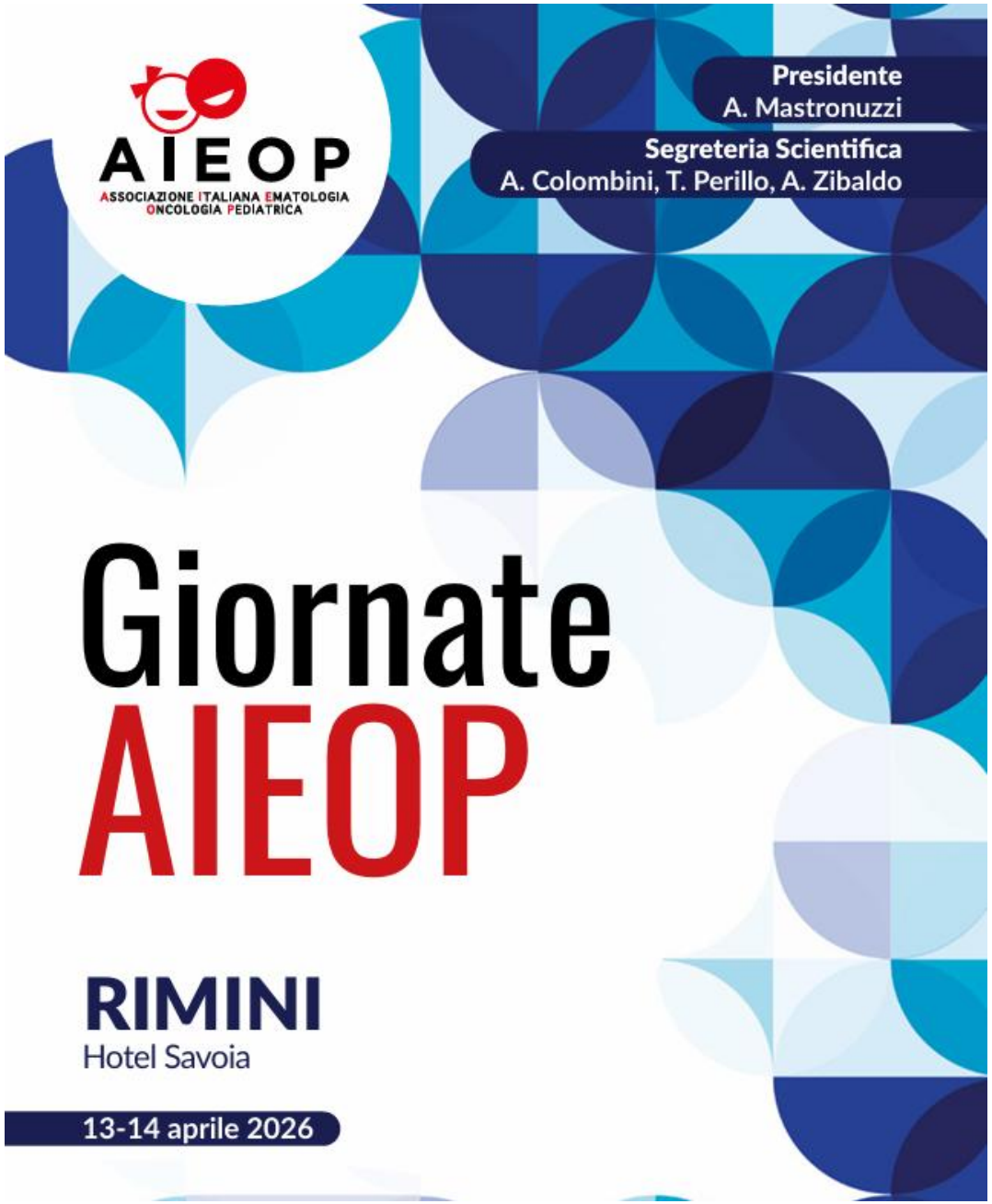


DIFETTI DELLA COAGULAZIONE

Paola Giordano, MD

paola.giordano@uniba.it

Giuseppe Lassandro, MD PhD

giuseppe.lassandro@uniba.it

UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

European Reference Network | Hematological Diseases (ERN EuroBloodNet)

ASSETTO 2025-2027 GdL DIFETTI DELLA COAGULAZIONE

Componenti

Gorio Chiara
Ospedale: Brescia – ASST Ospedali Civili

Lassandro Giuseppe
Ospedale: Bari – Pediatrica Universitaria Policlinico-Giovanni XXIII

Luciani Matteo
Ospedale: Roma – Ospedale Bambino Gesù

Marzollo Antonio
Ospedale: Padova – Azienda Ospedale Università

Molinari Angelo Claudio
Ospedale: Genova – Ospedale Gaslini

Spinelli Marco
Ospedale: Monza – AO San Gerardo

GIORDANO PAOLA (Coordinatore)
Ospedale: Bari – Pediatrica Universitaria Policlinico-Giovanni XXIII
E-mail: paola.giordano@uniba.it

Consulenti

Del Borrello Giovanni
Ospedale: Torino – Ospedale Regina Margherita

Del Vecchio Giancarlo
Ospedale: Bari – Pediatrica Universitaria Policlinico-Giovanni XXIII

Farruggia Piero
Ospedale: Palermo – ARNAS Civico

Notarangelo Lucia Dora
Ospedale: Brescia – ASST Ospedali Civili

Palumbo Giuseppe
Ospedale: Roma – Ospedale Bambino Gesù

Russo Giovanna
Ospedale: Catania – Policlinico

AREE D'INTERESSE GdL DIFETTI DELLA COAGULAZIONE

DIFETTI PIASTRINICI

- PIASTRINOPENIE IMMUNI
- PIASTRINOPENIE EREDOFAMILIARI
- PIASTRINOPATIE

MALATTIE EMORRAGICHE CONGENITE

- EMOFILIA A/B
- MALATTIA DI VON WILLEBRAND
- DIFETTI RARI DELLA COAGULAZIONE

TROMBOSI

- DISORDINI TROMBOFILICI
- TROMBOSI IN ETA' PEDIATRICA
- TROMBO-PROFILASSI
- ANTICOAGULAZIONE

COLLABORAZIONI INTERSOCIETARIE GdL DIFETTI DELLA COAGULAZIONE

AIEOP
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

AICE
Associazione Italiana Centri Emofilia

SISET
Società Italiana per lo Studio dell'Emostasi e della Trombosi

R.I.T.I
REGISTRO ITALIANO TROMBOSI INFANTILE

GSP

ALT Onlus
Associazione per la Lotta alla Trombosi e alle malattie cardiovascolari

GRUPPO DI STUDIO PIASTRINE

PROGETTI IN CORSO GdL DIFETTI DELLA COAGULAZIONE

Studio PRIMA: La PRofilassi nei pazIenti pediatrici affetti da EMofilia A nell'ambito dei centri AIEOP: studio retrospettivo.

Obiettivo primario:
il tipo di profilassi nei soggetti in età pediatrica o adolescenziale con emofilia A in cura presso i Centri AIEOP.

Obiettivi secondari:

1) Conoscere il numero di pazienti in profilassi con Fattore VIII

2) conoscere il numero di pazienti in profilassi con farmaci non sostitutivi (emicizumab o altro sperimentale)

3) conoscere le motivazioni del mantenimento o del passaggio da una profilassi sostitutiva con fattore VIII a una profilassi non sostitutiva con emicizumab

4) acquisire dati "real world" di efficacia della profilassi

5) acquisire dati "real world" di tollerabilità e sicurezza della profilassi

Emofilia A: un mondo in cambiamento

- Emofilia A: incidenza di 13.8 casi per 100.000 maschi
- Da malattia cronica, debilitante, difficile da controllare a condizione «*costituzionale*» con occasionali picchi di «*malattia*»

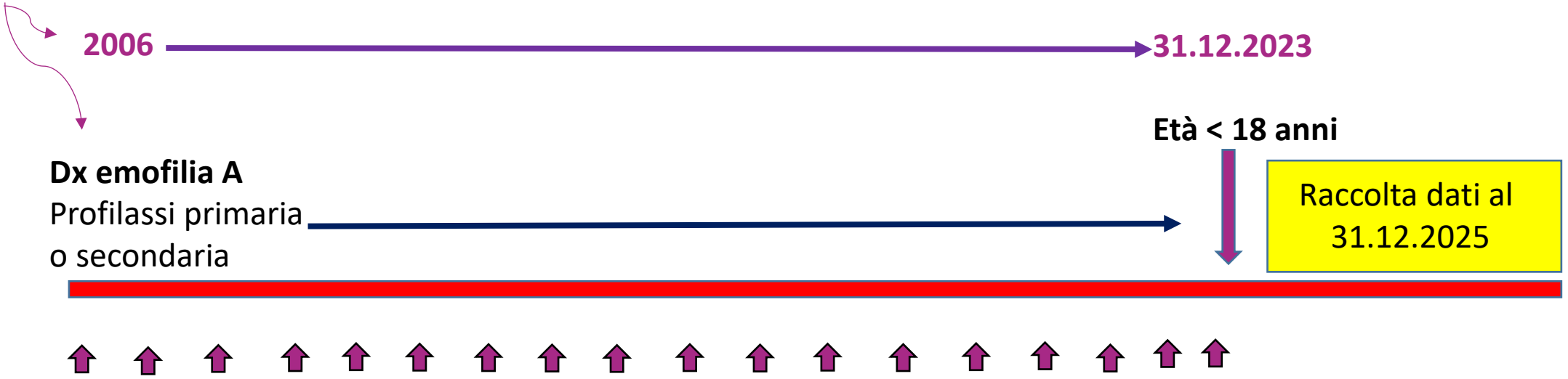
I fattori del cambiamento intervenuti negli ultimi 15 anni sono:

- Profilassi primaria nei pazienti gravi e moderati (con fenotipo grave)
- Inizio precoce della profilassi: < 2°a. → < 1 a.
- Disponibilità di farmaci sicuri e sempre più maneggevoli: FVIII plasmaderivato → FVIII ricombinante
- Disponibilità di prodotti a lunga emivita: rEHL, emicizumab
- Disponibilità di FVIII mimetici: emicizumab

- Terapia genica ?

Studio PRIMA: La PRofilassi nei pazIenti pediatrici affetti da EMofilia A nell'ambito dei centri AIEOP: studio retrospettivo.

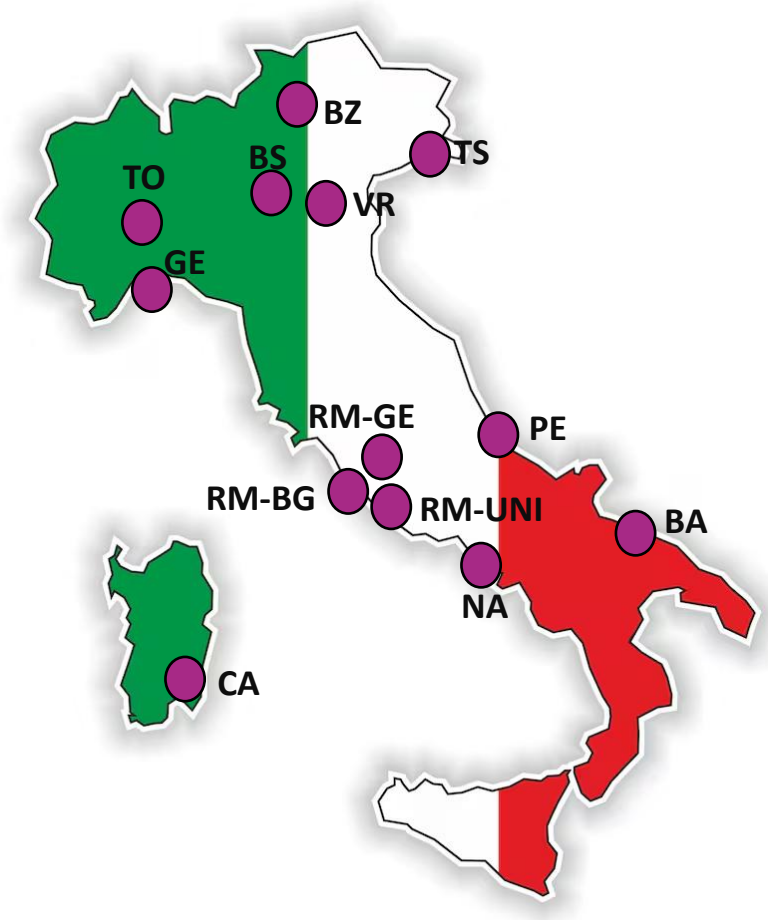
Studio retrospettivo, osservazionale, multicentrico



Per ogni paziente inserito:
- scheda di registrazione (dati essenziali)
- scheda di f-up annuale (modifiche annuali, ABR, salute articolare, tipo di complicanze)

Centri partecipanti- GdL Coagulazione AIEOP

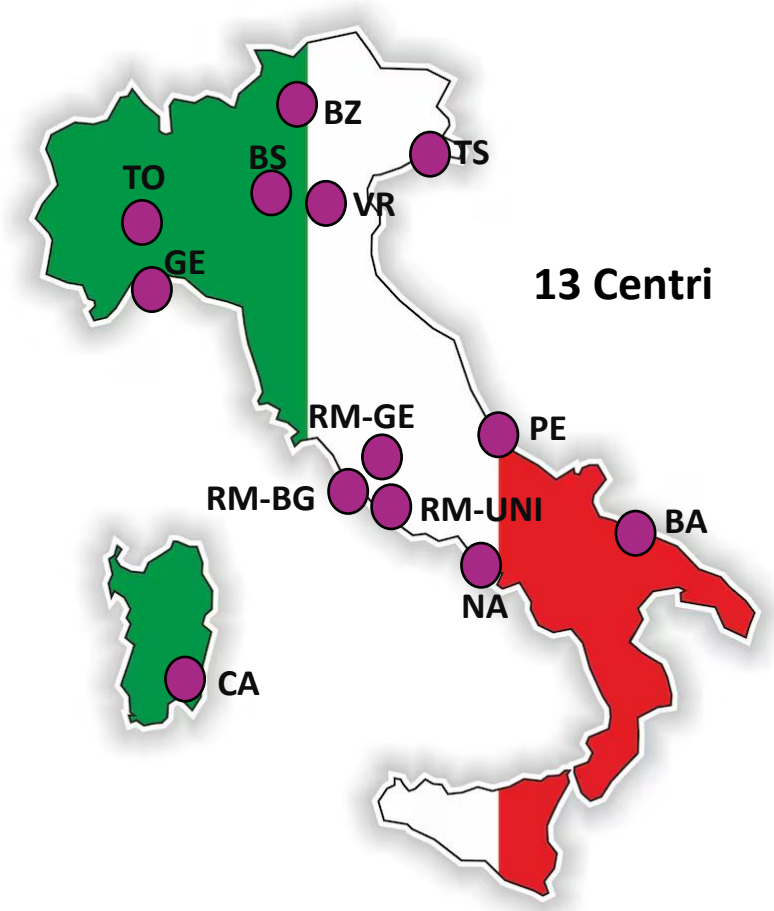
Centro	N° pz.	%
Bari	22	12.6
Brescia	21	12
Bolzano	8	4.6
Cagliari	3	1.7
Genova	3	1.7
Napoli	25	14.3
Pescara	6	3.4
Roma BG	29	16.6
Roma Gemelli	6	3.4
Roma Univ.	23	13.1
Torino	17	9.7
Trieste	3	1.7
Verona	9	5.1
Totale	**175**	**100**



