Strategie per la gestione di pazienti con concomitante rischio emorragico e trombotico

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Outlines

Patients at haemorrhagic risk (not exhaustive list of conditions)

- Chemotherapy related thrombocytopenia
- Haematologic malignancies

- Immune thrombocytopenic purpura (ITP)

- Congenital bleeding disorders

Inferior vena cava filters – ACCP 2012 Recommendations

- **2.13.1. In patients with acute DVT of the leg, we recommend against the use of an IVC filter in addition to anticoagulants** (Grade 1B) **.**

- **2.13.2. In patients with acute proximal DVT of the leg and contraindication to anticoagulation, we recommend the use of an IVC filter** (Grade 1B) **.**

- **2.13.3. In patients with acute proximal DVT of the leg and an IVC filter inserted as an alternative to anticoagulation, we suggest a conventional course of anticoagulant therapy if their risk of bleeding resolves** (Grade 2B) **.**

Complications of IVC filters

- Mortality Rate 0.3%
- Complications related to the insertion process (bleeding, pain etc.)
- Venous thrombosis at the site of insertion (up to 40%)
- Filter migration
- Filter erosion through the IVC wall
- IVC obstruction (5-18%)

Temporary IVC filters

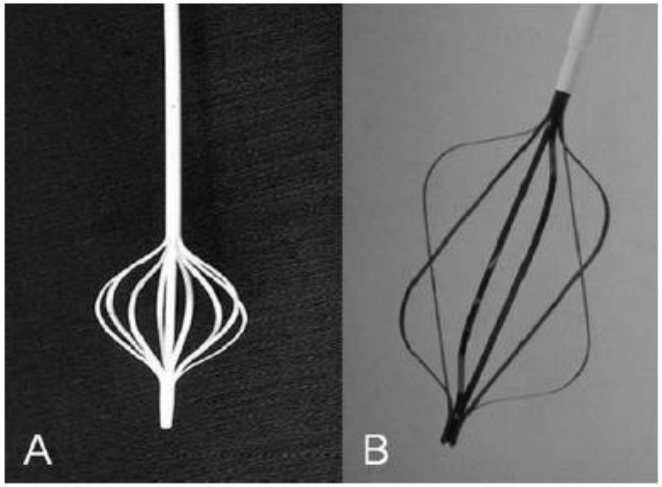


Fig 1. A, Neuhaus Protect filter. **B,** Antheor filter.

Table II. Outcome

Duration of placement	10.6±7.0 days	
Filter thrombosis	4 (12.1%)	3 resolved by catheter-directed thrombolytic therapy; 1 removed under venotomy at the insertion site
Pulmonary embolism	0	During filter protection and retraction

Miyahara et al, J Vasc Surg 2006

- Temporary filters remain attached to a wire or catheter that can be removed through the skin, and the advantage of these filters is their ease of insertion and removal.

- However, the external fixation is a potential pathway for infection, which would render such devices highly inappropriate for neutropaenic patients.

- Furthermore, temporary filters are often difficult to manage and present frequent complications such as thrombosis or migration.

- In addition, the limited duration of use that can be achieved with temporary filters is insufficient to recover the platelet count after high-dose chemotherapy. If needed, they could be replaced by another temporary filter or a retrievable filter, but this procedure is susceptible to increase the risks for the patient.

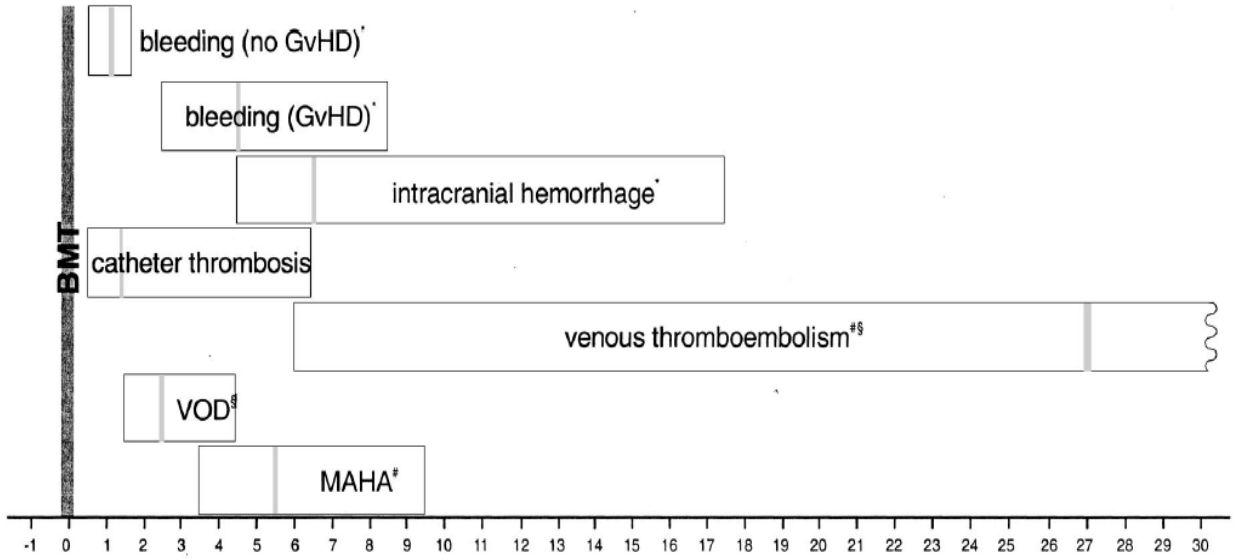
Chemotherapy related thrombocytopenia

Haematologic malignancies

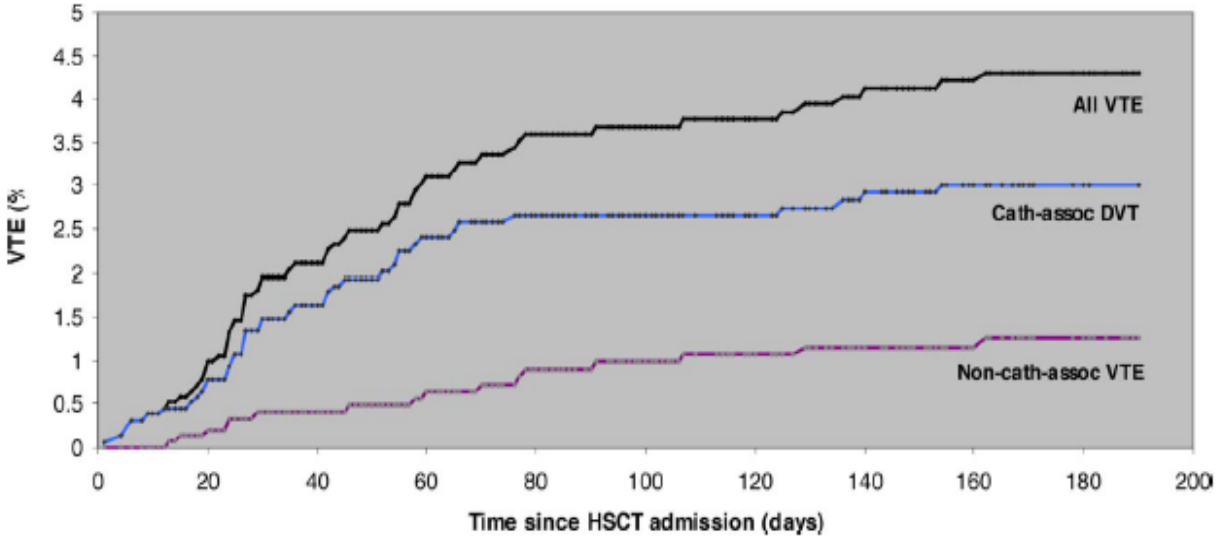
VTE in hematopoietic stem cell transplantation (HSCT)

Reference	*Type of HSCT*	*Patients (n)*	*CVC-thrombosis*	*VTE*	*Platelets < 50,000*	*Platelets < 20,000*
Pihusch, 2002	***Auto***	**83**	**3.6%**	**1.2%**	**44.2%**	**n.r.**
	Allo	**364**	**4.1%**	**5.8%**	**(overall)**	
Gerber, 2008	***Auto_***	**928**	**3.6%**	**1.3%**	**34%**	**13%**
	Allo	**586**	**(overall)**	**(overall)**	**(overall)**	**(overall)**
Gonsalves, 2008	***Auto***	**382**	**2.4%**	**0.5%**	**n.r.**	**n.r.**
	Allo	**207**	**2.6%**	**2.4%**	**n.r.**	**n.r.**
Labrador, 2013	***Allo***	**431**	**1.6%**	**4.4%**	**n.r.**	**n.r.**

Patients without VTE not receiving anticoagulation had major bleeding in 14.3%, fatal in 3.6%. Patients receiving anticoagulation had a 3.1-fold increase in risk of bleeding
(Gerber et al, Blood 2008)



Pihusch et al, Transplantation 2002



Gerber et al, Blood 2008

Treatment of VTE in hematological patients with thrombocytopenia

1. Drakos et al, Cancer 1992 (n= 4)
2. Herishanu et al, Leuk Lymphoma 2004 (n= 5)
3. Imberti, Tumori 2004 (n= 4)
4. Tousovska et al, Blood Coagul Fibrinol 2009 (n= 17)
5. Stine et al, Clin Appl Thromb Hemost 2007 (n= 2)

6. De Stefano et al, J Thromb Haemost 2005 (n= 24)
7. Schimmer et al, Bone Marrow Transplant 1998 (n= 10)
8. Ibrahim et al, Bone Marrow Transplant 2005 (n= 25)
9. Boeras et al, Blood Coagul Fibrinolys 2008 (n= 1)

10. Uderzo et al, J Clin Oncol 1995 (n= 17)

- Out of 22 patients with CVC-related DVT described in detail, all had a platelet count < 40,000 /mmc.

- In 9 cases LMWH was reduced (50% to 75% of the therapeutic dose); in the remaining cases therapeutic dose of LMWH was fully administered together with platelet transfusion if platelets were lower than 40,000/mmc.

- No patient had major bleeding. Two patients had rethrombosis, in one case after withdrawal of heparin, in another during LMWH 150 U/kg qd.

- Out of 10 patients with DVT not CVC-related described in detail, all had a platelet count < 50,000 /mmc.

- Full therapeutic dose of LMWH was administered together with platelet transfusion if platelets were lower than 20-40,000/mmc.

- No patient had major bleeding. One patient had rethrombosis (during LMWH 150 U/kg qd)

Critical Reviews in Oncology/Hematology 105 (2016) 92–99

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Safety of anticoagulation in the treatment of venous thromboembolism in patients with haematological malignancies and thrombocytopenia: Report of 5 cases and literature review

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In a series of 379 patients with acute leukaemia, treatment for 20 patients who had one (n=16) or two (n= 4) VTE events was enoxaparin 100 U/kg bid; in the case of a platelet count <50,000 /mmc or in the clinical suspicion of bleeding risk the dose was reduced to 100 U/kg qd or 50 U/kg bid.

Alternatively, the patients received a continuous i.v. infusion of UFH to obtain aPTTs in the lower therapeutic range (1.5 times greater than the basal value).

Secondary prophylaxis was based on the administration of enoxaparin 100 U/kg qd in the case of ongoing chemotherapy or VKA (INR between 2 and 3) otherwise. In general, the length of secondary prophylaxis was not longer than six months .

De Stefano et al, J Thromb Haemost 2005

EXPERTS' OPINION

Experts and the AIEOP suggested that:

1) the first two weeks of treatment should consist of the administration of full- dose LMWH (anti-factor Xa level 0.5-1 U/ml), maintaining the platelet count > 50,000/mmc.
2) After the first two weeks, halving the dose is recommended if the platelet count is between 20 and 50,000 /mmc.
3) If the platelet count is <20,000 /mmc, it is advised that the LMWH therapy be discontinued until the platelet count recovers.

Bajzar et al, Curr Opin Pediatr 2006

Giordano et al, Recent Pat Cardiovasc Drug Discov 2007

Falanga & Rickles, Hematology ASH Educ Program 2007

Journal of Thrombosis and Haemostasis, **11**: 1760–1765 DOI: 10.1111/jth.12338

RECOMMENDATIONS AND GUIDELINES

Management of challenging cases of patients with cancer-associated thrombosis including recurrent thrombosis and bleeding: guidance from the SSC of the ISTH

M. CARRIER,* A. A. KHORANA,† J. I. ZWICKER,‡ S. NOBLE,§ A. Y. Y. LEE¶ and ON BEHALF OF THE SUBCOMMITTEE ON HAEMOSTASIS AND MALIGNANCY FOR THE SSC OF THE ISTH

**Thrombosis Program, Division of Hematology, Department of Medicine, University of Ottawa, Ottawa, ON, Canada; †Department of Solid Tumor Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; ‡Division of Hemostasis and Thrombosis, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; §Royal Gwent Hospital, Newport, UK; and ¶Division of Hematology, Department of Medicine, University of British Columbia, Vancouver, BC, Canada*

Guidance statement:

1 We recommend giving full therapeutic doses of anticoagulation without platelet transfusion in patients with CAT and a platelet count of $\geq 50 \times 10^9\ L^{-1}$.

