192.5 months). The female:male ratio of primary immune thrombocytopenia patients was 1.4:1. Platelet count data were available for 694 (64.9%) patients with the primary immune thrombocytopenia.

Differences in the prevalence of several co-morbidities at baseline were noted between adult patients with and without primary immune thrombocytopenia, including diabetes (100 [9.3%] *vs.* 231 [5.4%], $P<0.001$), chronic renal failure (30 [2.8%] *vs.* 56 [1.3%], $P<0.001$), previous venous thromboembolic events (64 [6.0%] *vs.* 198 [4.6%], $P=0.066$), and previous arterial thromboembolic events (105 [9.8%] *vs.* 280 [6.5%], $P<0.001$).

Oral corticosteroid usage within a one-year period prior to study entry was noted in 200 (18.7%) members of the primary immune thrombocytopenia cohort; a further 25 (2.3%) patients within this group had already undergone splenectomy. By two years post-index, the proportion of oral corticosteroid-treated and splenectomized adult patients with primary immune thrombocytopenia had climbed to 294 (37.7%) and 53 (6.8%), respectively. [Oral corticosteroid-treated and splenectomized proportions were reflective of the 779 (72.8%) of adult patients with

Table 2. Incidence rates of venous and arterial thromboembolic events by diagnostic code.

Codes	Primary ITP Cohort			Primary ITP-Disease Free Cohort		
	Patients at risk	Events	Incidence rate (95% CI)	Patients at risk	Events	Incidence rate (95% CI)
Venous TE						
Idiopathic Codes						
Read						
Idiopathic thrombocytopenic purpura D313000 & D313012						
ITP-Idiopathic thrombocytopenic purpura 42P2.11	932	29	67.47 (45.18, 96.90)			
OXMIS Idiopathic thrombocytopenia 2871C				4,082	82	42.45 (33.76,52.70)
Autoimmune Codes						
Read Autoimmune thrombocytopenia D313.12	74	2	56.06 (6.79, 202.50)			
Arterial TE						
Idiopathic Codes						
Read Idiopathic thrombocytopenic purpura D313000 & D313012						
ITP-Idiopathic thrombocytopenic purpura 42P2.11	897	40	94.28 (67.36 128.93)			
				4,000	128	67.40 (56.23,80.14)
OXMIS Idiopathic thrombocytopenia 2871C						
Autoimmune Codes						
Autoimmune thrombocytopenia 288599	68	4	124.75 (33.99, 319.40)			

Incidence expressed per 10,000 patient-years.

Table 3. Stratified incidence rates of venous thromboembolic events.