85% dei paz. eleggibili (surveypre-studio: 207)

Centri partecipanti- GdL Coagulazione AIEOP

Età dx (a.)	mediana 0.5	0-13.4
Età al 31.12.25 (a.)	mediana 10.7	2.2-24.5
Peso (ultimo f-up)	mediana 25 kg	5-89
Gravità	2 Lieve 16 Moderata 154 Grave	2.9% 9.1% 88%
Profilassi (ultimo f-up)	175	**100%**
Profilassi primaria	134	76.6%
Profilassi secondaria	41	23.4%
Intervallo dx-prof. Prim. (a.)	0.6 a	0-12-2
Intervallo dx-prof. Secon. (a.)	3.8 a.	0-15.9
Inibitore (storia)	48	27.4%
Inibitore attuale	20	**11.4%**
Intervallo dx-inibitore (a.)	0.5	**0-8.9**
Età inibitore (a)	1.6	**0.3-13.6**



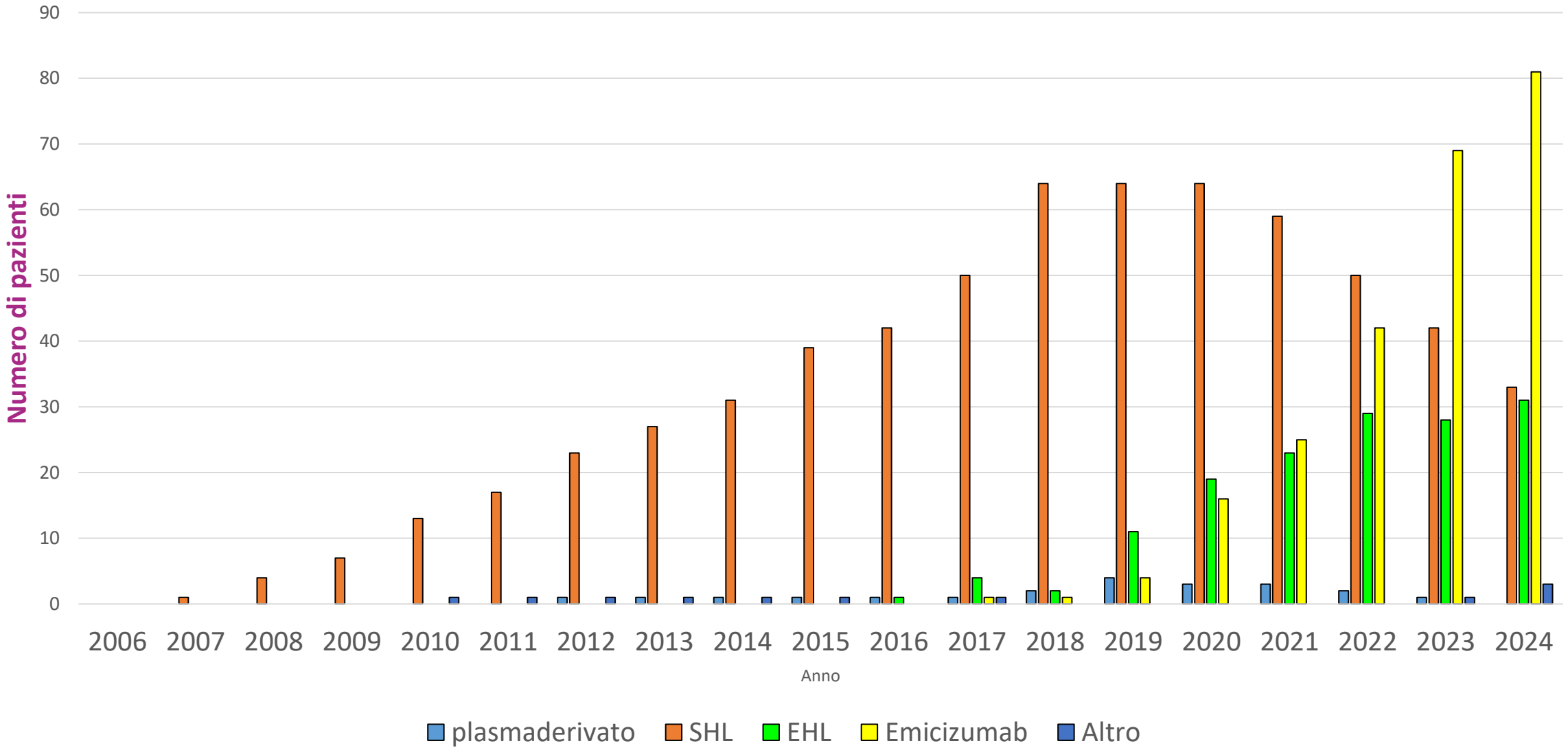
Follow-up annuale: quale profilassi usata?

Anni di f-up con informazioni: 1311 in 163 paz. (8 a./paz) - numero atteso di anni di f-up: 1336 su 175 pazienti

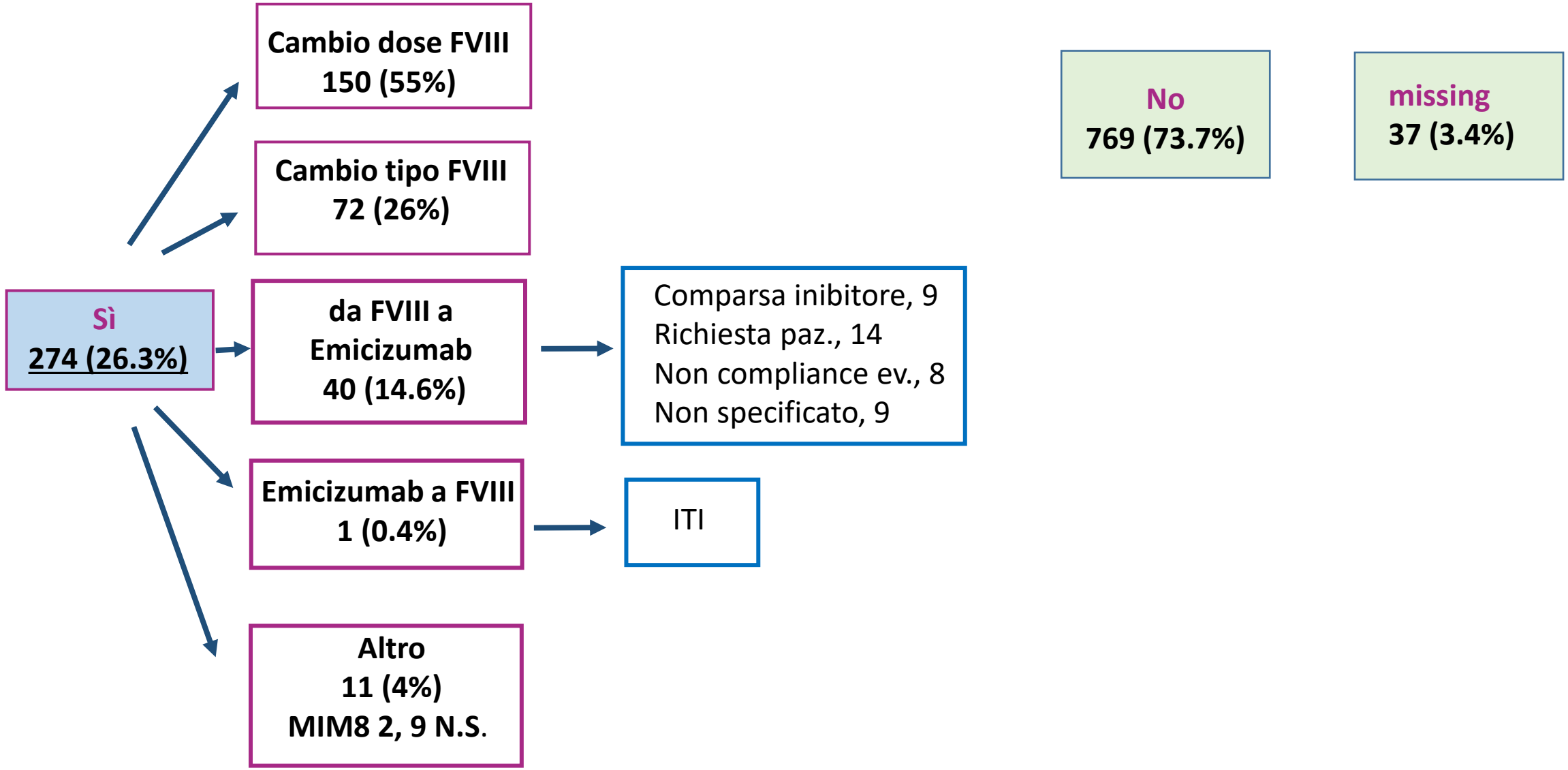
Anni di f-up con profilassi: 1080 (82.8%)

Tipo profilassi	N° anni f-up, (%)	Tipo prodotto
Plasmaderivato	21 (2.0%)	Haemate P 14, Klott 4, Alphanate 3
SHL	630 (60.1%)	Octocog 470, moroctocog in 52, turoctocog 47, simoroctocog37, lonoctog18, rurioctocog 4, N.S. 2
EHL	148 (14.1%)	Efmoroctocg 117, damocotocog alpha peg 13, ruriococtog alpha peg 12, turoctocog alpha peg 6
Emicizumab	239 (22.8%)	
Altro	11 (1.0%)	novoseven+octocog 6, MIM8 in 4, novoseven1