2 For acute CAT and thrombocytopenia ($< 50 \times 10^9\ L^{-1}$):

i We recommend full therapeutic doses of anticoagulation with platelet transfusion to maintain a platelet count of $\geq 50 \times 10^9\ L^{-1}$.

ii If platelet transfusion is not possible or is contraindicated, we suggest insertion of a retrievable filter and removal of the filter when the platelet count recovers and anticoagulation can be resumed.

3 For subacute or chronic CAT and thrombocytopenia ($< 50 \times 10^9\ L^{-1}$):

i We suggest reducing the dose of LMWH to 50% of the therapeutic dose or using a prophylactic dose of LMWH in patients with a platelet count of 25–$50 \times 10^9\ L^{-1}$.

ii We suggest discontinuing anticoagulation in patients with a platelet count of $< 25 \times 10^9\ L^{-1}$.

Consensus paper on: “Platelet cut-off for anticoagulant therapy in cancer patients with venous thromboembolism and thrombocytopenia”

Giorgia Saccullo[1], Marco Marietta[2], Monica Carpenedo[3], Valerio De Stefano[4], Anna Falanga[5], Augusto B. Federici[6], Francesco Rodeghiero[7], Alberto Tosetto[7] and Sergio Siragusa[1]

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Consensus

According to the results of rating, in cancer patients the experts consider as <u>Appropriate</u>:

- Full dosage of LMWH, in **acute VTE** (including catheter-related VTE) and platelets count >50.000 <100.000 **(9/9)**

- LMWH reduced to 50% of full dosage, in cancer patients with **acute VTE** and stable platelets count ≥ 30.000 < 50.000

- The discontinuation of LMWH treatment and positioning of a vena cava filter, in **acute VTE** and platelets count < 30.000 **(6/9)**

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche.

Clinical Practice in the prophylaxis and treatment of arterial and venous thromboembolism in patients with hEmatological NEoplasms and LOw PlatElets (PENELOPE Observational Study)

GIMEMA EMATO 0213

ClinicalTrial.gov Identifier NCT01855698

Study Responsibilities:

For GIMEMA Foundation:

Sponsor according to European Directives:	**GIMEMA Foundation, Rome**
Study Coordinator	**Valerio De Stefano**
Coordinating Centre:	**Institute of Hematology, Catholic University, Rome**
Writing Committee:	**Giuseppe Avvisati (Rome), Giancarlo Castaman (Vicenza), Laura Contino (Alessandria), Anna Falanga (Bergamo), Marco Marietta (Modena), Sergio Siragusa (Palermo), Alberto Tosetto (Vicenza)**
Study and Project Management:	**GIMEMA Data Centre, Rome**
GIMEMA WP Hemostasis and Thrombosis Chairman	**Valerio De Stefano**
Legal representative of the GIMEMA Foundation:	**Prof. Franco Mandelli**

Checklist

Assign record to a Data Access Group? -- select a group --

Adding new Record ID **4**

Record ID	4

Clinical Practice in the prophylaxis and treatment of arterial and venous thromboembolism in patients with hEmatological NEoplasms and LOw PlatElets (PENELOPE Observational Study)

Inclusion Criteria

diagnosis of hematologic neoplasm independently of the stage of disease or treatment * must provide value	○ Yes ○ No	reset
platelet count < 70 x10^9/L at the time of starting antithrombotic prophylaxis or platelet count < 70 x10^9/L at the time of diagnosis of arterial or venous thromboembolism objectively proven or platelet count >70 x10^9/L at time of thrombosis but subsequent thrombocytopenia < 70 x10^9/L while receiving antithrombotic treatment * must provide value	○ Yes ○ No	reset

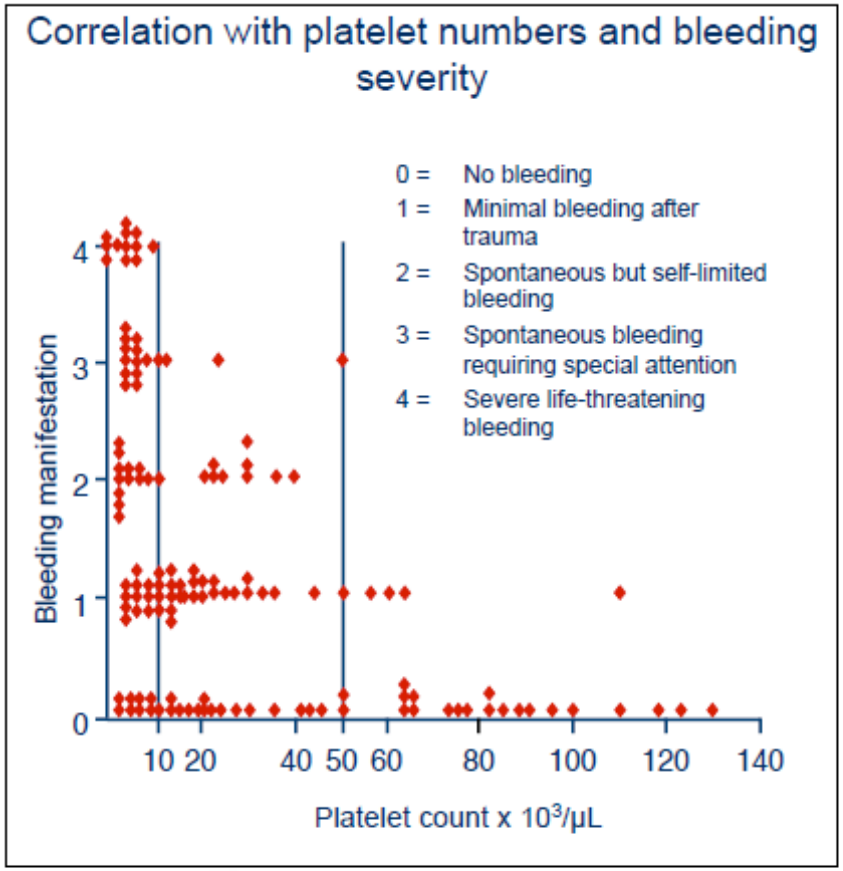
Exclusion criteria

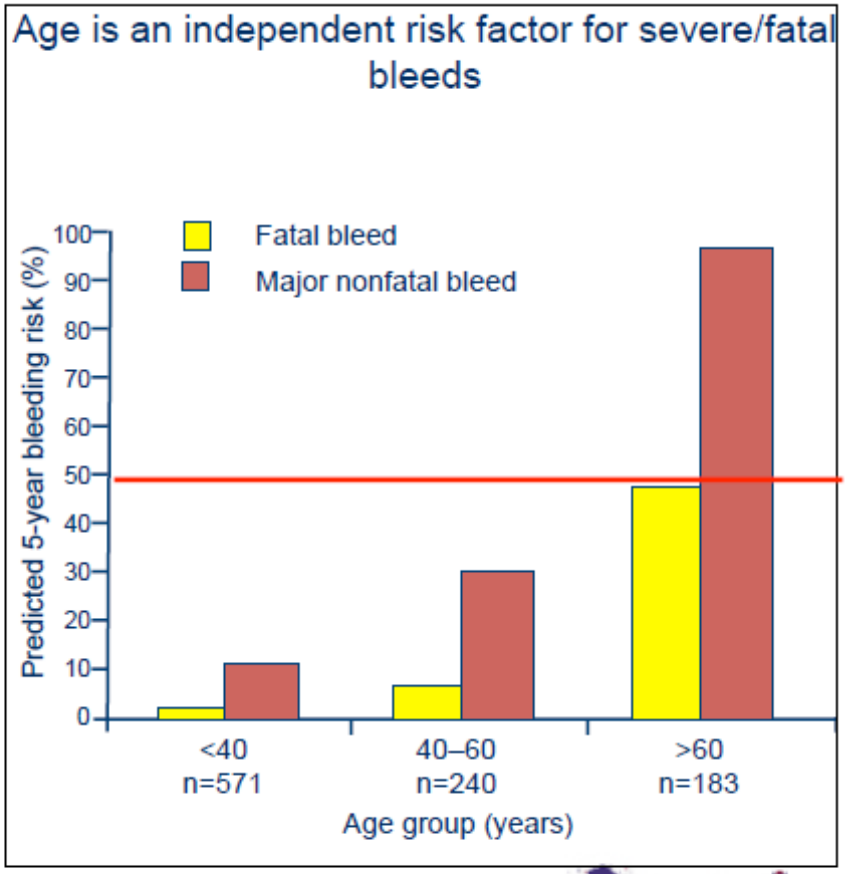
transient ischemic attack without CT and/or NMR signs * must provide value	○ Yes ○ No	reset
superficial vein thrombosis without Doppler ultrasound examination showing evidence of thrombosis * must provide value	○ Yes ○ No	reset
antithrombotic prophylaxis only local for central venous lines (i.e. CVC flushing with heparin) * must provide value	○ Yes ○ No	reset
occlusion of the central venous cathether * must provide value	○ Yes ○ No	reset
eligibility	0 View equation Disclaimer	

Diagnosis of thrombosis

Immune thrombocytopenic purpura (ITP)

Bleeding risk in adult patients





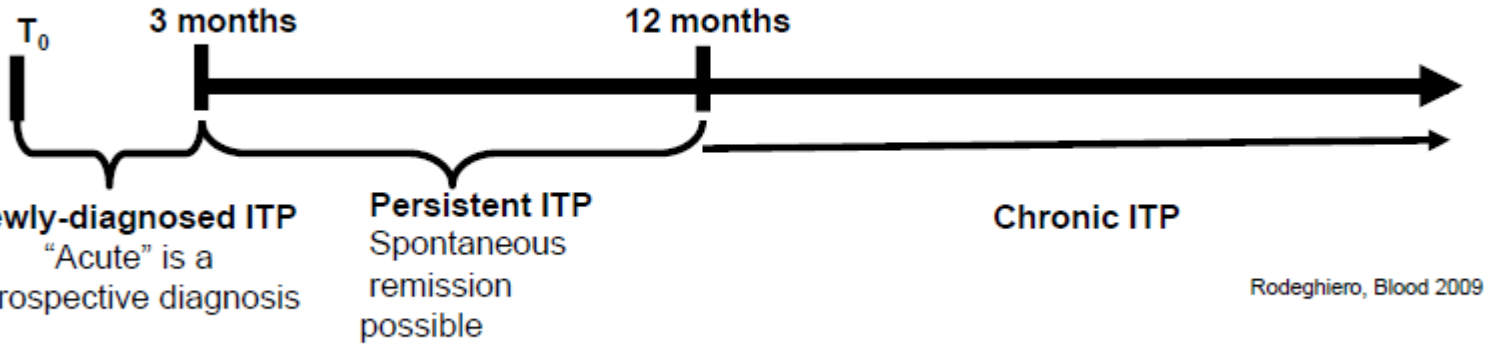
Lacey & Penner. *Semin Thromb Hemost* 1977;3:160–174

Cohen YC et al. Arch Intern Med 2000;160:1630–1638

REvolution on Thrombocytopenia Management

Courtesy of W. Barcellini

ITP: phases of the disease



Steroids/Ivlg

rituximab??

TPO mimetics ??

Steroids/Ivlg

TPO mimetics as bridge to splenectomy?

rituximab?

Manage/cure(?)

Splenectomy -TPO mimetics – rituximab

Low dose steroids, pulse Ivlg

What if….?

Your patient needs:

- ASA
- Double antiplatelet therapy
- VKA
- DOAC

But he/she has ITP?

- Prevalence of atrial fibrillation in the general population: 2%
- The incidence of VTE in the general population is 0.1-0.2 per 100 pt-years, and 0. 4 per 100 pt-years over 60 years
- The incidence of arterial thrombosis in the general population is 0.3-0.4 per 100 pt-years.

Trattamento anticoagulante nei vari paesi

Country	Total population	Patients on OAT	% monitored in ACCs	% monitored in routine medical care	Drug in use
Canada	32,000,000	275,000	5%	95%	Warfarin
England	63,000,000	750,000	80%	20%	Warfarin
France	60,000,000	600,000	0%	100%	Phenindione 61%, Aenocoumarol 38%, Warfarin 1%
Italy	60,000,000	650,000	25%	75%	Warfarin 80% Acenocoumarol 20%
The Netherlands	16,300,000	325,072	100%	0%	Acenocoumarol 71% Phenprocoumon 21%
Spain	42,000,000	400,000	90%	5%	Acenocoumarol
USA	280,000,000	2,500,000	25%	75%	Warfarin

Pengo V. *J Tronb Trombolysis* 2006

ITP and risk of VTE

- The incidence of VTE among ITP patients in population-based studies has been estimated as high as 4.2 to 5.3 /1,000 pt-years (Sarpatwary et al, Haematologica 2010; Severinsen et al, BJH 2010), with a risk-ratio of 1.5-2.6 in comparison with the reference population.

- In a multicenter retrospective cohort of 986 ITP patients, the annualized rates for 1,000 pt-years were 11.4, 3.9 and 7.1 for total, venous and arterial thrombosis. Older subjects, patients presenting vascular risk factors or using steroids and particularly those who have undergone splenectomy are at increased risk (Ruggeri et al, JTH 2014).

