I TPO-mimetici nella «real life»

ITP e trattamento antitrombotico

Marco Ruggeri

UOC Ematologia, Vicenza

Platelet count and thrombosis

- There are clinical examples where low platelet count correlates with the risk of thrombosis:
  - Thrombotic thrombocytopenic purpura
  - Heparin-induced thrombocytopenia
  - Antiphospholipid syndrome
- Is this the case also for ITP?
  - Role of the actual platelet count
  - Relation with phase of disease, treatment, splenectomy status
  - Risk factors

Why this interest in the relationship between ITP and thrombosis?

- Thrombosis with human recombinant thrombopoietin and megakaryocytes development factor (PEG-rHuMGDF)
- Thrombosis reported in the registrative studies of romiplostim and eltrombopag in ITP

Risk of pulmonary embolism in patients with autoimmune disorders: a nationwide follow-up study from Sweden

Bengt Zöller, Xinjun Li, Jan Sundquist, Kristina Sundquist

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	<1 year of follow-up		1–5 year of follow-up		5–10 years of follow-up		≥10 years of follow-up		All	
	O	SIR (95% CI)	O	SIR (95% CI)	O	SIR (95% CI)	O	SIR (95% CI)	O	SIR (95% CI)
Addison's disease	32	7·75 (5·30–10·95)*	24	1·79 (1·14–2·66)*	16	2·02 (1·15–3·29)*	6	0·96 (0·34–2·10)	78	2·46 (1·94–3·07)*
Amyotrophic lateral sclerosis	57	5·14 (3·89–6·66)*	23	1·54 (0·98–2·32)	9	0·96 (0·43–1·83)	19	1·26 (0·76–1·97)	108	2·14 (1·76–2·58)*
Ankylosing spondylitis	30	4·27 (2·88–6·11)*	45	1·27 (0·93–1·70)	28	0·91 (0·60–1·32)	60	0·88 (0·67–1·14)	163	1·16 (0·99–1·35)
Autoimmune haemolytic anaemia	27	11·07 (7·29–16·12)*	34	3·73 (2·58–5·22)*	18	3·16 (1·87–5·00)*	5	0·70 (0·22–1·64)	84	3·44 (2·74–426)*
Behçet's disease	42	9·03 (6·51–12·22)*	55	2·05 (1·55–2·67)*	26	1·05 (0·68–1·54)	78	1·23 (0·97–1·54)	201	1·68 (1·45–1·93)*
Celiac disease	35	6·29 (4·38–8·76)*	48	1·71 (1·26–2·27)*	26	1·09 (0·71–1·61)	55	1·10 (0·83–1·44)	164	1·53 (1·30–1·78)*
Chorea minor	2	16·67 (1·57–61·29)*	1	1·03 (0–5·91)	0		1	1·67 (0–9·55)	4	1·77 (0·46–4·58)
Chronic rheumatic heart disease	233	4·21 (3·69–4·79)*	234	0·98 (0·86–1·11)	121	0·61 (0·51–0·73)*	118	0·51 (0·42–0·61)*	706	0·97 (0·90–1·05)
Crohn's disease	142	8·71 (7·34–10·27)*	101	1·34 (1·09–1·63)*	66	1·12 (0·87–1·43)	95	0·98 (0·79–1·20)	404	1·63 (1·48–1·80)*
Diabetes mellitus type I	12	6·38 (3·28–11·18)*	16	1·28 (0·73–2·09)	23	0·98 (0·62–1·48)	58	0·86 (0·65–1·11)	109	1·03 (0·85–1·25)
Discoid lupus erythematosus	12	12·00 (6·17–21·03)*	12	1·94 (1·00–3·40)*	7	1·60 (0·63–3·32)	13	1·50 (0·80–2·57)	44	2·18 (1·58–2·92)*
Graves' disease	346	6·50 (5·84–7·23)*	440	1·30 (1·18–1·43)*	348	1·08 (0·97–1·21)	665	1·01 (0·94–1·09)	1799	1·31 (1·25–1·37)*
Hashimoto's thyroiditis	331	5·26 (4·83–5·73)*	667	1·33 (1·23–1·47)*	323	1·20 (1·08–1·34)*	287	1·10 (0·97–1·23)	1748	1·62 (1·54–1·70)*
Immune thrombocytopenic purpura	49	10·79 (7·98–14·28)*	34	2·02 (1·40–2·82)*	15	1·32 (0·74–2·18)	13	0·79 (0·42–1·35)	111	2·25 (1·85–2·71)*
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Lupoid hepatitis	8	13·33 (5·69–26·40)*	4	1·78 (0·46–4·60)	1	0·56 (0–3·24)	3	0·49 (0·09–1·45)	16	1·49 (0·85–2·42)
Multiple sclerosis	106	7·68 (6·28–9·29)*	87	1·72 (1·38–2·13)*	37	1·15 (0·81–1·59)	64	1·15 (0·88–1·47)	294	1·93 (1·72–2·17)*
Myasthenia gravis	30	7·21 (4·86–10·31)*	17	1·11 (0·64–1·78)	12	1·18 (0·61–2·07)	15	1·11 (0·62–1·84)	74	1·71 (1·35–2·12)*
Pernicious anaemia	183	3·92 (3·37–4·53)*	284	1·17 (1·03–1·31)*	170	1·00 (0·85–1·16)	182	1·09 (0·94–1·26)	819	1·31 (1·22–1·40)*
Polyarteritis nodosa	37	13·26 (9·33–18·29)*	22	1·92 (1·20–2·91)*	12	1·39 (0·71–2·43)	16	1·46 (0·83–2·38)	87	2·57 (2·06–3·17)*
Polymyalgia rheumatica	580	7·86 (7·23–8·53)*	637	1·76 (1·62–1·90)*	345	1·33 (1·20–1·48)*	389	1·17 (1·05–1·29)*	1951	1·90 (1·81–1·98)*
Polymyositis/ dermatomyositis	37	16·44 (11·57–22·69)*	24	3·03 (1·94–4·52)*	17	2·89 (1·68–4·64)*	14	1·23 (0·67–2·07)	92	3·36 (2·70–4·12)*
Primary biliary cirrhosis	28	7·37 (4·89–10·66)*	19	2·01 (1·21–3·15)*	7	1·19 (0·47–2·48)	15	1·59 (0·89–2·63)	69	2·42 (1·88–3·06)*
Psoriasis	134	4·84 (4·06–5·73)*	267	1·66 (1·47–1·87)*	160	1·22 (1·04–1·42)*	243	0·96 (0·84–1·09)	804	1·40 (1·31–1·50)*
Reiter's disease	3	9·38 (1·77–27·75)*	1	0·51 (0–2·91)	2	0·94 (0·09–3·47)	1	0·43 (0–2·47)	7	1·04 (0·41–2·16)
Rheumatic fever	38	10·08 (7·13–13·85)*	38	1·71 (1·21–2·35)*	55	2·15 (1·62–2·80)*	87	1·08 (0·87–1·34)	218	1·65 (1·44–1·89)*
Rheumatoid arthritis	830	5·99 (5·59–6·41)*	921	1·78 (1·66–1·90)*	360	1·18 (1·06–1·31)*	389	1·12 (1·01–1·23)*	2500	1·91 (1·83–1·98)*
Sarcoidosis	94	8·93 (7·21–10·93)*	104	1·97 (1·61–2·39)*	71	1·10 (0·86–1·39)	183	1·11 (0·95–1·28)	452	1·54 (1·40–1·69)*
Sjögren's syndrome	33	7·40 (5·09–10·40)*	33	1·64 (1·13–2·31)*	18	1·57 (0·93–2·49)	16	1·66 (0·95–2·70)	100	2·19 (1·78–2·66)*
Systemic lupus erythematosus	99	10·23 (8·31–12·45)*	76	2·11 (1·67–2·65)*	45	1·56 (1·14–2·09)*	56	1·10 (0·83–1·42)	276	2·20 (1·95–2·47)*
Systemic sclerosis	74	7·09 (5·57–8·91)*	106	1·91 (1·56–2·31)*	72	1·35 (1·06–1·70)*	118	1·07 (0·89–1·29)	370	1·61 (1·45–1·79)*
Ulcerative colitis	250	10·26 (9·03–11·62)*	207	1·67 (1·45–1·91)*	145	1·43 (1·20–1·68)*	211	1·29 (1·12–1·48)*	813	1·97 (1·83–2·11)*
Wegener's granulomatosis	186	6·57 (5·66–7·58)*	270	1·55 (1·37–1·75)*	184	1·05 (0·90–1·21)	238	0·97 (0·85–1·10)	878	1·41 (1·31–1·50)*
All	4308	6·38 (6·19–6·57)*	4803	1·53 (1·48–1·57)*	2757	1·15 (1·11–1·20)*	3739	1·04 (1·00–1·07)	15 607	1·59 (1·56–1·61)*

Adjusted for age, sex, period, hospital admission for chronic obstructive pulmonary disease, obesity, alcoholism and alcohol-related liver disease, coronary heart disease, stroke, hypertension, sepsis, varicose veins, peripheral vascular disease, and congestive heart failure. O=observed number of cases. SIR=standardised incidence ratio. *95% CI does not include 1·00.