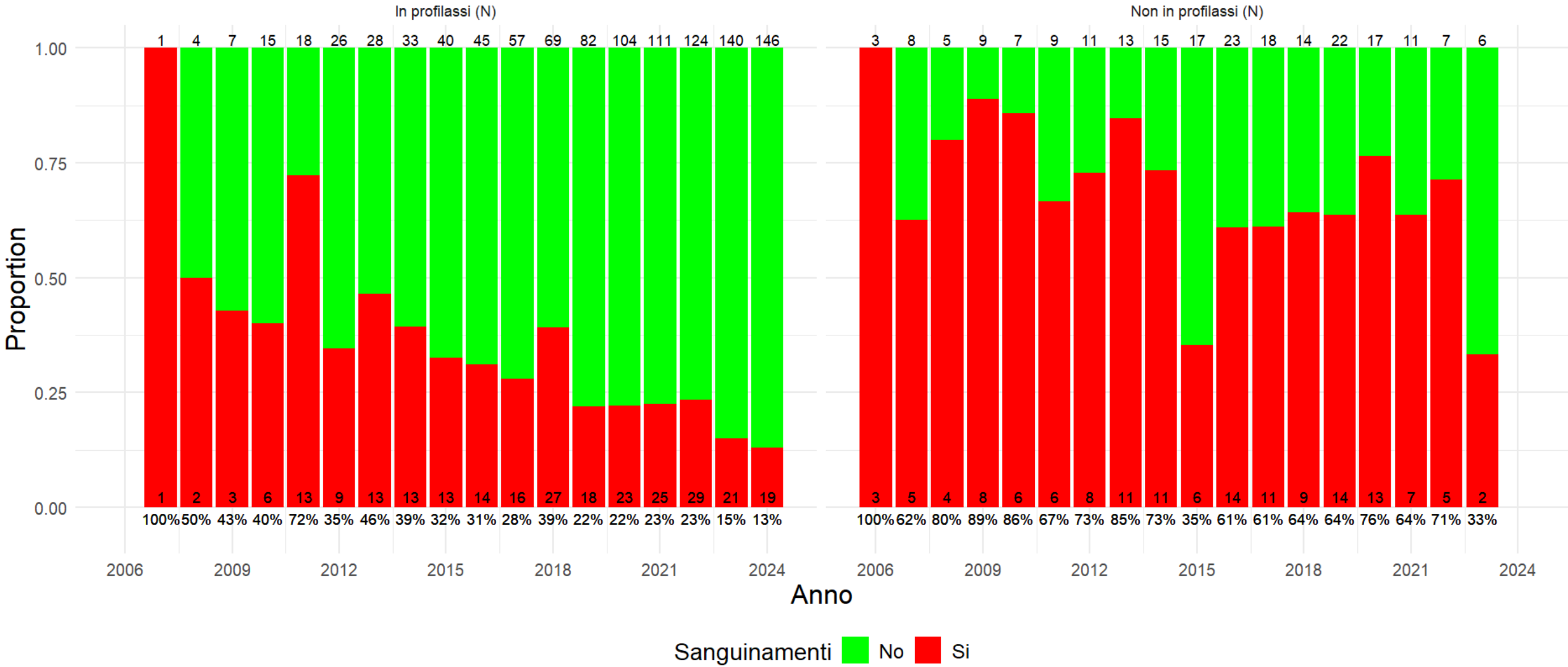
Profilassi in uso per anno



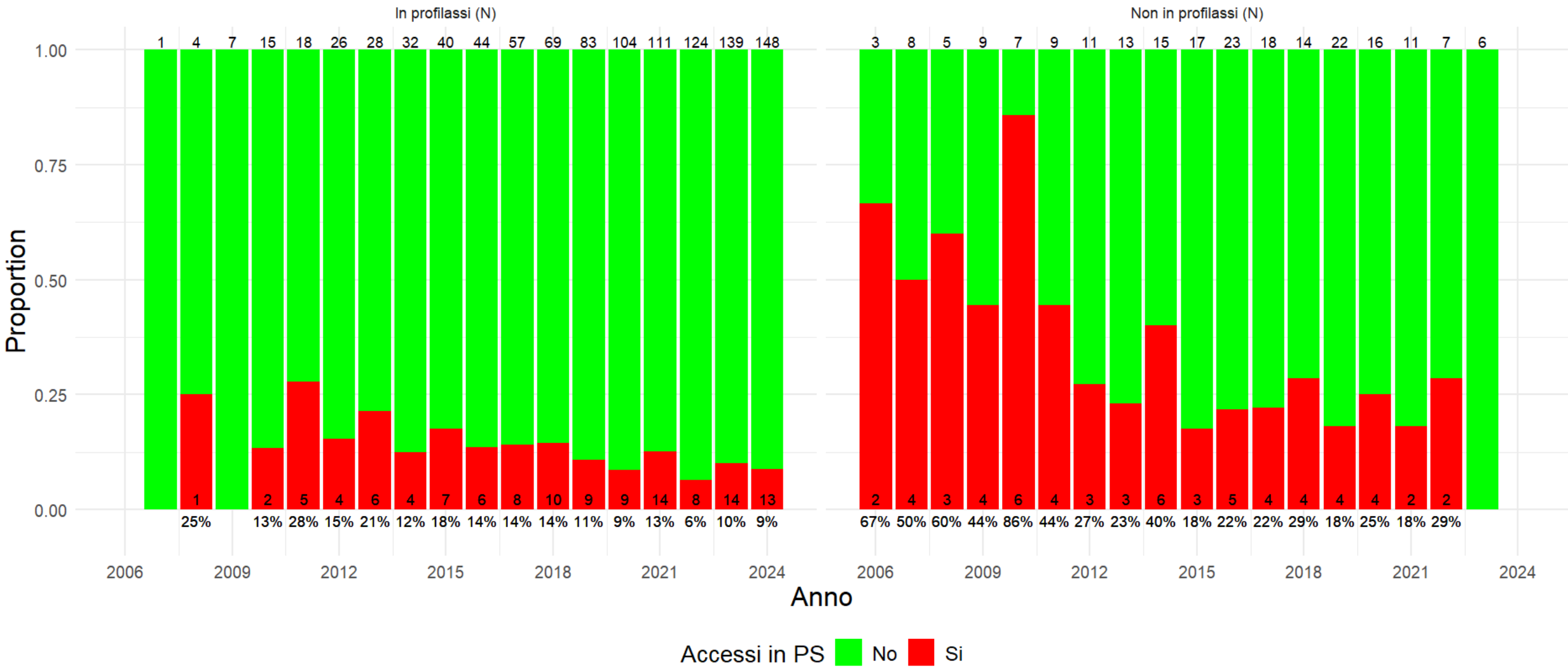
Follow-up annuale: modifica della profilassi usata?



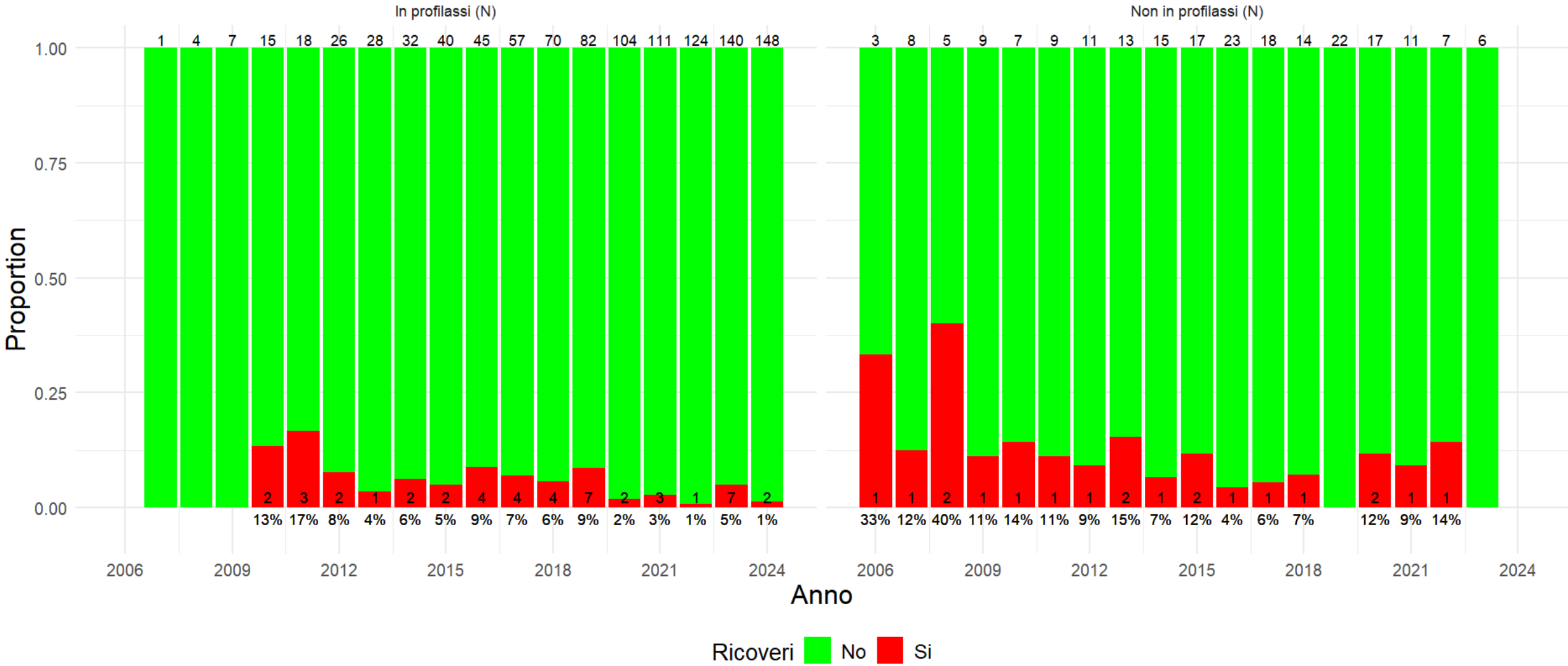
Sanguinamenti



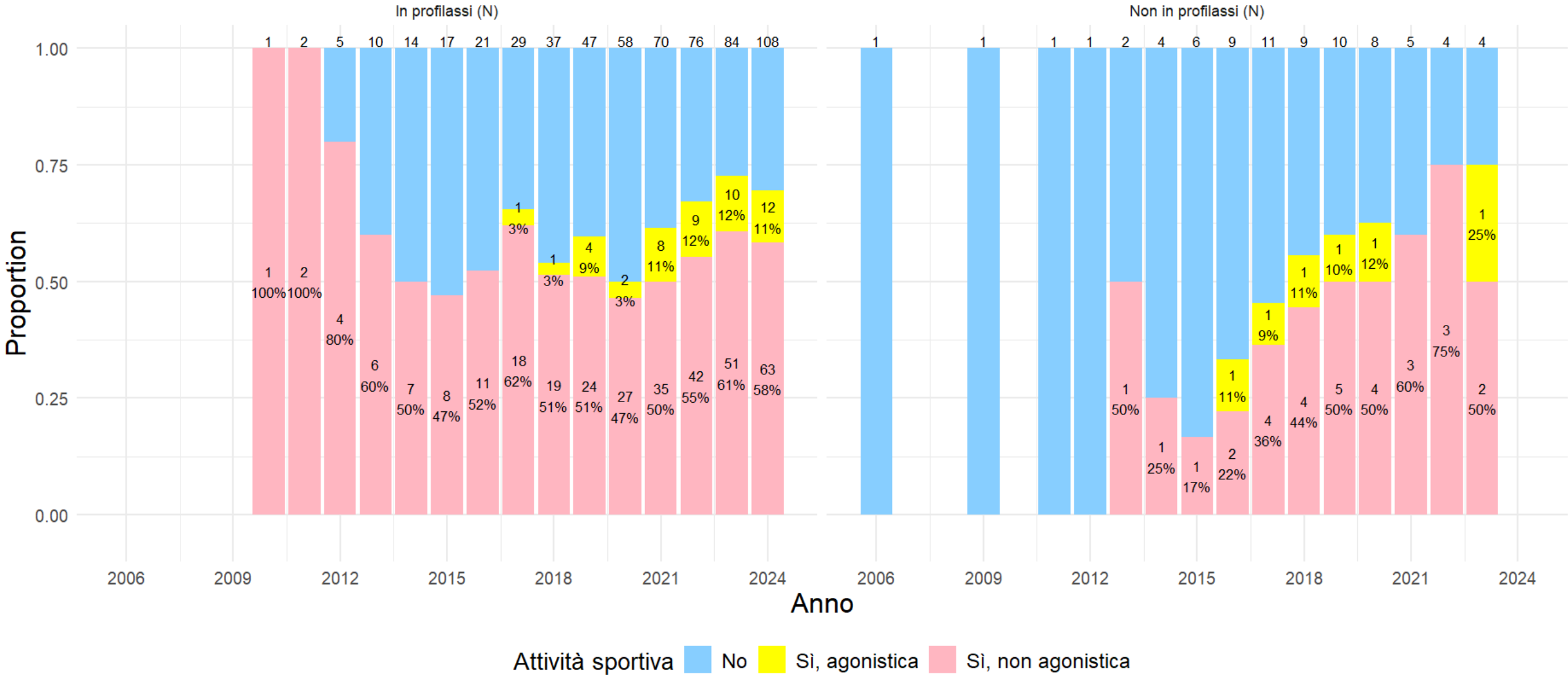
Accessi in PS



Ricoveri


In profilassi (N)
Non in profilassi (N)
1 4 7 15 18 26 28 32 40 45 57 70 82 104 111 124 140 148
3 8 5 9 7 9 11 13 15 17 23 18 14 22 17 11 7 6
2 3 2 1 2 2 4 4 4 7 2 3 1 7 2
1 1 2 1 1 1 1 2 1 2 1 1 1 2 1 1
13% 17% 8% 4% 6% 5% 9% 7% 6% 9% 2% 3% 1% 5% 1%
33% 12% 40% 11% 14% 11% 9% 15% 7% 12% 4% 6% 7% 12% 9% 14%
1.00
0.75
0.50
0.25
0.00
Proportion
2006
2009
2012
2015
2018
2021
2024
Anno
Ricoveri
No
Si

Attività sportiva



Conclusioni

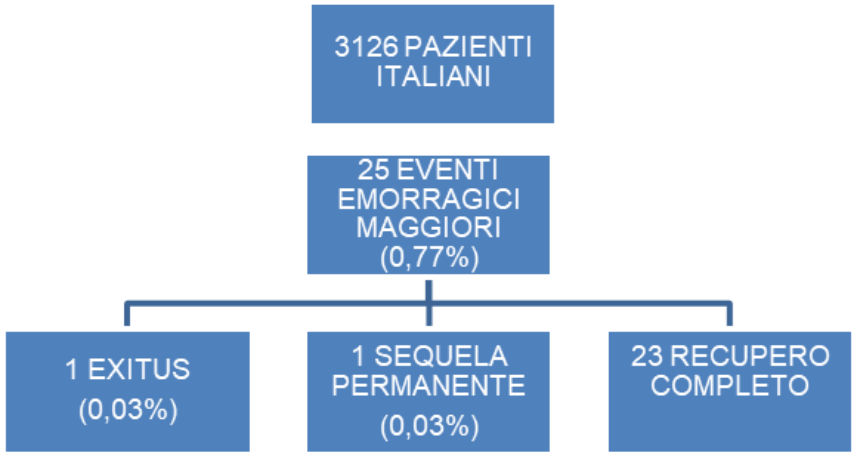
- **La profilassi è uno standard of care: riduce i sanguinamenti, ricoveri e accessi urgenti PS**
- **Osservato la preferenza recente per la terapia non sostitutiva con Emicizumab**
- **Persiste l'uso di FVIII SHL , ma in riduzione**
- **Lento incremento di uso del FVIII EHL**
- **Inibitore: 11%**
- **Sfida futura: preservazione del benessere articolare e attività motoria**

PROGETTI IN CORSO GdL DIFETTI DELLA COAGULAZIONE

Milano, 10/03/2026

GdL Coagulazione AIEOP

Incidenza e fattori di rischio degli eventi emorragici severi nella trombocitopenia immune primaria pediatrica:
risultati di uno studio multicentrico su 3126 pazienti italiani (2010-2024)



Conclusioni

- Incidenza cumulativa eventi emorragici severi in ITP di nuova diagnosi: 0,5%
- Incidenza cumulativa emorragia cerebrale: 0,2%
- Exitus: 1 (0,03%)
- PTL <10.000/mmc: 80%
- Nuova insorgenza: 62% - Cronica: 38%

Lavoro in fase di stesura definitiva e sottomissione a Pediatric Blood&Cancer

PROGETTI IN CORSO GdL DIFETTI DELLA COAGULAZIONE

GdL AIEOP
Difetti della coagulazione
10/03/2026

SARS-CoV2 vaccination and Immune Thrombocytopenia in children

Study rationale

SARS-CoV-2 infection associated with the development or exacerbation of several autoimmune diseases[1], also autoimmune cytopenias,

mainly AIHA and ITP[2]

Most cases of ITP described in **adults**[3]

De novo ITP or the worsening of pre-existing ITP has rarely been reported following COVID-19 vaccination[4,5]

Again, especially in **adult patients**[4,5]

No exclusively pediatric studies
This is the first italian multicenter study

[1]Tzang CC. et al. Clin Rev Allergy Immunol 2025; Gil AM. et al. Semin Arthritis Rheum 2025; [2]Taherifard E. et al. Hematology 2021; [3]Zulfiqar A.A. et al. N. Engl. J. Med. 2020; Lévesque V. et al. Int. J. Hematol. 2020; Mahévas M. et al. Br. J. Haematol. 2020; [4]Welsh K.J. et al. Vaccine. 2021; Kuter D.J. Br J Haematol. 2021; [5]Sharma K. et al. Cureus. 2022; Kaicker S. et al. Pediatr Blood Cancer 2023, Hillier K. et al. Pediatr Blood Cancer. 2022; Visser C. et. al. Blood Adv. 2022; Lee EJ et al. Blood 2022; Bidari A, et al. European Journal of Haematology. 2022; Jacobs JW, et al. British Journal of Haematology. 2023; Woolley P, et al. JTH. 2022; Woo EJ., Dimova R.B. Vaccine. 2022.