Immune Thrombocytopenia Patients Requiring Anticoagulation—Maneuvering Between Scylla and Charybdis

Axel Matzdorff,[a] and Juerg-Hans Beer[b]

Immune thrombocytopenia (ITP) is no longer a disorder of young people. Half of the patients are older than 50 and comorbidities become more common with age. Anticoagulation has to be discussed when an ITP patient develops atrial fibrillation, venous or arterial thromboembolism, myocardial infarction, or stroke. At the same time low platelet counts often prohibit therapeutic anticoagulation. Guidelines do not give guidance for these situations. This article summarizes experiences from case reports and small series and suggests an approach to ITP patients with thrombocytopenia and an indication for anticoagulation.
Semin Hematol 50:S83–S88.

- Give corticosteroids and IVIg to raise platelet counts rapidly to a safe level (ie, >30,000–50,000/μL).
- Start TRAs to maintain platelet counts in a safe range when corticosteroids are tapered and the effect of IVIg starts to wear off.
- Do not give anticoagulation, no matter what the platelet count, in patients with life-threatening bleeding or bleeding requiring transfusion (World Health Organization [WHO] grade III/IV). Consider a vena cava filter in DVT patients.
- In all other ITP patients (no bleeding, petechiae, hematomas, stable hemoglobin

authors tried to raise platelet counts to safe levels before starting anticoagulation.[55,57]

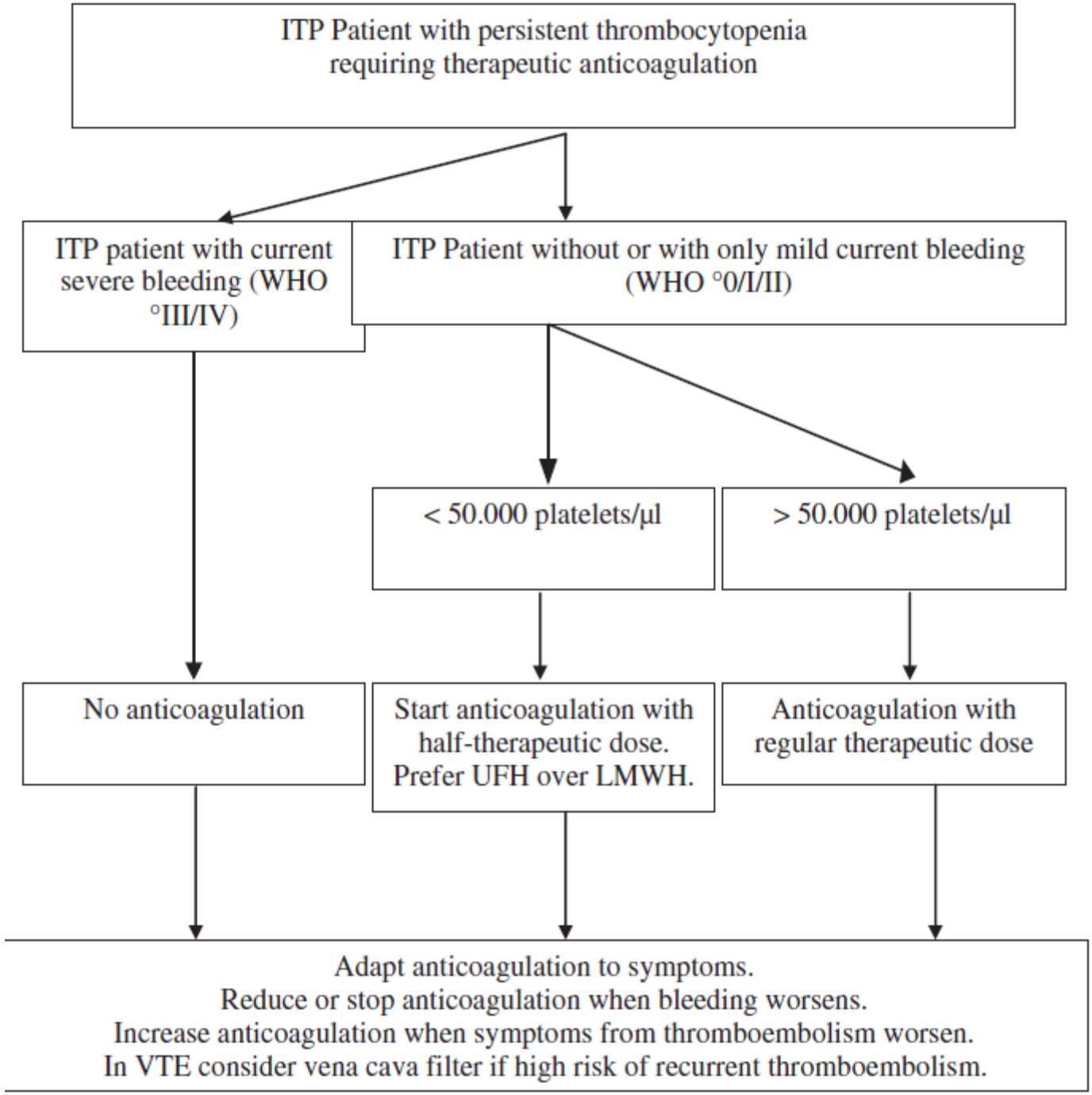

ITP Patient with persistent thrombocytopenia requiring therapeutic anticoagulation
ITP patient with current severe bleeding (WHO °III/IV)
ITP Patient without or with only mild current bleeding (WHO °0/I/II)
< 50.000 platelets/µl
> 50.000 platelets/µl
No anticoagulation
Start anticoagulation with half-therapeutic dose. Prefer UFH over LMWH.
Anticoagulation with regular therapeutic dose
Adapt anticoagulation to symptoms.
Reduce or stop anticoagulation when bleeding worsens.
Increase anticoagulation when symptoms from thromboembolism worsen.
In VTE consider vena cava filter if high risk of recurrent thromboembolism.

Table 3. Individual agents for treatment of ITP and the time to the first and peak responses if using the reported dose range

Agent/treatment	Reported dose range	Time to initial response*	Time to peak response*
Prednisone[4,44]	1-4 mg/kg po daily × 1-4 wk	4-14 d	7-28 d
Dexamethasone[48,49]	40 mg po or iv daily × 4 d for 4-6 courses every 14-28 d	2-14 d	4-28 d
IVIg[41,46,50]	0.4-1 g/kg per dose iv (1-5 doses)	1-3 d	2-7 d
Anti-D[42,47]	75 μg/kg per dose iv	1-3 d	3-7 d
Rituximab[10,40,51]	375 mg/m^2 per dose iv (4 weekly doses)	7-56 d	14-180 d
Splenectomy[43]	Laparoscopic	1-56 d	7-56 d
Vincristine[4]	up to 2 mg/dose iv (4-6 weekly doses)	7-14 d	7-42 d
Vinblastine[4,45]	0.1 mg/kg per dose iv (6 weekly doses)	7-14 d	7-42 d
Danazol[4,52]	400-800 mg po daily	14-90 d	28-180 d
Azathioprine[52]	2 mg/kg po daily	30-90 d	30-180 d
AMG531[6,7,9]	3-10 μg/kg weekly sc	5-14 d	14-60 d
Eltrombopag[8]	50-75 mg po daily	7-28 d	14-90 d

In the times to the initial and peak responses, the first number of days is the first time that a response could be reasonably expected and the second number of days is the time after which a response to this particular agent becomes less likely when administered at the dose and schedule listed in the table. Dosages, where not given on kilogram/body weight basis, are intended for adults.

po indicates per os administration; iv, intravenous infusion; and sc, subcutaneous infusion.

Rodeghiero et al, Blood 2009

Clinical & Experimental Immunology
The Journal of Translational Immunology

Clinical and Experimental Immunology REVIEW ARTICLE doi:10.1111/j.1365-2249.2011.04389.x

The experience of Flebogammadif® in primary immune thrombocytopenia

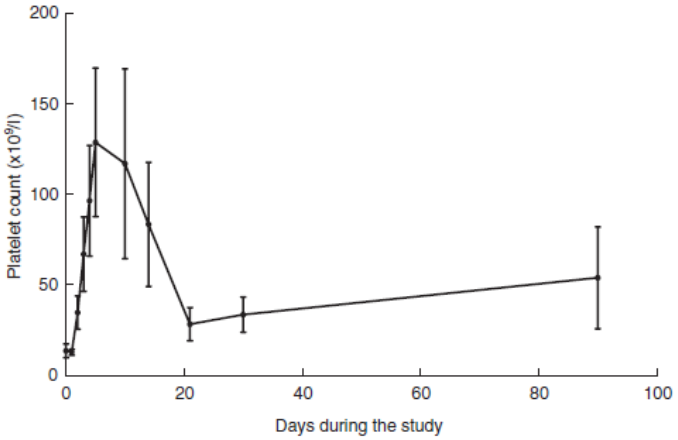


Fig. 1. Platelet counts for all patients who received at least one dose of Flebogammadif® (mean values and standard error bars). Values on day 0 indicate platelet count before the first infusion of the study product.

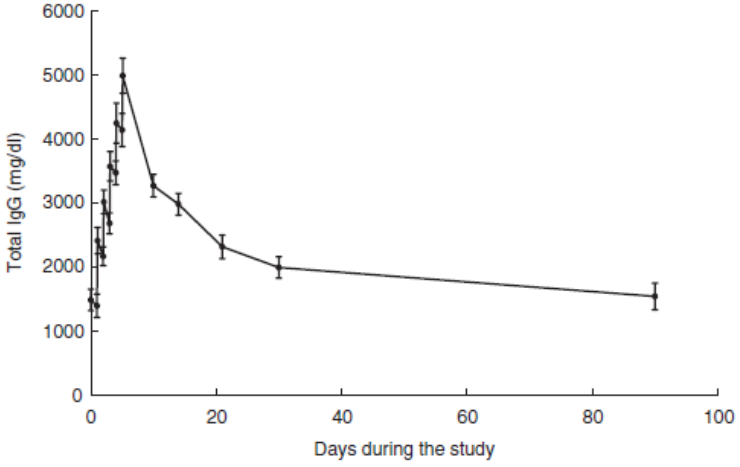


Fig. 2. Immunoglobulin G (IgG) levels for all patients who received at least one dose of Flebogammadif® (mean values and standard error bars). Values on day 0 indicate levels of IgG before the first infusion of study product.

High-dose Dexamethasone

Table 1. Univariate Analysis of Clinical and Laboratory Variables Associated with the Outcome at Six Months among the 106 Patients with an Initial Response.*

Variable	Sustained Response at 6 Mo	Relapse within 6 Mo	P Value
Age (yr)	46.7±18.2	45.8±18.5	0.80
Sex (no.)			0.31
Female	33	40	
Male	20	13	
Platelet count (per mm³)			
Pretreatment	12,300±11,600	13,500±11,800	0.63
Day 3	46,700±16,500	42,100±23,400	0.34
Day 10	132,600±41,900	84,700±37,000	<0.001
3 Mo	185,100±73,400	59,100±57,500	<0.001

* Plus–minus values are means ±SD.

Cheng et al, NEJM 2003

Therapy with high-dose dexamethasone (HD-DXM) in previously untreated patients affected by idiopathic thrombocytopenic purpura: a GIMEMA experience

Maria Gabriella Mazzucconi,[1] Paola Fazi,[2] Sayla Bernasconi,[1] Giulio De Rossi,[3] Giuseppe Leone,[4] Luigi Gugliotta,[5] Nicola Vianelli,[6] Giuseppe Avvisati,[7] Francesco Rodeghiero,[8] Angela Amendola,[1] Carlo Baronci,[3] Cecilia Carbone,[9] Stefano Quattrin,[10] Giuseppe Fioritoni,[11] Giulio D'Alfonso,[2] and Franco Mandelli,[1] for the Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA) Thrombocytopenia Working Party

