8ª GIORNATA DELLO SPECIALIZZANDO IN NEUROLOGIA

Maneuvering Between Scylla and Charybdis, management of antithrombotic therapy in thrombocytopenic patients with ischemic stroke

Dott. Matteo Grazzini
Clinica Neurologica Ospedale Policlinico San Martino, Genova

OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria

UNIVERSITÀ DEGLI STUDI
DI GENOVA

Background

Thrombocytopenia does not protect patients against thromboembolic disease.

Thrombocytopenic patients may experience cerebrovascular events and its management have to face off with the risk of bleeding due to low platelet count at the same time.

Thrombocytopenia is defined as a platelet count of less than $150\times10^3/\mu L$
(approximately 2.5 percent of the population).

People with incidentally discovered borderline thrombocytopenia may have a low incidence of progression to clinical disease.

Only 6.9% patients with platelet values between $100\times10^3/\mu L$ and $150\times10^3/\mu L$ develops more severe thrombocytopenia.

The most recognised platelet count referred for thrombocytopenia definition is $<100\times10^3/\mu L$ on current literature.

The incidence of thrombocytopenia in acute ischemic stroke (AIS) have been found in 7,9% of cases considering a platelet threshold $<150x10^9/L$.

It was lower if considering platelet count $<100x10^9/L$, ranging about 4%.
It was not suspected based on initial history in only 0.3% of patients

Degrees of thrombocytopenia can be further subdivided into mild (platelet count 100 to $150\times10^3/\mu L$), moderate (50 to $99\times10^3/\mu L$), and severe ($<50,000\times10^3/\mu L$).
*However, it must be interpreted in the context of the underlying disease, and higher or lower values may be appropriate for certain conditions.

Current guidelines

AHA/ASA Guideline

2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

ESO EUROPEAN STROKE ORGANISATION

ESO Stroke Guidelines

forward 20 1997/2017

SPREAD

Stroke Prevention And Educational Awareness Diffusion

VIII Edizione

Ictus cerebrale:

linee guida italiane di prevenzione e trattamento

Raccomandazioni e Sintesi

According to current US and European guidelines, PC < 100×10^9/L is a contraindication for IVT.

While US guidelines recommend initiating IVT treatment before PC is available, European guidelines do not, according to the criteria of the previous randomized IVT trials.

2.3. Other Diagnostic Tests	COR	LOE	New, Revised, or Unchanged
1. Only the assessment of blood glucose must precede the initiation of IV alteplase in all patients.	**I**	**B-R**	Recommendation reworded for clarity from 2013 AIS Guidelines. Class unchanged. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
10. Given the extremely low risk of unsuspected abnormal platelet counts or coagulation studies in a population, it is reasonable that urgent IV alteplase treatment not be delayed while waiting for hematologic or coagulation testing if there is no reason to suspect an abnormal test.	**IIa**	**B-NR**	Recommendation and Class unchanged from 2015 IV Alteplase. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.

Coagulopathy	The safety and efficacy of IV alteplase for acute stroke patients with platelets <100 000/mm³, INR >1.7, aPTT >40 s, or PT >15 s are unknown, and IV alteplase should not be administered.† (*Class III: Harm; LOE C-EO*)‡§ (In patients without history of thrombocytopenia, treatment with IV alteplase can be initiated before availability of platelet count but should be discontinued if platelet count is <100 000/mm³. In patients without recent use of OACs or heparin, treatment with IV alteplase can be initiated before availability of coagulation test results but should be discontinued if INR is >1.7 or PT is abnormally elevated by local laboratory standards.) (Recommendation wording modified to match Class III stratifications.)

Current guidelines

AHA/ASA Scientific Statement

Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke

A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

Stroke February 2016

A platelet count <100 000/mm^3 is a contraindication for the administration of intravenous alteplase for acute ischemic stroke.

This threshold was derived from expert consensus. The risk of hemorrhagic complications is expected to be increased in the setting of severe thrombocytopenia, but the precise relationship between platelet count and bleeding risk is not well studied.

Whether a platelet count of 100 000 mm^3 is a justified threshold for withholding intravenous thrombolysis remains unclear. Of 14306 stroke patients treated with intravenous alteplase, 21 patients have been reported with details, sICHwas documented in 1 of these 21 patients (4.8%). The extremely small number of published cases precludes solid conclusions.

Table 13. Thrombocytopenia

Study	Study Design	n/Total Lysed, N	Any ICH, n	sICH, n	mRS Score of 0–2
Frank et al[52]	Data pooled from observational studies	10/2755	NA	0	NA
Meretoja et al[157]	Observational, single-center registry	7/985	NA	1	3
Brunner et al[155]	Observational, single-center registry	3/688	0	0	NA
Kvistad et al[156]	Observational, single-center registry	1/265	NA	0	NA
Gensicke et al	**Observational multicenter**	**44/7533**	**NA**	**3**	**NA**

Outcome and in-hospital mortality

Journal of the Neurological Sciences

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

Outcomes after acute ischemic stroke in patients with thrombocytopenia or thrombocytosis

Julio C. Furlan [a,b,c,*], Jiming Fang [d], Frank L. Silver [a,b,e]

