50 MINUTES ON...

50 Minutes on: ITP LAB
Multidisciplinary approach and open discussion
Special lectures, special guests

WEBINAR

2. THROMBO-EMBOLISM IN ITP: HOW TO SELECT AND TREAT PATIENTS AT RISK
June 18, 2024

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Disclosures

- Research support: Bayer, Pfizer, UCB.
- Speaker fees: Amgen, Novartis, Pfizer, Bristol Myers Squibb, SOBI, Grifols, Sanofi.
- Advisory boards: Amgen, Novartis, Pfizer, Principia Biopharma Inc- a Sanofi Company, Sanofi, SOBI, Grifols, UCB, Argenx, Cellphire, Hutchmed.

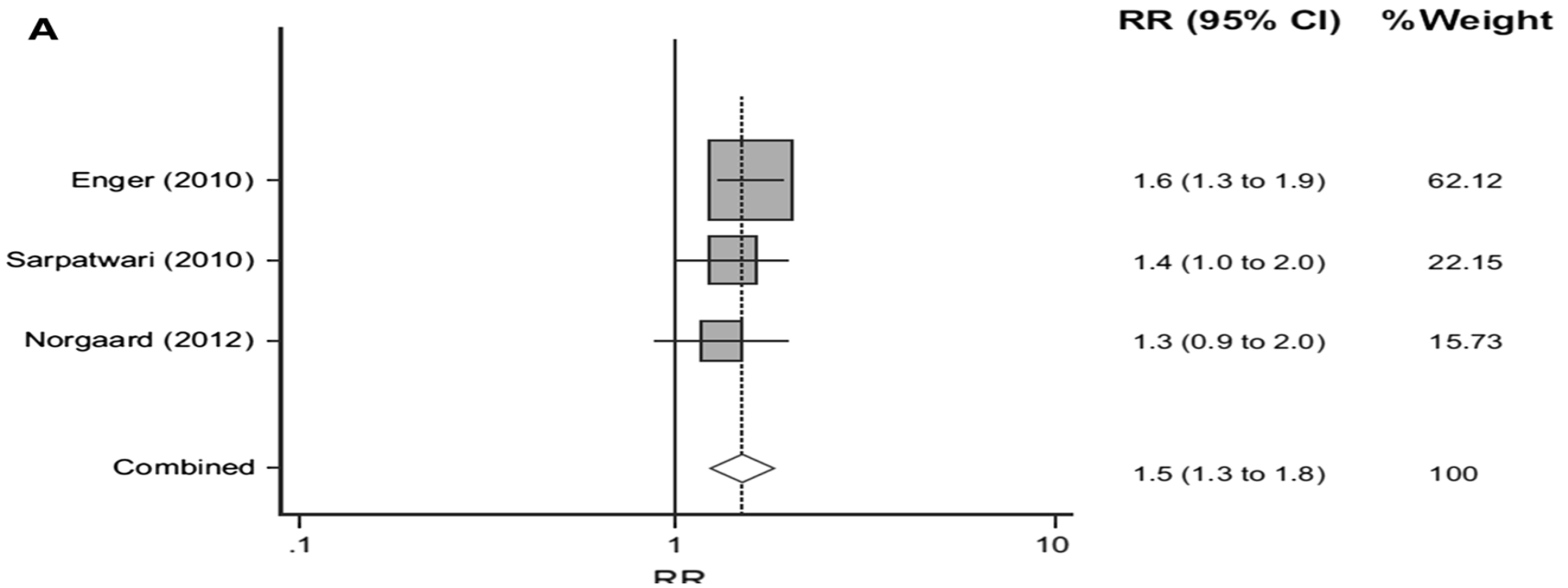
Case

- 50-year-old female, a chronic ITP, steroid responsive
- Recurrent drop platelets down to single digits by response to steroids.
- Started her on TPO-RA. One week later developed headache.
- MRI scan and CT: sagittal sinus thrombosis.
- Currently on Apixaban.
- What do you think and advise?

The risk and consequences of thromboembolism in ITP

Evidence from epidemiological studies

Thromboembolism in patients with ITP: a meta-analysis of observational studies

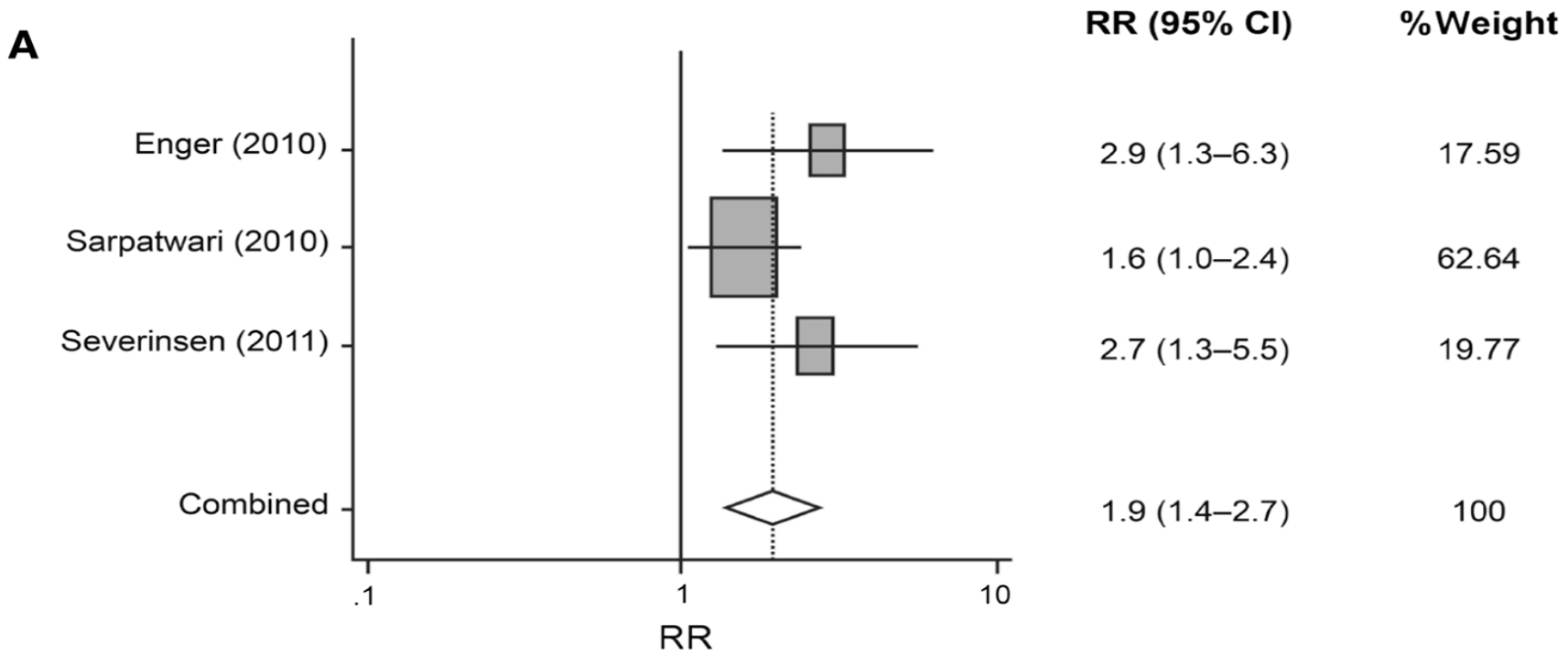


Incidence of ATE / 100 PY among:

ITP patients	1.0 - 2.8
Population	0.7 - 1.8
Rate Ratio	**1.5 (95 % CI 1.3, 1.8)**