Table 3: **SIRs for subsequent pulmonary embolism in patients with autoimmune disorders without previous hospital admission for venous thromboembolism or coexisting venous thromboembolism**

Thrombo-Embolic Events in adults with ITP

	CUMULATIVE INCIDENCE AFTER ENTRY GPRD		HAZARD RATIO (ADJUSTED)
	ITP CASES (%)	ITP-FREE PATIENTS (%)	
Venous	2.9	1.9	**1.58 (1.01-2.48)**
Arterial	4.1	3	1.37 (0.94-2)
Venous & Arterial	6.1	4.6	**1.41 (1.04-1.91)**

Sarpatwari A et al: Haematologica et al, 2010

Risk of **venous thromboembolism** in patients with primary chronic immune thrombocytopenia

	Chronic ITP cohort			Reference cohort			
	Number of VTEs	Person-years	IR per 1000 person-years (95% CI)	Number of VTEs	Person-years	IR per 1000 person-years (95% CI)	Adjusted IRR (95% CI)
Total	10	1879	5·32 (CI: 2·86–9·89)	33	16 196	2·04 (CI: 1·45–2·87)	2·65 (CI: 1·27–5·50)
Unprovoked VTE	5	1879	2·66 (CI: 1·11–6·39)	18	16 195	1·11 (CI: 0·70–1·76)	2·26 (CI: 0·81–6·30)
Provoked VTE	5	1879	2·66 (CI: 1·11–6·39)	15	16 195	0·93 (CI: 0·56–1·54)	3·16 (CI: 1·11–8·98)
Female	3	1247	2·41 (CI: 0·78–7·46)	21	10 605	1·98 (CI: 1·29–3·04)	1·20 (CI: 0·35–4·14)
Male	7	632	11·07 (CI: 5·28–23·23)	12	5591	2·15 (CI: 1·22–3·78)	5·23 (CI: 1·99–13·75)
Age ≤ 60 years	4	1243	3·22 (CI: 1·21–8·57)	11	10 137	1·09 (CI: 0·60–1·96)	2·86 (CI: 0·91–8·97)
Age > 60 years	6	636	9·44 (CI: 4·24–21·01)	22	6059	3·63 (CI: 2·39–5·51)	2·51 (CI:0·97–6·50)
Charlson score = 0	5	1380	3·62 (CI: 1·51–8·70)	18	11 362	1·58 (CI: 1·00–2·51)	2·32 (CI: 0·85–6·35)
Charlson score ≥ 1	5	498	10·04 (CI: 4·18–24·12)	15	4833	3·10 (CI: 1·87–5·15)	3·10 (CI: 1·06–9·07)

Severinses M et al; Br J Haematol, 2011

Risk of **arterial thrombosis** in patients with primary chronic immune thrombocytopenia

	cITP patients			Comparison cohort			cITP *versus* comparisons
	ATs (*n*)	Person-years	IR per 1000 person-years (95% CI)	ATs (*n*)	Person-years	IR per 1000 person-years (95% CI)	Adjusted IRR (95% CI)
Total	29	2551	11·37 (7·90–16·36)	254	27 902	9·10 (8·05–10·29)	1·32 (0·88–1·98)
Women	21	1698	12·37 (8·06–18·97)	120	18 533	6·48 (5·41–7·74)	2·27 (1·40–3·69)
Men	8	852	9·38 (4·69–18·77)	134	9369	14·30 (12·07–16·94)	0·58 (0·27–1·25)
Age ≤ 60 years	7	1796	2·39 (0·77–7·42)	35	18 372	1·91 (1·37–2·65)	2·17 (0·95–4·93)
Age > 60 years	22	755	29·14 (19·19–44·26)	219	9529	22·98 (20·13–26·24)	1·16 (0·73–1·85)
No comorbidity	15	1933	7·76 (4·68–12·87)	126	20 083	6·27 (5·27–7·47)	1·26 (0·71–2·22)
Comorbidity present	14	618	22·67 (13·43–38·28)	128	7819	16·37 (13·77–19·47)	1·39 (0·79–2·46)

Norgaard M et al; Br J Haematol, 2012

Thrombo-Embolic Events in ITP: data from prospective study of 82 patients (APA assayed)

Type of thombosis	ITP patients (n)		p
	APA + (31)	APA – (51)	
Venous	5	1	
Arterial	6	1	
Combined	11	2	
Cumulative incidence *	35%	4%	0.001
Cumulative thrombosis free survival*	39%	97%	0.04

*= 5 years

Kukcukkaya RD et al; Blood, 2001

Thrombo-Embolic Events in ITP: data from pros retrospective study of 215 patients (APA assayed)

Type of thombosis	ITP patients (n)		p
	APA + (55; 26%))	APA – (160; 74%)	
Venous	3	7	
Arterial	1	3	
Combined	4	10	
Cumulative incidence *	7.2%	6.25%	0.7

*= median follow up 31 months

Pierrot-Deseilligny Despujol C et al; Br J Haematol, 2008

Thrombo-Embolic Events in ITP associated to splenectomy: data from a systematic review

Kojouri K et al; Blood ,2004

	Laparotomy	Laparoscopy
Death*		
Articles, no.	81	29
Mortality rate, % (no. patients who died/total no. evaluable patients)	1 (48/4955)	0.2 (3/1301)
Causes of death		
Postoperative bleeding, no.	11	1 (intraabdominal)
Gastrointestinal, no.	5	—
Intracranial, no.	5	—
Not specified, no.	1	—
Cardiovascular, no.	10	1 (aortic aneurysm)
Cardiac, no.	7	—
Stroke, no.	2	—
Aortic aneurysm, no.	1	—
Infectious, no.	6	1 (sepsis)
Pneumonia, no.	2	—
Sepsis, no.	2	—
Subdiaphragmatic abscess, no.	1	—
Viral hepatitis, no.	1	—
Venous thromboembolism, no.	5	—
Pancreatitis, no.	3	—
Miscellaneous, no.	3	—
Not reported, no.	10	—
Complications*		
Articles, no.	35	19
Complication rate, % (no. patients with complications/total no. evaluable patients)	12.9 (318/2465)	9.6 (88/921)

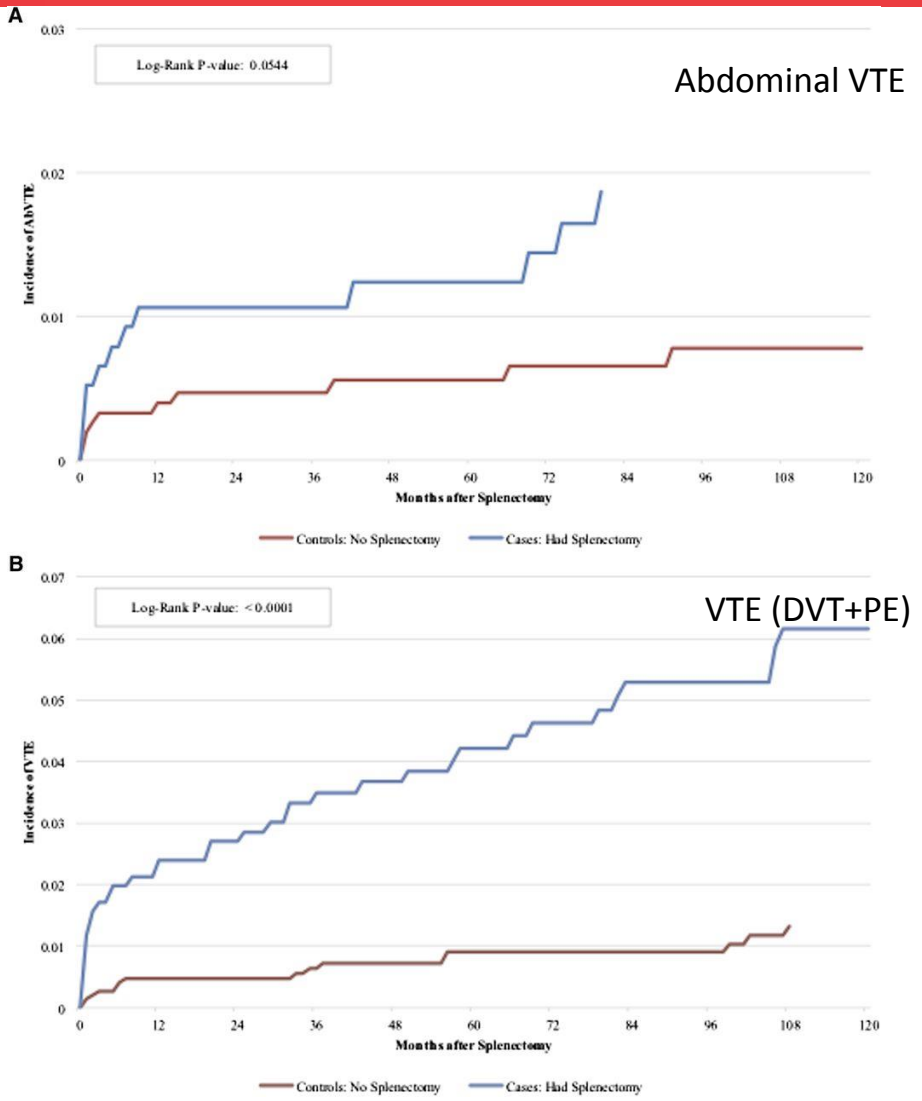
Impact of splenectomy on thrombotic risk

Boyle S et al; Blood, 2013

- Administrative data (California).
  Retrospective observational cohort in patients with index hospitalization for ITP from 1990 to 2009:
  - Cases: 1762 splenectomized (after index hospitalization)
  - Controls: 8214 not splenectomized (after index hospitalization)
  - Median FU 5 years
  - Unadjusted overall prevalence:
    - Abdominal VTE: 1.6% splenectomized vs 1% not splenectomized
    - DVT and PE: 4.3% splenectomized vs 1.7% not splenectomized