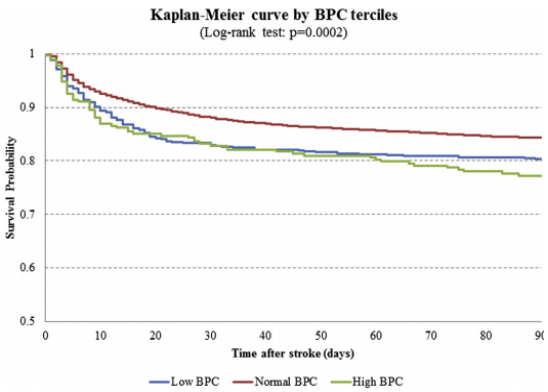
Thrombocytopenia and In-hospital Mortality Risk among Ischemic Stroke Patients

Jason J. Sico, MD,*†‡ Michael S. Phipps, MD,*† John Concato, MD,‡§‖
Carolyn K. Wells, MPH,‡‖ Albert C. Lo, MD, PhD,*¶# Steven E. Nadeau, MD,**††
Linda S. Williams, MD,‡‡§§ Aldo J. Peixoto, MD,‡§ Mark Gorman, MD,‖‖
John L. Boice, MD,¶¶## and Dawn M. Bravata, MD‡‡##

Abnormal blood platelet count (BPC) on admission is correlated with greater 30-day and 90-day mortality after an acute ischemic stroke.

Sico et al. reported that thrombocytopenia on admission is independently associated with in-hospital mortality following acute ischemic stroke, even after adjusting for NIHSS and comorbidities.

Admission thrombocytopenia among patients presenting with acute ischemic stroke predicts in-hospital mortality.



Tohgi et al found that decreasing platelet counts are negatively correlated with infarct size.

There is a paucity of studies focused on the potential association between BPC and outcomes or mortality after AIS.

Thrombocytopenia and its relationship with AIS

Etiologies of Thrombocytopenia

Decreased platelet production
- Bone marrow failure (e.g., aplastic anemia, paroxysmal nocturnal hemoglobinuria, Shwachman-Diamond syndrome)
- Bone marrow suppression (e.g., from medication, chemotherapy, or irradiation)
- Chronic alcohol abuse*
- Congenital macrothrombocytopenias (e.g., Alport syndrome, Bernard-Soulier syndrome, Fanconi anemia, platelet-type or pseudo–von Willebrand disease, Wiskott-Aldrich syndrome)
- Infection† (e.g., cytomegalovirus, Epstein-Barr virus, hepatitis C virus, HIV, mumps, parvovirus B19, rickettsia, rubella, varicella-zoster virus)
- Myelodysplastic syndrome
- Neoplastic marrow infiltration
- Nutritional deficiencies (vitamin B_{12} and folate)

Increased platelet consumption
- Alloimmune destruction (e.g., posttransfusion, neonatal, posttransplantation)
- Autoimmune syndromes (e.g., antiphospholipid syndrome, systemic lupus erythematosus, sarcoidosis)
- Disseminated intravascular coagulation*/severe sepsis*
- Drug-induced thrombocytopenia

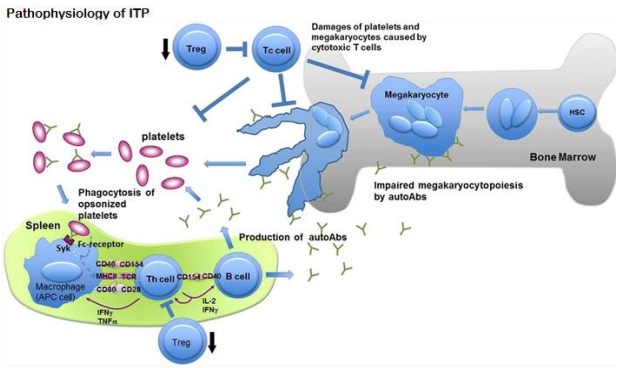
Increased platelet consumption *(continued)*
- Heparin-induced thrombocytopenia
- Immune thrombocytopenic purpura*
- Infection† (e.g., cytomegalovirus, Epstein-Barr virus, hepatitis C virus, HIV, mumps, parvovirus B19, rickettsia, rubella, varicella-zoster virus)
- Mechanical destruction (e.g., aortic valve, mechanical valve, extracorporeal bypass)
- Preeclampsia/HELLP syndrome
- Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome

Sequestration/other
- Chronic alcohol abuse*
- Dilutional thrombocytopenia (e.g., hemorrhage, excessive crystalloid infusion)
- Gestational thrombocytopenia
- Hypersplenism (e.g., distributional thrombocytopenia)
- Liver disease (e.g., cirrhosis, fibrosis, portal hypertension)
- Pseudothrombocytopenia
- Pulmonary emboli
- Pulmonary hypertension

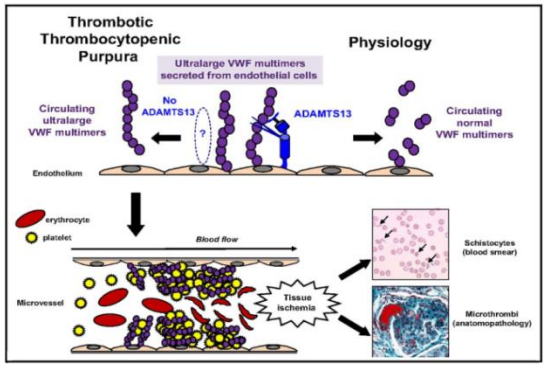
Several disorders can lead to thrombocytopenia.
Only some of these conditions cause prothrombotic state directly.
These disorders may also be overlapping.
Several hematologic disorders leads to the risk of thrombotic events.