Langeberg et al. Int J Hematol 2016;103: 655-664

Thromboembolism in patients with ITP: a meta-analysis of observational studies

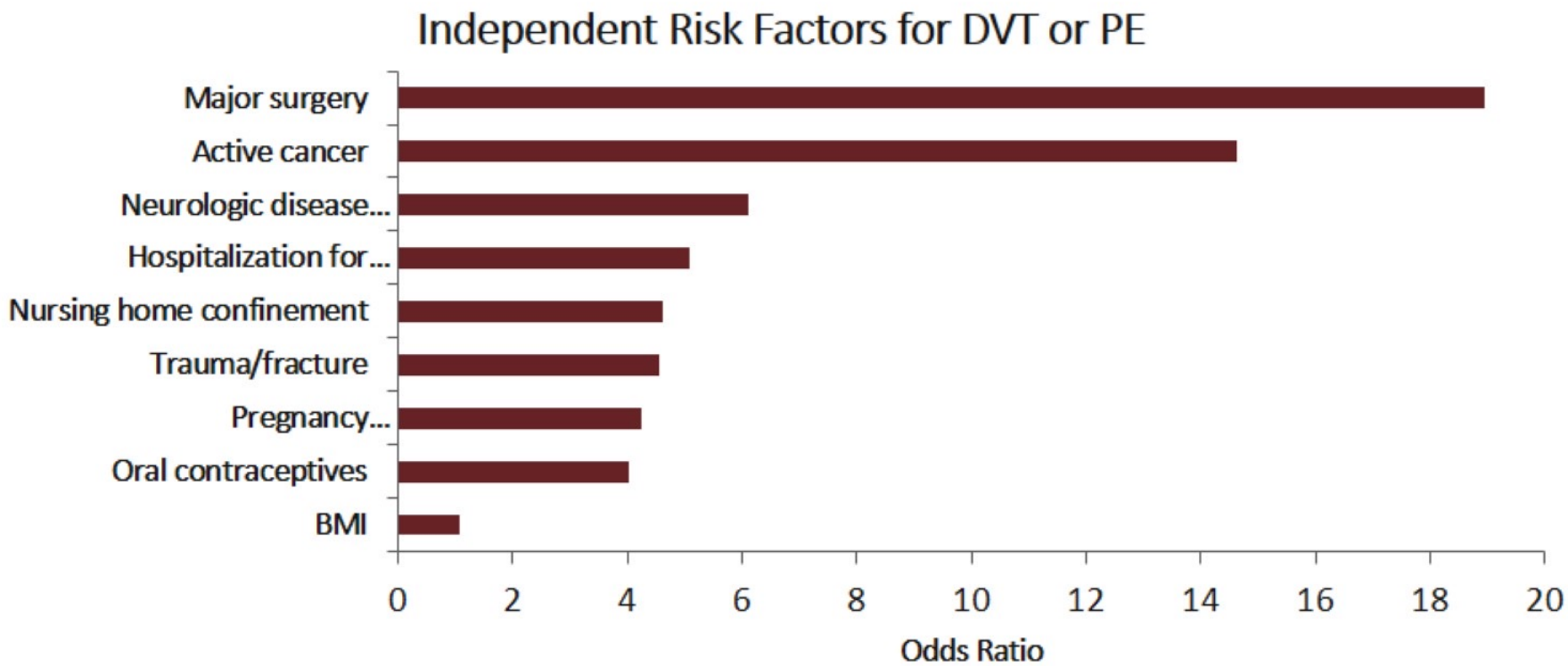


Incidence of VTE / 100 PY among:

ITP patients	0.4 – 0.7
Population	0.1 – 0.4
Rate Ratio	**1.9 (95 % CI 1.4, 2.7)**

Langeberg et al. Int J Hematol 2016;103: 655-664

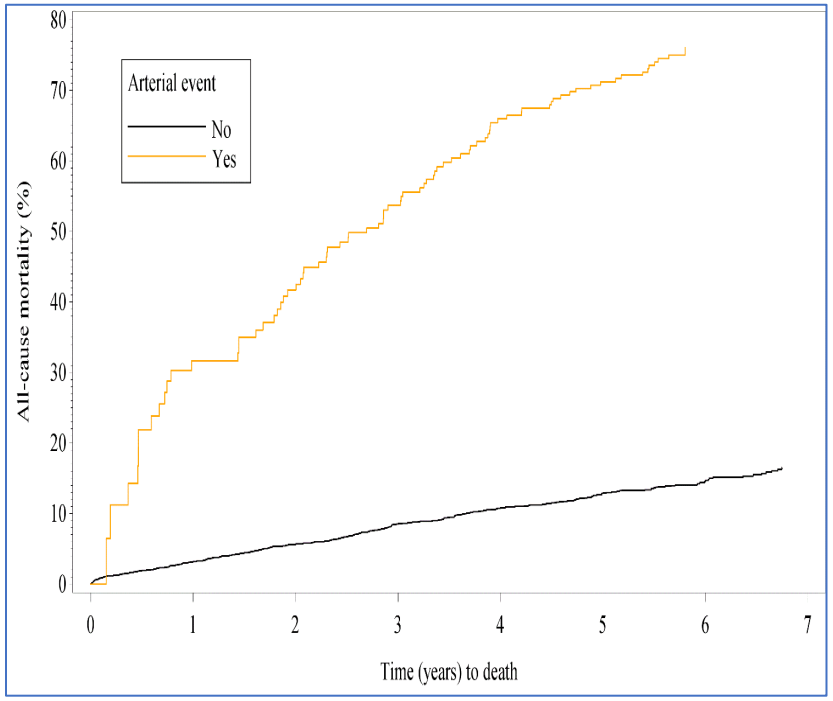
Independent VTE Risk Factors

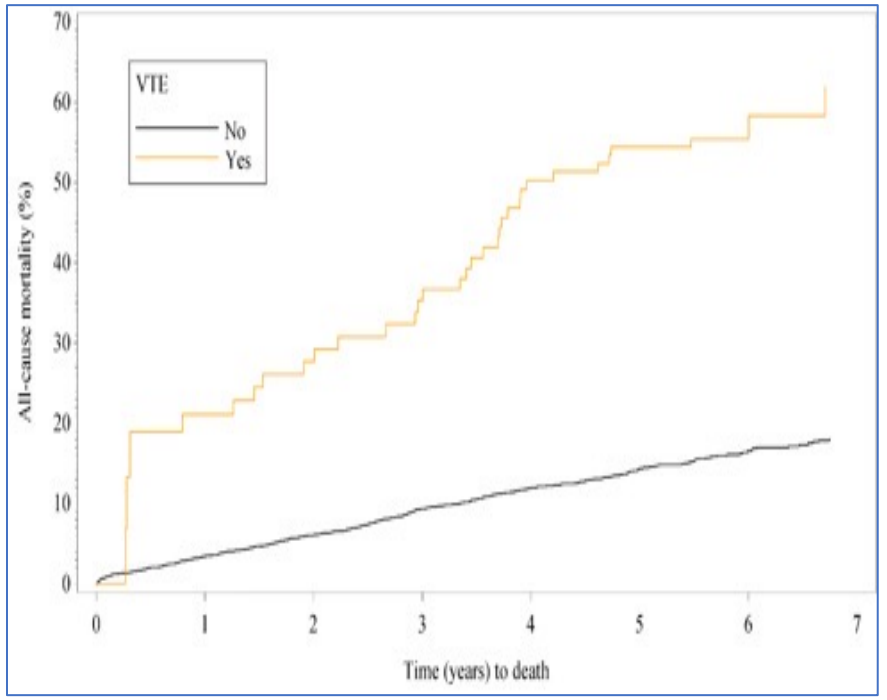


Intrinsic (patient-centered) risk factors also play a great role in contributing to the overall VTE risk along with the type of surgery or medical illness

Heit JA, et al. *J Thromb Thrombolysis*. 2016;41:3-14.

Consequences of thromboembolism in ITP





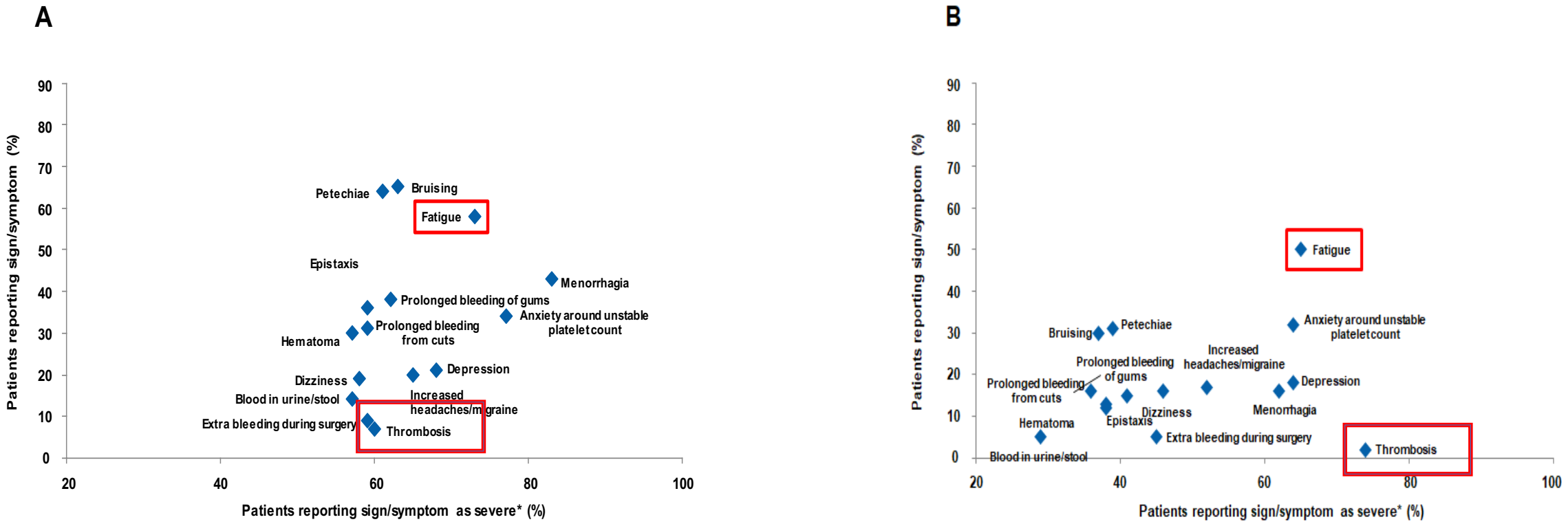
Arterial Thrombosis

Venous Thromboembolism

All-cause mortality in chronic ITP

Adelborg K et al. J Thromb Haemost. 2019 ;17:912-924

Consequences of thromboembolism in ITP



Patient perception at diagnosis (A) and time of survey completion (B) of occurrence and severity of ITP signs and symptoms

Cooper N, *et al. Am J Hematol.* 2021;96:188–98.