Incidence of AbVTE and VTE by splenectomy status

Boyle S et al; Blood 2013



Splenectomy vs no splenectomy Hazard ratio (CI 95%)	
AbVTE < 90 days from splenectomy	5.4 (2.3 – 12.5)
AbVTE ≥ 90 days from splenectomy	1.5 (0.9 – 2.6)
VTE < 90 days from splenectomy	5.2 (3.2 – 8.5)
VTE ≥ 90 days from splenectomy	2.7 (1.9 – 3.8)

Thrombotic risk in chronic ITP patients exposed to romiplostim

Rodeghiero F et al; EJH, 2013

- Pooled analysis of 13 clinical trials – Mean age of pts 52 yrs
  - 653 pts received romiplostim for up to 5 yrs (922 pt-yrs)
  - 138 pts received placebo/SOC for up to 2 yrs (110 pt-yrs)
- Results
  - Romiplostim: 39 pts with at least 1 thrombotic episode (5.9%)
    Placebo/SOC: 5 pts with at least 1 thrombotic episode (3.6%)
  - Romiplostim annualized risk (first thrombotic episode): 4.2
    Placebo/SOC annualized risk (first thrombotic episode): 4.5

Kuter D et al; BJH, 2013

- Analysis restricted to 292 pts in long-term, single-arm, open-label study (614 pt-yrs)
  - Thrombosis in 19 patients (6.5%) (25 thrombotic events)
  - Annualized risk: 3.1 per 100 pt-yrs (first thrombotic episode)

Long-term treatment with romiplostim in pts with chronic ITP: safety and efficacy

Kuter D et al; BJH, 2013

Table IV. Thrombotic events.

Thrombotic event	Weeks on treatment in this study	Patient age (years)	Platelet count prior to event, $\times 10^9$ per litre	Days between platelet count and event
Cardiovascular				
Myocardial infarction*	14	61	217	24
Myocardial infarction	108	66	527†	3
Myocardial infarction	23	70	152	0
Myocardial infarction	104	70	5†	1
Myocardial infarction	45	80	274	10
Myocardial infarction	44	83	141	2
Myocardial infarction	60	83	103†	1
Myocardial infarction	84	83	7	1
Myocardial infarction	19	85	948	0
Myocardial infarction*	9	85	20	2
Neurological				
Hemiparesis	169	53	253	9
Transient ischaemic attack	22	57	49†	4
Transient ischaemic attack	26	58	125	4
Cerebrovascular accident	107	63	243	3
Transient blindness	15	63	187	0
Cerebrovascular accident	40	79	142	0
Venous thromboses				
Pulmonary embolism	50	40	312	0
Portal vein thrombosis*	118	44	473†	3
Catheter thrombosis	60	44	7	7
Deep vein thrombosis*	130	44	7†	11
Transverse sinus thrombosis*	52	63	293	5
Deep vein thrombosis	22	67	47	0
Thrombophlebitis	35	69	285	0
Deep vein thrombosis	23	70	152	0
Pulmonary embolism*	80	85	149†	6

*Considered by the investigator as possibly related to study treatment.
†Recorded within 8 weeks of rescue medication use.

Thrombotic risk in chronic ITP patients exposed to eltrombopag

Saleh NM et al; Blood, 2013

- Results from the long-term open-label EXTEND study
  - 299 patients treated up to 3 yrs (median exposure time 2 yrs, range 2-1267 days)
  - Median age 50 yrs
  - 20 thrombotic episodes in 16 patients (5.3%)
  - Thrombosis rate 3.2 per 100 pt-yrs (calculated on 20 events)

Thrombotic risk in chronic ITP patients exposed to eltrombopag

Saleh NM et al; Blood, 2013

Table 5. Thromboembolic events

Patient no.	Event	Baseline platelet count*	Platelet count prior to/day of the event	Maximum platelet count†	Days to onset	Outcome
1	TIA	13	27	301	59	Resolved
2	PE	15	407	407	58	Resolved
3	DVT	23	248	577	387	Resolved
4	CNS ischemia	25	60	122	971	Not resolved
	Subclavian/brachial vein thrombosis		Unknown		981	Not resolved
5	DVT	26	220	482	134	Resolved‡
	MI		420		362	Resolved
	DVT		482		387	Resolved
6	MI	21	197	364	476	Resolved
7	PE	9	246	246	143	Resolved‡
8	DVT	15	61	108	114	Resolved
9	DVT	13	40	55	279	Not resolved
10	MI	23	146	208	761	Resolved
11	Cerebral infarction	7	143	324	300	Resolved‡
12	Cerebral infarction	25	219	476	244	Resolved‡
13	PE	29	94	304	215	Resolved
	DVT		228	304	229	Resolved
14	Balance disorder, speech disorder, dizziness (suspected PRIND)	14	14	44	1	Resolved
15	DVT (8 d posttherapy)	6	28	40	45	Resolving
16	DVT (7 d posttherapy)	23	214	465	57	Resolved

CNS indicates central nervous system; DVT, deep vein thrombosis; MI, myocardial infarction; PE, pulmonary embolism; PRIND, prolonged reversible ischemic neurologic deficit; and TIA, transient ischemic event.

*Baseline platelet count of the study in which the patient was first exposed to eltrombopag.

†Maximum platelet count includes platelet counts across studies while exposed to eltrombopag (ie, prior study and EXTEND study).

‡Events reported as resolved with sequelae.

Abstract 1368 Hepatobiliary and Thromboembolic Events during Long-Term E.X.T.E.N.Ded Treatment with Eltrombopag in Adult Patients with Chronic Immune Thrombocytopenia (ITP)

Annual Meeting Program Information

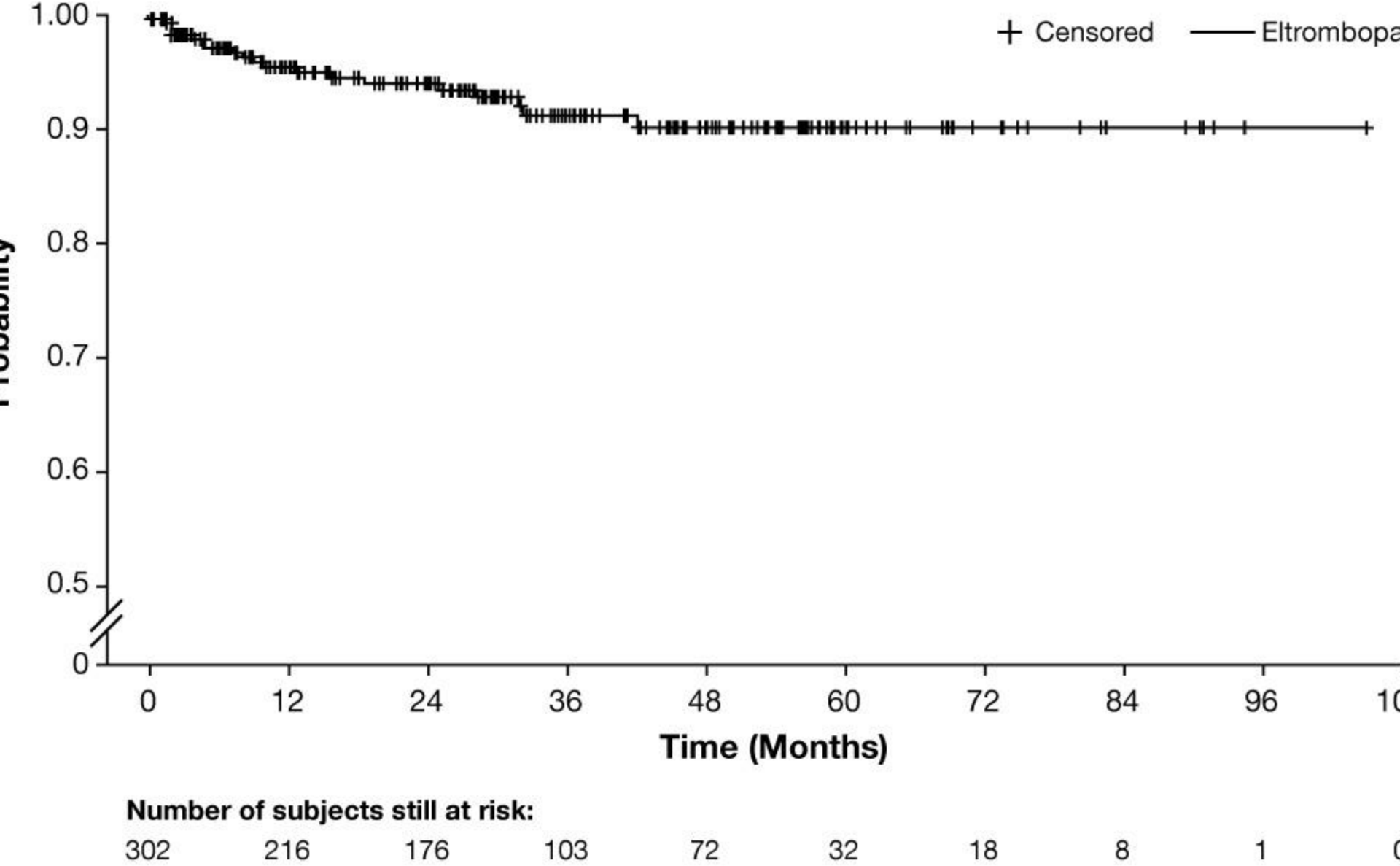
Saturday, December 3, 2016, 5:30 PM-7:30 PM
Hall GH (San Diego Convention Center)

Category: Disorders of Platelet Number or Function
Program: Oral and Poster Abstracts
Type: Poster
Session: 311. Disorders of Platelet Number or Function: Poster I

Mansoor N. Saleh[1], *James B Bussel, MD*[2], *Raymond SM Wong*[3*], *Balkis Meddeb*[4*], *Abdulgabar Salama*[5*], *Ali El-Ali*[6*], *Erhard Quebe-Fehling, PhD*[7*] *and Abderrahim Khelif*[8*]

- 19 (6.3%) patients experienced a total of 23 TEEs.
- Most events occurred in the first year , and none after year 4.
- TEEs included deep vein thrombosis (n=6), cerebral infarction (stroke) [n=3], myocardial infarction (n=4), transient ischemic attack (n=2), others (n=8, 1 occurrence of each).
- A clear association with elevated platelet counts was not observed.
- Platelets >200x10^9/L at the time of the TEE were recorded in 8/19 patients; 6/19 experienced the TEE at or shortly after achieving their maximum platelet count. In total, 10 patients discontinued because of TEEs.

gure B. Kaplan-Meier plot of time to first TEE



- Epidemiologic evidence and data from cohort studies suggest that ITP patients may be at increased risk of venous and arterial thromboembolic events.