Stroke has been identified in 1.27% of patients with hematologic disorders as presenting manifestation

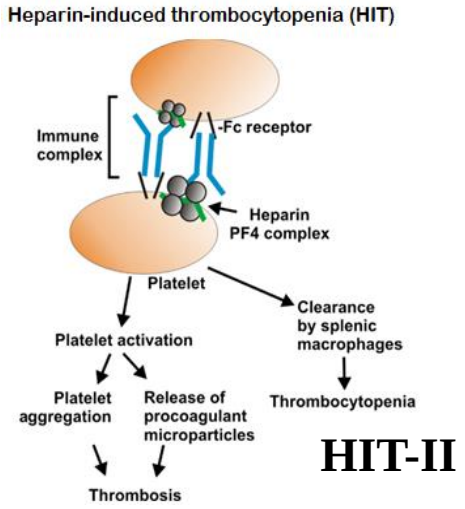
Thrombocytopenic disorders associated with increased thrombotic risk
Immune thrombocytopenia (ITP)
Thrombotic thrombocytopenic purpura (Moschcowitz syndrome, TTP)
Heparin-induced thrombocytopenia type II (HIT- II)
Antiphospholipid antibody syndrome (APS)
Disseminated intravascular coagulation (DIC)
Cancer-associated thrombocytopenia



ITP



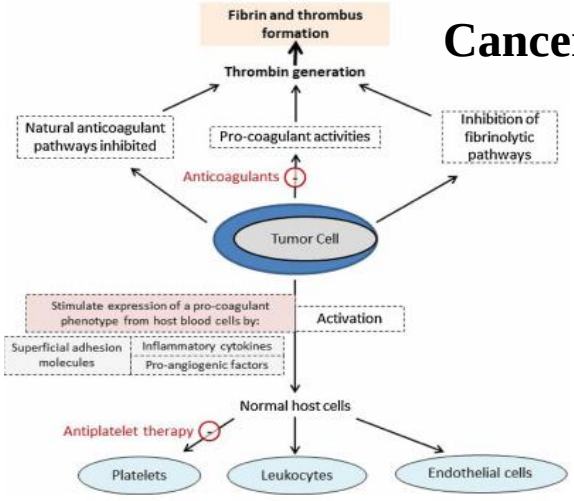
TTP



HIT-II

Several disorders can lead to thrombocytopenia with different mechanism, resulting in a prothrombotic state also and an increased risk of thrombosis.

Treatment is based on the etiology and, in some cases, treating the secondary cause results in normalization of platelet counts, reducing the thrombotic risk at the same time.



Cancer

DIC

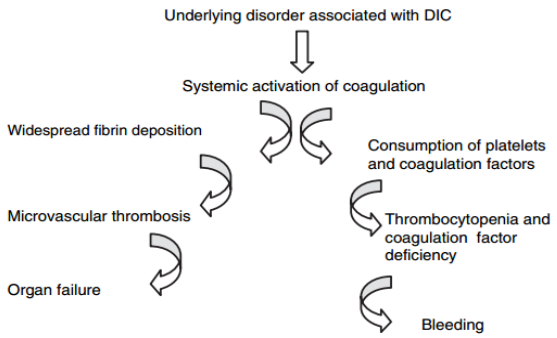
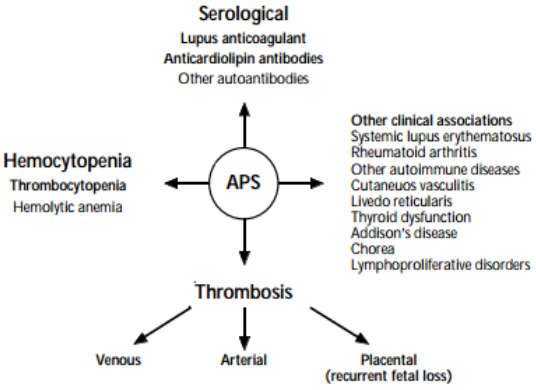


Fig 1. Processes in DIC.

APS



Aims

We intended to assess the incidence of association between AIS and thrombocytopenia in our patient cohort and on scientific available literature, in order to evaluate the management of antithrombotic therapy, their clinical outcome and its relationship with thrombocytopenia.

Material and methods

We performed a non-systematic literature review of the pubmed database researching for all current published article providing cases of AIS experiencing thrombocytopenia ($<100x10^9/L$) at the time of stroke onset. Overall 54 articles have been included.