Is it the disease or the treatment?

Case

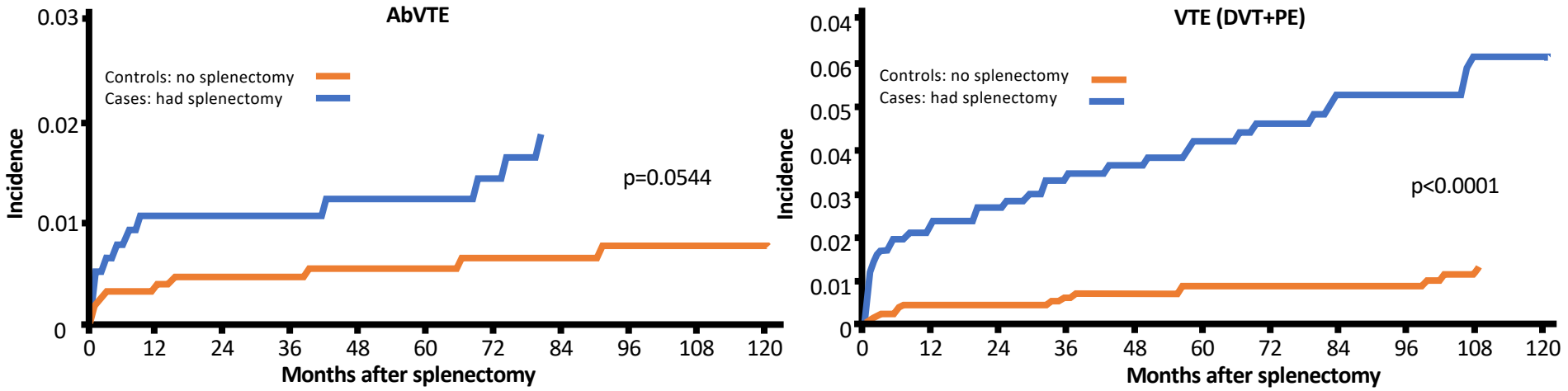
- I would like your opinion: 50-year-old female, a chronic ITP steroid responsive recurrent drop platelets down to single digits by response to steroids.

- Started her on TPO-RA one week later developed headache, MRI scan and CT sagittal sinus thrombosis.

- Currently in Apixaban. What do you think and advise?

- Advice: continue on Apixaban as long as platelet count is >50 $X10^9/L$
- Antiphospholipid antibodies?

Incidence of AbVTE and VTE by splenectomy status



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)

Boyle S, et al. Blood 2013;121:4782–90.

Log-rank p-values.
AbVTE, abdominal venous thromboembolism; DVT, deep venous thrombosis; PE, pulmonary embolus.

Case reports of Rituximab-induced myocardial infarction

Study	Age and sex	Rituximab dose	Indication	Cardiac risk factors	Type and time to MI	Outcome
Armitage, 2008	58, Male	First	CLL	Previous MI	Two have MI during the infusion (one of them was with a test dose of 25 mg) and the third at the completion of infusion	Survival
	61, Male		BL	+Risk factors		Survival
	72, Male		BLL	+Risk factors		Death
Arunprasath, 2011	60, Male	First	DLBCL	Diabetes	AWMI, 15 min after starting the infusion	Survival
Renard, 2013	52, Male	Third, 375 mg/m^2	MG	None	IWMI, 10 h after the infusion	Survival
Gogia, 2014	65, Male	First	SLVL	None	IWMI, after 5 min of starting the infusion	Survival
Van Stjl, 2014	70, Female	First and second	RA	Previous history of MI	ALWMI	Survival
	76, Female	Second	RA	None	AWMI	Survival
Keswani, 2015	46, Male	Second	DLBCL	Smoking: 25 pack-years	IWMI, halfway through the infusion	Survival
Verma, 2016	62, Male	First	NHL	None	IWMI, after 5 min of starting the infusion	Survival
Mehrpooya, 2016	52, Female	First dose, 375 mg/m^2	ITP	HTN, mild CAD	IWMI, 24 h	Survival
Arenja, 2016	36, Male	Not specified	PR3-ANCA-positive granulomatosis with polyangiitis	Smoking: 20 pack-years, HTN, hypercholesterolaemia	AWMI	Survival
Sharif, 2017	58, Male	Fifth dose of 1,000 mg	RA + Scleroderma	HTN, smoking: 30 pack-years	AWMI, during infusion	Survival

Al Rahhal et al, Frontiers in Medicine. 2024. DOI 10.3389/fmed.2024.134894

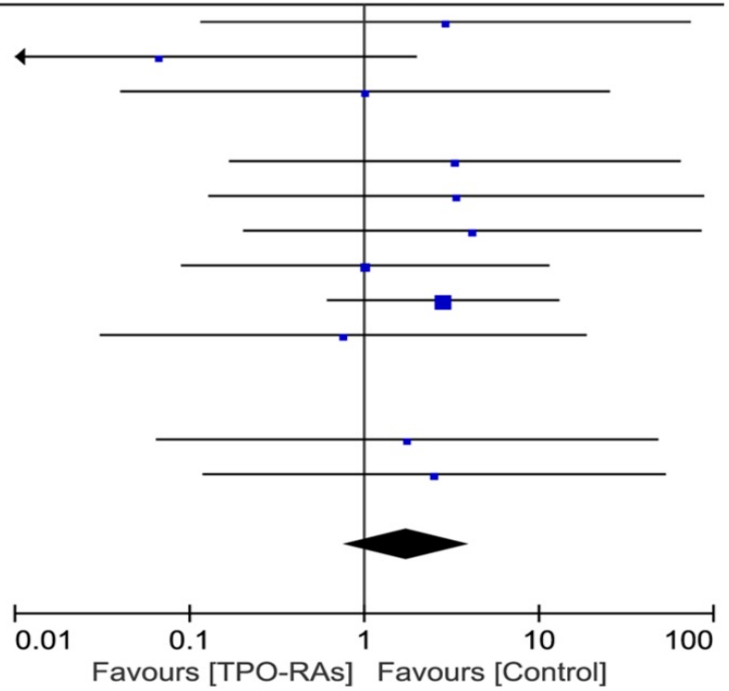
Risk of thromboembolism in TPO-RA treated patients – a meta-analysis of RCTs

Thromboembolic events were observed in most of the TPO-RA trials

Study or subgroup	TPO-RAs Events	TPO-RAs Total	Control Events	Control Total	Weight	Odds ratio M-H, Random, 95% CI
Arnold et al., 2020	1	38	0	36	6.4%	2.92 [0.12, 74.03]
Bussel et al., 2006	0	17	1	4	5.8%	0.07 [0.00, 2.00]
Bussel et al., 2007	1	88	0	29	6.5%	1.01 [0.04, 25.51]
Bussel et al., 2009	0	76	0	38		Not estimable
Cheng et al., 2011	3	135	0	62	7.6%	3.30 [0.17, 64.90]
Huang et al., 2018	1	17	0	18	6.3%	3.36 [0.13, 88.39]
Jurczak et al., 2018	3	32	0	17	7.4%	4.15 [0.20, 85.23]
Kuter et al., 2008	2	83	1	42	11.4%	1.01 [0.09, 11.50]
Kuter et al., 2010	11	157	2	77	28.7%	2.83 [0.61, 13.08]
Mei et al（1）, 2021	1	339	0	85	6.5%	0.76 [0.03, 18.76]
Mei et al（2）, 2021	0	48	0	48		Not estimable
Shirasugi et al., 2011	0	22	0	12		Not estimable
Tomiyama et al., 2012	1	15	0	8	6.1%	1.76 [0.06, 48.19]
Yang et al., 2017	2	104	0	51	7.2%	2.51 [0.12, 53.30]
Total (95% CI)		**1171**		**527**	**100.0%**	**1.76 [0.78, 4.00]**
Total events	26		4			

Heterogeneity: Tau² = 0.00; Chi² = 5.29, df = 10 (P = 0.87); I² = 0%

Test for overall effect: Z = 1.35 (P = 0.18)



OR=1.76, 95% CI: 0.78, 4.00, P=0.18

CI, confidence interval; OR, odds ratio; RCT, randomized controlled trial; TPO-RA, thrombopoietin receptor agonist.

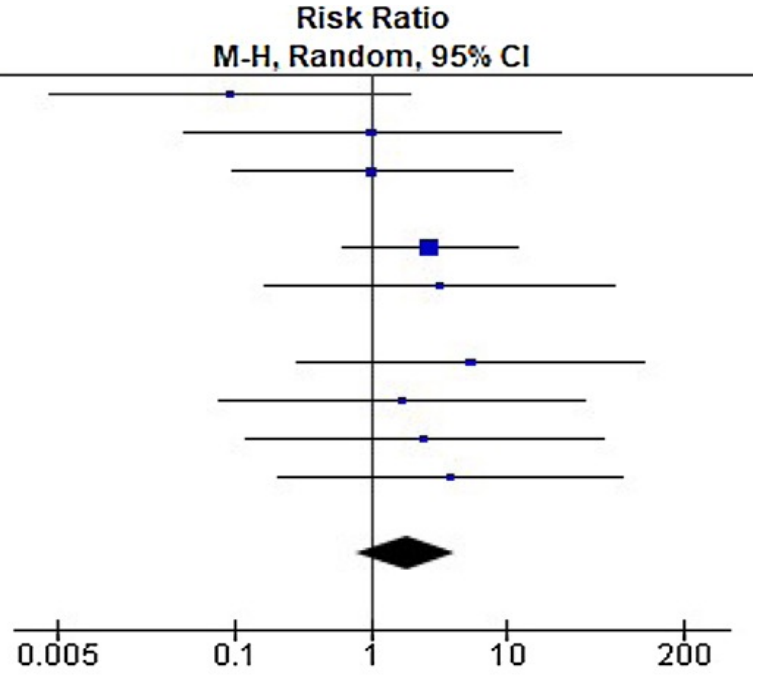
Shen N, et al. *Biomed Rep.* 2024;20(3):44.