- However, evidence from population-based studies could be hampered by some weakness, such as lack of standardization and validation in the definition of ITP, few data, if any, about phase of the disease, platelet count at events, and about ongoing specific therapy, lack of information about ITP out-patients outcome.

- Cohort studies are often mono-centric, with a sample size not adequate to obtain robust rate estimations.

Diz-Kukcukkaya RD et al; Blood 2001
Aledort L et al; Am J Hematol 2004
Kojouri K et al; Blood 2004
McMillan R et al; Blood 2004
Vianelli N et al; Haematologica 2005
Pierrot-Deseilligny Despujol C et al; Br J Haematol 2008
Sarpatwari A et al; Haematologica et al 2010
Gernsheimer TB et al; JTH 2010
Thomsen RV et al, JTH 2010
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Zoller B et al; Lancet 2011
Norgaard M et al; B J haematol 2012
Kuter DJ et al, Br J Haematol 2013
Saleh MN et al, Blood 2013
Boyle S et al, Blood 2013

Journal of Thrombosis and Haemostasis, **12**: 1266–1273 DOI: 10.1111/jth.12636

ORIGINAL ARTICLE

Thrombotic risk in patients with primary immune thrombocytopenia is only mildly increased and explained by personal and treatment-related risk factors

M. RUGGERI,* A. TOSETTO,* F. PALANDRI,† N. POLVERELLI,† M. G. MAZZUCCONI,‡ C. SANTORO,‡ G. GAIDANO,§ M. LUNGHI,§ F. ZAJA,¶ V. DE STEFANO,** R. SARTORI,†† P. FAZI,‡‡ and F. RODEGHIERO* FOR THE GRUPPO ITALIANO MALATTIE EMATOLOGICHE DELL'ADULTO (GIMEMA) ANEMIA AND THROMBOCYTOPENIAS WORKING PARTY. GIMEMA STUDY ITP0311

**Department of Cell Therapy and Hematology, San Bortolo Hospital, Vicenza; †Department of Hematology and Clinical Oncology 'L. and A. Seragnoli', S. Orsola-Malpighi Hospital, University of Bologna, Bologna; ‡Department of Biocellular Technology and Hematology, La Sapienza University, Roma; §Division of Hematology, Department of Translational Medicine, Amedeo Avogadro University of Eastern Piedmont and Maggiore Hospital, Novara; ¶Institute of Hematology, Transplant Center and Cellular Therapy 'Carlo Melzi' DISM, S. Maria Misericordia Hospital, University of Udine, Udine; **Institute of Hematology, Catholic University, Roma; ††Transfusion Service, Castelfranco Veneto Hospital, Castelfranco Veneto; and ‡‡GIMEMA Data Center, Roma, Italy*

- Data from 7 GIMEMA Centres was collected

- The original cohort consisted of 1.001 patients:

  15 individual were excluded by the coordinating centre because platelet count > 100 x 10^9/L at diagnosis (10) or absence of any specific treatment for ITP during the follow-up (5)

- 986 patients were included for the final evaluation, with a 3.888 patient-years observation time

	Unprovoked	Surgery in the preceding month	Total
	N (%)	N (%)	N (%)
Acute myocardial infarction	13 (30.2)	1 (2.3)	14 (32.6)
Stroke/TIA	8 (18.6)	-	8 (18.6)
Peripheral artery thrombosis	6 (13.9)	-	6(13.9)
Deep Vein thrombosis	10 (23.3)	-	10 (23.6)
Pulmonary Embolism	1 (2.3)	2 (4.7)	3 (6.9)
Superficial vein thrombosis	1 (2.3)	1 (2.3)	2 (4.7)
Total	39 (90)	4 (10)	43 (100)

Incidence of thromboembolic complications (per 100 pt/years) in the studied cohort. Values within brackets are 95% CI of the estimate

Age (years)	All events	Venous events	Arterial events
<40 years	0.23 (0.07-0.73)	0.15 (0.03-0.63)	0.07 (0.01-0.56)
40-60	0.66 (0.33-1.33)	0.33 (0.12-0.88)	0.24 (0.08-0.76)
>60 years	2.40 (1.68-3.41)	0.53 (0.25-1.12)	1.76 (1.17-2.65)
All ages	1.11 (0.82-1.51)	0.34 (0.19 – 0.59)	0.71 (0.48-1.04)

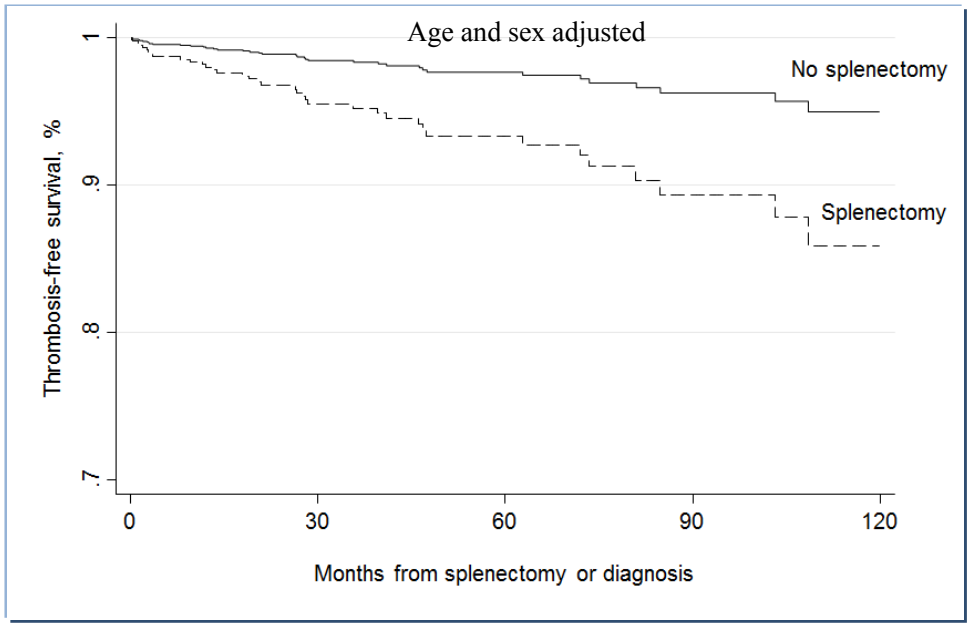
	No event (n=943)	Any thrombotic event (n=43)	p
Male/Female	349/594	19/24	0.34
Median age at diagnosis, years (range)	51 (10-95)	66 (30-90)	<0.001
Previous history of any thrombotic event, n (%)	41 (4.4)	6 (14.6)	0.003
Smoke, n (%) §	104 (12.3)	5 (12.5)	0.97
History of hypertension, n (%) §	245 (26.4)	29 (67.4)	<0.001
Hypercholesterolemia, n (%) §	57 (6.2)	9 (21.4)	<0.001
Diabetes n (%)§	87 (9.4)	14 (33.3)	<0.001
Hemoglobin at diagnosis, g/dL, mean (range)	13.4 (4.8-17.7)	13.6 (10.3-17.4)	0.818
White blood cell at diagnosis, $x10^9$/L, mean (range)	7.2 (6.5-47)	8.2 (3-16.7)	0.18
Platetet at diagnosis, $x10^9$/L mean (range)	35.1 (1-99)	24.1 (1-96)	0.04
Hemoglobin at event, g/dL, mean (range)	-	12.8 (6.6-17.2)	
White blood cell at event, $x10^9$/L mean (range)	-	10.2 (5-46.8)	
Platelet at event, $x10^9$/L mean (range)	-	141.4 (4-738)	
LA, n (%) ¶	(6.6)	29 (13.6)	0.20
ANA, n (%) ¶	17.7	37 (13.3)	0.57
APA, n (%) ¶	5.6	29 (9.1)	0.49
Treatment during follow-up			
Number of treatments, median (range)	2 (1-8)	3 (2-5)	0.006
Steroids n (%)	65.3	86.1	0.005
IVIg * n (%)	31.9	44.2	0.09
Splenectomy n (%)	13.2	25.5	0.02
Rituximab n (%)	16.1	11.6	0.42
TPO r.a. # n (%)	7.4	7.4	0.99
Immunosuppression n (%)	9.3	18.6	0.045