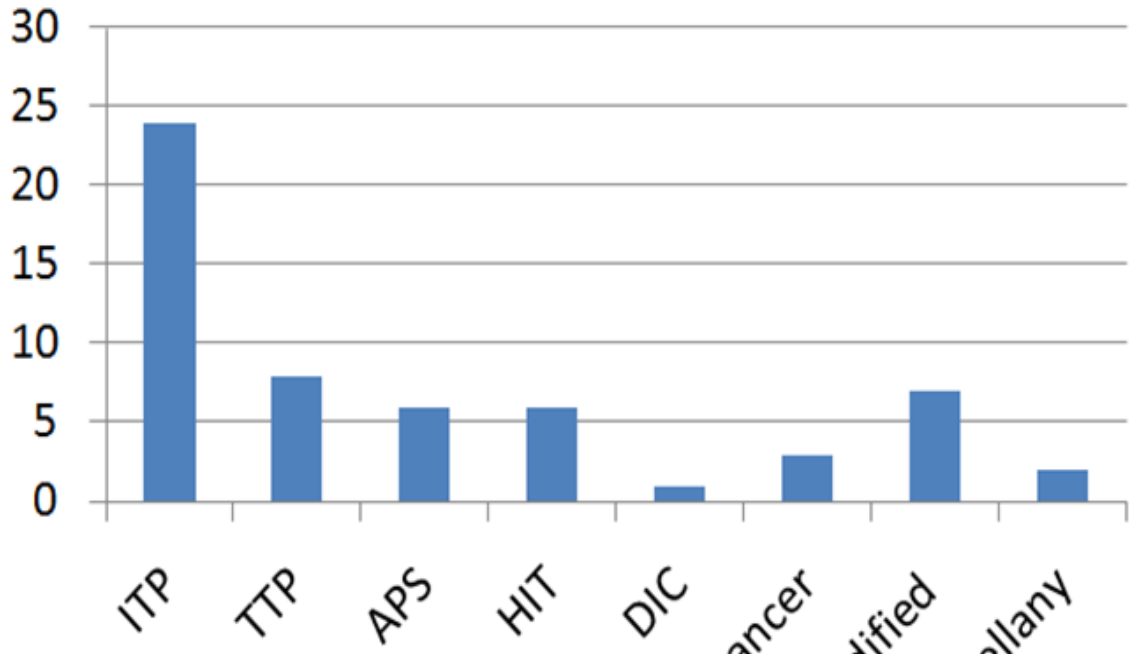
We furthermore performed retrospective analysis of available clinical records in our neurologic clinic by January 2002 until December 2018.

We assessed the incidence of this association in AIS patients on admission, in order to evaluate the management of antithrombotic therapy, their clinical outcome and its relationship with thrombocytopenia.

TOTAL CASES (n=58)	
Age (mean±SD)	51,8±19,6
platelet count at stroke onset, x10³/uL (mean±SD)	69,2±39,8
Cerebrovascular risk factors	Hypertension=8 (14%) Dyslipidemia n=4 (7%) AF n=6 (10%) DM n=3 (5%) Previous Stroke/TIA n=9 (15,5%) ACS n=2 (3%) Atherosclerosis n=2 (3%) Smoking n=3 (5%) Others n=8 (14%) None n= 18 (31%)
Treatment for thrombocytopenia	Steroid n=23 (40%) PEX n=9 (15,5%) IVIG n=11 (19%) PLT transfusion n= 5(9%) immunosuppressant n=10 (17%) Splenectomy n=6 (10%) EPO n=1 (1,7%) antithrombotic therapy discontinuation n=5 (9%) None n=9 (15,5%) NA n=15 (26%)
Treatment of AIS	ASA n=5 (8,6%) Clopidogrel n=1 (1,7%) Cilostazol n=1 (1,7%) Sodium ozagrel n=2 (3%) ASA+dipyridamole n=1 (1,7%) ASA+clopidogrel n=2 (3%) AP not specified n=3 (5%) Fondaparinux n=3 (5%) Argatroban n=1 (1,7%) Tirofiban n=1 (1,7%) ACO n=8 (14%) AP+ACO n=2 (3%) Heparin n=6 (10%) CEA n=2 (3%) IVT n=2 (3%) IA Thrombolysis n=1 (1,7%) Mechanical thrombectomy (MT) n=1 (1,7%) IAT+TM n=1 (1,7%) None n=8 (14%) NA n=13 (22%)
NIHSS at admission (mean)	8
NIHSS at discharge (mean)	4
TOAST classification	LAA n=10 (17%) SVO n=2 (3%) CE n=4 (7%) UD n= 20 (34%) OD n=6 (10%) NA n=16 (27,5%)
ICH	Yes n=5 (9%) No n=28 (48%) NA n=25 (43%)
Follow up (3 months mRS)	mRS0 n=7 (12%) mRS1 n=6 (10%) mRS2 n=2 (3%) mRS3 n=1 (2%) mRS4 n=2 (3%) mRS5 n=2 (3%) mRS6 n=4 (7%) NA n=34 (59%)

Causes of thrombocytopenia

Study population (n=58)

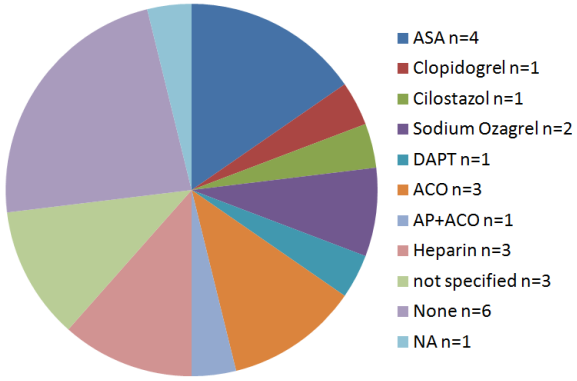


ICH (9%)

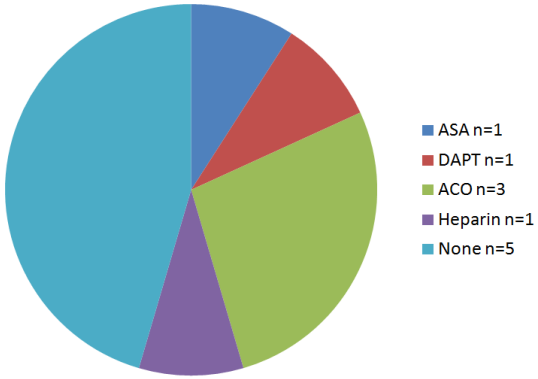
	ITP	TTP	APS	DIC	Unspedified
	n=1	n=1	n=1	n=1	n=1
Platelet count x10³/uL	90	113	23,6	48	<100