Meta-analysis: Thromboembolism in adults treated with TPO-RA vs placebo/SoC in the RCTs

Study or Subgroup	TPO-RA Events	TPO-RA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Bussel et al. 2006	0	17	1	4	7.7%	0.09 [0.00, 1.94]	2006
Bussel et al. 2007	1	88	0	29	7.1%	1.01 [0.04, 24.17]	2007
Kuter et al. 2008	2	83	1	42	12.7%	1.01 [0.09, 10.84]	2008
Bussel et al. 2009	0	76	0	38		Not estimable	2009
Kuter et al. 2010	11	157	2	77	32.4%	2.70 [0.61, 11.87]	2010
Cheng et al. 2011	3	135	0	62	8.2%	3.24 [0.17, 61.84]	2011
Shirasugi et al. 2011	0	22	0	12		Not estimable	2011
Haselboeck et al. 2012	2	11	0	12	8.3%	5.42 [0.29, 101.77]	2012
Tomiyama et al. 2012	1	15	0	8	7.4%	1.69 [0.08, 37.26]	2012
Yang et al. 2016	2	104	0	51	7.8%	2.48 [0.12, 50.64]	2016
Jurczak et al. 2018	3	32	0	17	8.4%	3.82 [0.21, 69.88]	2018
Total (95% CI)		**740**		**352**	**100.0%**	**1.82 [0.78, 4.24]**	
Total events	25		4				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.30$, $df = 8$ ($P = 0.73$); $I^2 = 0\%$

Test for overall effect: $Z = 1.39$ ($P = 0.16$)



RR 1.82 [0.78–4.24]); p = 0.16

25 thromboembolic (5 arterial, 8 venous, 12 unspecified) events occured in the TPO-RA group vs 4 in the comparator arm

Tjepkema et al. Clinical Reviews in Oncology/Hematology 2022; 171

VTE and AT Events in Romiplostim Studies

Study	Duration of follow-up (weeks)	TPO arm n/N (%)	Comparison arm n/N (%)	Remarks
Phase 2 and 3 studies				
Bussel et al. 2006[1]	6	0/41 (0.0%)	1/4 (25%)	1 DVT
Kuter et al. 2008[2]	24	2/83 (2.4%)	1/42 (2.4%)	1 VTE in each arm
Kuter et al. 2010[3]	52*	6/154 (3.9%)	2/75 (2.7%)	11 events in 6 patients on romiplostim and 2 in SOC (P=0.07)
Long-term follow-up studies				
Kuter et al. 2013[4]	110#	19/291 (6.5%)		16 ATE (0.04/100 p.w.) 9 VTE (0.03/100 p.w.)
Steurer et al. 2016[5]	102**	7/340 (2.0%)		10 thrombotic events

* 52-week long study and follow-up period of 6 months for patients who did not enter another romiplostim study;
# Mean duration of treatment
** Duration of exposure

- AT(E), arterial thromboembolism; DVT, deep vein thrombosis; p.w., patient-weeks; SOC, standard of care; TPO, thrombopoietin; VTE, venous thromboembolism
- 1. Bussel J, et al. N Engl J Med. 2006;355:1672-81; 2. Kuter D, et al. Lancet. 2008;371:395-403; 3. Kuter D, et al. N Engl J Med. 2010;363:1889-99; 4. Kuter D, et al. Br J Haematol. 2013;161:411-23; 5. Steurer M, et al. Eur J Haematol. 2017;98:112-20

VTE and AT Events in Eltrombopag Studies

Study	Duration of follow-up (weeks)	TPO-RA arm n/N (%)	Comparison arm n/N (%)	Remarks
Phase 2 and 3 studies				
Bussel et al. 2007[1]	6	0/88 (0.0%)	0/29 (0.0%)	
Bussel et al. 2009[2]	6	0/76 (0.0%)	0/38 (0.0%)	
Cheng et al. 2011[3]	26	3/135 (2.2%)	0/62 (0.0%)	3 VTE
Long-term follow-up studies				
Bussel et al. 2013[4]	–	0/65 (0.0%)		
Wong et al. 2017[5]	123*	19/302 (6.3%)		24 events; 10 VTE (2.69/100 patient years)
Other studies				
Cooper et al [6]	24*	6/105 (5.7%)		

* Median duration

- AT, arterial thromboembolism; TPO-RA, thrombopoietin receotor antagonist; VTE, venous thromboembolism
- 1. Bussel J, et al. N Engl J Med. 2007;357:2237-47; 2. Bussel J, et al. Lancet. 2009;373:641-8; 3. Cheng G, et al. Lancet. 2011;377:393-402; 4. Bussel J, et al. Br J Haematol. 2013;160:538-46; 5. Wong RSM, et al. Blood. 2017; 130(23):2527-36 . 6. Cooper et al 2023 AJH submitted

VTE and AT Events in the Avatrombopag Study

Study	Study duration (weeks)	TPO arm n/N (%)	Comparison arm n/N (%)	Remarks
Phase 3 core study				
Jurczak et al. 2018[1]	26	3/32 (10%)	0/17 (0.0%)	DVT (day 8), asymptomatic PE (day 154); cerebrovascular event (day 89)
Phase 3 extension study				
Jurczak et al. 2018[1]	104	1/39		Jugular vein thrombosis (day 335)

Of the 4 patients, 3 had multiple risk factors for thromboembolic disease, with the reported events associated with platelet counts from 39-271 × 10^9/L and doses of avatrombopag from 10 to 40 mg.

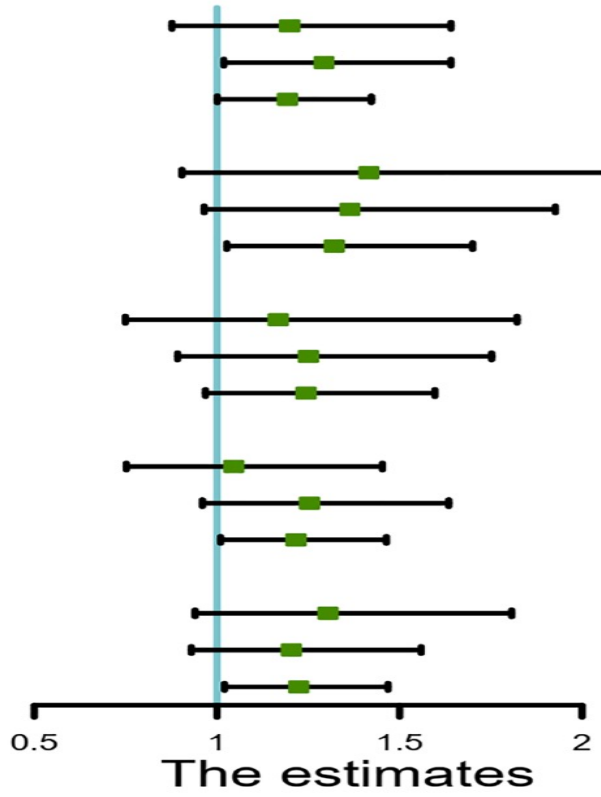
AT, arterial thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; TPO, thrombopoietin; VTE, venous thromboembolism

1. Jurczak W, et al. Br J Haematol. 2018;183:479-90

Risk of thromboembolism in TPO-RA treated patients – a Mendelian randomization analysis

Estimation of TPORD and TEE risk based on Mendelian Randomization analysis suggests an increased risk of TEEs, particularly VTE/DVT/STR

	Beta	P–value	OR(95%CI)
TPORDs & Venous thromboembolism			
MR Egger	0.182	0.267	1.199(0.877–1.641)
Weighted median	0.257	0.034	1.293(1.019–1.641)
Inverse variance weighted	0.177	0.049	1.193(1.001–1.423)
TPORDs & Deep vein thrombosis			
MR Egger	0.348	0.142	1.416(0.904–2.218)
Weighted median	0.31	0.078	1.364(0.965–1.927)
Inverse variance weighted	0.279	0.03	1.321(1.027–1.700)
TPORDs & Pulmonary embolism			
MR Egger	0.156	0.499	1.168(0.749–1.822)
Weighted median	0.223	0.195	1.250(0.892–1.752)
Inverse variance weighted	0.218	0.087	1.244(0.969–1.597)
TPORDs & Myocardial infarction			
MR Egger	0.045	0.793	1.046(0.752–1.453)
Weighted median	0.225	0.097	1.253(0.960–1.635)
Inverse variance weighted	0.196	0.039	1.216(1.010–1.464)
TPORDs & Ischaemic Stroke			
MR Egger	0.265	0.125	1.304(0.940–1.807)
Weighted median	0.185	0.159	1.204(0.930–1.559)
Inverse variance weighted	0.202	0.029	1.224(1.021–1.468)