Description	Primary ITP Cohort			Primary ITP-disease free cohort			
	Patients (95% CI)	Events	Incidence Rate (95% CI)	Patients	Events	Incidence rate (95% CI)	Incidence rate Ratio (95% CI)
All patients	1,006	31	66.59 (45.25,94.52)	4,082	82	42.45 (33.76,52.70)	1.57 (1.04,2.37)
Gender and age (years)							
Female	579	20	71.40 (43.61,110.27)	2,362	53	45.67 (34.21,59.73)	1.56 (0.93,2.62)
Male	427	11	59.33 (29.62,106.16)	1,720	29	37.62 (25.19,54.02)	1.58 (0.79,3.16)
Female; 40-49	69	2	47.01 (5.69-169.80)	285	3	18.97 (3.91,55.44)	2.48 (0.41-14.83)
Female; 50-59	83	3	74.92 (15.45,218.96)	375	5	25.58 (8.31,59.69)	2.93 (0.70,12.26)
Female; 60-69	84	3	71.14 (14.67,207.91)	359	11	58.08 (29.00,103.93)	1.22 (0.34,4.39)
Female; 70-79	92	5	126.93 (41.21,296.22)	369	15	87.53 (48.99,144.36)	1.45 (0.53,3.99)
Female; 80-89	68	2	92.54 (11.21,334.30)	242	11	134.67 (67.22,240.95)	0.69 (0.15,3.10)
Male; 40-49	56	1	35.76 (0.91,199.24)	227	2	19.22 (2.33,69.42)	1.86 (0.17,20.52)
Male; 50-59	63	3	92.53 (19.08,270.42)	266	6	43.61 (16.01,94.93)	2.12 (0.53,8.48)
Male; 60-69	66	0		276	8	59.66 (25.76,117.55)	
Male; 70-79	113	3	70.07 (14.45,204.77)	437	11	57.21 (28.56,102.37)	1.22 (0.34,4.39)
Male; 80-89	43	3	274.45 (56.60,802.07)	170	1	20.91 (0.53,116.53)	13.12 (1.36,126.16)
Baseline platelet count (x10^9/L)							
< 50	164	1	15.08 (0.38,84.00)	1	0		
50-75	128	2	48.35 (5.86,174.67)	0	0		
75-150	233	5	61.80 (20.07,144.22)	29	1	95.92 (2.43,534.41)	0.64 (0.08,5.52)
No data available	354	20	87.56 (53.49,135.24)	3,030	63	39.95 (30.70,51.11)	2.19 (1.33,3.62)
ITP-specific treatment							
Corticosteroid Yes	474	14	60.37 (33.00,101.29)	641	16	51.16 (29.24,83.08)	1.18 (0.58,2.42)
Corticosteroid No	532	17	72.77 (42.39,116.52)	3,441	66	40.77 (31.53,51.87)	1.78 (1.05,3.04)
IVIg Yes	2	0		8	0		
IVIg No	1,004	31	66.93 (45.48,95.00)	4,074	82	42.56 (33.85,52.83)	1.57 (1.04,2.38)
Splenectomy Yes	79	3	67.96 (14.01,198.60)	3	0		
Splenectomy No	927	28	66.45 (44.16,96.04)	4,079	82	42.48 (33.79,52.73)	1.56 (1.02,2.40)
Thromboembolic event (TE) history							
TE Yes	101	4	117.03 (31.89,299.65)	255	5	49.38 (16.03,115.23)	2.37 (0.64,8.83)
TE No	905	27	62.60 (41.25,91.08)	3,827	77	42.07 (33.20,52.58)	1.49 (0.96,2.31)

Incidence expressed per 10,000 patient-years.