Antithrombotic therapies

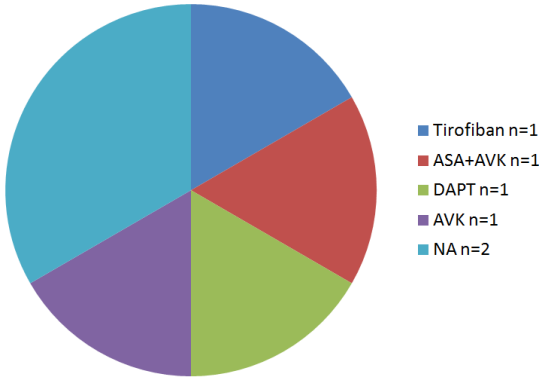
ITP n=24



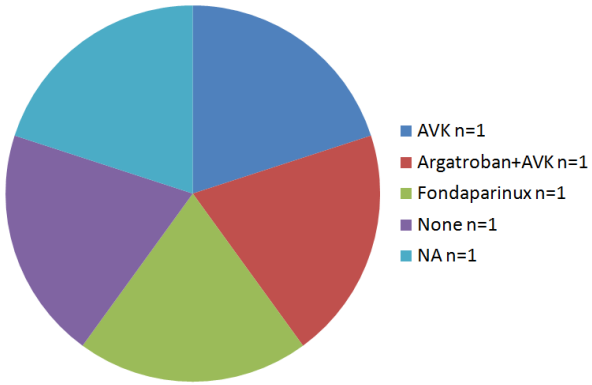
TTP n=8



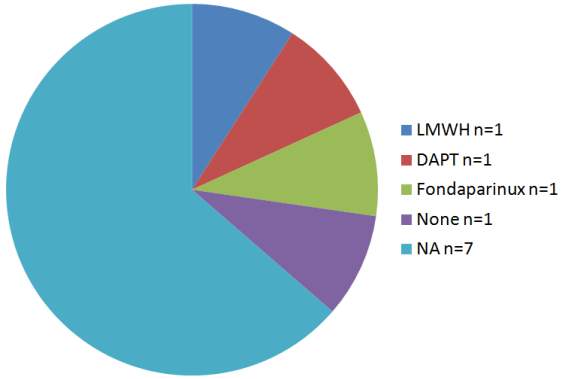
APS n=6



HIT n=6



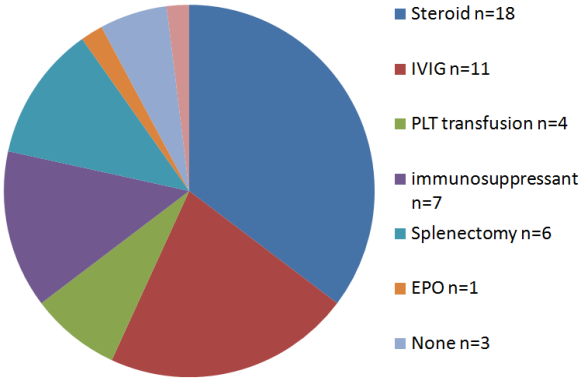
Other etiologies n=13



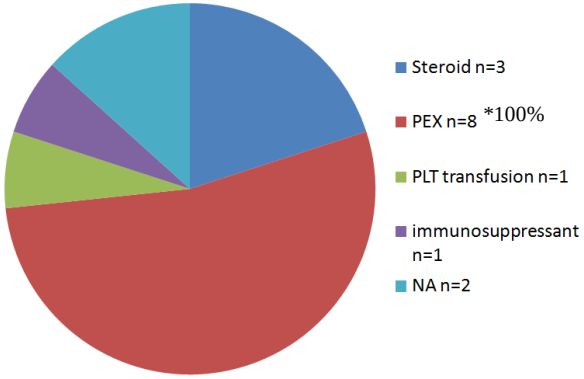
In a relevant percentage of patients having less than $50x10^9$/L platelet none antithrombotic therapy was administered.