TPORD= Thrombopoietin receptor agonist related drugs; TEE= Thromboembolic events; VTE= venous thrmboembolism; DVT= Deep vein thrombosis; STR= stroke

Liang et al. Ther Adv Drug Saf 2024;15:1–13

VTE and AT Events in fostamatinib and rilzabrutinib studies

Study	Study duration (weeks)	Active drug arm n/N (%)	Comparison arm n/N (%)	Remarks
Fostamatinib				
Bussel et al. 2018[1]	229*	1/146(0.7%)	0 (0.0%)	TIA
Kuwana et al. 2023[3]	24	0/24	0 (0.0%)	
Rilzabrutinib				
Kuter et al. 2022[2]	24	0/60	-	

Cooper et al Ther Adv Hematol 2021;12: 1-12; Kuter et al NEJM 2022: 386: 1421; Kuwana et al BJH 2023. 200

Risk factors for thrombosis in ITP

Evidence from various studies

Impact of risk factors on the occurrence of arterial thrombosis and venous thromboembolism in adults with primary ITP –Results from 2 nationwide cohorts

- 9715 ITP
- France and Sweden (2009–2015/2016)
- Arterial Thrombosis
  - Stroke, MI, CAD, others
  - IR: 1.5 / 100 person-years
  - **Risk factors of AT: male sex, age >60 y, history of AT**
- Venous Thromboembolism
  - DVT, PE, thrombophlebitis, SVT, Splanchnic VT
  - IR 0.7 / 100 person-years
  - **Risk factors: age >60 y, history of VTE, cancer**

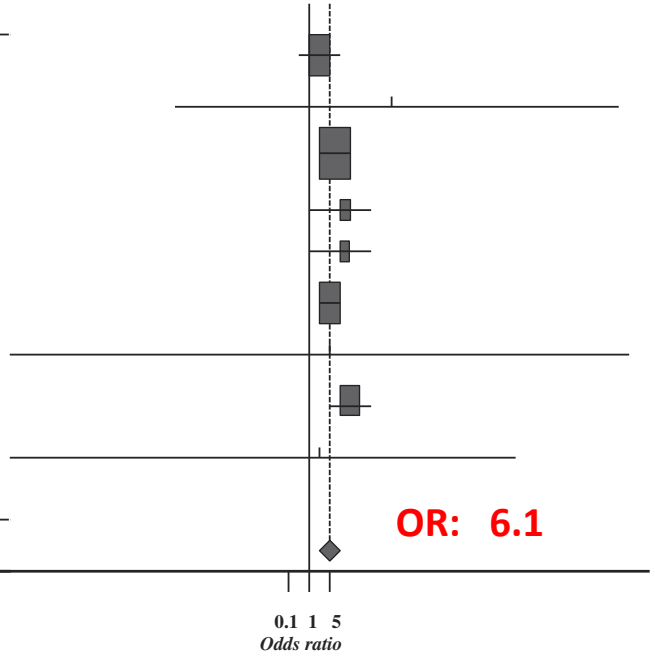
Ekstrand C et at. T Thromb Res 2018; 178:

IR= incidence rate

Risk of thrombosis in patients with ITP and antiphospholipid antibodies

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-Küçükkaya	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%



- Risk of arterial thrombosis associated with LA: 5.52 (2.40–2.70)
- Risk of venous thrombosis associated with LA: 5.13 (2.31–11.40)
- Risk of all thrombosis associated with aCL: 2.14 (1.11–4.12)

Moulis G, et al. Autoimmun Rev 2016;15:203–9.

aCL, anticardiolipin; LA, lupus anticoagulant; OR, odds ratio.

Risk and factors associated with thromboembolism in ITP

A single center experience

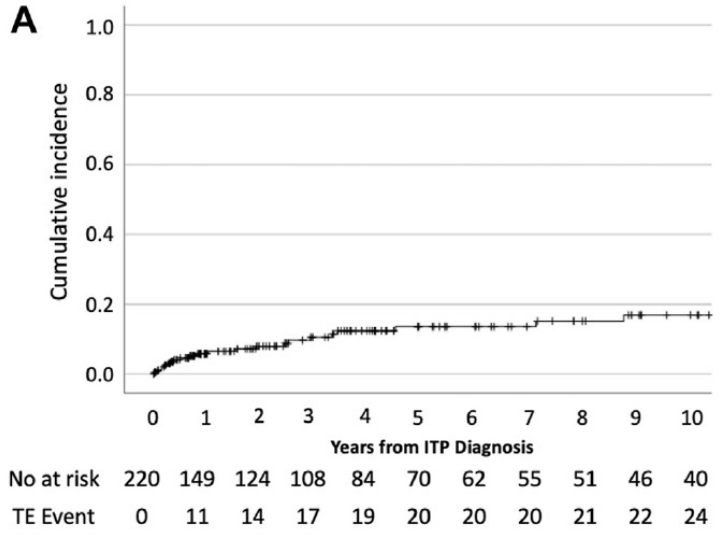
37 thrombotic event in 26/220 patients

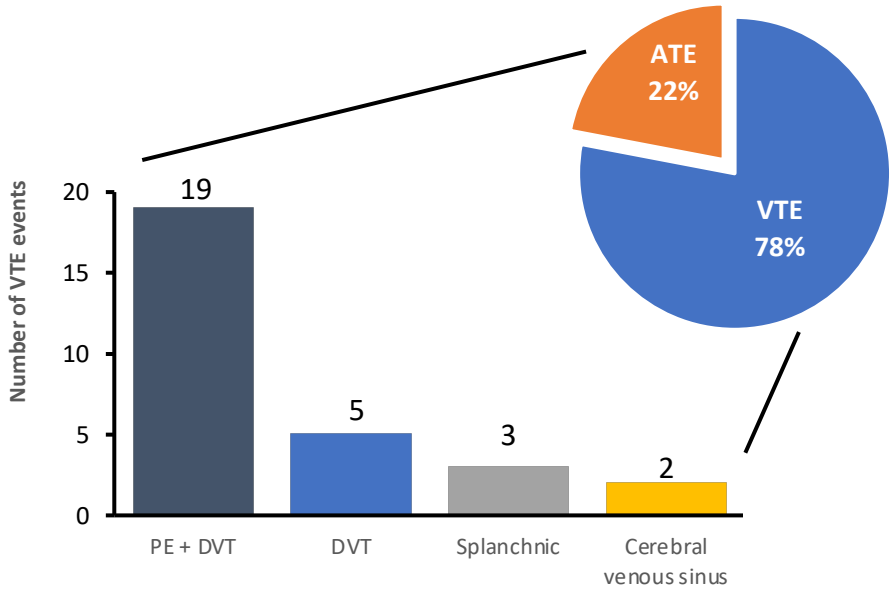
Incidence rate index:

- VTE =2.05 per 100 person-years (95% CI 1.42–2.95)
- ATE= 0.66 per 100 person-years (95% CI 0.33–1.26)

In the multivariable Cox regression, the following factors predicted thrombosis:

- Age >60 years
  (HR 1.04; 95% CI 1.02–1.06; P≤0.04)
- Secondary ITP status
  (HR 2.40; 95% CI 1.10–5.21; P=0.02)
- Multiple prior ITP therapies
  (HR 1.29; 95% CI 1.12–1.48; P≤0.001)
- TPO-RA
  (HR 2.96; 95% CI 1.36–6.44; P≤0.001)





ATE, arterial thromboembolism; CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; ITP, immune thrombocytopenia; PE, pulmonary embolism; TPO-RA, thrombopoietin receptor agonist; VTE, venous thromboembolism.

Goncalves I, et al. *Res Pract Thromb Haemost.* 2024;8(1):102342.