Study rationale

ITP in adults patients vaccinated with mRNA vaccine	ITP in adults patients vaccinated with adenovirus-based vaccines	Children vaccinated with mRNA vaccine
0.80 per million[1]	1:100,000[2]	Data regarding ITP in pediatric patients are extremely limited[3]

Compared to adults, children have a lower incidence of post-vaccination ITP, less severe clinical symptoms, and a more benign course, with favorable outcomes and no major complications[4]

[1]Welsh K.J. et al. Vaccine. 2021
[2]Woo EJ., Dimova R.B. Vaccine. 2022
[3]Bidari A, et al. European Journal of Haematology. 2022; Lee EJ, et al. Blood. 2022; Feng Y, et al. Human Vaccines & Immunotherapeutics. 2022; Kaicker S. et al. Pediatr Blood Cancer 2023
[4]Rodriguez et al. Journal of Autoimmunity. 2022; Jacobs JW. Et al. British Journal of Haematology. 2023

Study objectives

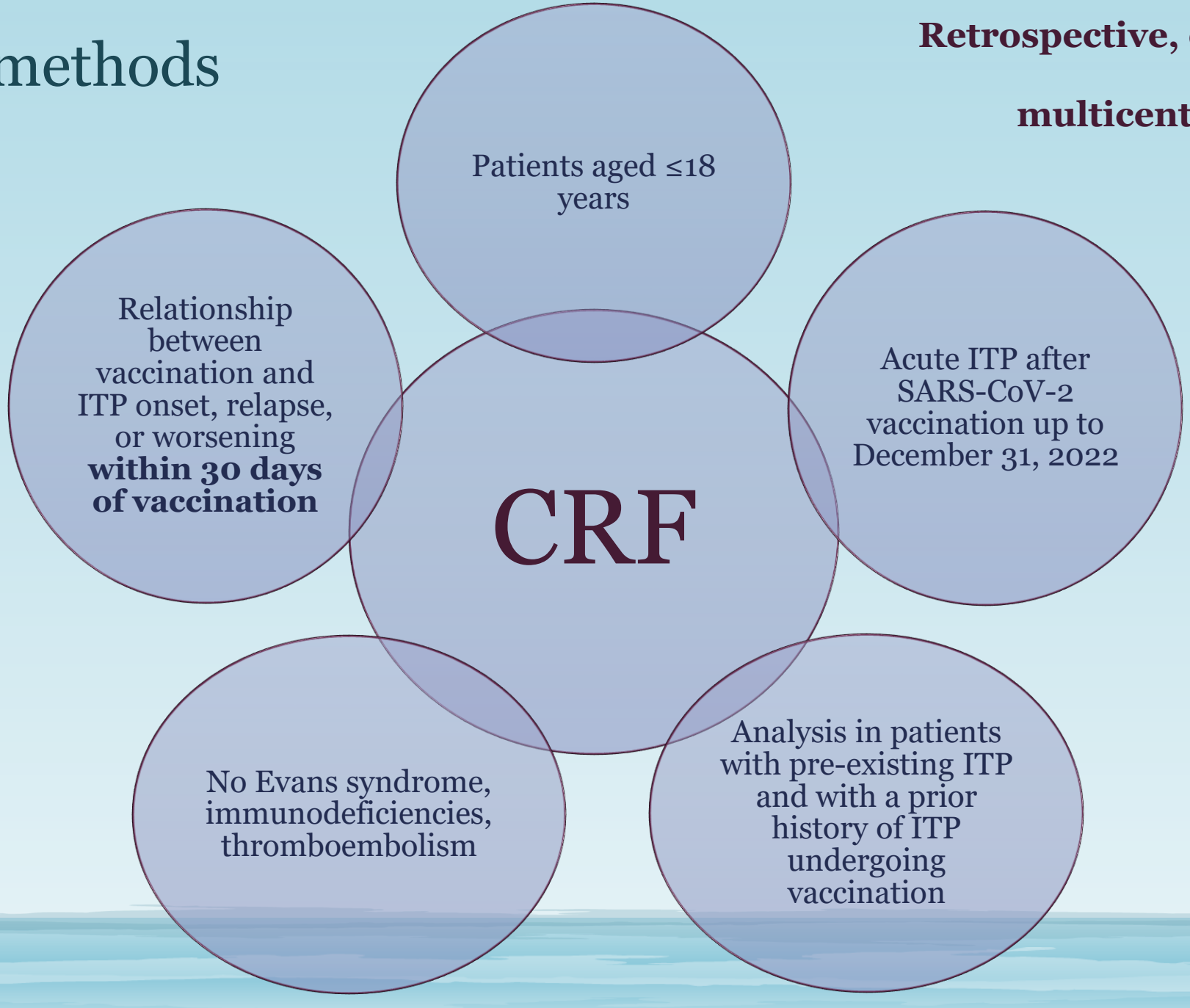
To assess the incidence, clinical characteristics, and outcomes of ITP newly diagnosed in children and adolescents after SARS-CoV-2 vaccination.

To analyze the outcome (worsening of thrombocytopenia and/or clinical symptoms, no influence, need for treatment changes/new treatment, complications) of patients with chronic, persistent or recurrent ITP after COVID-19 vaccination.

To analyze the outcome (relapse, need for treatment, complications, no influence) of patients with previous (and resolved) ITP after COVID-19 vaccination.

Material and methods

Retrospective, observational multicenter study



Results

Table 1. Characteristics of patients with newly diagnosed ITP following SARS-CoV-2 vaccination

Median age at ITP onset (years)	14.8
Timing of ITP onset	80% (= 4 patients) after first vaccine dose 20% (= 1 patients) after the second dose
Median time from vaccination to ITP onset (days)	27 (range 14-30)
Median platelet count at diagnosis	6,000/mm^3
Bleeding severity	40% (= 2 patients) score A 60% (= 3 patients) score B
First line treatment	80% (= 4 patients) immunoglobulins 20% (= 1 patients) no treatment
Response to first-line treatment (4 patients)	50% (= 2 patients) complete response 25% (= 1 patient) partial response 25% (= 1 patient) no response
Median follow up (months)	9.5
Status at last follow up	60% (= 3 patients) off therapy 40% (= 2 patients) on therapy (80% with normal platelet count)

15 partecipating Centers

Results

Table 2. Characteristics of patients with pre-existing ITP who received SARS-CoV-2 vaccination

Number of patients analyzed with complete data	164
Type of ITP	95.7% (= 157 patients) chronic ITP 3.1% (= 5 patients) persistent ITP 1.2% (= 2 patients) recurrent ITP
ITP worsening and/or new bleeding manifestations after vaccination	8.5% (= 14 patients)
Median platelet count at ITP exacerbation	46,000/mm³ (range: 5,000–78,000/mm³)
Bleeding severity	64.3% (= 9 patients) score A 35.7% (= 5 patients) score B
Treatment status at time of vaccination	79% (= 11 patients) on treatment 21% (= 3 patients) off therapy
Treatment status at 3-month follow-up in 11 patients with available data	64% (= 7 patients) on treatment 36% (= 4 patients) off therapy
Treatment status at 12-month follow-up in 10 patients with available data	50% (= 5 patients) on treatment 50% (= 5 patients) off therapy

No relapses were observed among the 34 patients with recovered ITP who were under active follow-up at the participating centers

Conclusions

ITP following SARS-CoV-2 vaccination in pediatric patients is an exceptionally rare event (1 < 500,000), usually mild and associated with a favorable outcome.

Our data also suggest that COVID vaccination in children with preexisting or past ITP appears to be safe.

Given the substantial morbidity and mortality associated with COVID-19 infection, the benefits of vaccination in children and adolescents clearly outweigh the minimal risk of vaccine-related ITP.

Under submission

GRAZIE!

PROGETTI IN CORSO GdL DIFETTI DELLA COAGULAZIONE

ITP refrattaria: iniziative

Dott. Antonio Marzollo
Dott.ssa Chiara Gorio
Dott. Giovanni Del Borrello
Dott. Giuseppe Lassandro

ITP refrattarie: il problema

Un porzione dei pazienti con ITP risultano refrattari ai trattamenti

- Alto rischio di sanguinamenti gravi
- Peggioramento della qualità di vita
- Non è definita la migliore strategia di trattamento
- Nuovi farmaci sono in studio, soprattutto nell'adulto

ITP refrattarie: definizione

La definizione di ITP refrattaria è oggetto di dibattito, soprattutto per le ITP persistenti/croniche

Non si applica più la definizione storica IWG: «lack to response to splenectomy»

Definizioni di refrattarietà: ITP di recente diagnosi

Definizione LG AIEOP:

"children with persistent, clinically significant active bleeding and consistently low platelet counts (no response according to IWG criteria) **despite first-line treatments (i.e., IVIG and steroids)**"

Definizione ICON (USA):

"Refractory to emergent therapy is defined as no platelet response after treatment with all eligible **emergent pharmacotherapies (corticosteroids, IVIG, anti-D immune globulin)**.

Definizione omogenea

Definizione di refrattarietà: ITP persistente/cronica

Aieop:

1) children with persistent, clinically significant active bleeding and consistently **low platelet counts** (no response according to IWG criteria) despite first-line treatments (i.e., IVIG and steroids) or **rescue therapies (other immunosuppressive agents, TPO-RAs, or splenectomy)**

2) children who are not entirely unresponsive to first-line treatments but require **frequent therapeutic interventions** to maintain a sustained clinical response, experiencing disease worsening and medication-induced toxicities

ICON/ICIS (USA):

Pediatric patients with ITP who are platelet nonresponsive and/or continue to demonstrate high disease burden **despite treatment with multiple classes of disease-modifying therapies (≥2 mechanisms of action)** represent a challenging subset of ITP.

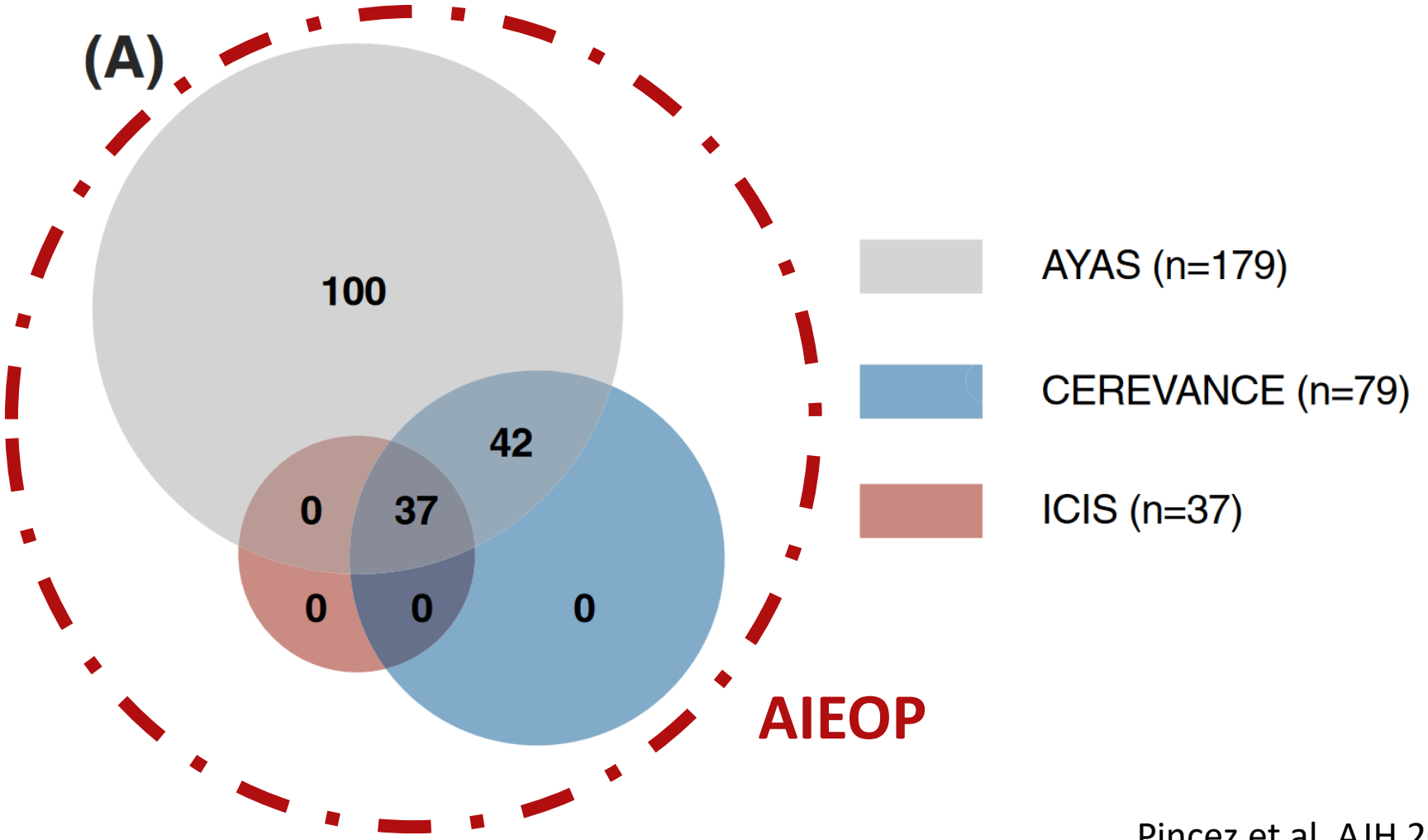
Definizione di refrattarietà: ITP persistente/cronica

CEREVANCE (Francia)

Administration of **≥3-4 second-line treatments considering the nine main second-line treatments** (eltrombopag, romiplostim, rituximab, cyclosporine, sirolimus, azathioprine, mycophenolate mofetil, hydroxychloroquine, and splenectomy)

AYAS (Francia, adolescenti):

≥3 different lines of therapy given that two different first-line treatments (e.g., corticosteroids and IVIG) were considered as only one line of therapy



Pincez et al, AJH 2024

Survey

BACKGROUND:

Non esistono evidenze per suggerire un trattamento o un altro per le piastrinopenie refrattarie.

Non esistono definizioni condivise di piastrinopenia refrattaria

Non è noto quanto la pratica clinica sia variabile tra i centri.