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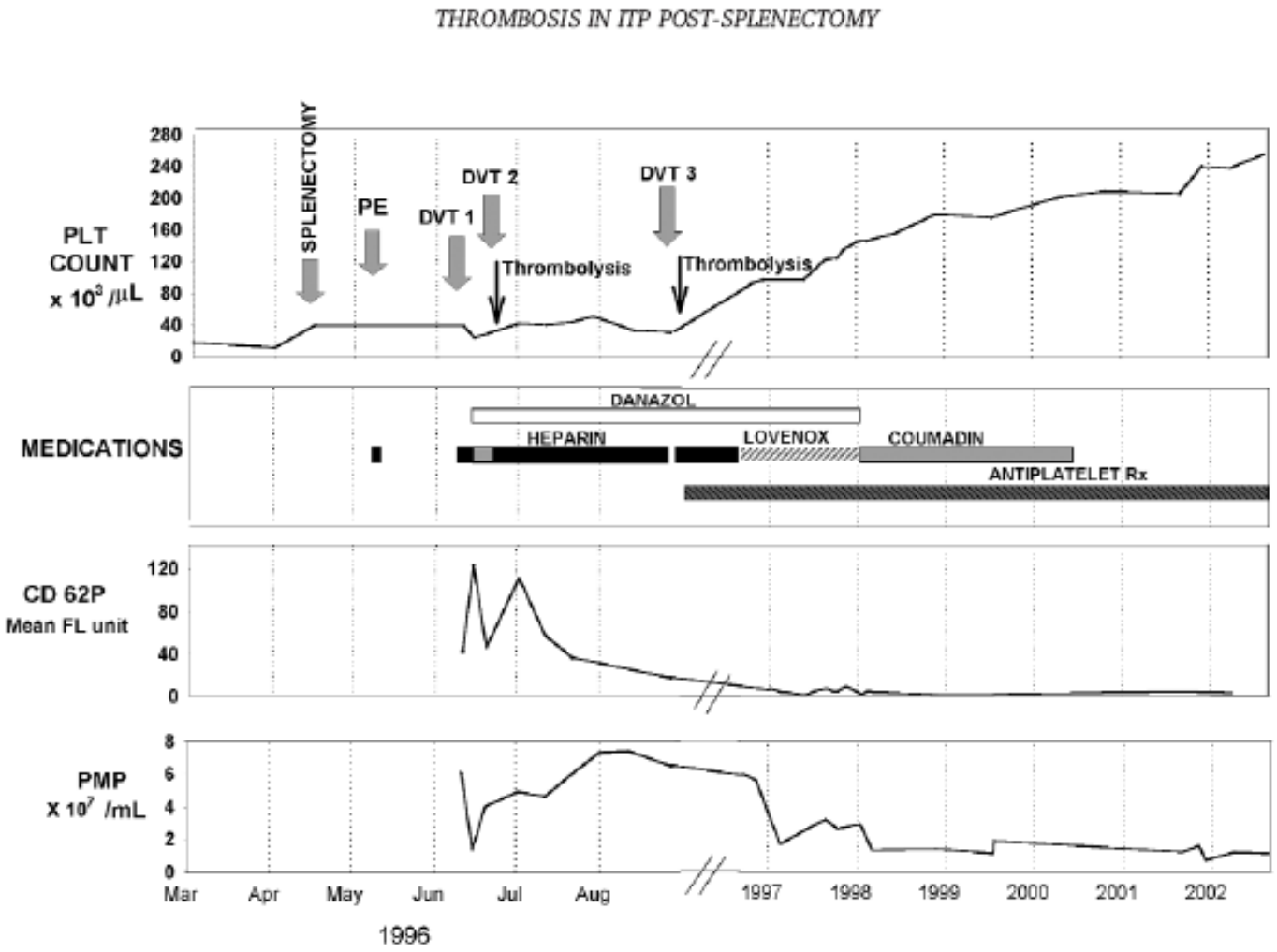
Table 5. GIMEMA multicenter pilot study: platelet count of evaluable patients after the end of the first therapy course

		At least 18 years of age through 70 years of age	At least 2 years of age through 17 years of age		
	Total		Total	Less than 10	10 or greater
Evaluable patients, n	90	48	42	32	10
Median platelet count at fourth day of the first therapy cycle, $\times 10^9$/L (range)	92 (2-370)	87 (2-290)	99 (7-370)	98 (7-271)	110 (28-370)
Platelets $> 20 \times 10^9$/L, no. patients (%)	68/75* (91)	35/38* (92)	33/37* (89)	25/29* (86)	8/8* (100)
Platelets $> 30 \times 10^9$/L, no. patients (%)	76/90 (84)	42/48 (87)	34/42 (81)	26/32 (81)	8/10 (80)
Platelets $\geq 50 \times 10^9$/L, no. patients (%)	66/90 (73)	38/48 (79)	28/42 (67)	21/32 (66)	7/10 (70)

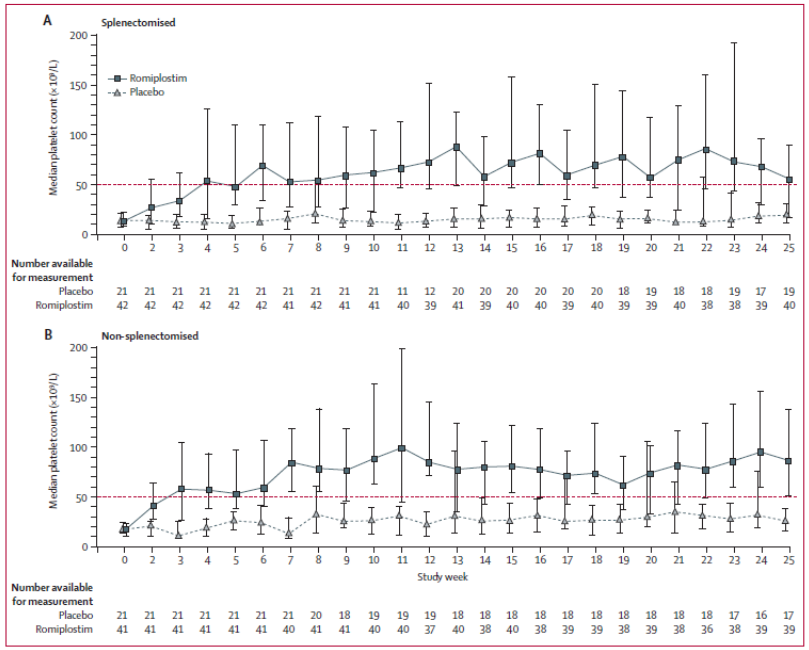
NA indicates not applicable; NS, not significant.
*Patients with platelet count $\leq 20 \times 10^9$/L at enrollment.

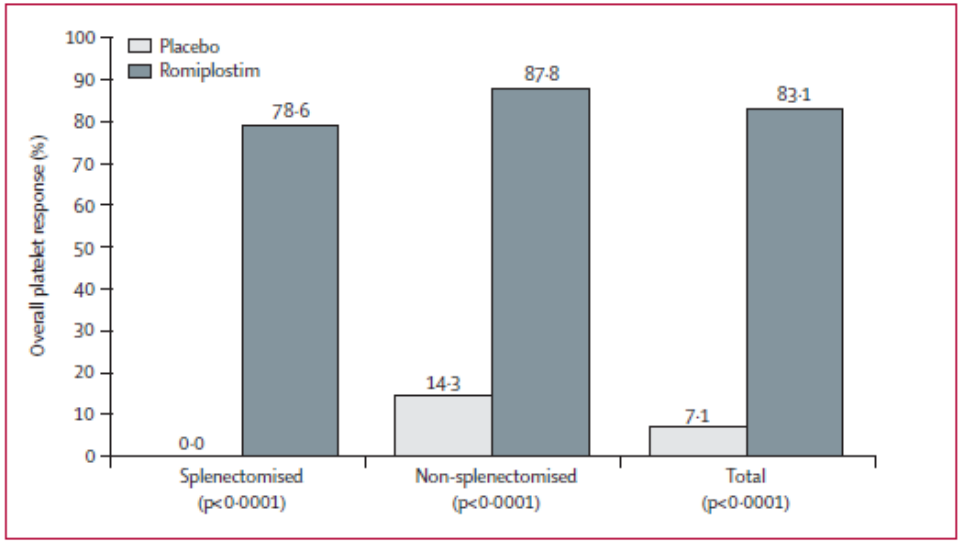
Blood 2007

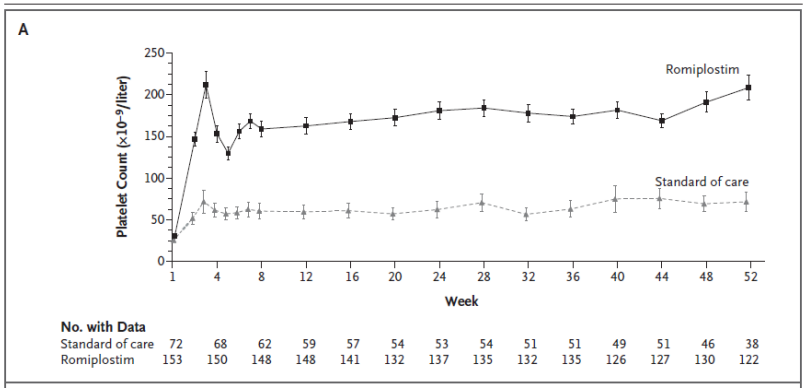


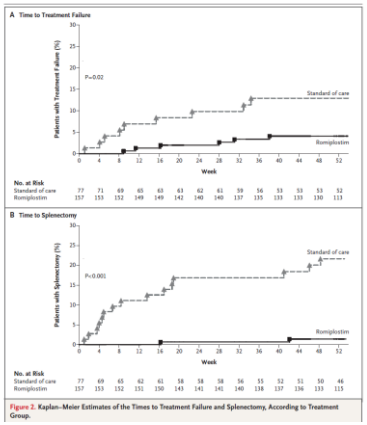
Tiede et al, Clin Appl Thromb Hemostas 2005

TPO-RECEPTOR AGONISTS





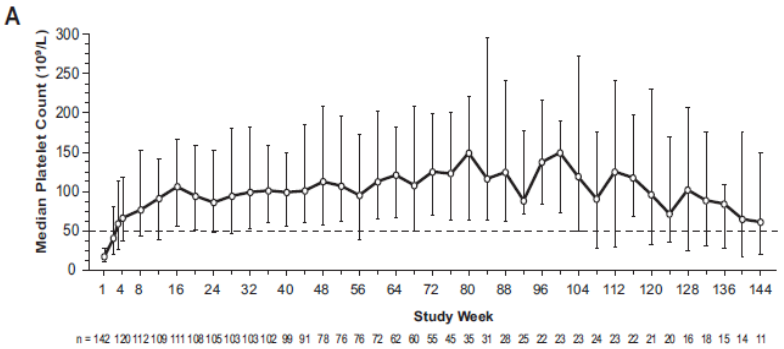


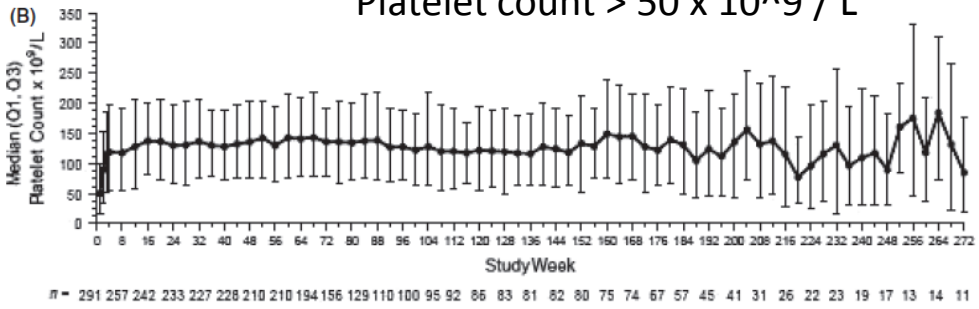


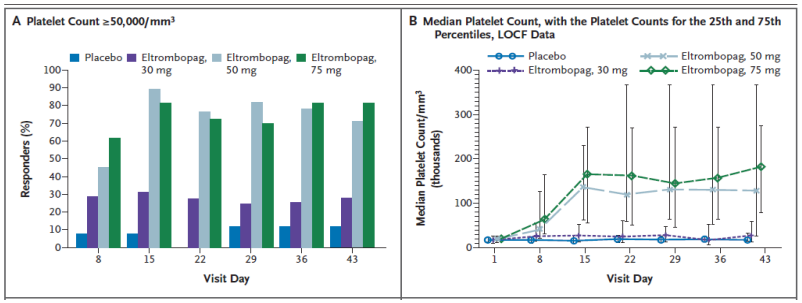
ROMIPLOSTIM

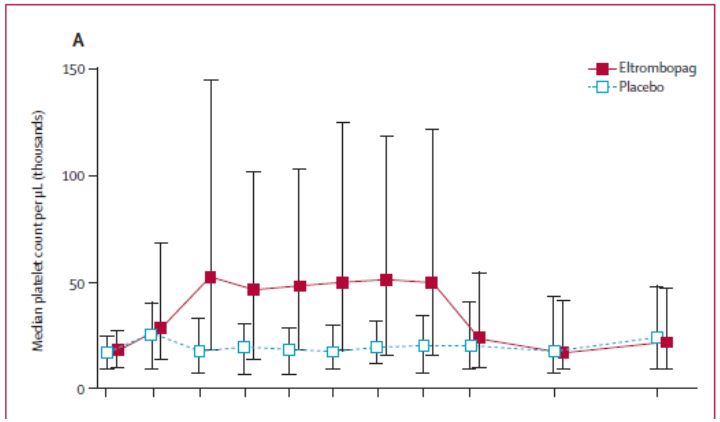
Kuter et al, Lancet 2008
Bussel et al, Blood 2009
Kuter et al, NEJM 2010
Kuter et al, Br J Hematol 2013

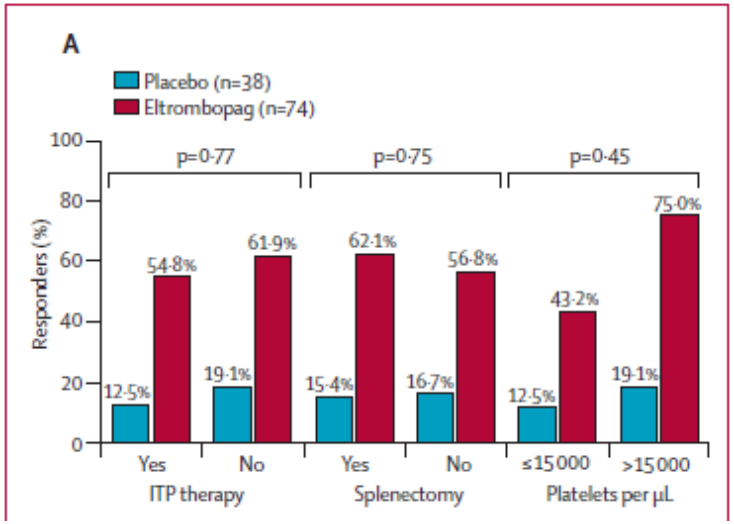
Definition of response:
Platelet count > 50 x 10^9 / L