Risk factors for thrombosis in ITP

- Age >60–70 years[1]
- Treatment
  - Splenectomy (VTE/AT)[1]
  - TPO-RA (VTE/AT) - (not drug/ dose / response /timing – related)
  - Steroid[1] **?**
  - IVIg[2] **?** (doses >35g/day)
- Comorbidity[1,3]
  - Diabetes, hypercholesterolaemia, hypertension, smoking, atrial fibrillation, valvular disease, history of TE, obesity[1,3]
- Gender
  - Males/Females (AT)[4]
- Presence of antiphospholipid antibodies
- Previous VTE

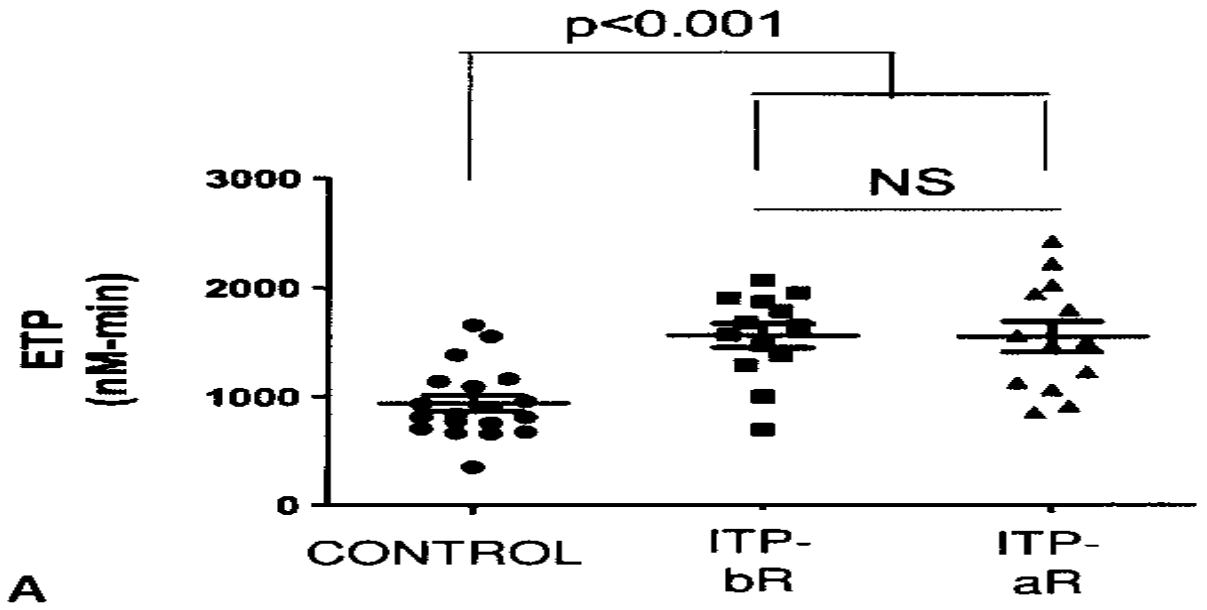
1. Ruggeri M, et al. J Thromb Haemost 2014;12:1266–73; 2. Paran D, et al. Blood Coagul Fibrinolysis 2005;16:313–8;
3. Kuter D, et al. Br J Haematol 2013,161:411–23; 4. Nørgaard M, et al. Br J Haematol 2012;159:109–11.

Case

- 50-year-old female, a chronic ITP steroid responsive recurrent drop platelets down to single digits by response to steroids.
- Started her on TPO-RA one week later developed headache, MRI scan and CT sagittal sinus thrombosis.
- Currently in Apixaban. What do you think and advise?
- Advice: continue on Apixaban as long as platelet count is >50 $X10^9/L$
- Triple positive APA
- Advice:
  - Is this APS?
  - Should we switch over to warfarin?
  - Should we change treatment of ITP? Fostamatinib, rituximab

Hypercoagulability in ITP

Plasma procoagulant activity measured by Calibrated Automated Thrombogram

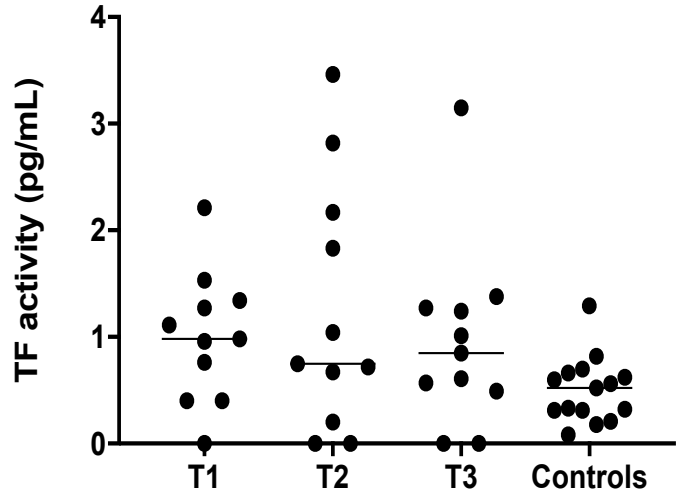


Increase thrombin generation in ITP

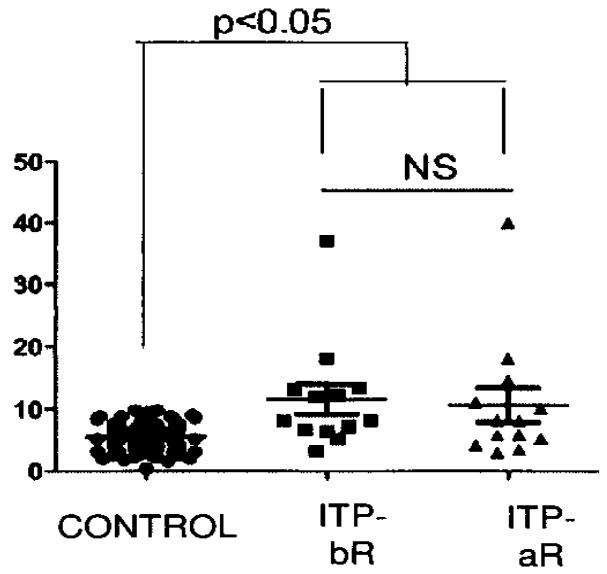
Alvarez Roman M, et al. Thromb Haemost 2014;112;65–72;

ETP= endogenous thrombin potential

Microparticle associated procoagulant activity in TPO-RA treated patients



Tissue Factor activity



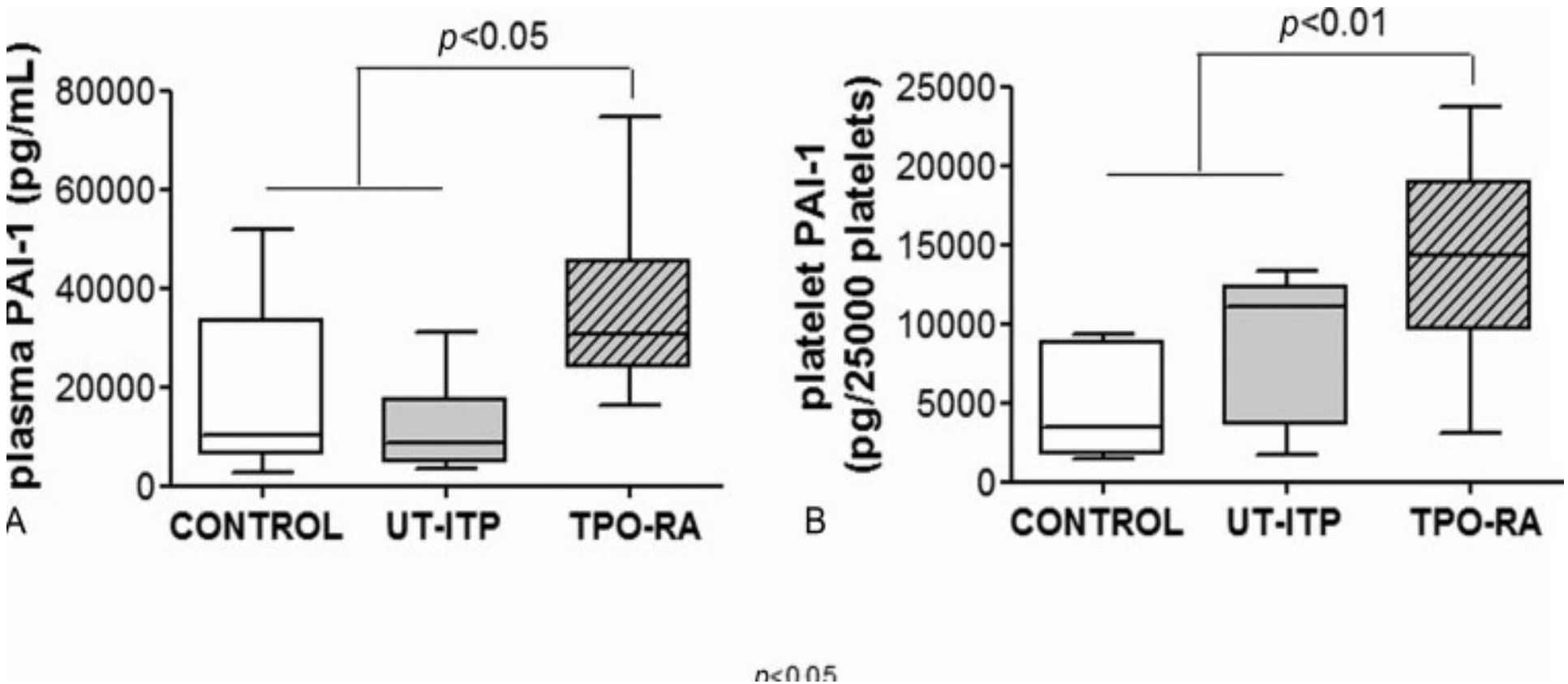
Phospholipid activity

T1= pretreatment; T2 = 2 weeks after TPO-RA; T3= 6 weeks after TPO-RA

Garabet L et al. Platelets 2019: PMID: 31280643

Alvarez Roman M, et al. Thromb Haemost 2014;112;65–72;