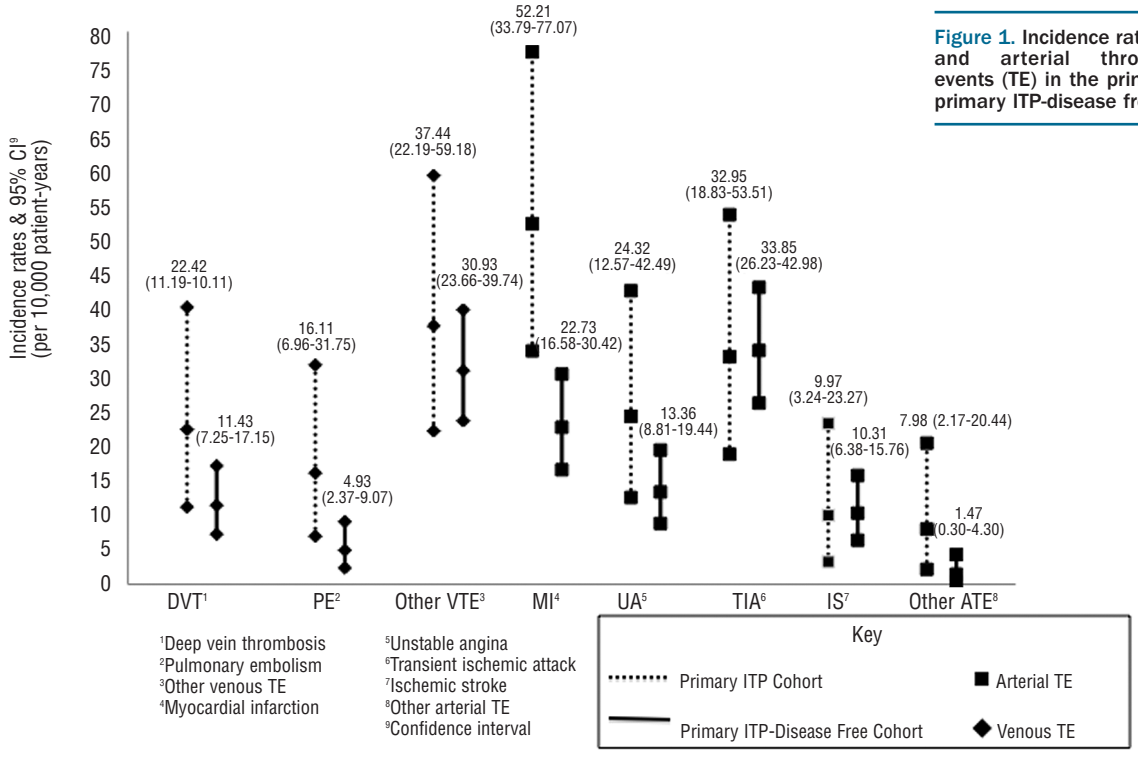

Figure 1. Incidence rates of venous and arterial thromboembolic events (TE) in the primary ITP and primary ITP-disease free cohorts.

primary immune thrombocytopenia still under follow-up two-years post-index.] The General Practice Research Database did not, however, capture the administration of IVIg, an acute treatment administered in hospital care settings.

The cumulative incidence of first venous, arterial and combined thromboembolic events during the study was 2.9%, 4.1%, and 6.1% in the primary immune thrombocytopenia cohort and 1.9%, 3.0%, and 4.6% in the primary immune thrombocytopenia disease free cohort, respectively.

Incidence rates (expressed per 10,000 patient-years) of venous (IR: 66.59 [95% CI, 45.25-94.52]) *vs.* 42.45 [95% CI, 33.76-52.70]) and arterial thromboembolic events (IR: 96.42 [95% CI, 70.06-129.45]) *vs.* 67.40 [95% CI, 56.23-80.14]) were elevated among patients with primary immune thrombocytopenia, an increased risk seen across the autoimmune (Read: 42P2.11) and idiopathic ([Read: D313.12, D313000 & D313012] and OXMIS [2871C]) coding strata (Table 2). Sub-grouping shown in Figure 1 depicts increased rates of myocardial infarction (IR: 52.21 *vs.* 22.73), unstable angina (IR: 24.32 *vs.* 13.36), other arterial thromboembolic events (IR: 7.98 *vs.* 1.47), deep vein thrombosis (IR: 22.42 *vs.* 11.43), pulmonary embolism (IR: 16.11 *vs.* 4.93), and other venous thromboembolic events (IR: 37.44 *vs.* 30.93). Overlap was noted between the 95% Confidence Intervals of the latter five sub-group estimates for the two cohorts. No cases of portal vein thrombosis were identified within the study population during the defined follow-up period.

Results from the stratification of venous (Table 3) and arterial (Table 4) thromboembolic events by baseline characteristics, respectively, demonstrated noticeable disparities in the incidence rate ratio of both types of events in women and men, in patients with and without a past history of thromboembolic events, and in patients taking and not taking oral corticosteroids.

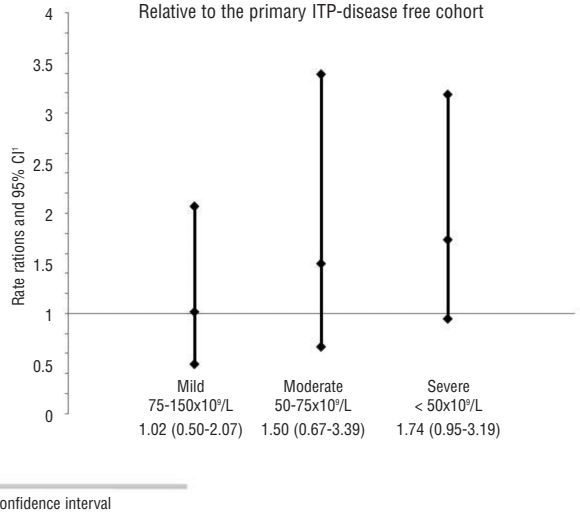

Figure 2. Incidence rate ratios of combined thromboembolic events by baseline platelet count subgroups.