Survey

SCOPO:

Identificare le attuali pratiche per i pazienti con piastrinopenia refrattaria nei centri AIEOP

RISPOSTE DA 26 CENTRI

rITP di recente insorgenza

rITP di recente insorgenza

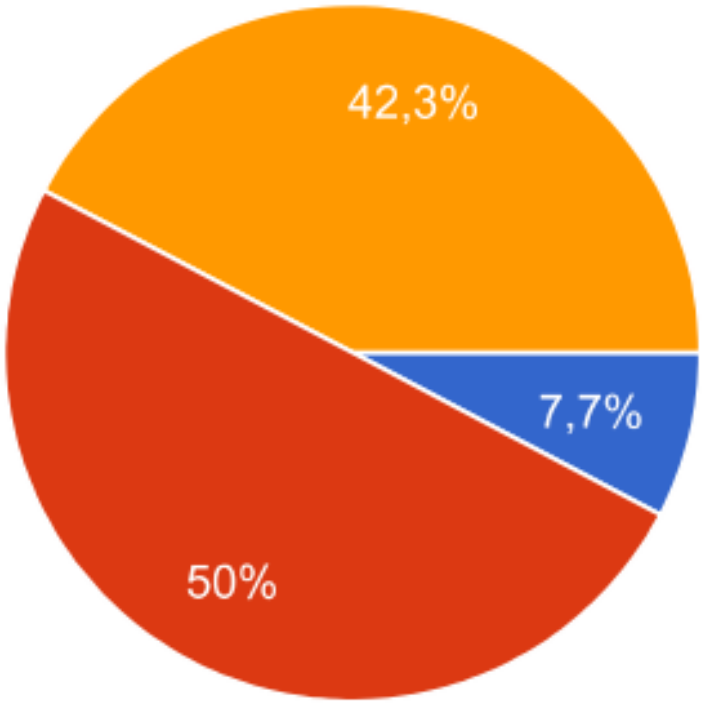
DEFINIZIONE:

Refrattaria se mancata risposta a IgIV **E** steroide

ACCERTAMENTI:

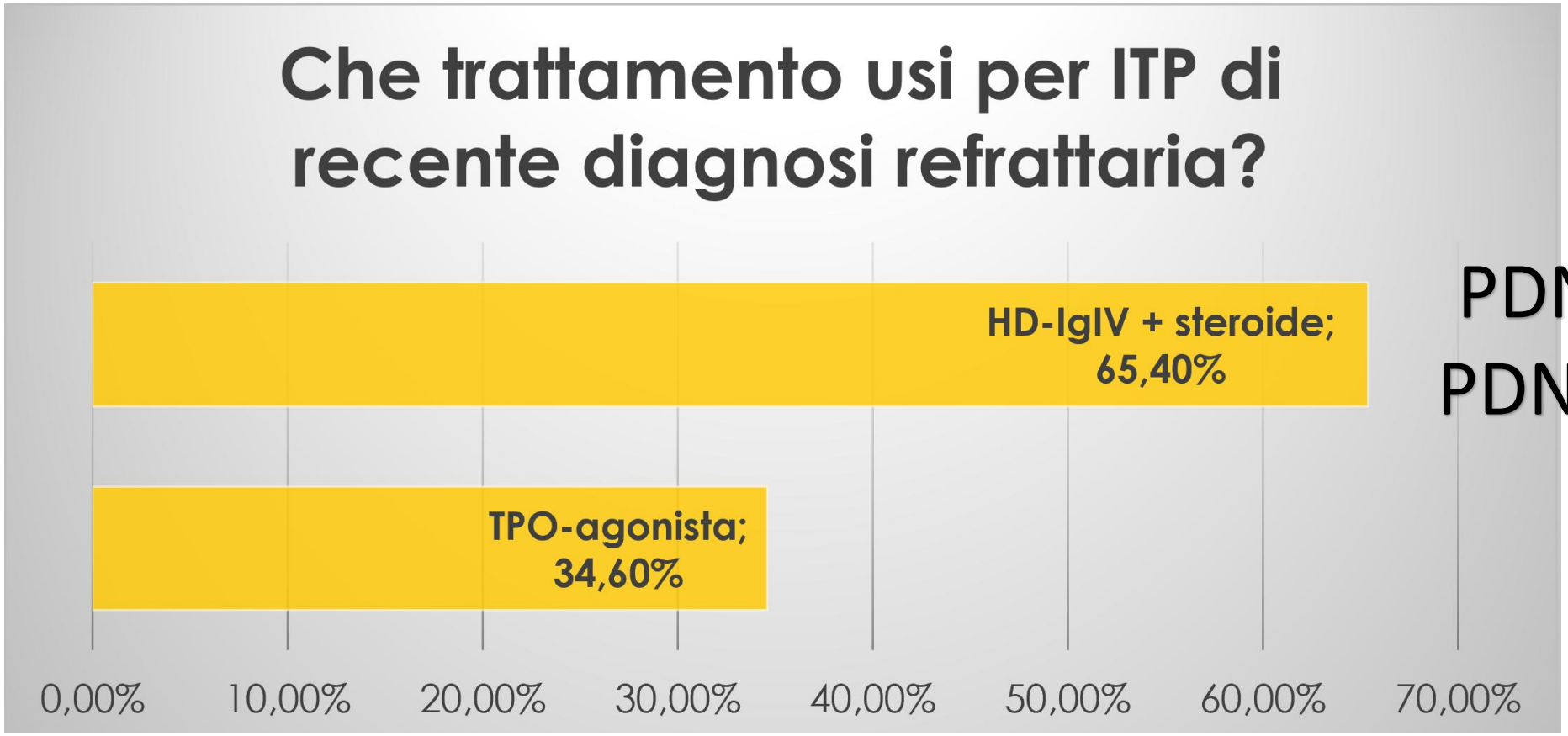
- Aspirato midollare
- Dosaggio immunoglobuline
- Screening auto-immunità
- Immunofenotipo linfocitario esteso

rITP di recente insorgenza: Obiettivi



- Wait and see, tollerando sanguinamento attivo (con score B&A fino a 3)
- Trattamento fino a risoluzione della sintomatologia, e poi wait and see indipendentemente dalla conta piastrinica
- Trattamento fino a risoluzione della sintomatologia e fino a raggiungere sufficiente conta piastrinica (ad es. > 30.000/uL)

rITP di recente insorgenza: Trattamento



PDN 2 mg/kg

PDN 20 mg/kg

rITP di recente insorgenza: Consigli

65% consentono attività fisica a basso rischio (27% vietano completamente attività fisica)

42% non consentono Asilo/scuola materna ma solo scuola dell'obbligo

15% caschetto nella vita quotidiana

60% sospendono vaccini

rITP cronica/persistente

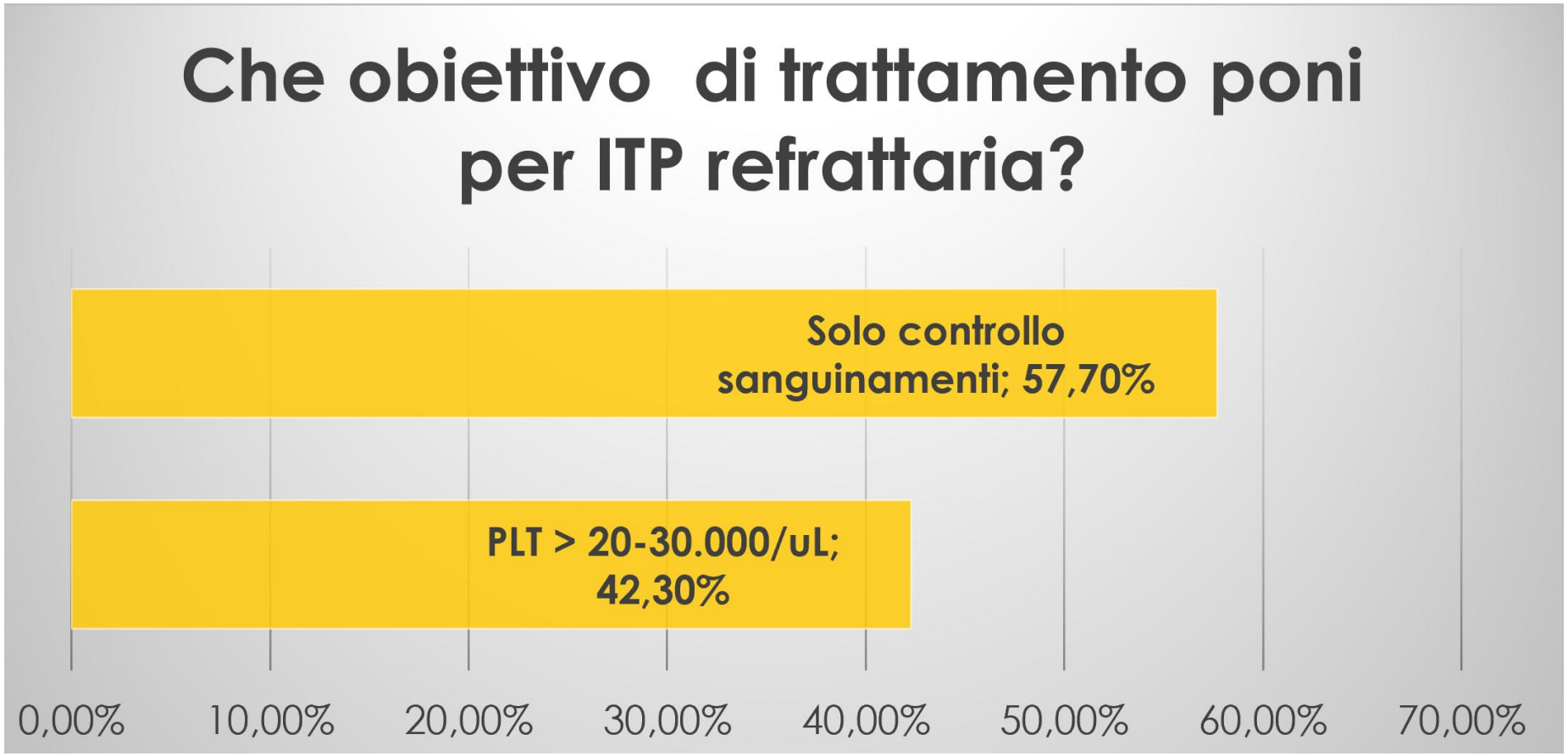
rITP persistente/cronica: definizione

rITP cronica/persistente: esami

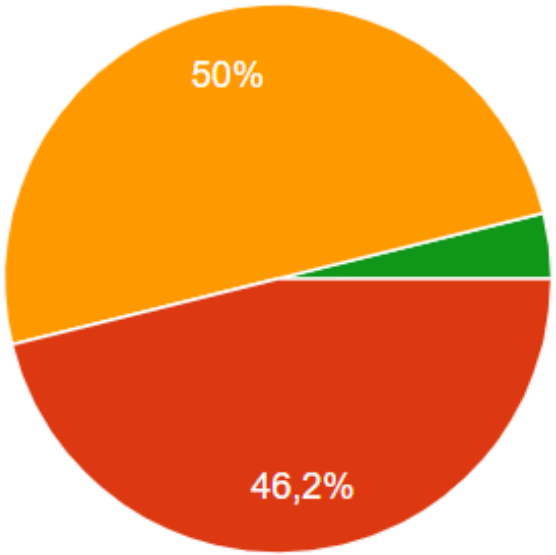
Condivisi

- Aspirato midollare
- Dosaggio immunoglobuline,
- Screening auto-immunità
- Immunofenotipo linfocitario esteso
- **Sequenziamento genetico** per difetti dell'immunità e per piastrinopenia eredofamiliare

rITP cronica/persistente: obiettivi

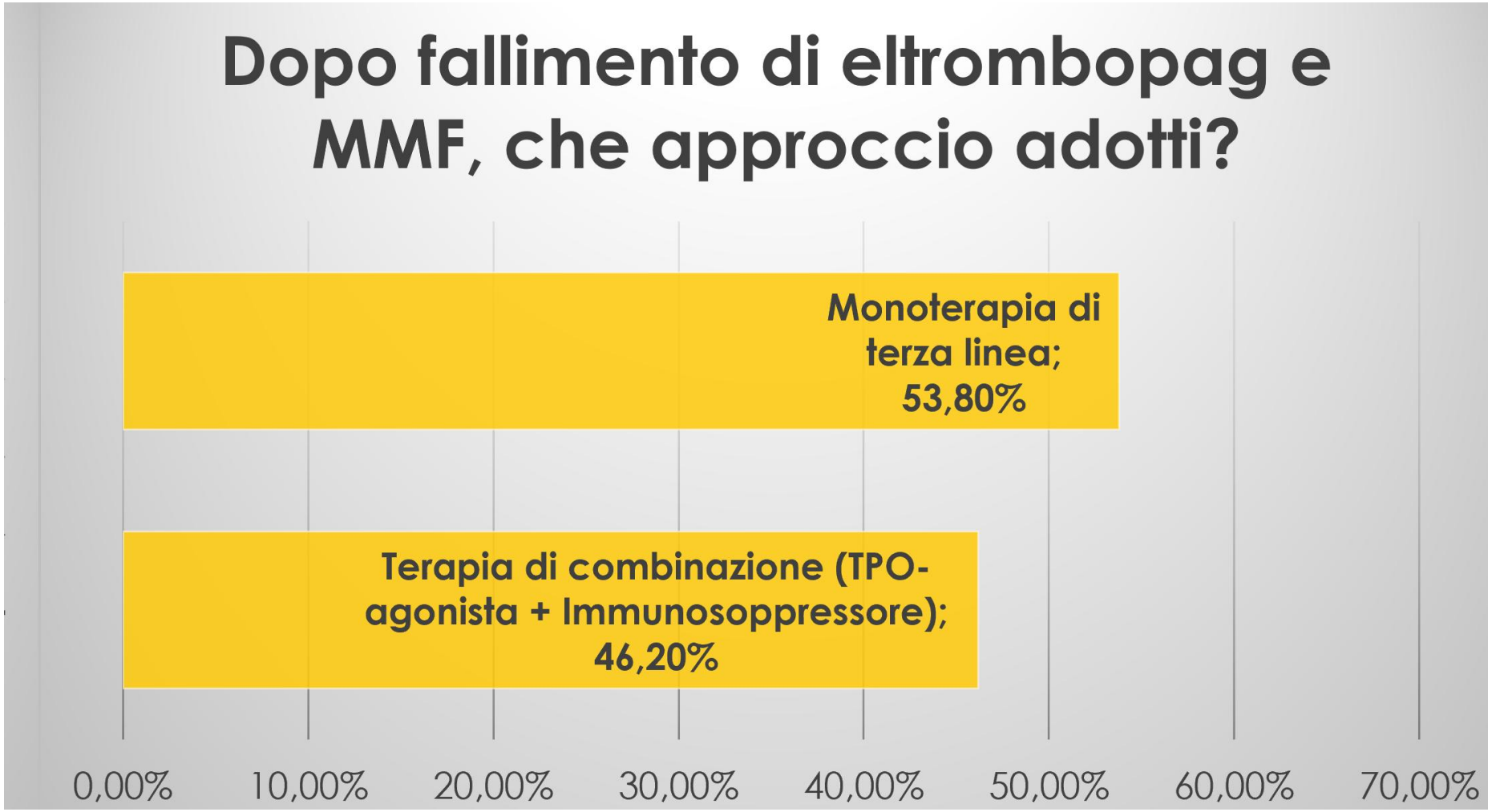


rITP refrattaria a Eltrombopag



- Continuare unicamente con terapia rescue al bisogno (steroide/ immunoglobuline), senza terapia cronica
- Sospendere Eltrombopag e iniziare un'altra terapia
- Mantenere Eltrombopag e associare un secondo farmaco (terapia combinata)
- romilopostim + aggiunta di immunosoppressore (Micofenolato o sirolimus) se non risposta al romilopos…