PAI-1 in TPO-RA treated patients

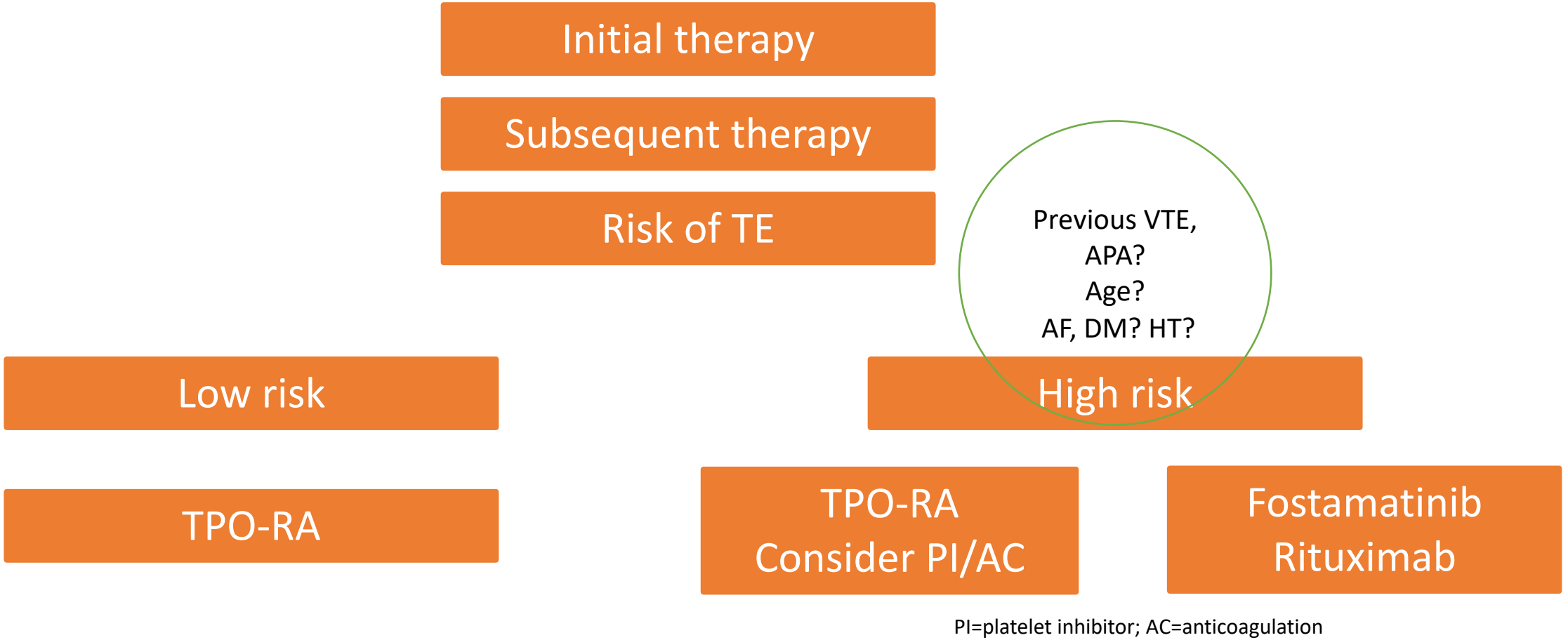


p<0.05

Justo Sanz et al TH 2018:

Managing thromboembolism in ITP

Managing ITP – should we individualize the patient according to the risk of TE?

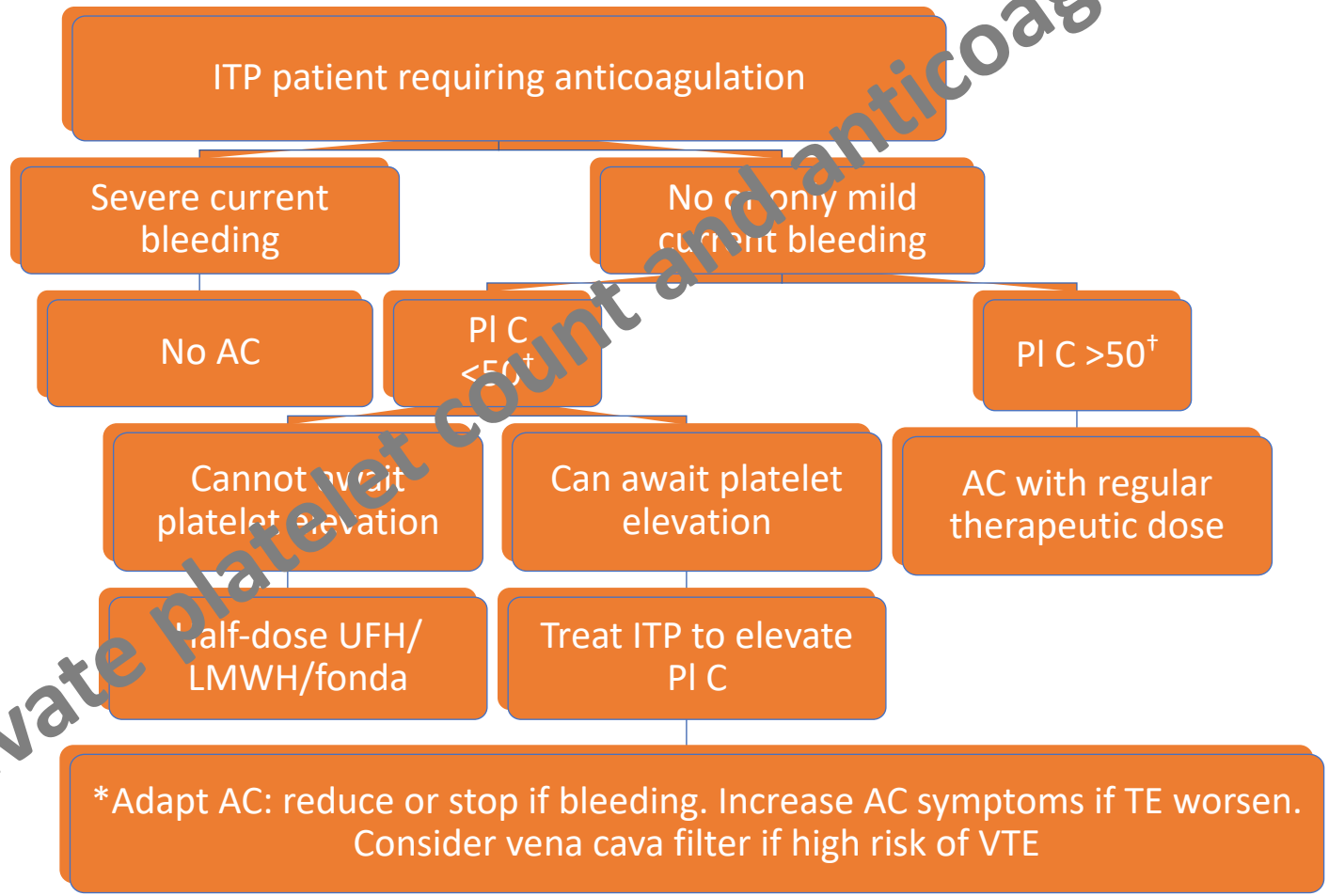


PI=platelet inhibitor; AC=anticoagulation

TE, thromboembolism; APA, antiphospholipid antibodies; AF, atrial fibrillation; DM, diabetes mellitus; HT, hypertension; PI, platelet inhibitors; AC, anticoagulation

Created by W. Ghanima.

Approach to ITP patients who require anticoagulation



Elevate platelet count and anticoagulate

Adapted from Matzdorff A, et al. Seminars of Hematology 2015;50:s83–88.

*Depends on bleeding risk/treatment response.
†Pl C, platelet count ×10^9/L; AC, anticoagulation

Recommended platelet levels for anticoagulation and platelet inhibitors

Anticoagulation	Platelet count
Single anti-platelet agent or anticoagulant (i.e. one antiplatelet agent, warfarin or DOAC)	$\geq$30-50 X 10^9/L
Dual anti-platelet or anticoagulant (i.e. two anti-platelet agents or one anti-platelet agent plus warfarin or DOAC)	$\geq$50-70 X 10^9/L

Prova et al. Blood Advances 2019; in press

Managing antithrombotic therapy in ITP - development of the TH2 risk assessment score

Risk assessment Score	Score
Thrombotic risk factors	
High thrombotic risk*	**+1**
Recent ITP treatment†	**+1**
Bleeding risk factor	
Platelets ≤20X 109/L	**- 1**
Major bleed (excluding skin) at presentation‡	**- 1**
Overall score	Nil or positive (excess thrombotic risk); negative (excess bleeding risk)

*AF, CHF, hypertension, age ≥75 years, diabetes, prior stroke, vascular disease, age 65 to 74 years, and sex category >5; unprovoked, recurrent, or cancer-associated thrombosis; antiphospholipid antibody syndrome.
†IVIG within 2 weeks or TPO-RA or splenectomy within 4 weeks.
‡Grade 2, by the ITP Bleeding Score