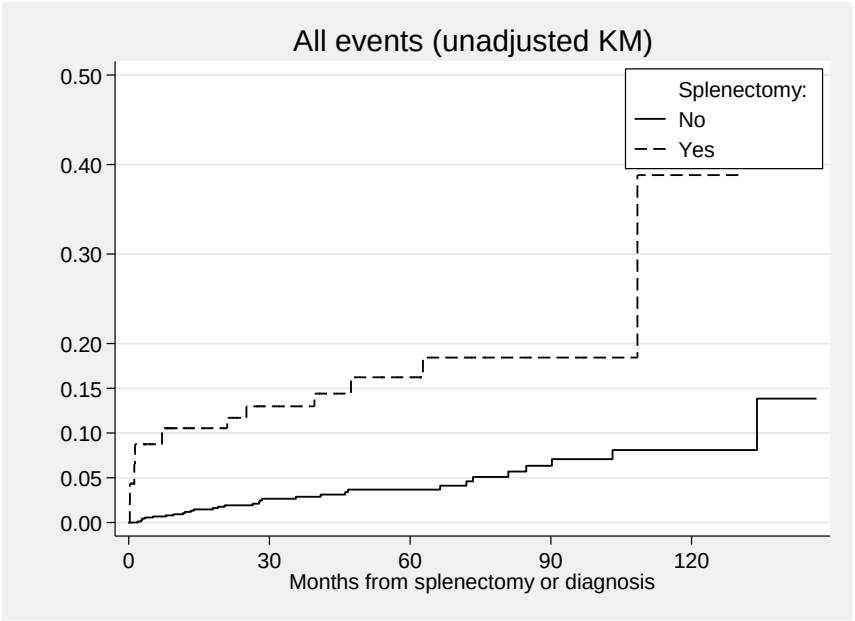
Cox regression estimates of Hazard Ratios (and 95% CI) for the considered risk factors (986 patients)

Risk factor	Hazard Ratio (95% CI)		
	All events (N. 43*)	VTE	Arterial
Age			
<40 years (32.6%)	1	1	1
40-60 years (29.0%)	1.7 (0.4 - 6.8)	1.4 (0.2 - 8.2)	2.1 (0.2 - 21.2)
>60 years (38.4%)	5.8 (1.6 - 21.1)	2.7 (0.5 - 16.2)	12.0 (1.5 – 98.5)
Number of risk factors present at diagnosis			
No risk factors	1	1	1
One	1.6 (0.7 - 3.9)	1.8 (0.5 - 7.0)	1.6 (0.5 - 5.0)
Two	1.9 (0.7 - 5.3)	0.8 (0.1 - 8.8)	2.6 (0.7 – 8.9)
Three or more	13.7 (4.5 - 41.1)	11.8 (2.0 - 70.7)	14.9 (3.6 - 60.6)
Prednisone use (vs. no prednisone use)	3.3 (1.0 - 11.0)	2.2 (0.5 - 10.4)	5.3 (0.9 - 40.6)
Splenectomy (vs. no splenectomy)	3.5 (1.6 - 7.6)	4.1 (1.1 - 15.7)	3.2 (1.2 - 8.6)

* 11 splenectomized

Probability of thrombotic events





- Annualized thrombotic risk 2.9% (CI 1.6 – 5.4) - 1.1% venous, 1.9% arterial constant over time
- After 5 yrs FU, not adjusted incidence: venous 6.6%, arterial 10.2%
- Risk ratio in keeping with Boyle et al, 2013 and Thomsen et al, 2010 (RR ~3)

Table 4 Platelet count at the time of thrombotic event

Platelet count ($\times 10^9$ L^{-1})	Thrombotic events	
	n	%
4–19	3	7
20 ≤ 49	6	14
50 ≤ 99	14	33
100 ≤ 399	17	39
≥ 400	3	7
Total	43	100

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Review

Risk of thrombosis in patients with primary immune thrombocytopenia and antiphospholipid antibodies: A systematic review and meta-analysis

Guillaume Moulis [a,*], Alexandra Audemard-Verger [b], Laurent Arnaud [c], Cécile Luxembourger [d], François Montastruc [e], Amelia Maria Gaman [f], Elisabet Svenungsson [g], Marco Ruggeri [h], Matthieu Mahévas [i], Mathieu Gerfaud-Valentin [j], Andres Brainsky [k], Marc Michel [i], Bertrand Godeau [i], Maryse Lapeyre-Mestre [e], Laurent Sailler [a]

[a] Internal Medicine Department, Toulouse University Hospital; UMR 1027 Inserm—University of Toulouse, France
[b] Internal Medicine Department, Caen University Hospital, France
[c] Inserm UMRS, 1136 Paris, France
[d] Rheumatology Department, Toulouse University Hospital, France
[e] Clinical and Medical Pharmacology Department, Toulouse University Hospital, UMR 1027 Inserm—University of Toulouse, France
[f] Department of Pathophysiology, University of Medicine and Pharmacy of Craiova, Department of Hematology, Filantropia City Hospital, Craiova, Romania
[g] Rheumatology Unit, Department of Medicine Solna, Karolinska University Hospital, Stockholm, Sweden
[h] Department of Hematology, San Bortolo Hospital, Vicenza, Italy
[i] Department of Internal Medicine, French National Center for Autoimmune Cytopenias, Créteil, France
[j] Department of Internal Medicine, Lyon University Hospital, France
[k] GlaxoSmithKline, Clinical Research, RD Projects Clinical Platforms & Sciences, Collegeville, PA, United States

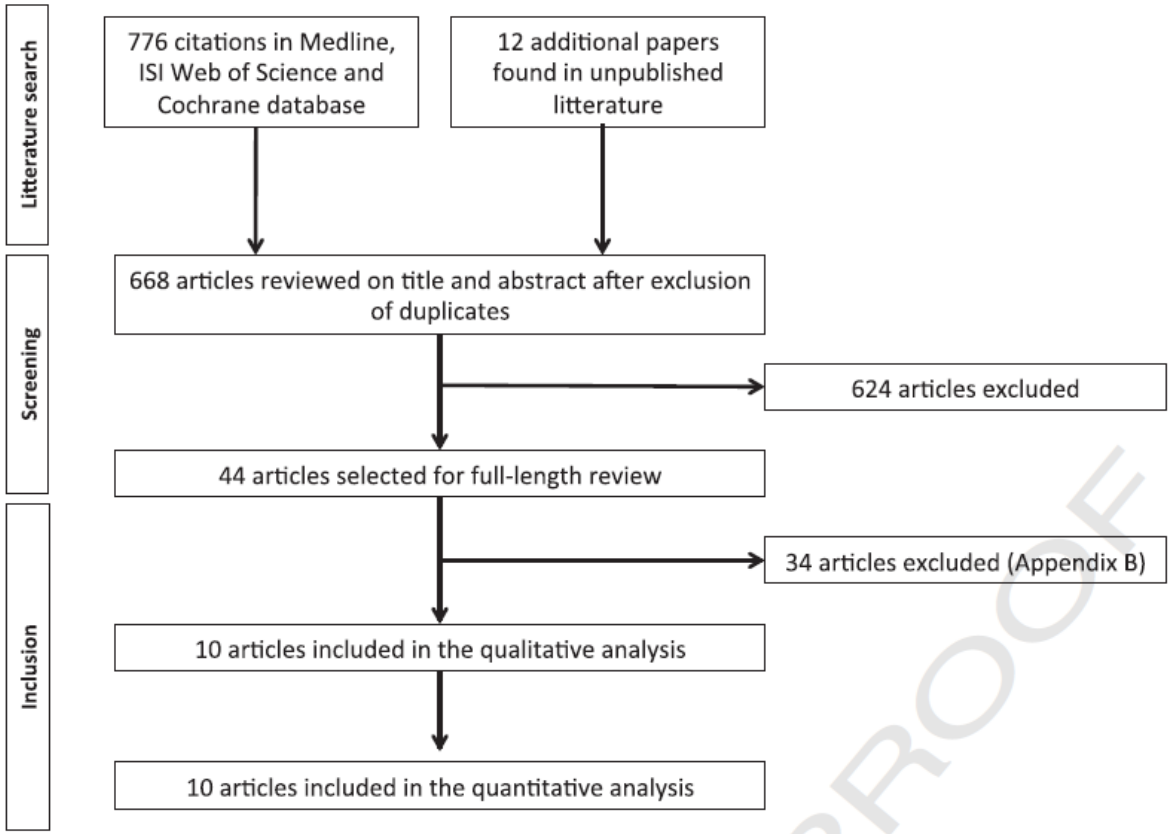


Fig. 1. Flowchart illustrating the study selection process.

Table 1
Characteristics of the 10 studies included in the meta-analysis.

Article	Design	Number of participants	Age, years	Female gender, %	Follow-up, months	Antiphospholipid antibody, n (%)			Outcome, n (%)		
						LA (+)	aCL (+)	aβ2GP1 (+)	Total	Arterial	Venous
Ruggeri et al., 2014	Retro.	564[a] b, c	52 (median)	62.7	38.2 (median)	39	– [b]	–	22	11	11
Wong et al., 2014	Pros.	167	41(median)	65.0	24	43	– [c]	– [c]	6	1	5
Kim et al., 2013	Retro.	165		30.9	53.4 (mean)	48	39	29	21	12	9
Gaman et al., 2013	Retro.	29	34 (median)	80.0	60	–	4	–	2	1	1
Yang et al., 2011	Pros.	70	48 (median)	64.3	19.6 (median)	5	17	–	2	1	1
Moulis et al., 2011	Retro.	93	46 (median)	74.2	36 (median)	6	20	4	2	0	2
Pierrot-Desseiligny et al., 2008	Retro.	215	44 (mean)	66.0	30 (median)	16	54	–[d]	14	4	10
Dash et al., 2004	Pros.	40	7 (median)	80.6	>6 months for 67.5%	11	–	–	0	0	0
Diz-Küçükkaya et al., 2001	Pros.	82	31 (median)	80.6	32 (median)	20	22	–	12	6	6
Stasi et al., 1994	Pros.	149	49 (median)	63.7	31 (median)	54	–[e]	–	0	0	0

Abbreviations: aβ2GP1: anti-β2GP1 antibody; aCL: anticardiolipin antibody; LA: lupus anticoagulant; NOS: Newcastle–Ottawa scale; Pros.: prospective; Retro.: retrospective.