rITP refrattaria a Eltrombopag e **MMF**



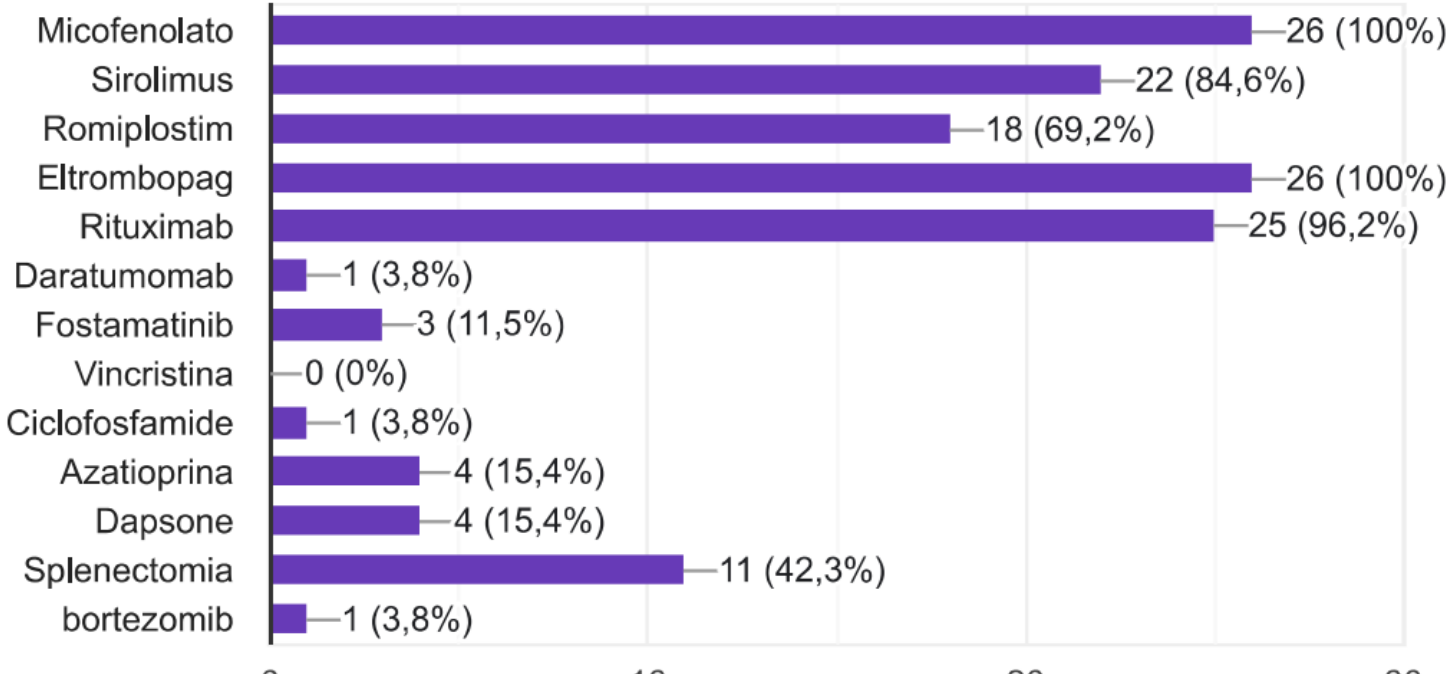
rITP cronica refrattaria
Opzioni di monoterapia

OPZIONI UTILIZZATE

- Sirolimus/MMF
- Shift ad altro TPO agonista
- Rituximab
- Splenectomia (poco)

OPZIONI POCO UTILIZZATE

- Fostamatinib
- Agenti anti plasmacellule
- Altri farmaci



PROGETTI IN CORSO GdL DIFETTI DELLA COAGULAZIONE

Studio Osservazionale Prospettico CHIPS & sottostudio µCHIPS

Coordinamento:

Dott. Giuseppe Lassandro (Bari)

giuseppelassandro@live.com

3392007395

&

Prof.ssa Paola Giordano, Dott.ssa Valentina Palladino, Dott. Luigi Moscogiuri (Bari)

&

Dott.ssa Michela Faleschini (Trieste)

European Reference Network | Hematological Diseases (ERN EuroBloodNet)

Policlinico di Bari Ospedale Giovanni XXIII

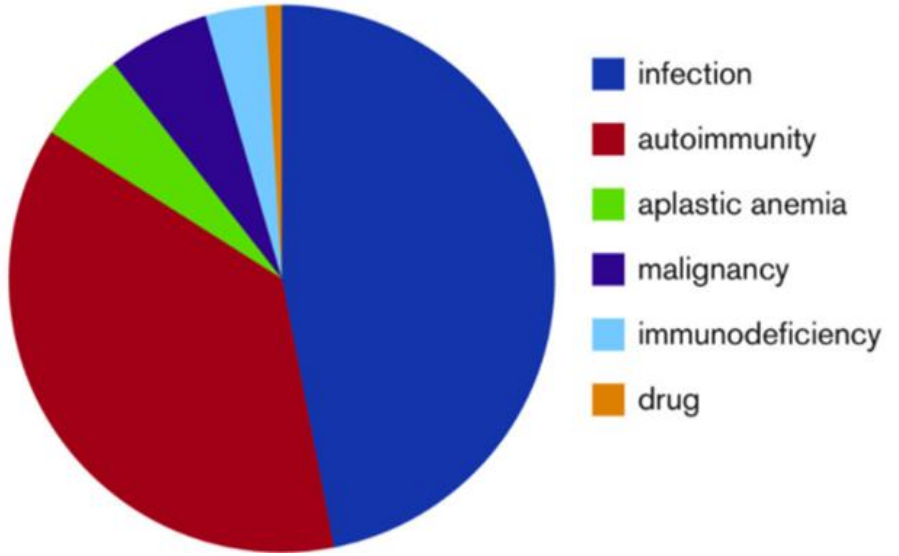
Multicenter Study > Blood Adv. 2021 Mar 23;5(6):1617-1626.
doi: 10.1182/bloodadvances.2020003004.

Misdiagnosed thrombocytopenia in children and adolescents: analysis of the Pediatric and Adult Registry on Chronic ITP

Alexandra Schifferli [1], Andrea Heiri [2], Paul Imbach [1], Susanne Holzhauer [3], Markus G Seidel [4], Diane Nugent [5], Marc Michel [6], Thomas Kühne [1]

3974 bambini di età compresa tra 3 mesi e 16 anni. ITP secondaria e non-IT sono stati riportati in 113 pazienti

2,8%



Causes of secondary ITP or non-IT in children misdiagnosed with primary ITP. Infection: HIV, n = 5; Chagas disease, n = 1; herpes zoster, n = 1; no information, n = 47. Autoimmunity: systemic lupus erythematosus, n = 16; Evans syndrome, n = 11; autoimmune lymphoproliferative syndrome, n = 2; autoimmune bicytopenia (thrombocytopenia and neutropenia), n = 5; mixed connective tissue disease, n = 2; diabetes mellitus type 1, n = 1; scleroderma, n = 1; no information, n = 4. Malignancy: myelodysplastic syndrome, n = 3; Hodgkin lymphoma, n = 1; myeloproliferative disease, n = 2; no information, n = 1. Immunodeficiency: DiGeorge syndrome, n = 1; primary chronic granulomatous disease, n = 1; not determined, n = 2.

J Pediatr Hematol Oncol. 2003 Jul;25(7):548-52.

Misdiagnosis of chronic thrombocytopenia in childhood.

Bader-Meunier B[1], Proulle V, Trichet C, Debray D, Gabolde M, Yvart J, Dreyfus M.

Patient/ sex	Family history	Age at onset of thrombocytopenia/ final diagnosis	Initial clinical features	Platelet count (range)	PaIgG (IgG/ platelet)	MAIPA assay (direct/ indirect)	Treatments/response to the treatment	Referring diagnosis/ final diagnosis
1/M	Parents first-degree relatives	2 years/4.5 years	Epistaxis, ecchymosis	30×10^9/L–50×10^9/L	ND	ND	IVIgG (1 g/kg/ 4 courses)/NR Steroids (2 mg/kg during 2 weeks and tapering)/NR	AITP/Bernard-Soulier disease
2/F	None	4 years/11 years	Fortuitous	30×10^9/L–50×10^9/L	2,000	Negative	IVIgG (1 g/kg;3 courses)/NR Steroids (2 mg/kg during 4 weeks)/NR α Interferon (3 U/m^2 × 3/week during 8 weeks)/NR	AITP/Bernard-Soulier disease
3/F	Paternal thrombocytopenia	5 months/ 5 years	Fortuitous	30×10^9/L–250×10^9/L	11,800	ND	IVIgG (1 g/kg; 1 course)/NR	AITP/von Willebrand disease
4/F	None	7 years/ 12.3 years	Fortuitous	30×10^9/L–50×10^9/L	>25,000	Negative/ Negative	IVIgG (1 g/kg; 4 courses)/PR after 2 courses in association with steroids (1.5 mg/kg during 2 weeks and tapering during 2 weeks); NR after the 2 other courses	AITP/von Willebrand disease
5/F	None	7 years/7.1 years	Epistaxis	8×10^9/L–20×10^9/L	3,300	ND	IVIgG (1 g/kg; 1 course)/NR	AITP/May-Hegglin disease
6/M	Maternal platelet autoimmunity	6 months/ 9 months	Fortuitous	15×10^9/L–50×10^9/L	ND	Negative/ Positive (1bIX)	IVIgG (0.8 g/kg/ 7 courses) and steroids (2 mg/kg during 4 weeks, progressively tapered)/CR	AITP/Wiskott-Aldrich disease
7/M	None	5 months/ 3 years	Fortuitous	5×10^9/L–70×10^9/L	ND	Negative/ Positive (1bIX)	IVIgG (0.8 g/kg; >10 courses) and steroids (2 mg/kg during 4 weeks, progressively tapered)/CR	AITP/Wiskott-Aldrich disease

7 di 58 bambini con diagnosi ITP cronica avevano una forma ereditaria di trombocitopenia

Front Pediatr. 2022 Nov 22:10:967417. doi: 10.3389/fped.2022.967417. eCollection 2022.

"CHildren with Inherited Platelet disorders Surveillance" (CHIPS) retrospective and prospective observational cohort study by Italian Association of Pediatric Hematology and Oncology (AIEOP)

Giuseppe Lassandro [1], Valentina Palladino [1], Michela Faleschini [2], Angelica Barone [3], Gianluca Boscarol [4], Simone Cesaro [5], Elena Chiocca [6], Piero Farruggia [7], Fiorina Giona [8], Chiara Gorio [9], Angela Maggio [10], Maddalena Marinoni [11], Antonio Marzollo [12], Giuseppe Palumbo [13] [14], Giovanna Russo [15], Paola Saracco [16], Marco Spinelli [17], Federico Verzegnassi [2], Francesca Morga [1], Anna Savoia [2] [18], Paola Giordano [1]

Affiliations + expand

PMID: 36507135 PMCID: PMC9728612 DOI: 10.3389/fped.2022.967417

Abstract

Background: Inherited thrombocytopenias (ITs) are rare congenital bleeding disorders characterized by different clinical expression and variable prognosis. ITs are poorly known by clinicians and often misdiagnosed with most common forms of thrombocytopenia.

Material and methods: "CHildren with Inherited Platelet disorders Surveillance" study (CHIPS) is a retrospective - prospective observational cohort study conducted between January 2003 and January 2022 in 17 centers affiliated to the Italian Association of Pediatric Hematology and Oncology (AIEOP). The primary objective of this study was to collect clinical and laboratory data on Italian pediatric patients with inherited thrombocytopenias. Secondary objectives were to calculate prevalence of ITs in Italian pediatric population and to assess frequency and genotype-phenotype correlation of different types of mutations in our study cohort.

Results: A total of 139 children, with ITs (82 male - 57 female) were enrolled. ITs prevalence in Italy ranged from 0.7 per 100,000 children during 2010 to 2 per 100,000 children during 2022. The median time between the onset of thrombocytopenia and the diagnosis of ITs was 1 years (range 0 - 18 years). A family history of thrombocytopenia has been reported in 90 patients (65%). Among 139 children with ITs, in 73 (53%) children almost one defective gene has been identified. In 61 patients a pathogenic mutation has been identified. Among them, 2 patients also carry a variant of uncertain significance (VUS), and 4 others harbour 2 VUS variants. VUS variants were identified in further 8 patients (6%), 4 of which carry more than one variant VUS. Three patients (2%) had a likely pathogenic variant while in 1 patient (1%) a variant was identified that was initially given an uncertain significance but was later classified as benign. In addition, in 17 patients the genetic diagnosis is not available, but their family history and clinical/laboratory features strongly suggest the presence of a specific genetic cause. In 49 children (35%) no genetic defect were identified. In ninetyseven patients (70%), thrombocytopenia was not associated with other clinically apparent disorders. However, 42 children (30%) had one or more additional clinical alterations.

Conclusion: Our study provides a descriptive collection of ITs in the pediatric Italian population.

“CHildren with Inherited Platelet disorders Surveillance” study (CHIPS) is a retrospective–prospective observational cohort study conducted between January 2003 and January 2022 in 17 centers affiliated to the Italian Association of Pediatric Hematology and Oncology (AIEOP)

Centri aderenti = 17

N° CENTRI	17
BARI	Paola Giordano Giuseppe Lassandro Valentina Palladino Francesca Morga
TRIESTE	Anna Savoia Federico Verzegnassi
BOLZANO	Gianluca Boscarol
BRESCIA	Chiara Gorio
CATANIA	Giovanna Russo
FIRENZE	Elena Chiocca – Ilaria Fotzi
MONZA	Marco Spinelli
PAVIA	Marco Zecca
PADOVA	Antonio Marzollo
PALERMO	Piero Faruggia
PARMA	Angelica Barone
ROMA	Fiorina Giona
ROMA BG	Giuseppe Palumbo
SAN GIOVANNI ROTONDO	Saverio Ladogana
TORINO	Paola Saracco
VARESE	Maddalena Marinoni
VERONA	Simone Cesaro

CHIPS

Lassandro G, et a. Front Pediatr. 2022 Nov 22;10:967417.