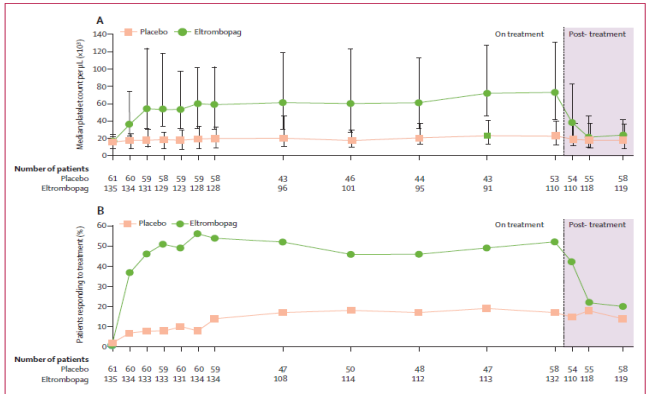


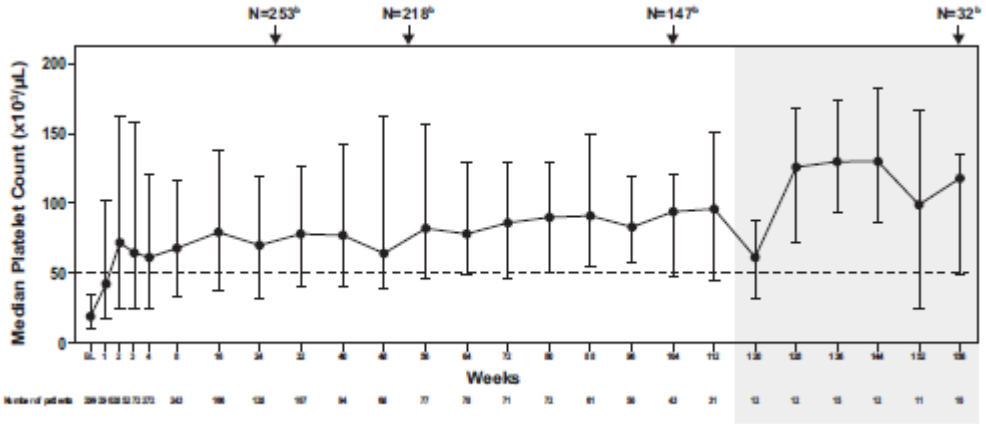












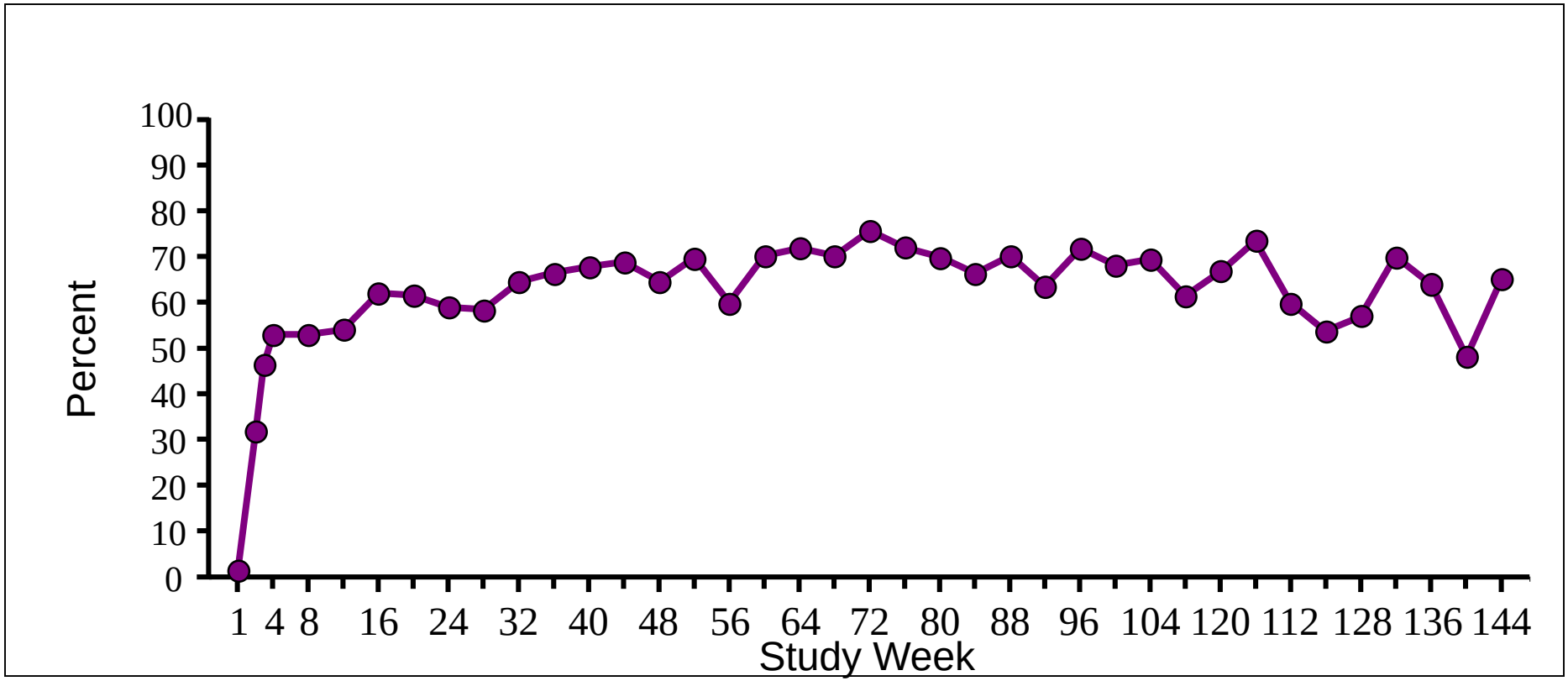
ELTROMBOPAG

Bussel et al, NEJM 2007
Bussel et al, Lancet 2009
Cheng et al, Lancet 2011
Saleh et al, Blood 2013

Definition of response:
Platelet count > 50 x 10^9 / L

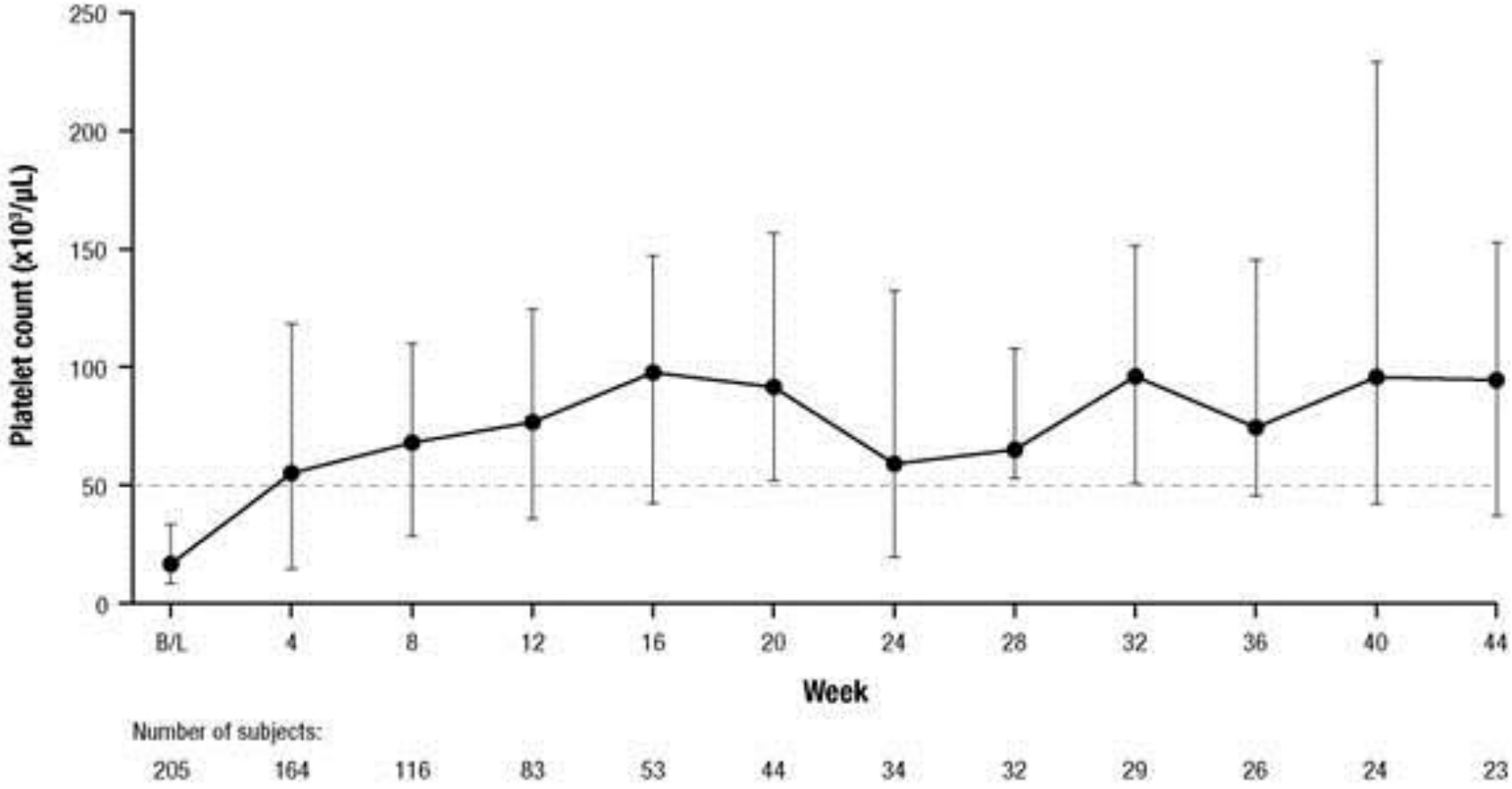
Romiplostim - Durability
Platelet Response in Long-term Extension Study