Further subgroup analyses of combined thromboembolic events by baseline platelet count suggest the possibility of a direct relationship between disease severity and thrombosis (Figure 2). Restriction of the primary immune thrombocytopenia cohort to adult patients with present-

ing counts less than 100×10^9/L, a threshold recently advocated by Rodeghiero *et al.*[22] to exclude asymptomatic, mildly thrombocytopenic patients from disease categorization, resulted in an elevated incidence rate ratio of 1.55 (95% CI, 0.97-2.43) for combined thromboembolic events. Moreover, incidence rate ratio point estimates for combined thromboembolic events were increasingly elevated for moderately (50-75$\times10^9$/L: 1.50 [95% CI, 0.67-

Table 4. Stratified incidence rates of arterial thromboembolic events.

Description	Primary ITP cohort			Primary ITP-disease free cohort			
	Patients	Events	Incidence rate (95% CI)	Patients	Events	Incidence rate (95% CI)	Incidence rate Ratio (95% CI)
All patients	965	44	96.42 (70.06,129.45)	4,000	128	67.40 (56.23,80.14)	1.43 (1.02,2.02)
Gender and Age (Years)							
Female	583	20	69.33 (42.35,107.08)	2,375	71	60.34 (45.52,74.05)	1.15 (0.70,1.89)
Male	382	24	142.98 (91.61,212.74)	1,625	57	78.89 (59.75,102.22)	1.81 (1.12,2.92)
Female; 40-49	73	0		291	4	24.74 (6.74,63.35)	
Female; 50-59	92	2	44.78 (5.42,161.75)	379	6	30.12 (11.05,65.55)	1.49 (0.30,7.37)
Female; 60-69	91	7	149.80 (60.23,308.64)	362	16	83.92 (47.97,136.29)	1.78 (0.73,4.34)
Female; 70-79	89	6	160.41 (58.87,349.14)	365	24	138.23 (88.56,205.67)	1.16 (0.47,2.84)
Female; 80-89	55	3	164.83 (33.99,481.71)	236	19	240.70 (144.92,375.88)	0.68 (0.20,2.31)
Male; 40-49	56	0		227	5	48.91 (15.88,114.14)	
Male; 50-59	62	3	97.56 (20.12,285.12)	262	7	51.49 (20.70,106.09)	1.89 (0.49,7.33)
Male; 60-69	61	9	353.18 (161.49,670.44)	251	6	50.89 (18.67,110.76)	6.94 (2.47,19.50)
Male; 70-79	92	9	260.52 (119.13,494.55)	400	27	158.28 (104.31,230.29)	1.65 (0.77,3.50)
Male; 80-89	29	2	247.53 (29.98,2,894.15)	144	11	268.17 (133.87,479.83)	0.92 (0.20,4.16)
Baseline platelet count (x10^9/L)							
< 50	156	10	161.54 (77.46,297.07)	1	0		
50-75	119	6	156.60 (57.47,340.85)	0	0		
75-150	219	5	66.23 (21.50,154.55)	27	0		
No data available	348	19	81.32 (48.96,126.99)	2,995	89	57.15 (45.90,70.33)	1.42 (0.87,2.33)
ITP-specific treatment							
Corticosteroid Yes	448	22	96.51 (60.48,146.11)	626	23	74.28 (47.09,111.46)	1.30 (0.72,2.33)
Corticosteroid No	517	22	96.34 (60.38,145.86)	3,374	105	66.06 (54.03,79.97)	1.46 (0.92,2.31)
IVIg Yes	2	0		8	0		
IVIg No	963	44	96.72 (70.28,129.84)	3,992	128	67.57 (56.37,80.34)	1.43 (1.02,2.02)
Splenectomy Yes	81	5	113.41 (36.82,264.66)	3	0		
Splenectomy No	884	39	94.61 (67.28,129.33)	3,997	128	67.45 (56.27,80.19)	1.40 (0.98,2.01)
Thromboembolic event (TE) history							
TE Yes	60	6	261.81 (96.08,569.84)	173	12	168.31 (86.97,294.00)	1.56 (0.58,4.14)
TE No	905	38	87.68 (62.05,120.35)	3,827	116	63.46 (52.44,76.12)	1.38 (0.96,1.99)