Treatment for thrombocytopenia

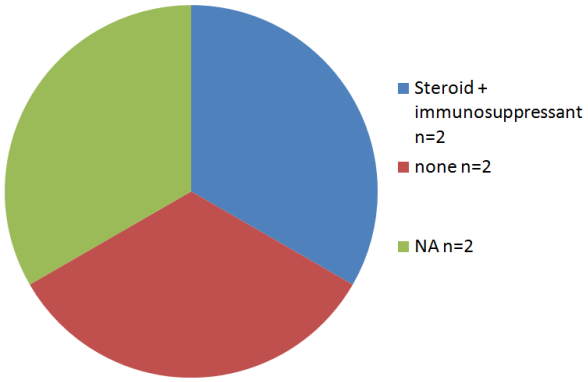
ITP n=24



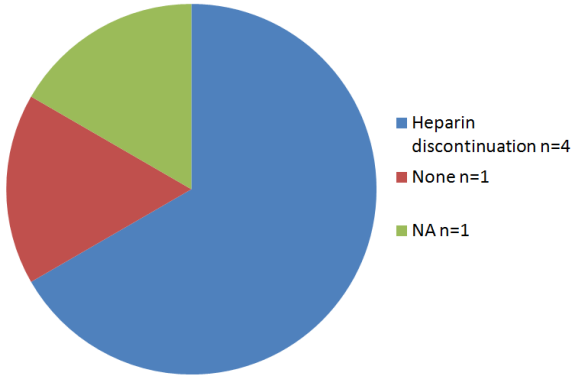
TTP n=8



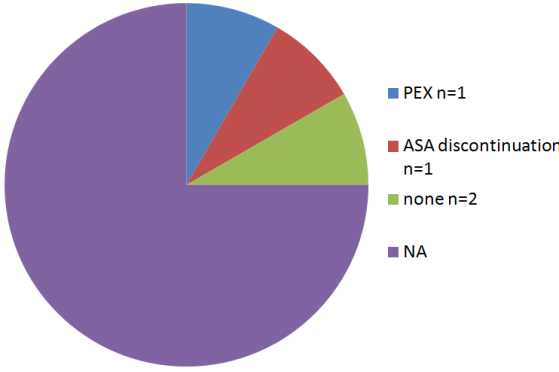
APS n=6



HIT n=6

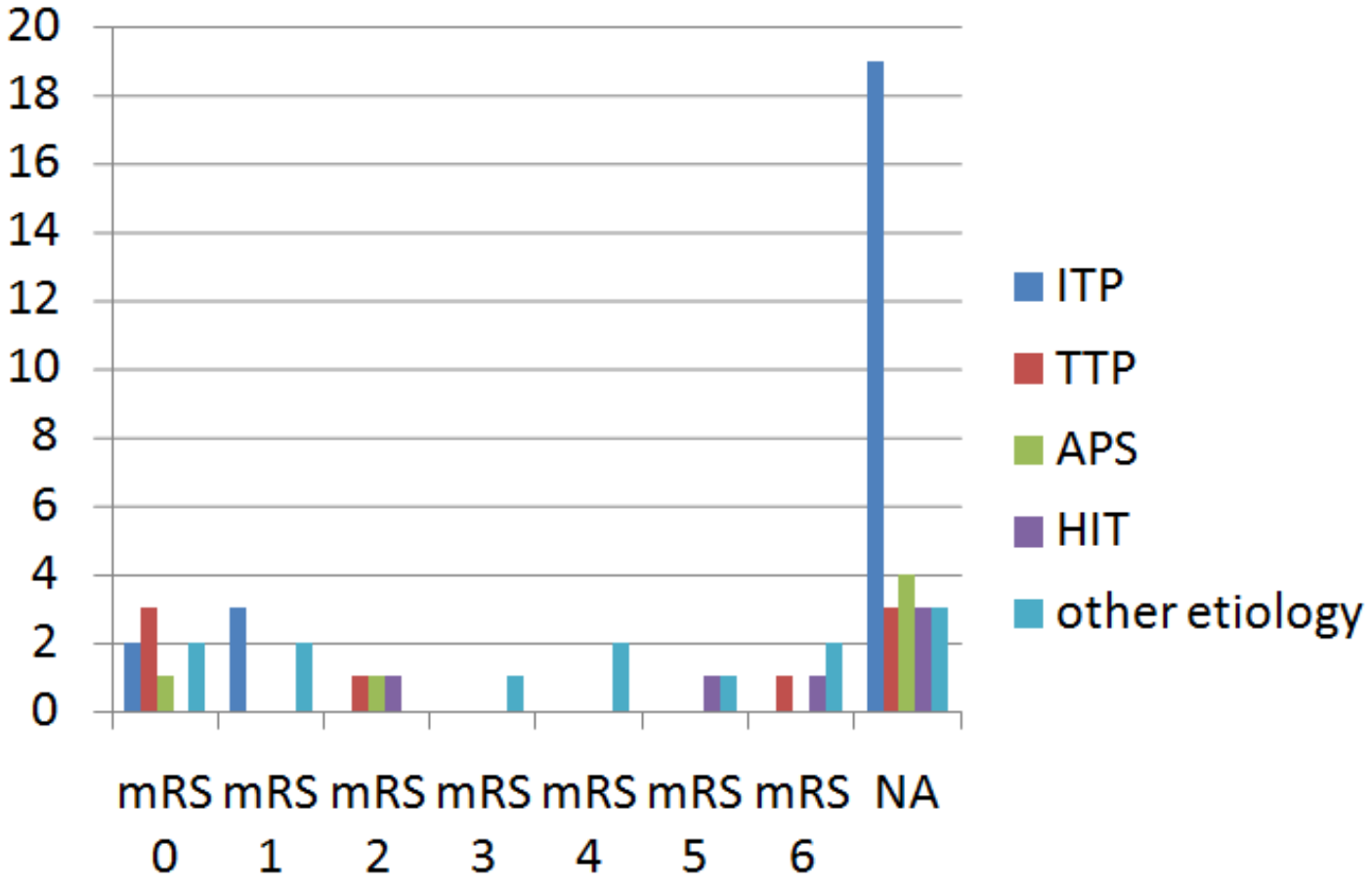


Other etiologies n=13



ITP patients experienced AIS soon after IGV therapy in several cases.
Many TTP patient were treated only with PEX and no antithrombotic therapy.