Platelet Counts ≥ 50 x 10^9/L and Double the Baseline Value

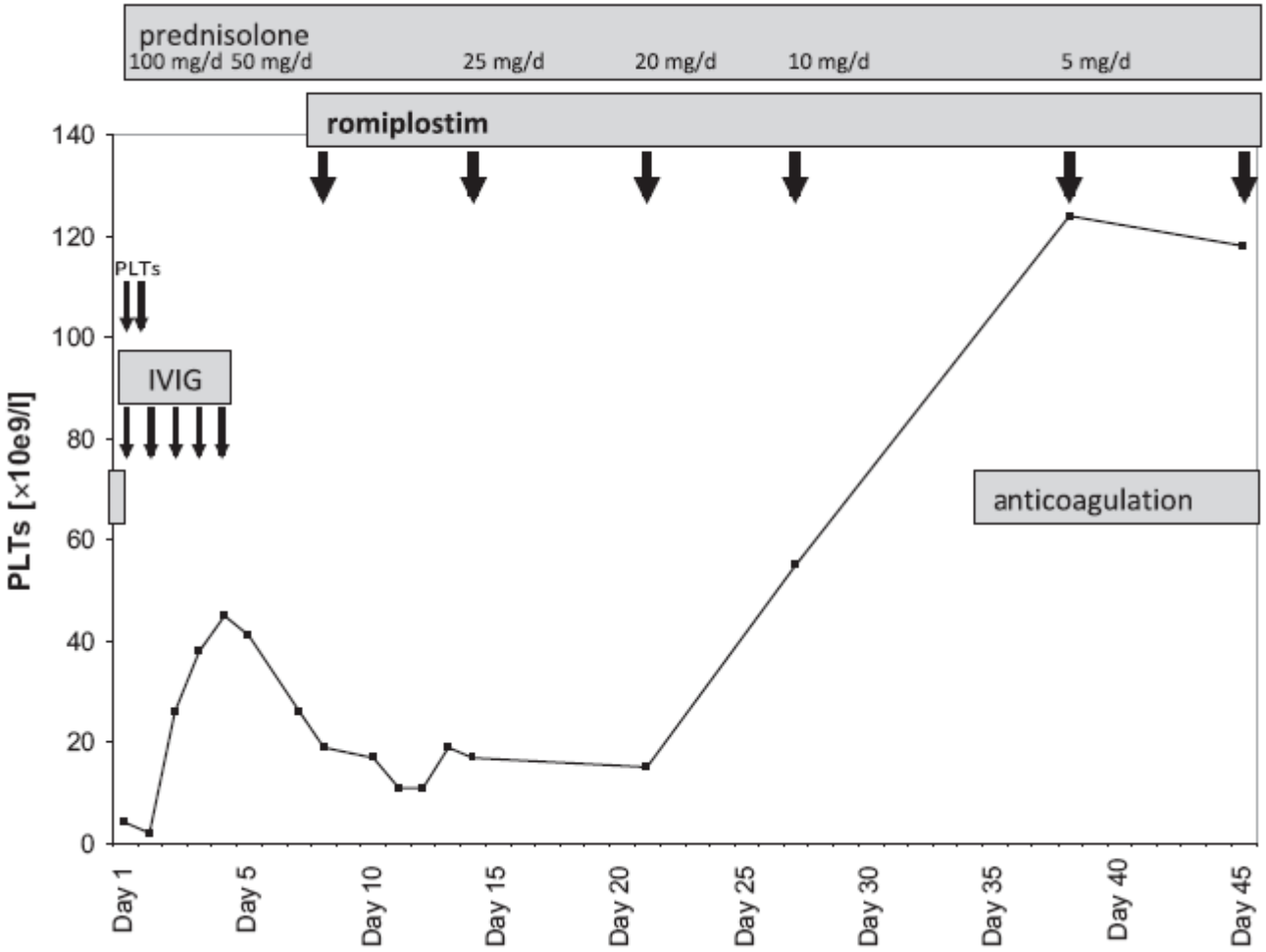


Bussel J et al, Blood 2009

Eltrombopag
Durability Platelet Response in Long-term EXTEND trial



Bussel J et al, ASH 2010



Cantoni N et al , Br J Haematol 2012

Platelets, May 2013; 24(3): 242–243

ISSN 0953-7104 print/ISSN 1369-1635 online
DOI: 10.3109/09537104.2012.686074

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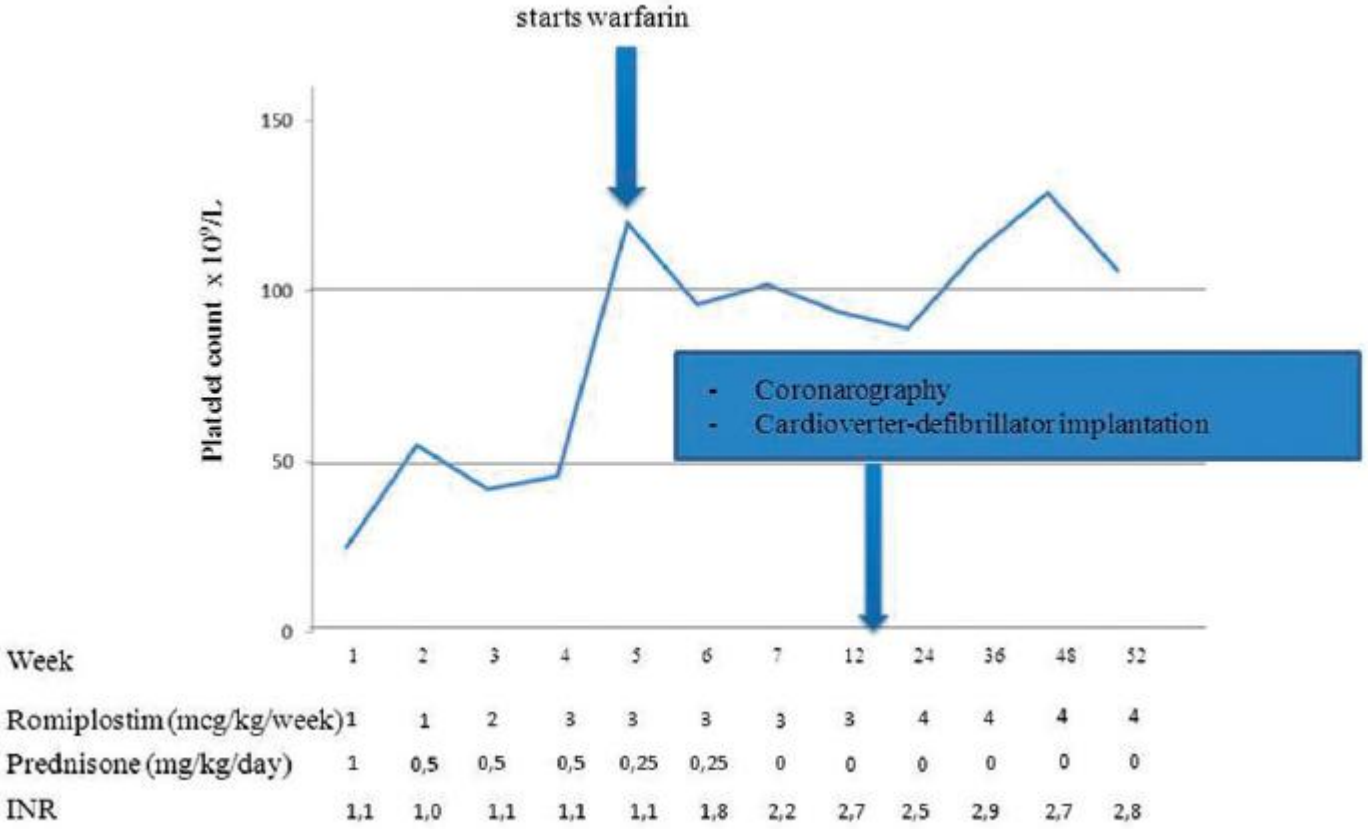
LETTER TO THE EDITOR

Long-term follow-up of concomitant treatment with romiplostim and warfarin in a patient with immune thrombocytopenia and severe cardiac comorbidities

Simone Baldini, Luigi Rigacci, Valentina Carrai, Rajmonda Fjerza, Renato Alterini & Alberto Bosi

Hematology Unit, University of Florence, Azienda Ospedaliero-Universitaria Careggi, viale Morgagni 85, Florence, Italy



Week	1	2	3	4	5	6	7	12	24	36	48	52
Romiplostim (mcg/kg/week)	1	1	2	3	3	3	3	3	4	4	4	4
Prednisone (mg/kg/day)	1	0,5	0,5	0,5	0,25	0,25	0	0	0	0	0	0
INR	1,1	1,0	1,1	1,1	1,1	1,8	2,2	2,7	2,5	2,9	2,7	2,8

platelets

http://informahealthcare.com/plt
ISSN: 0953-7104 (print), 1369-1635 (electronic)

Platelets, 2014; 25(4): 309–310
 DOI: 10.3109/09537104.2013.770137

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LETTER TO THE EDITOR

Feasible concomitant treatment with eltrombopag and oral anticoagulation in a patient with chronic immune thrombocytopenia and severe cardiac comorbidities

Blanca Sanchez-Gonzalez, Agueda Ancochea, Francesc Garcia-Pallarols, Carmen Jimenez, Carme Pedro, and Carles Besses

Department of Hematology, Hospital del Mar-IMIM, Barcelona, Spain

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CHMP positive opinion, december 2015

- Romiplostim®Nplate is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) ~~splenectomised~~ patients who are refractory to other treatments (e.g. corticosteroids, or immunoglobulins). ®~~Revolade may be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated.~~'

- Romiplostim®Nplate is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CHMP positive opinion, december 2015

- Eltrombopag (®Revolade) is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) ~~splenectomised~~ patients who are refractory to other treatments (e.g. corticosteroids, or immunoglobulins). ~~®Revolade may be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated.~~'

- Eltrombopag'®Revolade is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)

- Administration of high dose-immunoglobulins has been occasionally associated with VTE (Schiavotto et al, Haematologica 1993; Paran et al, Blood Coag Fibrinolys 2005; Tam et al, Am J Haematol 2008)

- Thrombotic events occurred in 5.9% and 5.3% of patients treated with romiplostim and eltrombopag, respectively (Rodeghiero et al, Eur J Hematol 2013; Saleh et al, Blood 2013)

- However, possible thrombotic risks associated with platelet increasing drugs should be balanced in ITP patients with acute VTE with the benefits of anticoagulation and with the risks due to the absence of anticoagulation

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Article original

Thromboses sous agonistes du récepteur de la thrombopoïétine au cours du purpura thrombopénique immunologique. Étude rétrospective multicentrique en France

Thrombosis during thrombopoietin receptor agonist treatment for immune thrombocytopenia. A French multicentric observational study

E. Weber[a,*], G. Moulis[b,c,d], M. Mahévas[e], C. Guy[f], B. Lioger[g], I. Durieu[h], M. Hunault[i], M. Ramanantsoa[j], B. Royer[k], A. Default[l], M.-C. Pérault-Pochat[m], L. Moachon[n], N. Bernard[o], G. Bardy[p], A.-P. Jonville-Bera[q], H. Geniaux[r], B. Godeau[e], P. Cathébras[a]

Tableau 1
Caractéristiques des patients ($n = 36$).

Variables	Valeurs
Caractéristiques démographiques	
Age au diagnostic de thrombose, médiane (extrêmes)	59 (19–94)
Sexe M/F (%)	14/22 (61)
PTI	
Primaire, *n* (%)	22 (61)
Secondaire, *n* (%)	13 (36)[b]
Inconnu, *n* (%)	1 (3)
Durée d'évolution[a], médiane (extrêmes)	6 ans (1 mois à 43 ans) (16 ND)
Accidents hémorragiques graves (O/N)	8/7 (21 ND)
Traitements antérieurs	
Splénectomie, *n* (%)	18 (50)
Corticostéroïdes, *n*	18 (17 ND)
Immunoglobulines intraveineuses, *n*	20 (16 ND)
Rituximab	13
Hydroxychloroquine	6
Azathioprine	4
Dapsone	5
Ciclosporine A	1
Danazol	2
Immunoglobulines anti-D	1
Cyclophosphamide	1
Vinblastine	2
ND	17
aRTPO	
Romiplostim, *n* (%)	20 (56)
Eltrombopag, *n* (%)	15 (42)
Romiplostim + eltrombopag, *n* (%)	1 (2)

Tableau 2
Localisation des événements thromboemboliques ($n = 41$).

Thromboses veineuses (n = 28, 68 %)	
Embolie pulmonaire + thrombose veineuse profonde, *n*	7
Embolie pulmonaire, *n*	7
Thrombose veineuse profonde[a], *n*	6
Thrombose veineuse cérébrale, *n*	2
Thrombose cave supérieure, *n*	2
Thrombose d'une veine rénale, *n*	1
Thrombose des corps caverneux, *n*	1
Thrombose veineuse superficielle, *n*	1
Thrombose de TIPS, *n*	1
Thromboses artérielles (n = 13, 32 %)	
Infarctus du myocarde, *n*	7
Accident vasculaire cérébral ischémique, *n*	3
Névrite optique ischémique antérieure aiguë, *n*	1
Ischémie aiguë de membre, *n*	1
Accident ischémique transitoire, *n*	1

TA : thrombose artérielle ; TIPS : dispositif de shunt intra-hépatique ; TV : thrombose veineuse.

[a] Dont une concomitante d'un accident vasculaire cérébral ischémique et une concomitante d'une thrombose veineuse cérébrale du sinus sagittal.

Tableau 3
Facteurs de risque artériels et veineux.

Thrombose veineuse	n (%)
Antécédent de MTEV	10[a] (28)
Néoplasie/hémopathie	9[b] (25)
Lymphome de Hodgkin	3
Lymphome B à grandes cellules	2
Leucémie aiguë myéloïde	1
Maladie de Waldenström	1
Antécédent de LZM	1
Antécédent de cancer du sein	1
Maladies inflammatoires et auto-immunes	8 (22)
Lupus érythémateux disséminé	5[c]
SAPL primaire	1
Syndrome d'Evans	2
Pathologies cardiovasculaires :	7 (19)
Cardiopathie rythmique	4
Cardiopathie ischémique	3
Infections	2 (5)
Sepsis	1
Pneumopathie	1
Autres	
Corticothérapie dans le mois précédent	9
Immunoglobulines dans le mois précédent	13
Insuffisance respiratoire chronique	1
Syndrome néphrotique	1
Shunt intrahépatique par voie transjugulaire	1
Contraception estro-progestative	1
Alitement, immobilisation	4
Chambre implantable	2
Chirurgie récente[d]	2
Voie veineuse centrale fémorale	1

Thrombose artérielle	
Hypertension artérielle	12
Obésité	8
Tabagisme actif	6
Diabète	6
Dyslipidémie	5

LZM : lymphome de la zone marginale ; MGUS : gammapathie monoclonale de signification indéterminée ; MTEV : maladie thromboembolique veineuse ; SAPL : syndrome des antiphospholipides.

[a] Un patient était sous traitement anticoagulant au moment de la thrombose, 2 patients n'avaient plus d'anticoagulant depuis une hémorragie digestive.

[b] Aucun patient n'était en cours de chimiothérapie.

[c] Dont 1 avec un syndrome d'Evans, 1 avec un syndrome de Gougerot-Sjogrën, aucun n'avait d'antiphospholipides

[d] Splénectomie, cholécystectomie (un mois avant la thrombose).