Incidence expressed per 10,000 patient-years.

3.39]) and severely (< 50×10⁹/L: 1.74 [95% CI, 0.95-3.19]) thrombocytopenic adult patients.

Unadjusted hazard ratios of 1.58 (95% CI, 1.05-2.39), 1.42 (95% CI, 1.01-2.00), and 1.42 (95% CI, 1.07-1.88) were obtained for venous, arterial, and combined thromboembolic events, respectively. Adjustment for immune thrombocytopenia treatment (oral corticosteroid usage, IVIg treatment, and splenectomy) and co-morbid status (hypertension, diabetes, chronic renal failure, and history of prior thromboembolic events) altered these ratios only slightly, resulting in hazard ratios of 1.58 (95% CI, 1.01-2.48), 1.37 (95% CI, 0.94-2.00), and 1.41 (95% CI, 1.04-1.91), respectively.

Discussion

Using a population-based data source,[18] our results provide evidence for an increased risk of venous thromboembolic events in adult patients with primary immune thrombocytopenia in comparison with adult patients without primary immune thrombocytopenia. An incidence rate ratio of 1.57 (95% CI, 1.04-2.37) was observed, and multivariate Cox's regression modeling yielded an adjusted, statistically significant hazard ratio of 1.58 (95% CI, 1.01-2.48). Furthermore, the incidence rate for each venous thromboembolic subgroup occurring during follow-up was higher among adult patients with primary immune thrombocytopenia, demonstrating a consistency of effect (Figure 1). Evidence for an elevated risk of arterial thromboembolic events among adult patients with primary immune thrombocytopenia is also present, though slightly less clear, with proportional hazards modeling yielding an adjusted hazard ratio of 1.37 (95% CI, 0.94-2.00). Particularly striking is a markedly increased incidence rate of myocardial infarction within the primary immune thrombocytopenia cohort (Figure 1). Owing to increasing challenges to the prevailing theory of distinct etiologies for venous and arterial thromboembolic events,[12,13] further analysis was conducted on combined thromboembolic events, with data supporting a statistically significantly increased hazard (adjusted HR=1.41 [95% CI, 1.04-1.91]).

An initial concern over our investigation centered on the external validity of the primary immune thrombocytopenia cohort and whether it is representative of adult patients under active management. Newly published data support its accurate classification. The positive predictive value of OXMIS and Read codes to identify patients with primary immune thrombocytopenia has recently been subject of a validation study by Schoonen *et al.*, who report a high point estimate of 91% (95% CI, 84-96%).[10] The codes utilized were incorporated into our study excluding four deemed likely less specific: Evans syndrome (Read: D313.11), platelet count (OXMIS: L 146N), platelet count (Read: 42P..00), and platelet count, nos (Read: 42PZ.00). As a result, the positive predictive value of our collection of codes should be commensurate, if not higher, than that of Schoonen *et al.*

Existence of two coding vocabularies (OXMIS and Read), as well as multiple codes for the same medical concept within these vocabularies, raises an additional question as to whether patients labeled with one of the five codes selected to identify adult patients with primary immune thrombocytopenia were systematically different from those classed under another. To investigate, we evaluated incidence rates of venous and arterial thromboembolic events across the two primary classes of primary immune thrombocytopenia codes, the autoimmune (Read: 42P2.11) and idiopathic ([Read: D313.12, D313000 and D313012] and OXMIS [2871C]) codes, as it is the coding description and not the coding number that are selected by general practitioners when entering data. Similar, elevated incidence rates for venous and arterial thromboembolic events in both of these strata suggest that no such differences were present (Table 2).