	90
Bari, Lassandro/Giordano/Palladino/Morga	21
Brescia, Gorio	5
Bolzano, Boscarol	1
Catania, Russo	14
Firenze, Chiocca	2
Monza, Spinelli	6
Padova, Marzollo	5
Parma, Barone	1
Roma BG, Palumbo	1
Roma Sapienza, Giona	6
Palermo, Farruggia	6
Pavia, Zecca	4
San Giovanni Rotondo, Maggio	2
Torino, Saracco	8
Trieste, Verzegnassi	4
Varese, Marinoni	3
Verona, Cesaro	1

CHIPS

AGGIORNAMENTO.

	90	119
Bari, Lassandro/Giordano/Palladino/Moscogiuri	21	21 + 5 NUOVI
Brescia, Gorio	5	5 NON AGGIORNATI
Bolzano, Boscarol	1	1 + 2 NUOVI
Catania, Russo	14	14 NON AGGIORNATI
Firenze, Chiocca	2	2 NON AGGIORNATI
Monza, Spinelli	6	6 + 2 NUOVI
Padova, Marzollo	5	5 NON AGGIORNATI
Parma, Barone	1	5 + 1 NUOVI
Roma BG, Palumbo	1	1 + 3 NUOVI
Roma Sapienza, Giona	6	6 NON AGGIORNATI
Palermo, Farruggia/Guarina	6	6 + 6 NUOVI
Pavia, Tolva	4	4 (2 NON AGGIORNATI) + 2 NUOVI
San Giovanni Rotondo, Maggio	2	2 + 3 NUOVI
Torino, Saracco	8	8 NON AGGIORNATI
Trieste, Verzegnassi	4	4 NON AGGIORNATI
Varese, Marinoni	3	3 NON AGGIORNATI
Verona, Cesaro	1	1 + 5 NUOVI

Michael Makris[1,2]

[1]Department of Infection, Immunity and Cardiovascular disease, University of Sheffield, and [2]Sheffield Haemophilia and Thrombosis Centre, Royal Hallamshire Hospital, Sheffield, UK

E-mail: m.makris@sheffield.ac.uk

doi:10.3324/haematol.2019.241786

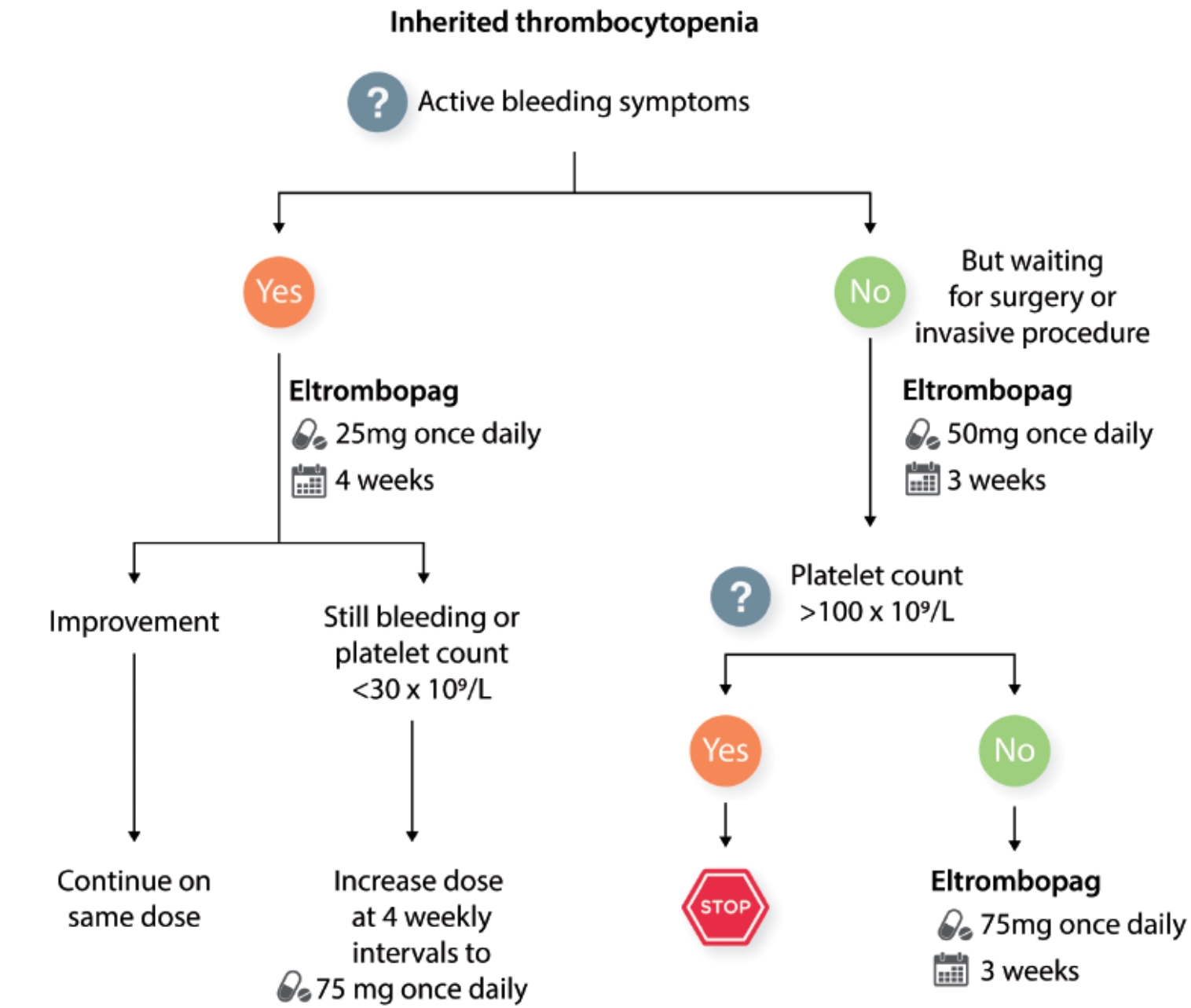


Figure 1. Outline of the phase II clinical trial using eltrombopag in patients with inherited thrombocytopenia.

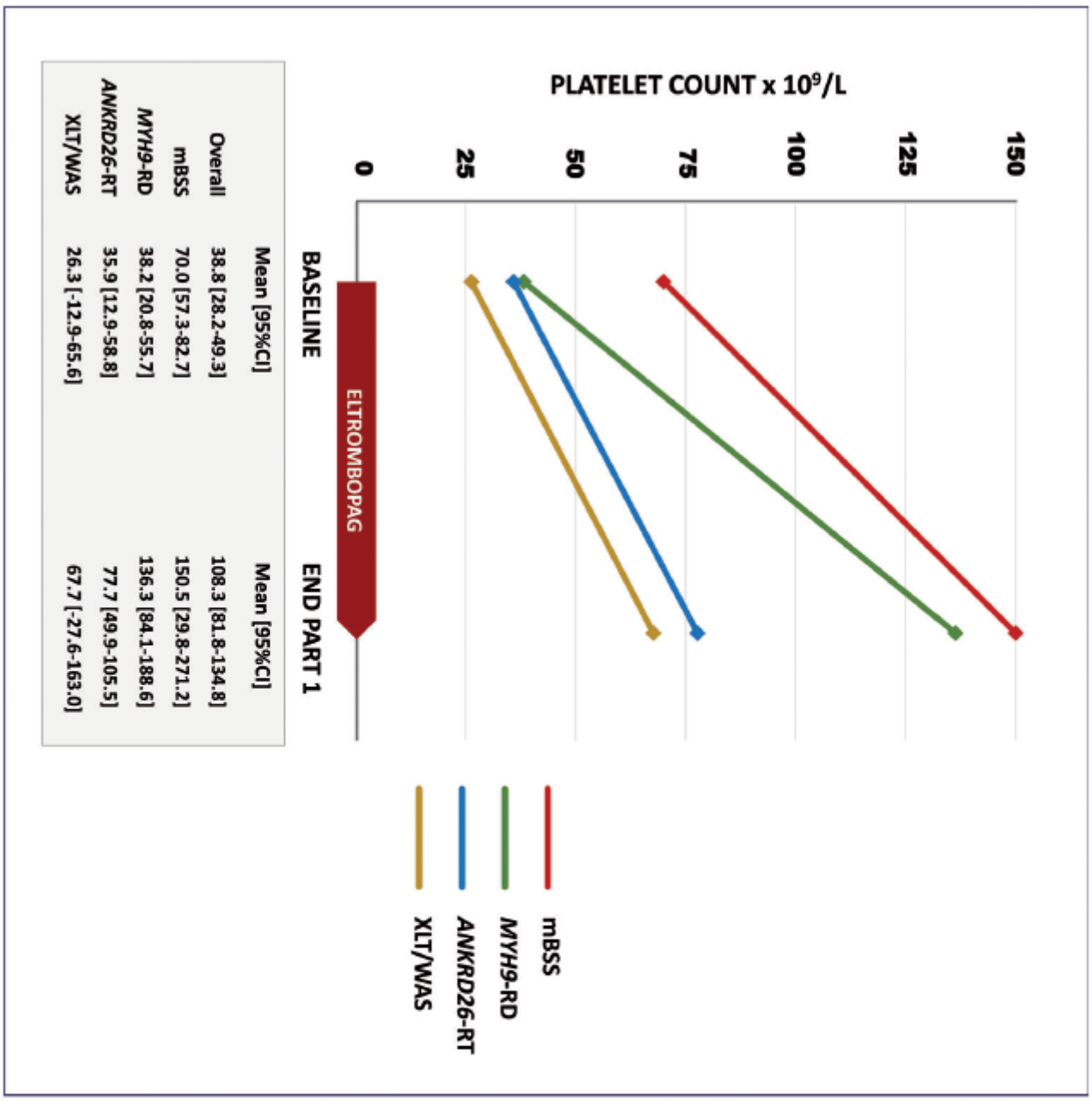
Ferrata Storti Foundation

Haematologica 2020
Volume 105(3):820-828

Eltrombopag for the treatment of inherited thrombocytopenias: a phase II clinical trial

Carlo Zaninetti,[1,2] Paolo Gresele,[3] Antonella Bertomoro,[4] Catherine Klersy,[5] Erica De Candia,[6,7] Dino Veneri,[8] Serena Barozzi,[1] Tiziana Fierro,[3] Maria Adele Alberelli,[6] Valeria Musella,[5] Patrizia Noris,[1] Fabrizio Fabris,[4] Carlo L. Balduini[1,9] and Alessandro Pecci[1]

[1]Department of Internal Medicine, IRCCS Policlinico San Matteo Foundation and University of Pavia, Pavia; [2]PhD course in Experimental Medicine, University of Pavia, Pavia; [3]Department of Medicine, University of Perugia, Perugia; [4]Department of Medicine, University of Padova, Padova; [5]Service of Clinical Epidemiology & Biometry, IRCCS Policlinico San Matteo Foundation and University of Pavia, Pavia; [6]IRCCS Policlinico Universitario A. Gemelli Foundation, Roma; [7]Institute of Internal Medicine and Geriatrics, Catholic University of the Sacred Heart, Roma; [8]Department of Medicine, Section of Hematology, University of Verona, Verona and [9]Ferrata-Storti Foundation, Pavia, Italy.



	Mean [95%CI]	Mean [95%CI]
Overall	38.8 [28.2-49.3]	108.3 [81.8-134.8]
mBSS	70.0 [57.3-82.7]	150.5 [29.8-271.2]
MYH9-RD	38.2 [20.8-55.7]	136.3 [84.1-188.6]
ANKRD26-RT	35.9 [12.9-58.8]	77.7 [49.9-105.5]
XLT/WAS	26.3 [-12.9-65.6]	67.7 [-27.6-163.0]

Figure 1. Mean increase in platelet count in the responders in part 1 of the study. Patients are categorized according to the diagnosis of the specific form of inherited thrombocytopenia. mBSS: monoallelic Bernard-Soulier syndrome; *MYH9*-RD: *MYH9*-related disease; *ANKRD26*-RT: *ANKRD26*-related thrombocytopenia. XLT/WAS: X-linked thrombocytopenia/Wiskott-Aldrich syndrome. Mean values of platelet count at baseline and at the end of part 1 of the treatment along with their 95% confidence intervals (95%CI) are reported in the gray box.

children

MDPI

Case Report

Successful Eltrombopag Therapy in a Child with MYH9-Related Inherited Thrombocytopenia

Giuseppe Lassandro [1], Francesco Carriero [2], Domenico Noviello [2], Valentina Palladino [1], Giovanni Carlo Del Vecchio [1], Maria Felicia Faienza [1,3] and Paola Giordano [1,2,*]

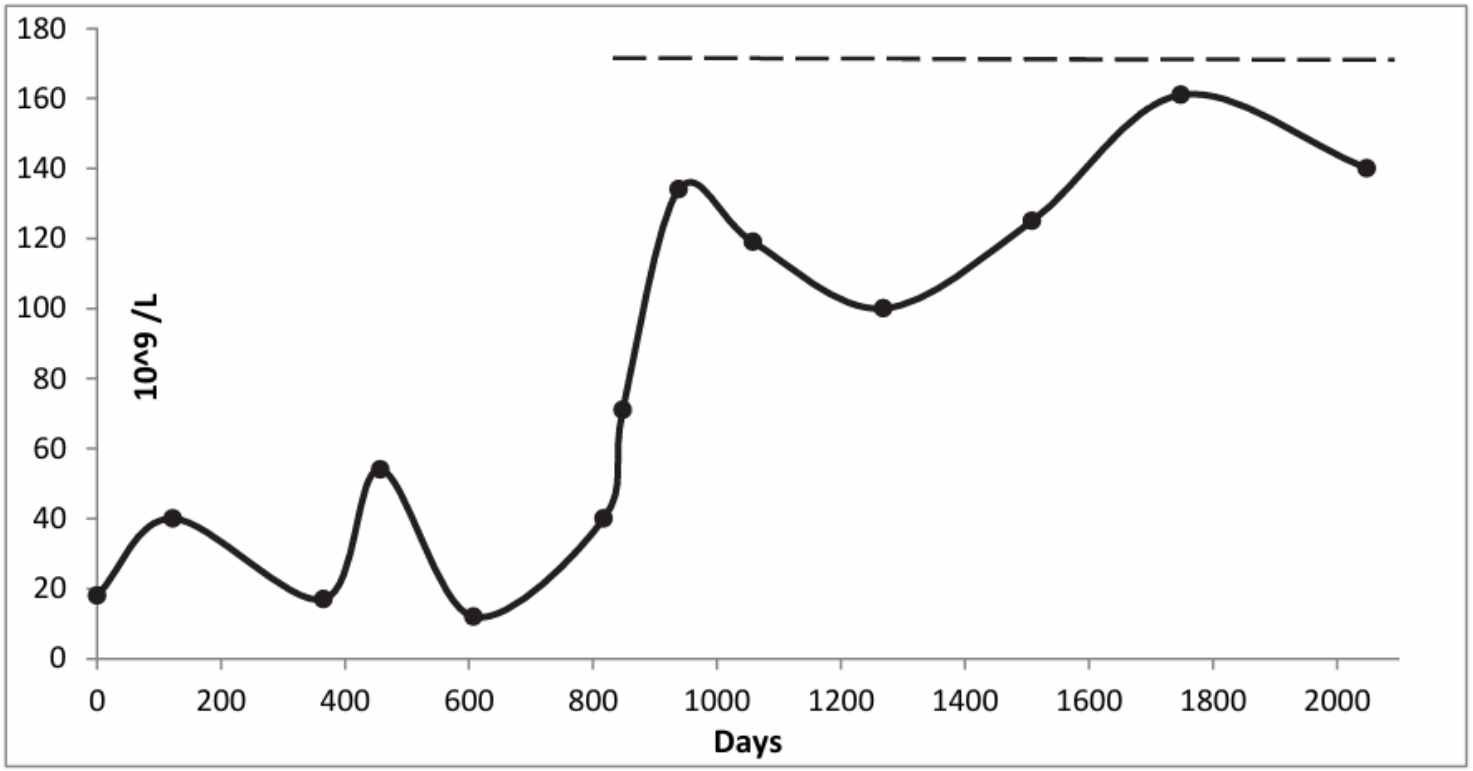


Figure 1. Platelet count during follow-up.