Événement thrombo-embolique	Traitement spécifique	Gestion aRTPO	Issue de l'épisode thrombo-tique	Pts G/L*	Durée de suivi	Statut du PTI **	Traitements du PTI depuis la thrombose	Hémorragies sous ACO ou AGG	Durée de ACO/AGG
IDM de l'IVA	biAG + stent	Arrêt 2 semaines	Favorable	10	25 mois	NR	ETP, MMF, Cs	N	6 mois double puis kardegic seul
TV cave Supérieure	RTX, S, Cs, IgIV,	Arrêt 3 semaines	ND	36	6 mois	ND	S, RTX, Cs, IgIV, RMP	–	–
PUIS TVC du sinus sagittal + TVP (2 mois après)	HBPM relais AVK	Maintien	Favorable §	49	4 mois	RC	AZA, Cs	N	HBPM 4 mois puis AVK 6–12 mois
TVP fémorale + iliaque externe + iliaque primitive gauche + EP LID et LSD	HNF relais fondaparinux 7,5 mg/j	Arrêt 16 mois, repris 1 mois	Favorable	134	42 mois	RC	Aucun	N	6 mois
Thrombose veine sous clavière + TV cave supérieure	Fondaparinux 7,5 mg/j	Maintien	Syndrome cave supérieur	69	26 mois	RC	RMP, AZA, IgIV, Cs	O (hématome de cuisse)	4 mois, relais fondaparinux 2,5 mg/j
Thrombose veine rénale gauche	Fondaparinux 7,5 mg/j	Arrêt 1 mois	Favorable	77	39,5 mois	ND	RMP, dapsone, AZA, RTX	N	3 mois
PUIS EP (sous fondaparinux préventif 3,5 mois après)	Fondaparinux 7,5 mg/j, relais AVK précoce	Arrêt quelques jours	ND	1049	36 mois	RC	Aucun (arrêt RMP après 7 mois puis arrêt AZA)	N	6 mois
IDM	AGG	ND	Cardiopathie ischémique	< 10	2 mois	ND	ND	ND	ND
TVP + EP	HBPM relais fondaparinux 7,5 mg/j	Arrêt	HTAP	36	2 ans et 2 mois	RC	AZA, Cs	N	2 ans
Thrombose TIPS (sous fondaparinux préventif)	Dilatation de TIPS	Arrêt	Favorable	527	5 mois	NR	RTX	N	–
AIT, Hémiparésie avec aphasie	AGG	Maintien	Favorable	118	30 mois	RC	RMP	N	Long cours
TVP bilatérale étendue	HBPM (tinzaparine)	Arrêt 2 mois	Favorable	176	16 mois	ND	ETP	N	–

Arterial thrombosis in ITP patients

Primary PCI for Acute Myocardial Infarction in a Patient with Idiopathic Thrombocytopenic Purpura

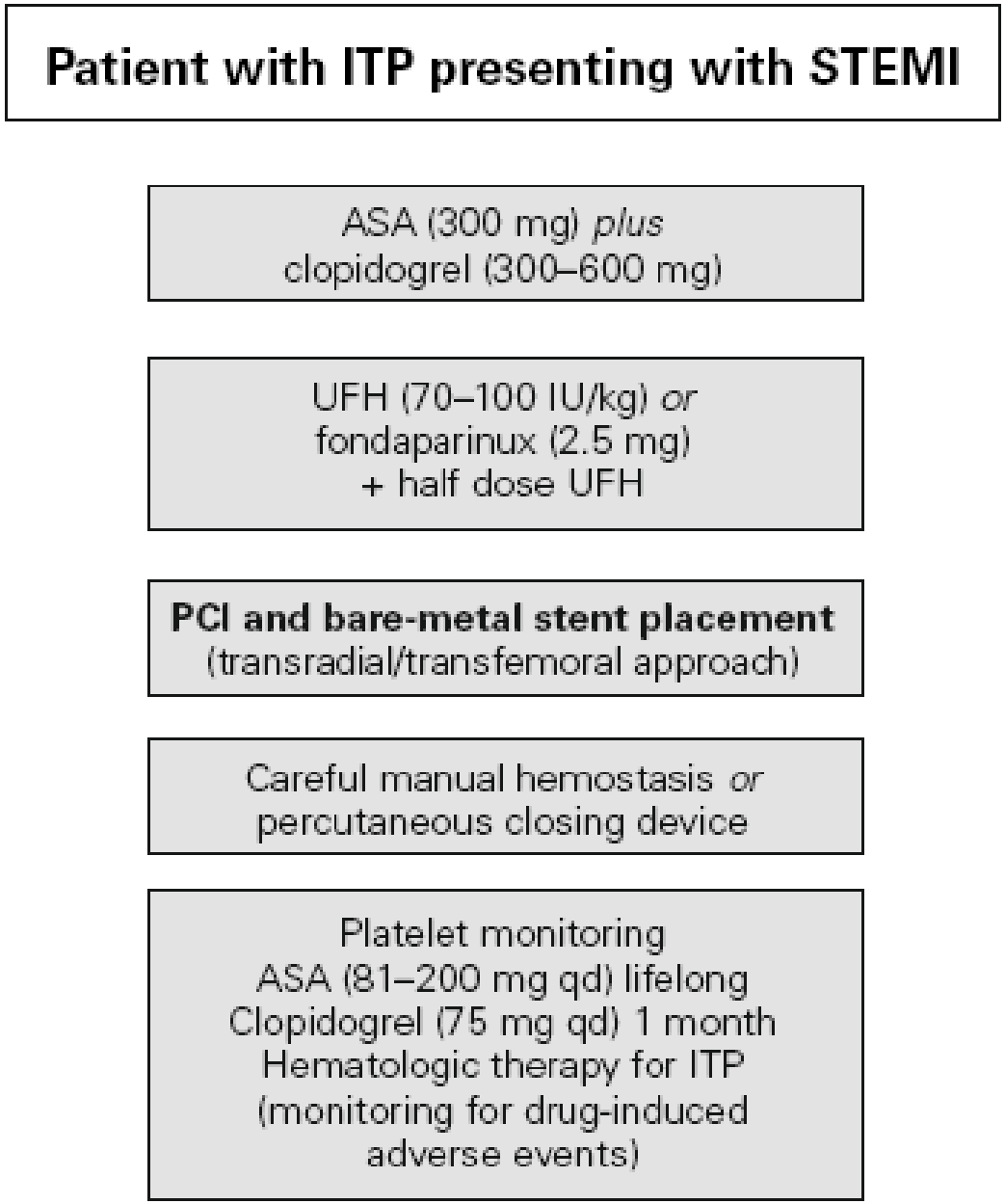
A Case Report and Review of the Literature

Aleksandar N. Neskovic[1], Ivan Stankovic[1], Predrag Milicevic[1], Aleksandar Aleksic[1], Alja Vlahovic-Stipac[1], Branko Calija[2], Biljana Putnikovic[1]

[1] Cardiac Catheterization Laboratory, Clinical Hospital Center Zemun, Belgrade University School of Medicine, Serbia,
[2] Dedinje Cardiovascular Institute, Belgrade, Serbia.

Received: June 8, 2009; accepted: August 24, 2009

Authors, year of publication	Patient age (years) and sex	Platelet count (× 10^9/l)	PCI Approach	UFH/LMWH during PCI	Antiplatelet agent
Fuchi et al., 1999 [24]	72, female	59	PCI Transfemoral	UFH	None
Kikuchi et al., 2002 [26]	68, female	22	PCI, stenting (–)	UFH	Ticlopidin
Kim et al., 2006 [31]	47, female	21	PCI, stenting Transfemoral	UFH	ASA Clopidogrel
Gracia et al., 2008 [32]	37, male	39	PCI, stenting Transfemoral	UFH	ASA Clopidogrel


Patient with ITP presenting with STEMI
ASA (300 mg) plus
clopidogrel (300–600 mg)
UFH (70–100 IU/kg) or
fondaparinux (2.5 mg)
+ half dose UFH
PCI and bare-metal stent placement
(transradial/transfemoral approach)
Careful manual hemostasis or
percutaneous closing device
Platelet monitoring
ASA (81–200 mg qd) lifelong
Clopidogrel (75 mg qd) 1 month
Hematologic therapy for ITP
(monitoring for drug-induced
adverse events)

Primary Percutaneous Coronary Intervention by a Stentless Technique for Acute Myocardial Infarction with Idiopathic Thrombocytopenic Purpura: A Case Report and Review of the Literature

Susumu Fujino, Satoru Niwa, Kensuke Fujioka, Tomohito Mabuchi, Yoshihiro Noji, Masato Yamaguchi and Takahiko Aoyama

Intern Med 55: 147-152, 2016 DOI: 10.2169/internalmedicine.55.4544

Table. Case Reports of AMI with Concomitant ITP in which Primary PCI Was Performed.

Reference No.	Nationality	Age	Gender	Device	Platelet count/μL	Major bleeding	Anti-platelet therapy
2	Japan	72	F	POBA	59,000	Yes	Ethyl icosapentate
3	UK	49	M	BMS	41,000	No	DAPT
4	Japan	68	F	BMS	22,000	No	Ticlopidine
5	USA	77	M	BMS	78,000	No	DAPT
6	Israel	46	M	POBA	24,000	No	ASA
7	Korea	47	F	BMS	21,000	No	DAPT
8	Spain	44	M	BMS	34,000	No	Clopidogrel
9	Spain	37	M	BMS	39,000	No	DAPT
10	Serbia	80	M	BMS	5,000	No	DAPT
11	Turkey	23	F	BMS	35,000	No	ASA
12	Turkey	42	M	BMS	41,000	No	DAPT
13	USA	55	M	DES	42,000	No	DAPT
14	Israel	60	F	BMS	29,000	No	DAPT
Current case	Japan	78	M	NSE	41,000	No	ASA

POBA: Plain old balloon angioplasty, BMS: Bare metal stent, DES: Drug eluting stent, DAPT: Dual antiplatelet therapy, ASA: Acetylsalicylic acid, NSE: Non-slip element balloon

PLATELET INCREASING STRATEGIES IN PATIENTS WITH IMMUNE THROMBOCYTOPENIA REQUIRING LONG-TERM ANTITHROMBOTIC PROPHYLAXIS

V. De Stefano, A. Ciminello, T. Za, S. Betti, F. Bartolomei, E. Rossi

(SISET 2016, PO117)

Characteristics of population (Hematology, Catholic University, 2000-2015)	
N patients (M/F); median age	18 (11/7); 52 yrs (47-90)
Indication to antithrombotic treatment	Treatment
Atrial fibrillation N= 4	VKA=2, DOAC=1, LMWH=1
Carotid stenosis N=2	Aspirin
Aortic valve replacement N=1	VKA followed by aspirin
Angioplasty of popliteal artery N=1	aspirin + clopidogrel
Coronary bypass N=1	Indobufene
Coronary stenting N=3	VKA=1, ASA+CPG=2
DVT of the legs N=3	LMWH (6 to 12 months)
Inferior caval vein thrombosis N=1	LMWH (4 months)
Portal vein thrombosis N=1	VKA
Retinal vein thrombosis N=1	LMWH (5 months)

Main results	
Platelet count before platelet-increasing treatment (median, range)	46 x 10*9/L (13-67 x 10*9/L)
TPO-RA N=11	Romiplostim N= 2, Eltrombopag N = 9
Steroids N=7 (in one case PDN+HD-IG)	PDN= 5, DEX = 2
Life-long antithrombotic treatment N= 13	
Plt count after platelet-increasing treatment	
➢ 100 x 10*9/L ➢ 90-100 x 10*9/L ➢ 50-90 x 10*9/L ➢ < 50 x 10*9/L	N=13 (TPO-RA=9, PDN=2, DEX=2) N= 2 (TPO-RA=2) N= 2 (PDN= 2) N= 1 (23 x 10*9/L after PDN+HD-IG)
Failure of platelet increasing treatment	n =1 (PDN+HD-IG) in IVC thrombosis (filter placement)
Withdrawal of treatment for ITP remission	N=6 (PDN=3, DEX=2, Eltrombopag=1)

All the 11 pts receiving TPO-RA reached plts >90 x 10*9/L vs 4/7 receiving steroids (p=0.04)

All patients with a plt count > 50 x 10*9/L received full doses of antithrombotic drugs

No thrombotic or bleeding complications occurred during treatment.

Proposal of Study

OBSERVATIONAL STUDY ON PLATELET INCREASING STRATEGIES IN PATIENTS WITH IMMUNE THROMBOCYTOPENIA REQUIRING LONG-TERM ANTITHROMBOTIC PROPHYLAXIS

PLatelet ENhancers in patients with Immune Thrombocytopenia requiring Antithrombotic Drugs

PLENITAD Study

SOCIETA' ITALIANA PER LO STUDIO EMOSTASI E TROMBOSI

SISET

XXIV
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NAZIONALE

Abano Terme, 9-12 novembre 2016

- **The primary objective** of the study is to gain information about the incidence of major bleeding in patients with ITP and platelet count < 100 $x10^9$/L requiring antithrombotic treatment including vitamin K-antagonists (VKA), direct oral anticoagulants (DOACs), unfractionated (UFH) or low molecular weight heparin (LMWH), fondaparinux, antiplatelet agents.

The secondary objectives are:

- To gain information about safety and efficacy in different clinical scenarios according to:
- Type of clinical situation requiring antithrombotic prophylaxis or treatment (atrial fibrillation, arterial stenosis, surgery, major arterial thrombosis and TIA, major venous thromboembolism and superficial vein thrombosis)
- Type of antithrombotic treatment (VKA, DOACs, UFH, LMWH, fondaparinux, antiplatelet agents)
- Type of management strategy: prednisone (PDN), high-dose dexamethasone (DEX), high-dose immunoglobulins (HD-IG), thrombopoietin receptor agonists (TPO-RA: eltrombopag ETP, romiplostim RPL). Patients treated with observation or with platelet transfusions will be included too.
- Level of platelet count
- Dosage of the antithrombotic drugs above listed

Congenital bleeding disorders

Haemophilia

Haemophilia (2012), 18, e173–e187 DOI: 10.1111/j.1365-2516.2012.02758.x

REVIEW ARTICLE *von Willebrand disease (VWD)*

Thrombotic adverse events to coagulation factor concentrates for treatment of patients with haemophilia and von Willebrand disease: a systematic review of prospective studies

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Table 6. Summary of studies, patients, thrombotic adverse events and event rates.