[a] Restricted to patients tested for LA.

[b] Only patients tested for LA were considered in these analyses, due to heterogeneity in aCL testing across the various centers participating in the study.

[c] Only patients tested for LA were considered in these analyses. Indeed, exposure to aCL and aβ2GP1 antibodies was described by antibody isotype only, while thrombotic events were described regarding the overall aCL/aβ2GP1 antibody positivity whatever the isotype. Moreover, several thresholds of positivity were tested for aCL and aβ2GP1, without description of the association with thrombosis occurrence.

[d] aβ2GP1 antibodies were not tested in the overall study population.

[e] Only patients tested for LA were considered in these analyses. Indeed, exposure to aCL antibodies was described by antibody isotype only.

Study	Thromboses		OR (95% CI)
	LA pos.	LA neg.	
Ruggeri	3/39	19/525	2.22 (0.63-7.85)
Wong	6/43	0/124	-
Kim	13/48	8/117	5.06 (1.94-13.21)
Yang	1/5	1/65	16.00 (0.84-305.74)
Moulis	1/6	1/87	17.20 (0.93-317.35)
Pierrot-Deseilligny	4/16	10/199	6.30 (1.72-23.07)
Dash	0/11	0/29	-
Diz-Küççükkaya	10/20	2/62	30.00 (5.71-157.66)
Stasi	0/54	0/95	-
Total	**38/242**	**41/1303**	**6.11 (3.40-10.99)**

Test for overall effect: p<0.001
Heterogeneity: I^2=0%

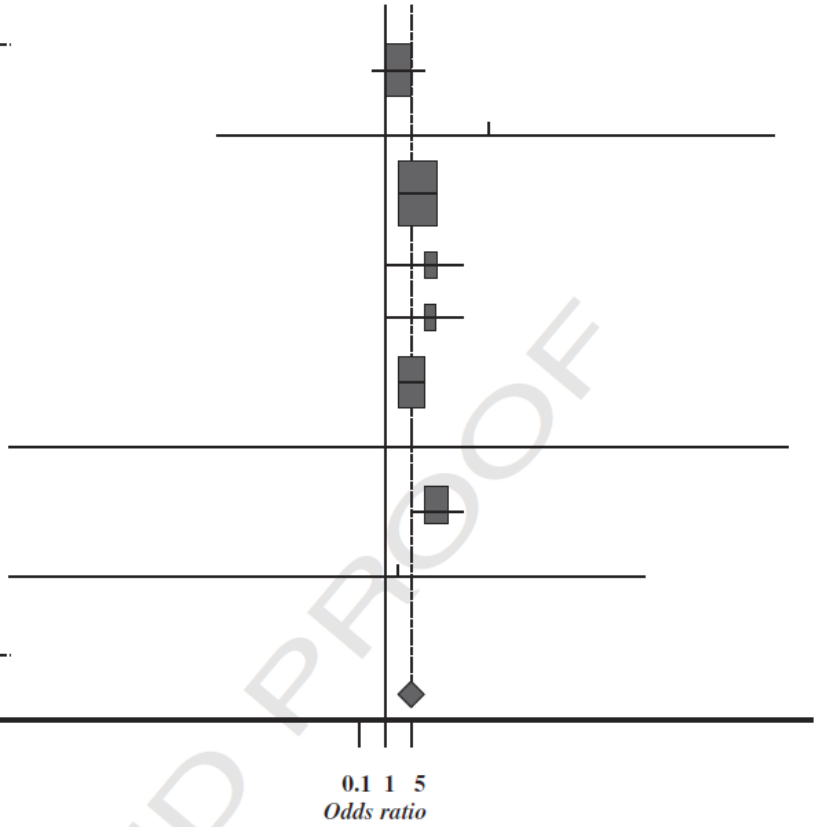
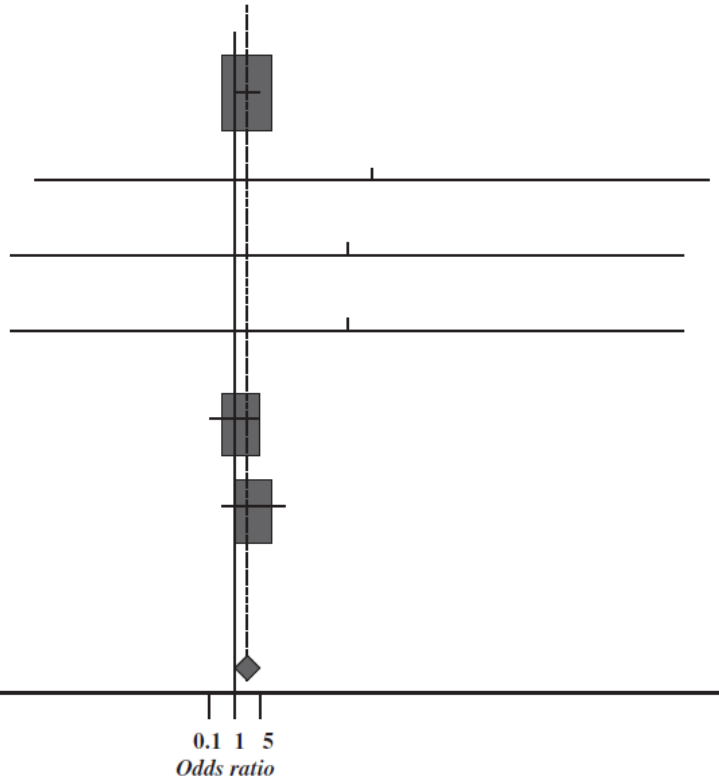


Fig. 2. Results of the meta-analysis assessing the risk of all thromboses in primary ITP patients in the presence of lupus anticoagulant. Abbreviations: CI, confidence interval; LA, lupus anticoagulant; OR, odds ratio; pos., positive; neg., negative.

Study	Thromboses		OR (95% CI)
	aCL pos.	aCL neg.	
Kim	8/39	13/126	2.24 (0.85-5.90)
Gaman	2/4	0/25	-
Yang	2/17	0/53	-
Moulis	2/20	0/73	-
Pierrot-Deseilligny	4/54	10/161	1.21 (0.36-4.02)
Diz-Küçükkaya	5/22	5/67	3.65 (0.94-14.08)
Total	**23/156**	**27/505**	**2.14 (1.11-4.12)**



Test for overall effect: p=0.023
Heterogeneity: I^2=0%

Fig. 3. Results of the meta-analysis assessing the risk of all thromboses in primary ITP patients in the presence of anticardiolipin antibodies. Abbreviations: aCL, anticardiolipin antibody; CI, confidence interval; OR, odds ratio; pos., positive; neg., negative.

Conclusions

Rodeghiero F; EJH, 2013

- Severe, even life-threatening or fatal, bleeding – although rare – remains the major risk in ITP (1-2% with available treatments)
- It is unclear at the moment if the recent awareness of a minimal increased risk of thrombosis in ITP, possibly aggravated by the exposure to TPO-ra or splenectomy, should mandate a change in the management algorithm
- Certainly, the focus of treatment should be aimed at minimizing thrombotic risk by reserving pharmacological or surgical treatment to patients at high risk of bleeding
- The main outcome of future studies should be more focused on bleeding control than on platelet count increase
- Stratification of patients according to their bleeding and thrombotic risk would require ad hoc prospective studies
- In the meantime, personalization of treatment by expert clinicians remains of paramount importance

bjh research paper

Procoagulant profile in patients with immune thrombocytopenia

María T. Álvarez-Román,[1] Ihosvany Fernández-Bello,[1] Víctor Jiménez-Yuste,[1,2] Mónica Martín-Salces,[1] Elena G. Arias-Salgado,[3] María I. Rivas Pollmar,[1] Raúl Justo Sanz[1] and Nora V. Butta[1]

[1]*Haematology and Haemotherapy Unit, University Hospital La Paz-IdiPaz,* [2]*Universidad Autónoma de Madrid, and* [3]*Advanced Medical Projects Madrid, Madrid, Spain*