Balitsky et a.Blood 2018; 132

Stepwise approach of the management of ITP co-existing with ACS

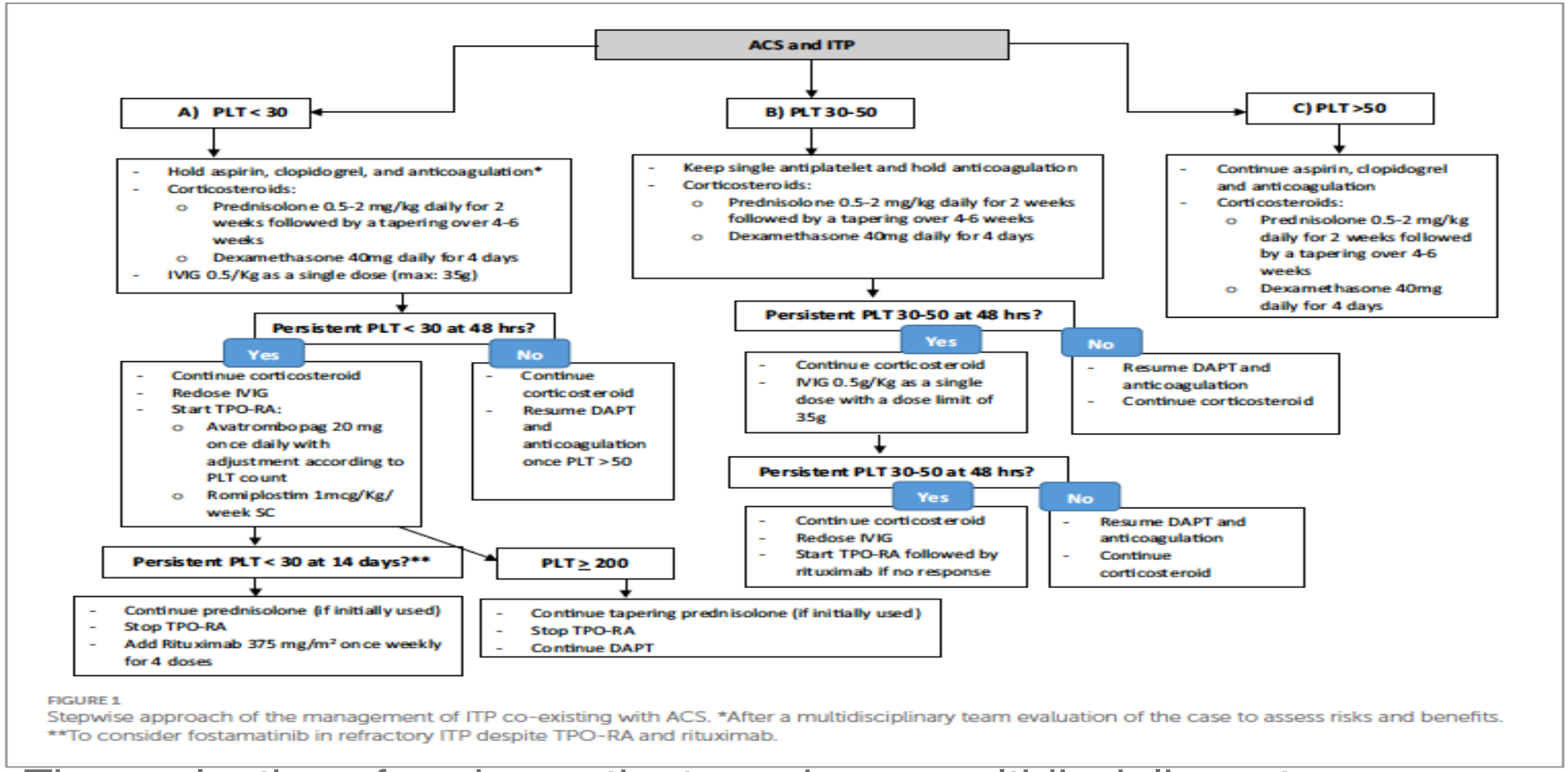


FIGURE 1
Stepwise approach of the management of ITP co-existing with ACS. *After a multidisciplinary team evaluation of the case to assess risks and benefits. **To consider fostamatinib in refractory ITP despite TPO-RA and rituximab.

The evaluation of such a patient requires a multidisciplinary team approach.

*After a multidisciplinary team evaluation of the case to assess risks and benefits. **To consider fostamatinib in refractory ITP despite TPO-RA and rituximab.

Al Rahhal et al, Frontiers in Medicine. 2024. DOI 10.3389/fmed.2024.134894

Conclusions

- Risk/benefit assessment
- Screening for and correction of patient-specific cardiovascular risk factors
- TPO-RAs seem to increases the risk of TE
- SYK and BTK inhibitors does not seem to increase the risk of TE
- Platelet count > 50 should be a safe threshold for anticoagulation /antiplatelet therapy
- Individualize therapy/anticoagulation dose in patients with platelet count <50

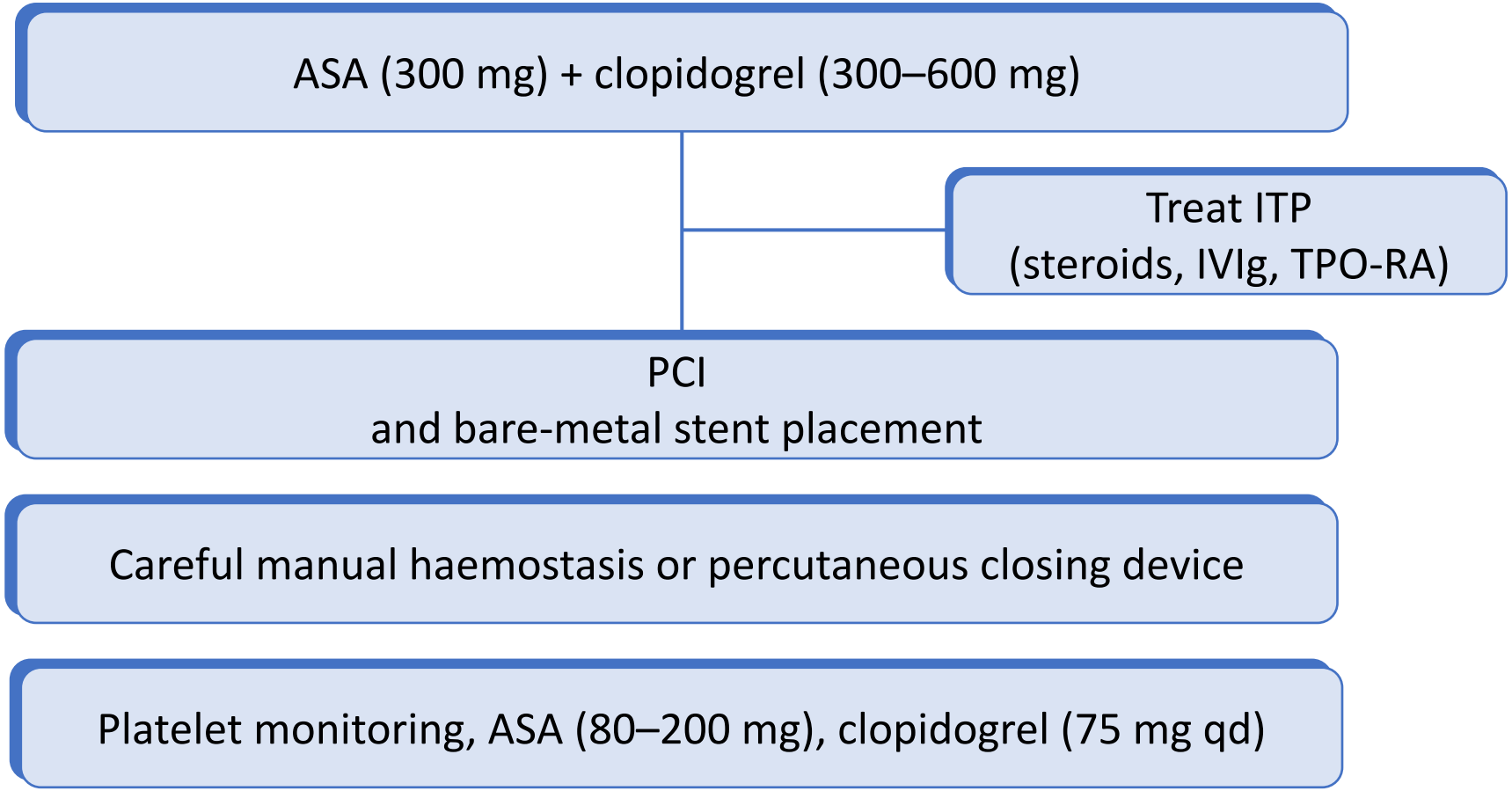
Thank you for your attention

Immune Thrombocytopenia – Current Diagnostics and Therapy: Recommendations of a Joint Working Group of DGHO, ÖGHO, SGH, GPOH, and DGTI

PL C <20	PL C 20-50	PL C >50
Individual decision when bleeding from thrombo-cytopenia is clinically leading anticoagulation When the symptoms of vascular obstruction are leading start with 1/2 therapeutic dose and then, depending on whether patient starts bleeding or not, adjust Dose or concentrates until count is >50 and then start full dose anticoagulation	Therapeutic anticoagulation e.g. 50% of standard heparin dose or antiplatelet agents every other day instead of daily If bleeding occurs If patient develops new vascular occlusions	Full standard dose anticoagulation If bleeding occurs reduce dose

Matzdorff et al . Oncol Res Treat 2018;41

ITP patient presenting with STEMI



Neskovic A, et al. Herz 2010;35:43–9; Li-Sha G, et al. BMC Cardiovasc Disord 2015;15:101.

STEMI, ST-elevation myocardial infarction.