Bleeding disorder	Patients *n* (studies)	Arterial thrombosis	Venous thromboembolism	Thrombophlebitis	Thrombotic AEs/patients (%)	Thrombotic AEs/infusions* (%)	Thrombotic AEs/Total AEs† (%)
Haemophilia A	4420 (45)	0	0	2‡	2/4420 (0.045)	1/502 743 (0.0002)	2/423 (0.47)
Haemophilia B	748 (15)	0	0	11§	11/748 (1.47)	1/17 642 (0.006)	2/104 (1.92)
von Willebrand disease	361 (11)	0	2	5¶	7/361 (1.94)	4/8368 (0.048)	7/50 (14.0)
All	5528 (71)	0	2	18	20/5528 (0.36)	6/528 753 (0.00113)	11/577 (1.91)

*Only data from studies reporting total number of concentrate infusions are considered (32 HA, 8 HB, 4 VWD).

†Only data from studies providing total number of AEs are considered (44 HA, 12 HB, 11 HA).

‡Reported in two studies; one occurred in a patient receiving factor concentrate continuous infusion; the relationship with an infusion site is not reported in the other patient.

§All events, reported in three studies, occurred at infusion sites; irritation or phlebitis (lacking further details) is reported in nine patients from a single study receiving continuous infusion.

¶Reported in five studies; in three patients the occurrence at infusion site is reported; one occurred in the leg, in the remaining case no detail is provided.

AE, adverse event.

J Thromb Thrombolysis 21(2), 175–178, 2006.

Arterial and venous thrombosis in patients with von Willebrand's disease: A critical review of the literature

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J Thromb Thrombolysis (2006) 21: 279–284
DOI 10.1007/s11239-006-6556-7

Non-catheter associated venous thrombosis in hemophilia A and B. A critical review of all reported cases

Antonio Girolami · Raffaella Scandellari · Ezio Zanon · Roberto Sartori · Bruno Girolami

Haemophilia (2006), **12**, 345–351 DOI: 10.1111/j.1365-2516.2006.01299.x

REVIEW ARTICLE

Arterial and venous thrombosis in rare congenital bleeding disorders: a critical review

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Haemophilia (2006), **12**, 87–89 DOI: 10.1111/j.1365-2516.2006.01179.x

CASE REPORT

Deep vein thrombosis in a patient with severe haemophilia A

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DVT of the left upper limb in a 25 y.o. man with severe hemophilia A

Treatment with FFP to achieve FVIII level of 30–40% for 4 days; the factor replacement therapy was withheld because of thrombosis of the left basilic vein

The patient was treated with enoxaparin 40 mg s.c. twice daily for 4 weeks and then enoxaparin 40 mg s.c. daily for next 5 months.

Table 1 Thrombotic events reported in patients with Glanzmann thrombasthenia

Authors	Age/sex	Gp IIb/IIIa levels; platelet count	Type of thrombosis	Associated risk factors	Bleeding tendency	Mutation	Therapy of thrombosis	Comments
George *et al.* [1]	33, F	<2%; n.r.	DVT	n.r.	Severe	n.r.	n.r.	Second case
Gruel *et al.* [20]	67, M	Low; n.r.	DVT	Long air travel	Moderate	Ser 752 Pro (β3)	Caval filter, LMWH	Good evolution
D'Orion *et al.* [2]	72, F	Low; normal	DVT	Old age, aFVII concentrate	Severe	n.r.	UH, LMWT	Intestinal resection for angiodysplasia
Ten Cate *et al.* [3]	48, M	Low; n.r.	Recurrent DVT	Smoking, Het Fv Leiden	Moderate	n.r.	LMWH	Long-term therapy with LMWH
Phillips and Richards [22]	2, F	Low; n.r.	DVT	Femoral vein catheter	Moderate	n.r.	Removal of catheter	Fair evolution
Tullu *et al.* [8]	6, M	Low; 240×10^3	Cardiothrombosis	Restrictive cardiomyiopathy	Moderate	n.r.	Platelet transfusion for bleeding	Fatal
Serenty *et al.* [7]	41, F	Low; n.r.	Pulmonary embolism	4-h immobilization in seated position	Moderate	n.r.	LMWH, coumadin	Good evaluation
Rezende [23] case 1	36, M	Low; n.r.	Recurrent DVT	Het Fv Leiden	Mild	n.r.	LMWH	
Case 2	41, M	Low; n.r.	Cerebral vein thrombosis	None	n.r.	n.r.	n.r.	No FV Leiden present in brother (second case)

aFVII, activacted factor VII; DVT, deep vein thrombosis; F, female; FV, factor V; Gp, glycoprotein; Het, heterozygote; LMWH, low molecular weight heparin; M, male; n.r., not reported; UH, unfractionated heparin.

Girolami et al, Blood Coagulation Fibrinolys 2013

Pulmonary embolism in a patient with congenital afibrinogenemia

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Haemophilia (2013), **19**, e358–e396

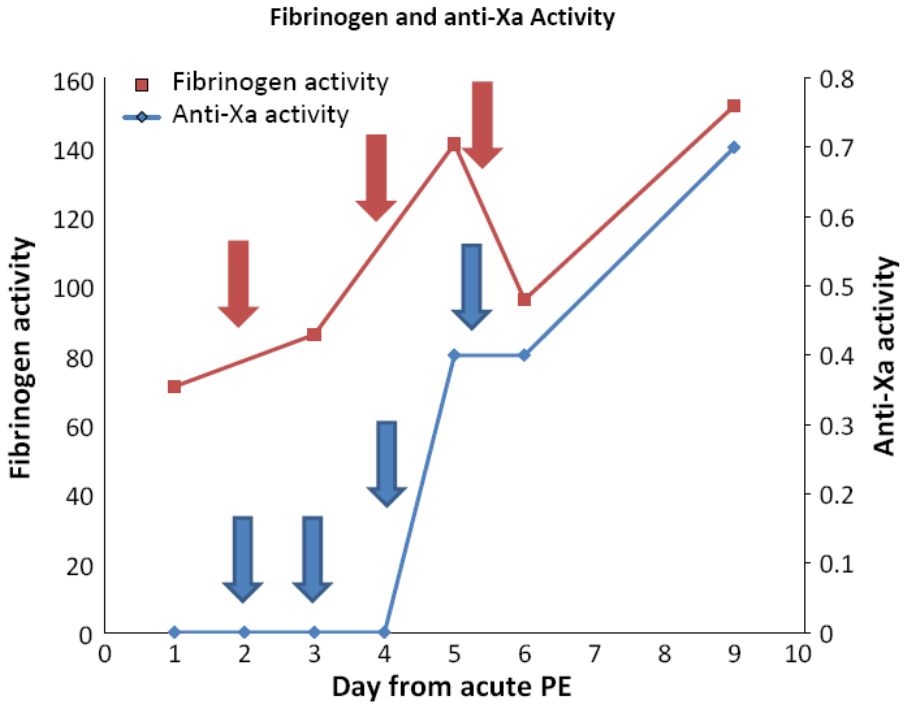

Fig. 1. Increased dosing of hFC is required with concomitant heparin dosing. Red arrows indicate dosing of hFC; blue arrows indicate enoxaparin (see text). Fibrinogen activity is shown on the left axis, anti-Xa activity on the right. Optimal anti-Xa activity was attained by day 9 after the acute pulmonary embolism (PE).

A case of peripheral arterial thrombosis in a patient with congenital afibrinogenemia has been reported at the XXIII Congress SISET*(Santoro et al, Poster 76)*

The patient is now treated with LMWH (100 IU/kg od) + ASA (100 mg od) + CPG (75 mg od) + FFP (twice a week)

Thrombosis Research 132 (2013) 8–14

Contents lists available at SciVerse ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Management of cardiovascular disease in haemophilia

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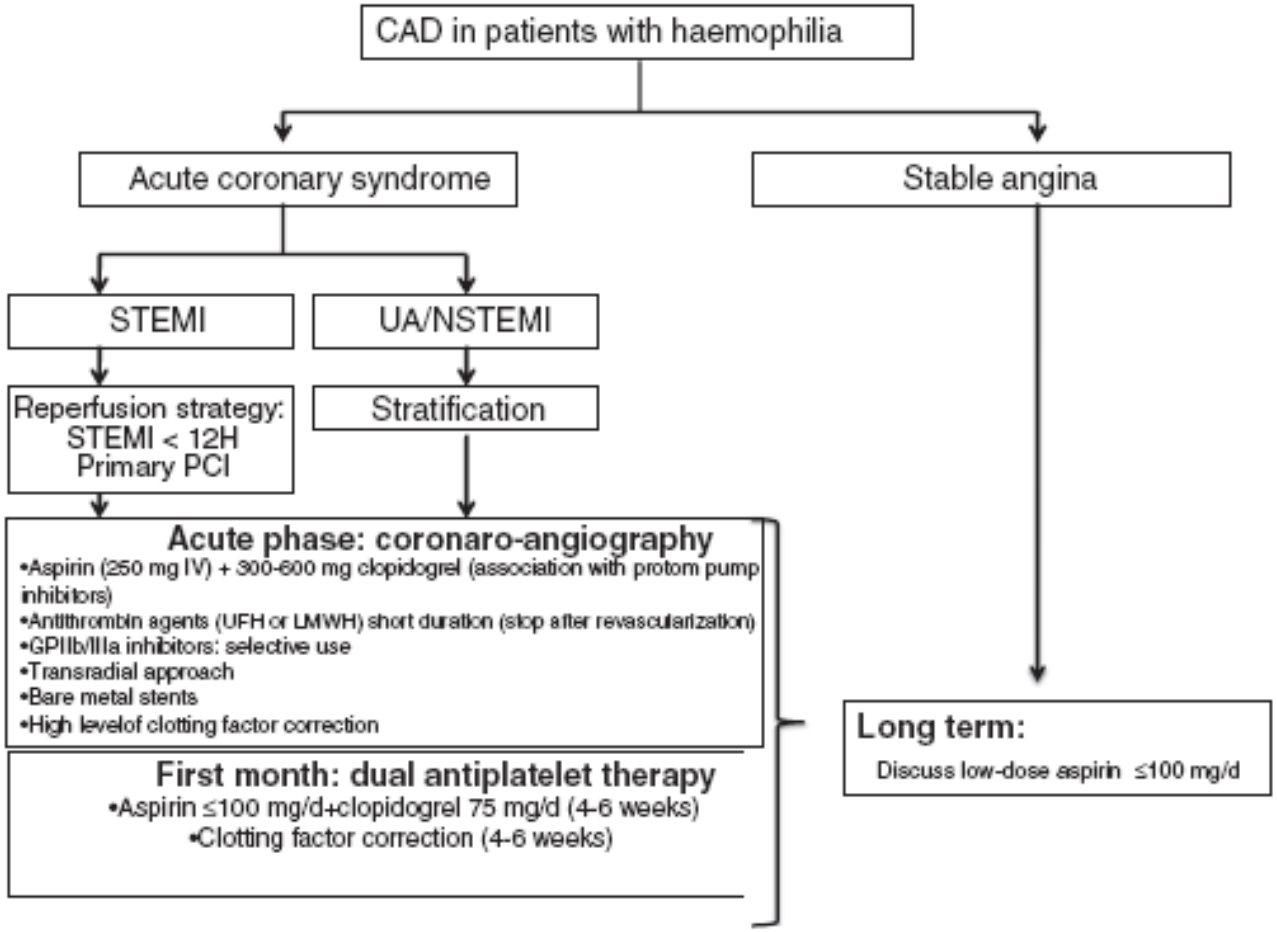

Table 2 **Thrombotic events described in patient with Bernard–Soulier syndrome**

Authors	Age/sex	Complex Gp I-IX-V levels; platelets count	Type of thrombosis	Associated risk factors	Bleeding tendency	Mutation	Therapy of thrombosis	Comments
Humphries *et al.* [9]	66, M	n.r.; 15×10^3	Unstable angina	None	Moderate	n.r.	CABG	Invasive procedure carried out after platelet transfusion
Girolami *et al.* [12] case 1	62, M	40%; 50×10^3	MI	Heavy smoking, Hypertension	Mild	N41H (Gp Ibα chain)	PTCA, stent ticlopidine, ASA	
Case 2	51, M	45%; 45×10^3	MI	Light smoking, high cholesterol	Mild	N41H (Gp Ibα chain)	CABG ticlopidine, ASA	Cousin of the previous case

ASA, aspirin; CABG, coronary artery bypass graft; Gp, glycoprotein; M, male; MI, myocardial infarction; n.r., not reported; PTCA, percutaneous transluminal coronary angioplasty.

Girolami et al, Blood Coagulation Fibrinolys 2013

Arterial thrombosis in patients at high hemorrhagic risk

- Thrombolysis for acute coronary syndrome (ACS) or ischemic stroke is contraindicated in patients with ITP or inherited plasma deficiencies.
- In ITP patients with ACS, percutaneous coronary intervention and bare-metal stent placement (requiring a shorter period of dual antiplatelet therapy over drug-eluting stents) appear reasonable, and antiplatelet agents are advisable after therapies obtaining a platelet count $\geq 50 \times 10^9$/L (for some authors $\geq 30 \times 10^9$/L). A stentless approach has been also suggested.
- In patients with haemophilia, management of ACS is substantially the same as for the general population, but bare-metal stents should be preferred and clotting factor correction should be adopted if haemophilia is severe