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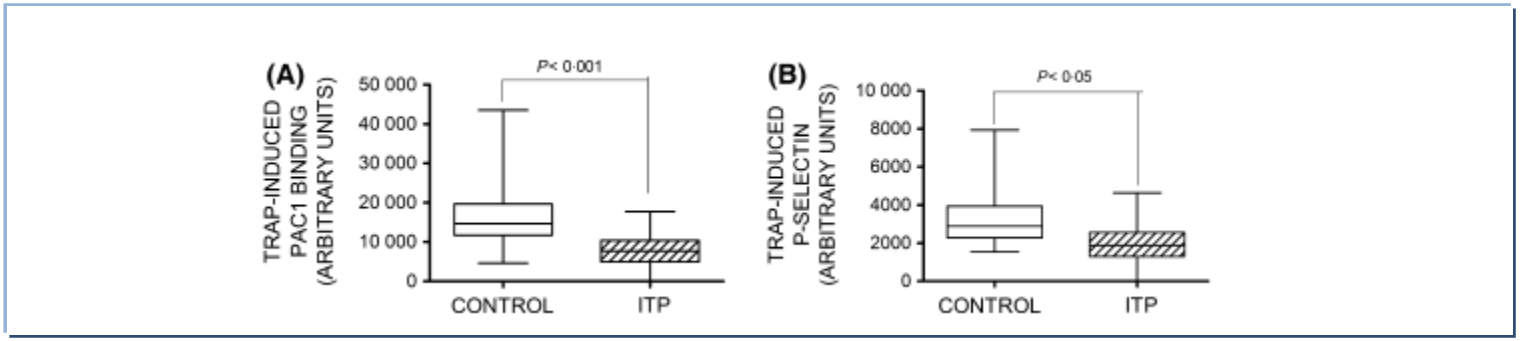
bjh BRITISH JOURNAL OF HAEMATOLOGY

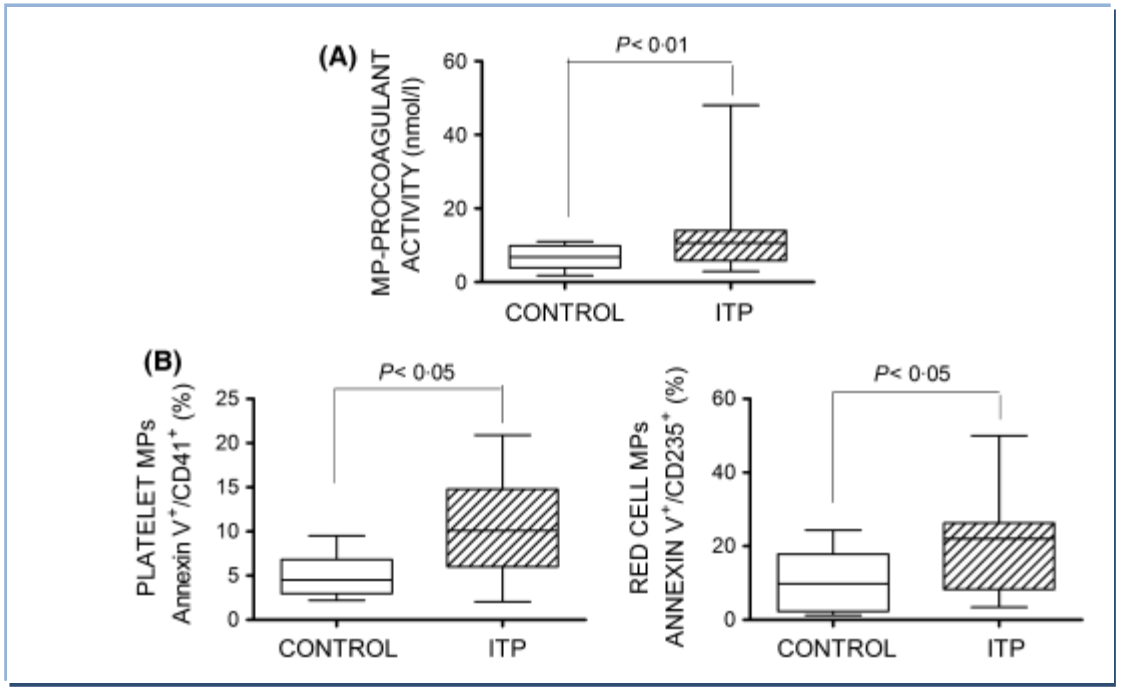
Studied population	42 chronic ITP patients and 35 healthy subjects
Methods	
1. Platelet activation	Flow analysis of: • activated conformation of fibrinogen receptor • P-selectin exposure
2. Plasma procoagulant activities	Determination of microparticle
3. Kinetics of clot formation	Rotational thromboelastometry
4. Thrombin generation	Calibrated automated thrombogram
5. Coagulation and fibrinolysys	Protein assay

Platelet activation



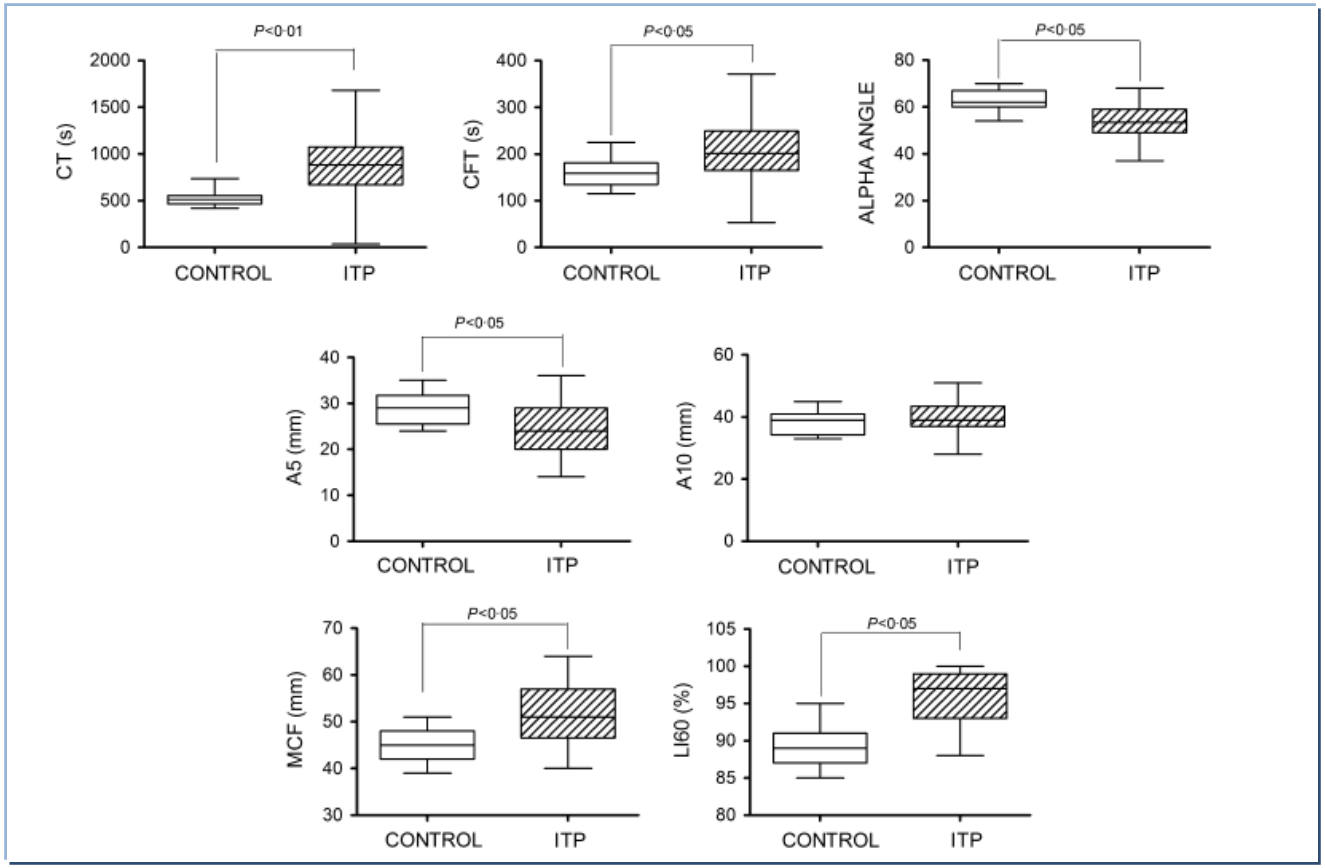
Platelet from ITP had a defect in their ability to be activated