Two limitations of our study should be noted. First, the available number of adult patients with primary immune thrombocytopenia in the General Practice Research Database may have hampered the power of the investigation to detect a statistically significant association between primary immune thrombocytopenia and arterial thromboembolic events. Although the 1,070 adult patients with primary immune thrombocytopenia included in our study constitutes one of the largest cohorts assembled for this condition, pre-investigation power calculations revealed the need for 8,120 patients to detect a twofold increase in the estimated annual incidence of arterial thromboembolic events in the Western world[21] at 80% 1- and 5%.

Second, the sparse platelet count and IVIg data noted in our study reflect a more general limitation of the General Practice Research Database in capturing specific, hospital-based information such as acute treatment and routine laboratory test results. However, as numerous investigative teams have shown for a variety of conditions, including primary immune thrombocytopenia,[10,21,23-24] this limitation does not diminish the accuracy of the data that are contained within the General Practice Research Database.

Importantly, the uncovered associations do not in themselves implicate primary immune thrombocytopenia as a causative agent for venous and combined thromboembolic events. Hospitalization, for instance, may have been more common among the primary immune thrombocytopenia cohort and is itself a widely recognized, independent risk factor for venous thromboembolic events.[25-26] Similarly, while statistically significant, increased hazards of venous and combined thromboembolic events persisted following adjustment for co-morbid conditions and immune thrombocytopenia treatment, it is possible that treatment modalities other than those included (oral corticosteroids, IVIg, and splenectomy) may have played a role in the creation of a pro-thrombotic environment.

Plausible mechanisms for primary immune thrombocytopenia induced venous thrombosis have been postulated, and include increased platelet microparticle thrombogenicity following peripheral destruction and the activity of antiphospholipid antibodies (APAs). The latter exhibit a high prevalence in adult patients with primary immune thrombocytopenia [27] and have been hypothesized to trigger increased platelet activation and decreased production of prostacylcin, nitric oxide, and protein C.[28] In a study of 82 consecutive adults with primary immune thrombocytopenia, for example, Diz-Küçükkaya *et al.* report a statistically significant difference in 5-year, thrombosis-free survival between APA-positive and negative patients.[29]

Knowledge of an elevated risk of venous thrombosis among adult patients with primary immune thrombocytopenia may possibly support increased utilization of thromboprophylactic treatment in patients at lower risk of hemorrhage. However, further work is first needed to con-

firm the uncovered association and to examine whether evidence exists implicating a causative role for primary immune thrombocytopenia pathogenesis in venous thrombus formation. Potentially fruitful next steps in exploring this topic include a meta-analysis of observational studies of adults with primary immune thrombocytopenia and *in vitro* investigation of differences in aggregation potential between APA-positive and negative platelets. Simultaneous efforts to establish an international consortium of immune thrombocytopenia specialists focused on the development of a prospective registry of adult patients with primary immune thrombocytopenia would also help, and would allow evaluation of a wider range of variables and a longer-term follow-up than is presently available.

Authorship and Disclosures

ASa, DB, and ASh designed the study protocol; JWL and ASh performed the statistical programming; ASa, DB, KJB, JWL, ACN, SS, and DP analyzed the results and helped draft the manuscript.

ASa and ACN: honoraria from GlaxoSmithKline, institutional research support by GlaxoSmithKline; DB, JWL, ASh and KJB: ownership of stock of GlaxoSmithKline, employment by GlaxoSmithKline; DP: ownership of stock of GlaxoSmithKline, honoraria from GlaxoSmithKline, institutional research support by GlaxoSmithKline.

The other authors reported no potential conflicts of interest.

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