Clinical outcome

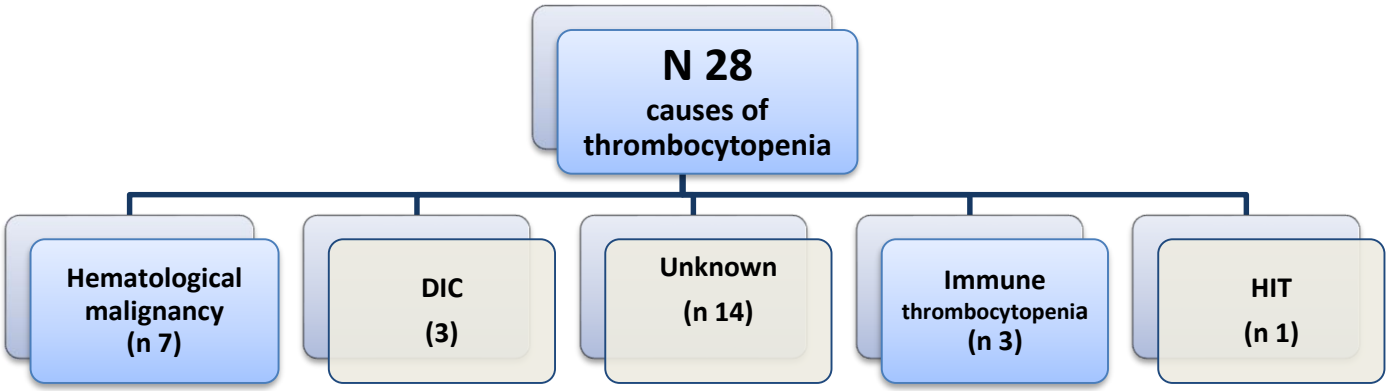


Reports on IVT-treated stroke patients with PC <100 × 10^9/L in current literature

Author	year of publication	number of cases/sex	Age	PLT x10^3/uL (Lowest)	NIHSS admission/ discharge	STN	Large vessels occlusion	ICH	SICH
Mowla A. et al	2017	5/2F	75 ± 18	63 ± 19	10 (range 5-17)	165' (n=1)	NA	n=1	n=1
Meretoja A. et al	2010	7/NA	72,7	<100	13 ± 4,7	153' ± 61'	NA	n=1	n=1
Brunner F. et al	2011	3/NA	NA	82 (59)	NA	NA	NA	no	no
Kvistad CE. Et al	2013	1/NA	77,4 ± 11,9	<100	9 (range 5–16)	NA	NA	no	no
Frank B. et al	2013	10/NA	NA	<100	NA	NA	NA	no	no
De Piazza C. et al	2016	1/F	63	71	9/14	210'	left MCA	yes	no
Camara-Lemarroy C.R. et al	2016	1/F	22	23,6	10/0	150' [rtPA using 0.6mg/kg]	right MCA	yes	no
Boattini M.	2013	1/M	39	27	4/0	100'	left MCA-M2	no	no
Breuer L et al	2013	3/1F	case 1 (65), case 2 (64), case 3 (78)	case 1: 59 case 2: 90 case 3: 96	case 1 (14), case 2 (5), case 3 (7)	NA	NA	no	no
Gensicke H et al	2018	44/12F	66 (59-79)	83 (29) , <50 n=2 not reporting ICH	13 (7-18 range)	NA	NA	NA	n=3

Tot n=76 SICH n=5 (PLT n1: 48x10^3/uL, n2 NA, n3 & n4 ≥50x10^3/uL)

Our study population

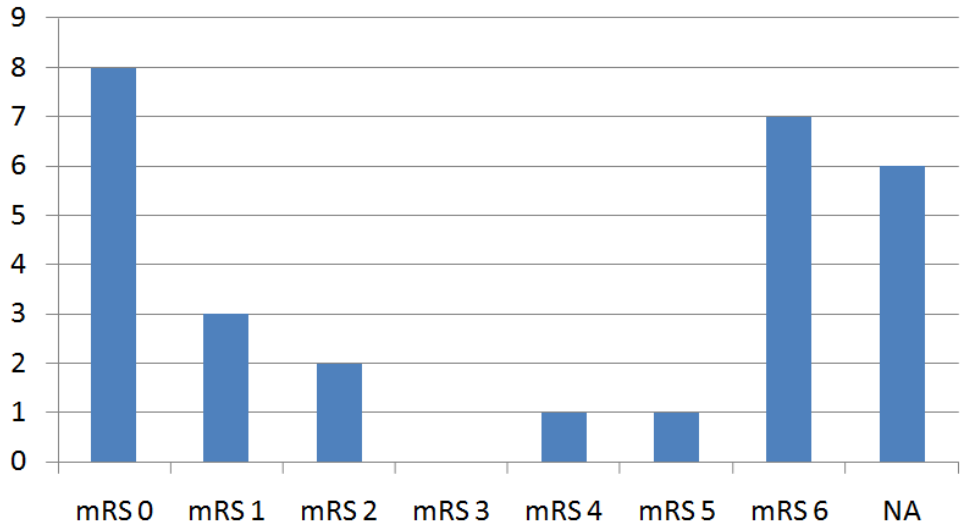


TOTAL CASES (n=28)	
Age (mean±SD)	51 ±20
platelet count at stroke onset, x10³/uL (mean±SD)	69±40
CHA_2DS_2-VASc Score (mean±SD)	4±2
Large Vessel intracranial Occlusion	n=8
NIHSS admission (mean±SD)	8±7
ICH	n=5
SICH	0
inhospital mortality	7 (25%)

PLT level (x10³/uL): 100 (n=2); 80 (n=1); 74 (n=1); 73 (n=1)

IVT-treated stroke patients with PC <100 × 10^9/L

N=5	Platelet count x10^3/uL	revascularization	NIHSS before/after treatment	ICH	mRS
Case 1	95	IVT+MT	21/3	no	2
Case 2	80	IVT+MT	8/4	HI2	2
Case 3	87	IV	5/2	no	0
Case 4	100	IV	23/19	HI1	5
Case 5	38	MT	20/20	no	6



Take home message I

In case of asymptomatic moderate thrombocytopenia, follow up and platelet count repetition in one to two weeks can be considered.