Plasma procoagulant activites



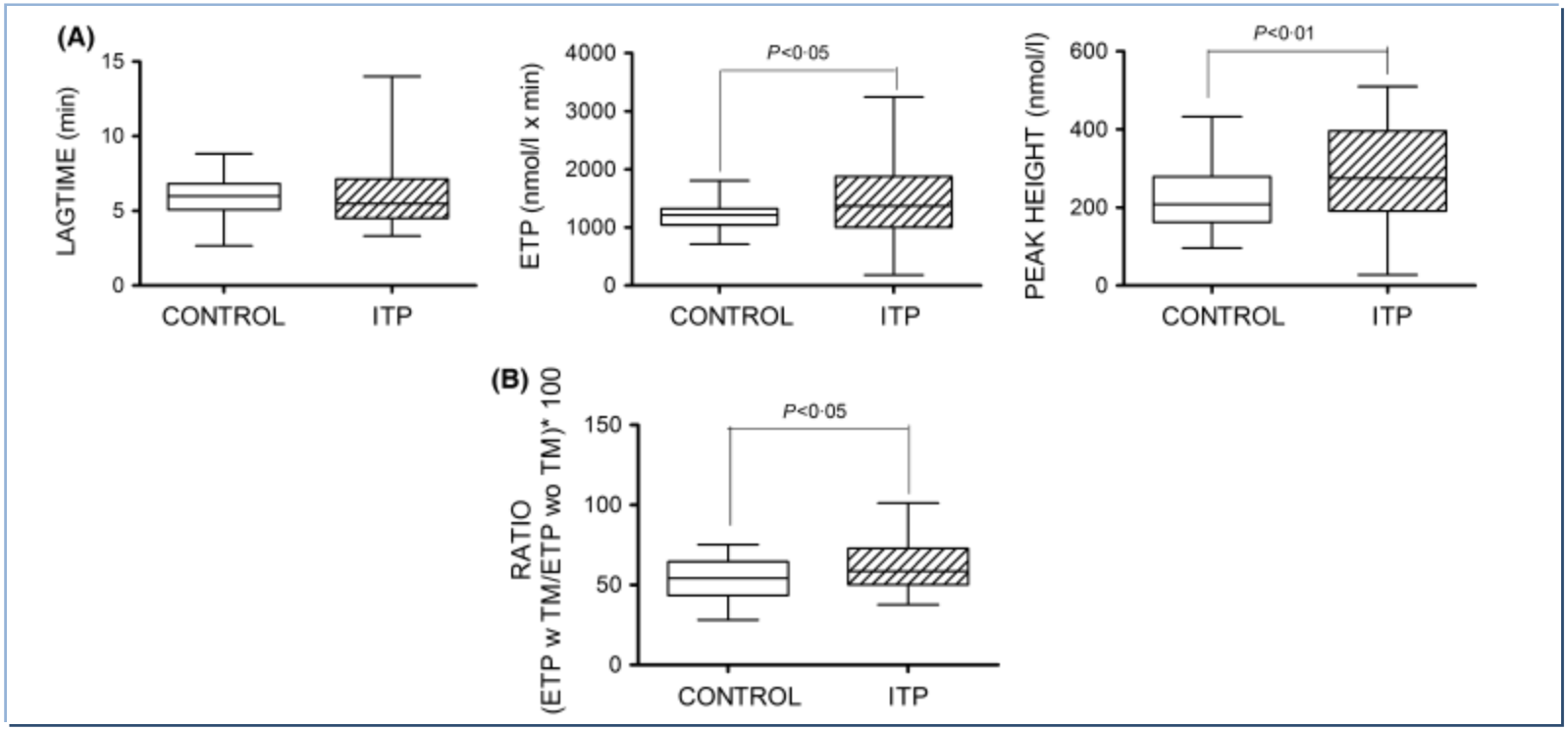
Microparticel – associated procoagulant capacity was higher in ITP than in controls

Kinetics of clot formation



Deferral in clot formation and a higher resistance to fibrinolysis

Thrombin generation



Plasma from ITP patients had a procoagulant profile

Clotting and fibrinolysis factors

Normal levels of fibrinogen and clotting factors

	Control median (range)	ITP median (range)
TAFI, % of activity	32·4 (28·79–37·0)	30·8 (28·0–35·2)
uPA, pg/ml	612·8 (539·9–749·9)	720·5 (634·9–808·8)
tPA, pg/ml	753·0 (578·6–959·0)	750·4 (565·9–912·2)
PAI-1, ng/ml	10·4 (6·6–23·4)	27·01 (16·2–43·8)*
E-Selectin, ng/ml	10·69 (6·57–14·47)	30·49 (17·53–45·33)*

Increase level of PAI-1

ITP patients presented a procoagulant profile due to:

- Increase amount of MP
- Increase resistance to activated Protein C
- Formation of a clot more resistant to fibrinolysis

Several pathogenesis:

- Increase platelet apoptosis
- Auto-antibodies activities
- Endothelial damage

Journal of Thrombosis and Haemostasis, **11**: 56–70 DOI: 10.1111/jth.12070

ORIGINAL ARTICLE

International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer

D. FARGE,*†[1] P. DEBOURDEAU,‡[1] M. BECKERS,§ C. BAGLIN,¶ R. M. BAUERSACHS,** B. BRENNER,††
D. BRILHANTE,‡‡ A. FALANGA,§§ G. T. GEROTZAFIAS,¶¶ N. HAIM,*** A. K. KAKKAR,†††
A. A. KHORANA,‡‡‡ R. LECUMBERRI,§§§ M. MANDALA,¶¶¶ M. MARTY,**** M. MONREAL,††††
S. A. MOUSA,‡‡‡‡§§§§ S. NOBLE,¶¶¶¶ I. PABINGER,***** P. PRANDONI,††††† M. H. PRINS,‡‡‡‡‡
M. H. QARI,§§§§§ M. B. STREIFF,¶¶¶¶¶ K. SYRIGOS,****** H. BOUNAMEAUX†††††† [1]
and H. R. BÜLLER‡‡‡‡‡‡ [1]

6 In cancer patients with thrombocytopenia, full doses of anticoagulant can be used for the treatment of established VTE if the platelet count is > 50 G L^{-1} and there is no evidence of bleeding; for patients with a platelet count below 50 G L^{-1}, decisions on treatment and dosage should be made on a case-by-case basis with the utmost caution [Best clinical practice, in the absence of data and a balance between desirable and undesirable effects depending on the bleeding risk vs. VTE risk].

7 In cancer patients with mild thrombocytopenia, platelet count > 80 G L^{-1}, pharmacological prophylaxis may be used; if the platelet count is below 80 G L^{-1}, pharmacological prophylaxis may only be considered on a case-by-case basis and careful monitoring is recommended [Best clinical practice, in the absence of data and a balance between desirable and undesirable effects depending on the bleeding risk vs. VTE risk].

blood

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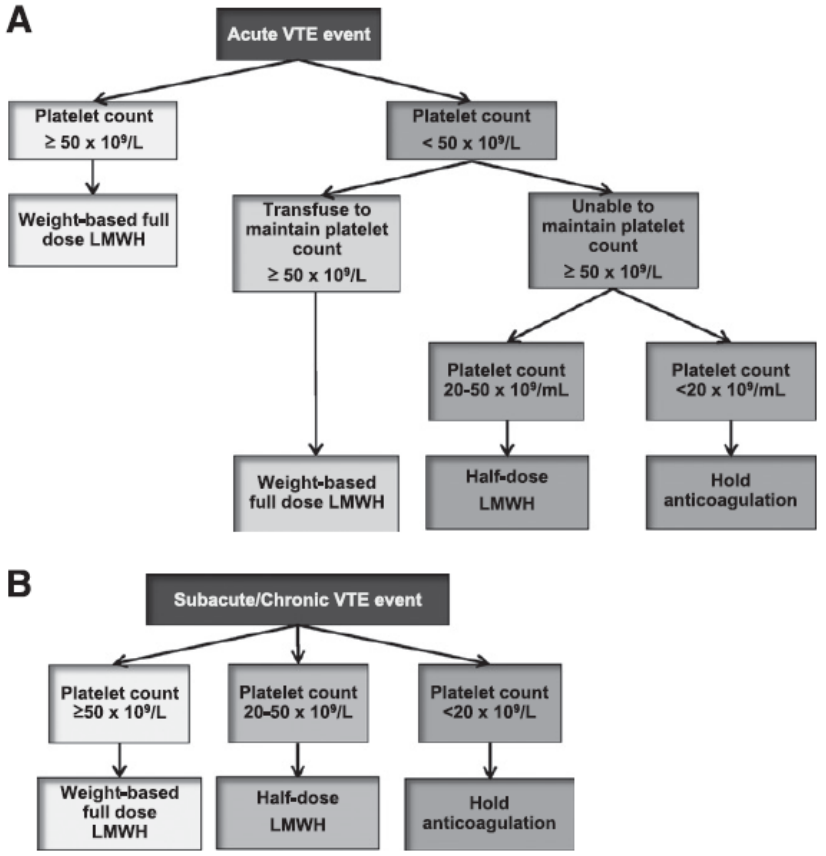
Treatment of cancer-associated thrombosis

Agnes Y. Y. Lee and Erica A. Peterson



Abstract 164 A Platelet Count <50 x10^9 Was Not Associated with Increased Rates of Major Bleeding Among Anticoagulated Patients

Annual Meeting Program Information

Saturday, December 3, 2016: 2:15 PM
Room 29 (San Diego Convention Center)

Category: Disorders of Platelet Number or Function
Program: Oral and Poster Abstracts
Type: Oral
Session: 311. Disorders of Platelet Number or Function: ITP II: Clinical and Biologic

Bethany T Samuelson, MD[1], *Roland B. Walter, MD, PHD*[2], *Terry Gernsheimer, MD*[3] *and David A Garcia, MD*[4]

[1]*Department of Medicine, Division of Hematology, University of Washington, Seattle, WA*
[2]*Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA*
[3]*Department of Medicine, Hematology, University of Washington, Seattle, WA*
[4]*University of Washington, Seattle, WA*

Retrospective chart review of cases of venous thrombosis, diagnosed between January 1, 2009 and December 31, 2014, during which the patient also experienced a ≥5-day period of moderate to severe (platelets $<50x10^9/L$) treatment-related thrombocytopenia within 30 days of diagnosis.

Inclusion criteria were: age ≥ 18 years old, new diagnosis of acute VTE and ≥ 5 days of treatment-related thrombocytopenia (platelet count < $50x10^9/L$ in the absence of transfusions) while undergoing HSCT for a hematologic malignancy or other curative-intent therapy for acute leukemia within 30 days of VTE diagnosis.

In the absence of evidence to guide management, the majority of providers maintain a platelet transfusion threshold of ≥ $50x10^9$/L for patients undergoing anticoagulation during periods of treatment-related thrombocytopenia.

While patients who experienced a platelet count below this goal for > 5 days had higher rates of minor (Grade 2) bleeding, increased rates of clinically significant (Grade 3/4 bleeding) were not observed.

Patients experienced a number of negative effects potentially related to transfusions, including transfusion reactions and volume overload and, in some cases, early discontinuation of anticoagulation due to difficulty adhering to the stated platelet goal.

Need for future trials designed to identify the optimal platelet transfusion threshold for patients who require anticoagulation.