In young patients experiencing CVE, hematological autoimmune disorders should be considered. Platelets aggregation and thrombosis are not wide spreading in early stages, therefore thrombocytopenia and other signs may not be clinically evident at first.

A systematic review estimated the frequency of aPL in young patients with cerebrovascular events (CVE) of undetermined origin at 17%, rising up to 22% for aCL in patients with stroke; its persistence with high title over time confers an higher thrombotic risk.

Patient older than 60 yrs with persistent thrombocytopenia should be evaluated for occult cancer.

Platelets destruction leads to quick turn-over and younger platelet are thrombotically more active, a quick raising on platelet counts may increases the risk of thrombotic complications. Therapies used to treat immune thrombocytopenia like intravenous immunoglobulin (IVIg) may also play a role.

It should be remembered that in case of HIT-II the risk of thrombosis remains high for 4–6 weeks after. Warfarin is not recommended because of the risk of paradox worsening and alternative anticoagulant should be given for up to 4 weeks, Fondaparinux is the more commonly available.

Take home message II

Reducing anticoagulation dose is possibly safe (bleeding), but efficacy (i.e. rates of thrombosis) is not known. Patients with platelet counts greater than 50 $\times 10^3/\mu L$ rarely have symptoms.

When platelets are above $50 \times 10^9/L$, full dose anticoagulation (OAC) appears safe, representing a trigger for changes in management of OAC. Current guidelines on VTE as well as the International Society on Thrombosis and Haemostasis (ISTH) guidelines recommend a minimum platelet count of $<50 \times 10^9/L$ for administer DOACs in patients with chemotherapy-induced thrombocytopenia.

In general, LMWH and direct oral anticoagulants (DOACs) are both acceptable treatment options for patients with cancer-associated thrombosis. Guidelines prioritize LMWH over DOACs in patients at high risk of bleeding. An algorithm derived from cancer patients, has been also proposed even for ITP patients (Matzdorff et al).

Management of OAC in those patients also affected with AF has only been described in anecdotal case reports. Decision making should take into account the individual thrombotic and bleeding risk. The risk benefit-ratio may change if the thrombocytopenia lasts more than several days to weeks.

However, patients with thrombocytopenia have been generally excluded from clinical trials and the generalizability of these data is limited. Clinical trials are needed to address pressing clinical questions related to the use of OAC in patients with thrombocytopenia.

Take home message III

Antiplatelet therapy increases bleeding risk, especially dual antiplatelet therapy (2.0% vs. 1.3% with antiplatelet monotherapy; P , 0.001), with bleeding rates that are similar to those on OAC.

In contrast, with ASA seems to be no difference in bleeding risk above and below 50×10^9/L, meaning that the risk for bleeding with ASA may increase at a lower platelet threshold.

The study by Feher et al, does however suggest that stopping all APT at count of 50×10^9/L may not be appropriate for all patients in this setting, and that a lower threshold could be considered.

The Society for Cardiovascular Angiography and Interventions proposed ASA administration with platelet counts above 10×10^9/L in patients with ACS and PCI, and reserved DAPT for counts above 30×10^9/L.

For patients with platelets counts of $50–100\times10^9$/L who undergo PCI, the authors recommended the following: restrict DAPT to one month post stenting. Protein pump inhibitors should be used in all patients continuing APT.

The choice of platelet transfusions in order to continuing APT or AC is not supported by any no evidence.
The multiple risks of platelet transfusion should to be keep in mind in order to prevent new ischaemic events.

Platelet transfusions have to be used prophylactically at a platelet threshold of $< 10 \times 10^9$/L to reduce bleeding risk. Higher thresholds may be considered in specific circumstances.

The relationship between platelet count and bleeding is complex and non linear.
Treatment of the underlying condition may lead to rising platelet count, reducing thrombotic risk and preventing the need for antithrombotic therapy withdrawal.

Conclusions

- Platelet count ranging between $50x10^9$/L may be an adeguate threshold for changes in anticoagulation and it may be lower for antiplatelet therapy.
- Platelet counts remain poor predictors of bleeding for mild to moderate reduced level and the risk-benefit ratio may changes in different setting.
- The proper therapeutic management should be tailored on each individual patient, taking into account their ischemic and bleeding risk as well as the underlying disease leading to thrombocytopenia.
- The relationship between platelet count and bleeding seems to be nonlinear, appearing a poor predictor of bleeding.

  perhaps IVT may be safe at moderate low platelet count at least in some patients.
- Little data are available yet and it precludes solid conclusions.

  Further evidence is needed to support this practice. Clinical guidelines are also needed to standardize and streamline clinical practice in these challenging setting.