ELTROMBOPAG,
UNA POSSIBILE OPPORTUNITA' TERAPEUTICA NELLE PIASTRINOPENIE EREDOFAMILIARI

G. Lassandro 1, V. Granberg 1, B. Bruschi 2, M. Chinello 3, C. Gorio 4, A. Marzollo 5, G. Palumbo 6, G. Russo 7, P. Giordano 1

1 AOUC Policlinico-Giovanni XXIII Università degli Studi di Bari Aldo Moro, 2 Azienda Ospedaliera delle Marche, 3 Azienda Ospedaliera Universitaria Integrata, 4 ASST-Spedali Civili, 5 Azienda Ospedale Università, 6 IRCCS Ospedale Pediatrico Bambino Gesù, 7 Università di Catania.

corrispondenza: *giuseppelassandro@live.com*

ABSTRACT AIEOP 2025

INTRODUZIONE: Le piastrinopenie eredofamiliari (PE), in un recente passato ritenute eccezionalmente rare, rappresentano oggi un interessante campo di ricerca genetico, cellulare e clinico. La comunità scientifica ha rapidamente acquisito conoscenze sui loro aspetti fisiopatologici facilitandone la diagnosi e garantendo un'attiva sorveglianza dei soggetti con forme evolutive verso condizioni oncologiche o disfunzione di altri organi. Le PE sono prevalentemente associate ad uno fenotipo emorragico lieve. Le terapie di supporto (concentrati piastrinici, tranexamico) sono, spesso, sufficienti a garantire un'adeguata emostasi. I farmaci mimetici della trombopoietina (Eltrombopag e Romiplostin) stimolando la produzione midollare hanno cambiato la storia della terapia nelle piastrinopenie immunomediate e, forse, possono avere un ruolo chiave nelle PE in caso di sanguinamento eccessivo o per prevenirlo nelle chirurgie.

MATERIALI E METODI: Raccolta di esperienze sull'uso off-label di Eltrombopag nei centri AIEOP afferenti al GdL Coagulazione. **RISULTATI: E' stato segnalato l'uso in 12 soggetti con PE (mutazioni: 5 WAS, 3 MYH9, 2 ANKRD26, 1 GNE, 1 MPL**

Motivazioni alla terapia: conta piastrinica ridotta, sanguinamento, avviamento all'attività sportiva.

Efficacia nell'incremento della conta piastrinica nel 92%.

Sicurezza nel 75%, segnalati due eventi avversi maggiori (trombosi venosa cerebrale ed encefalopatia iperammoniemica) ed uno minore (epigastralgia).

DISCUSSIONE: L'Eltrombopag, come già segnalato in letteratura, si conferma un'opportunità terapeutica efficace nelle PE. I dati di sicurezza meritano di ulteriori valutazioni perché i pochi eventi avversi maggiori appaiono correlati con la condizione clinica non riconducibile alla sola piastrinopenia. La limitazione dei dati impone di allargare la corte per ricercare le mutazioni che meglio possano beneficiare di Eltrombopag.

PAPER IN DRAFT

Email del 26/02/2026

Title:

Efficacy and safety of Eltrombopag in hereditary thrombocytopenias: italian pediatric hematologists experience.

Authors:

Giuseppe Lassandro[1], Vanja Granberg[1], Barbara Bruschi[2], Matteo Chinello[3], Chiara Gorio[4], Antonio Marzollo[5], Giuseppe Palumbo[6], Giovanna Russo[7], Paola Giordano[1]

Affiliations:

[1]AOUC Policlinico-Giovanni XXIII Università degli Studi di Bari Aldo Moro, Bari, Italia; [2]Azienda Ospedaliera delle Marche, Ancona, Italia; [3]Azienda Ospedaliera Universitaria Integrata, [4]ASST-Spedali Civili,Brescia, Italia; [5]Azienda Ospedale Università,Padova, Italia; [6]IRCCS Ospedale Pediatrico Bambino Gesù, Roma, Italia; [7]Università di Catania, Catania, Italia

PROGETTI IN CORSO GdL DIFETTI DELLA COAGULAZIONE

Assesment

heavy

Menstrual

Bleeding

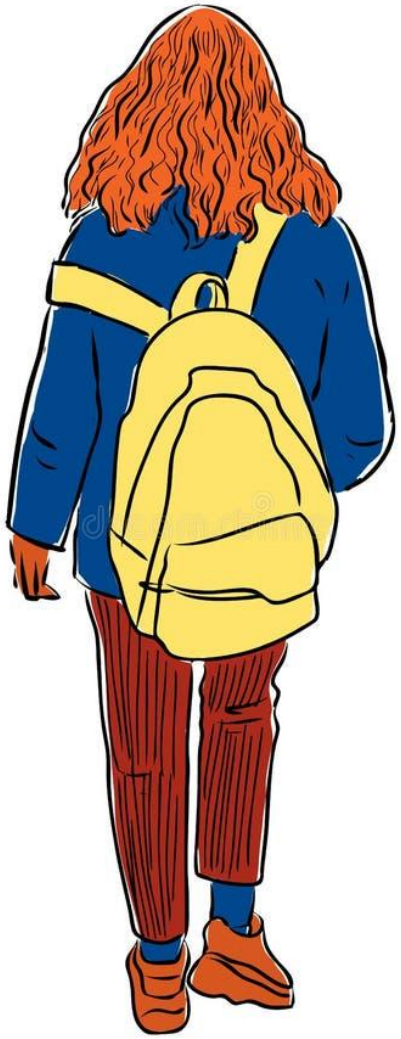
in italian

giRls

to search

Allied

hematological disordes



AMBRA

Coordinamento:

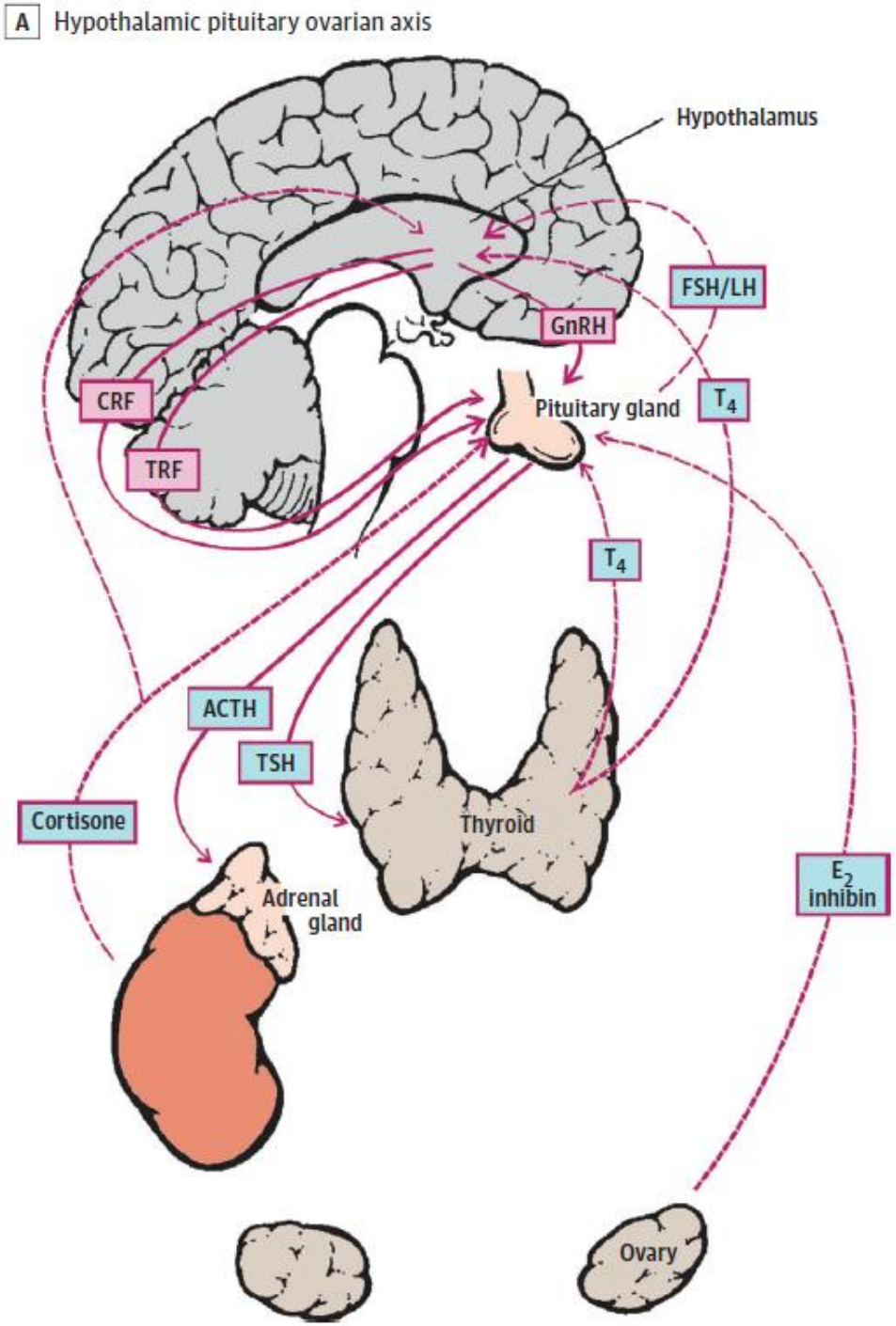
Dott. Giuseppe Lassandro (Bari)

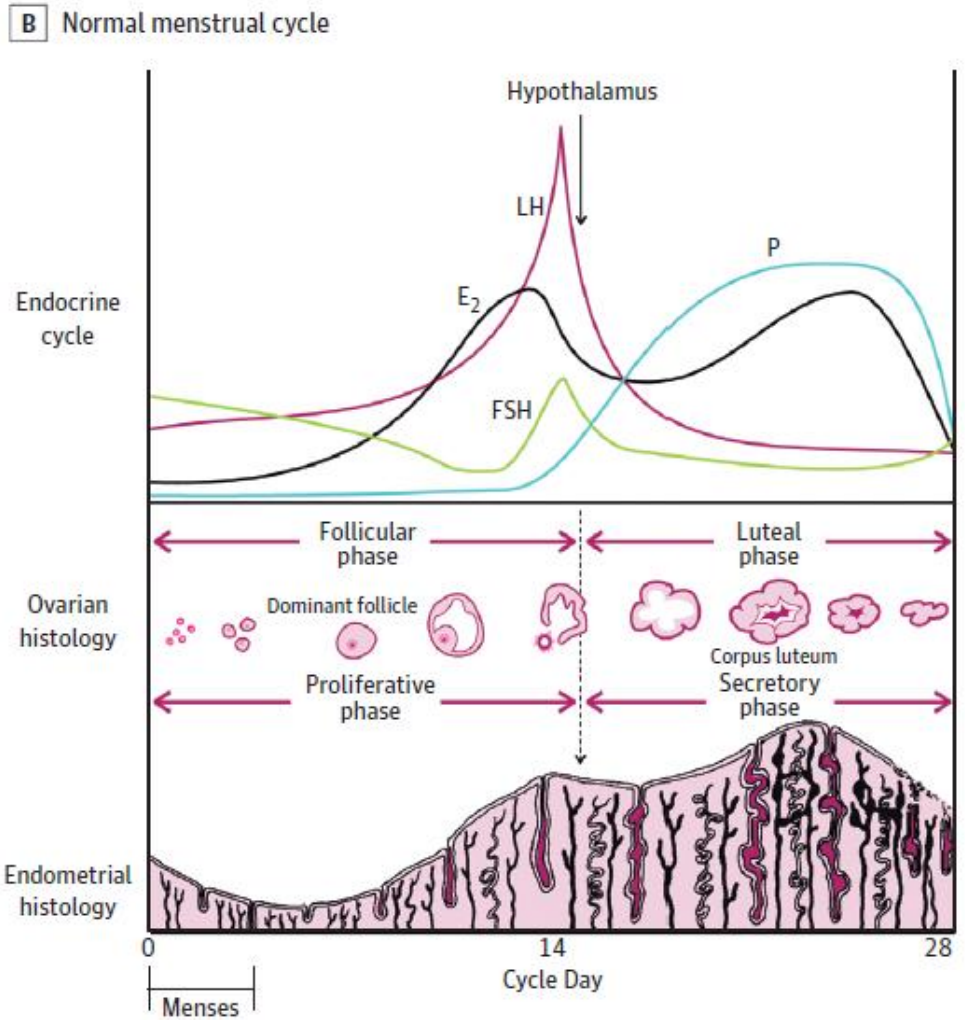
giuseppelassandro@live.com

3392007395

European Reference Network | Hematological Diseases (ERN EuroBloodNet)

Policlinico di Bari
Ospedale Giovanni XXIII





Borzutzky C, Jaffray J. Diagnosis and Management of Heavy Menstrual Bleeding and Bleeding Disorders in Adolescents. JAMA Pediatr. 2020 Feb 1;174(2):186-194.

ACOG American College of Obstetricians and Gynecologists

ETA' MEDIA DEL MENARCA: 12,5 ANNI (USA)

INTERVALLO CICLO MESTRUALE: 21-45 giorni (media 32 giorni)

DURATA FLUSSO MESTRUALE: 7 giorni o meno

UTILIZZO IN GIORNI DI TAMPONI: 3-6 giorni

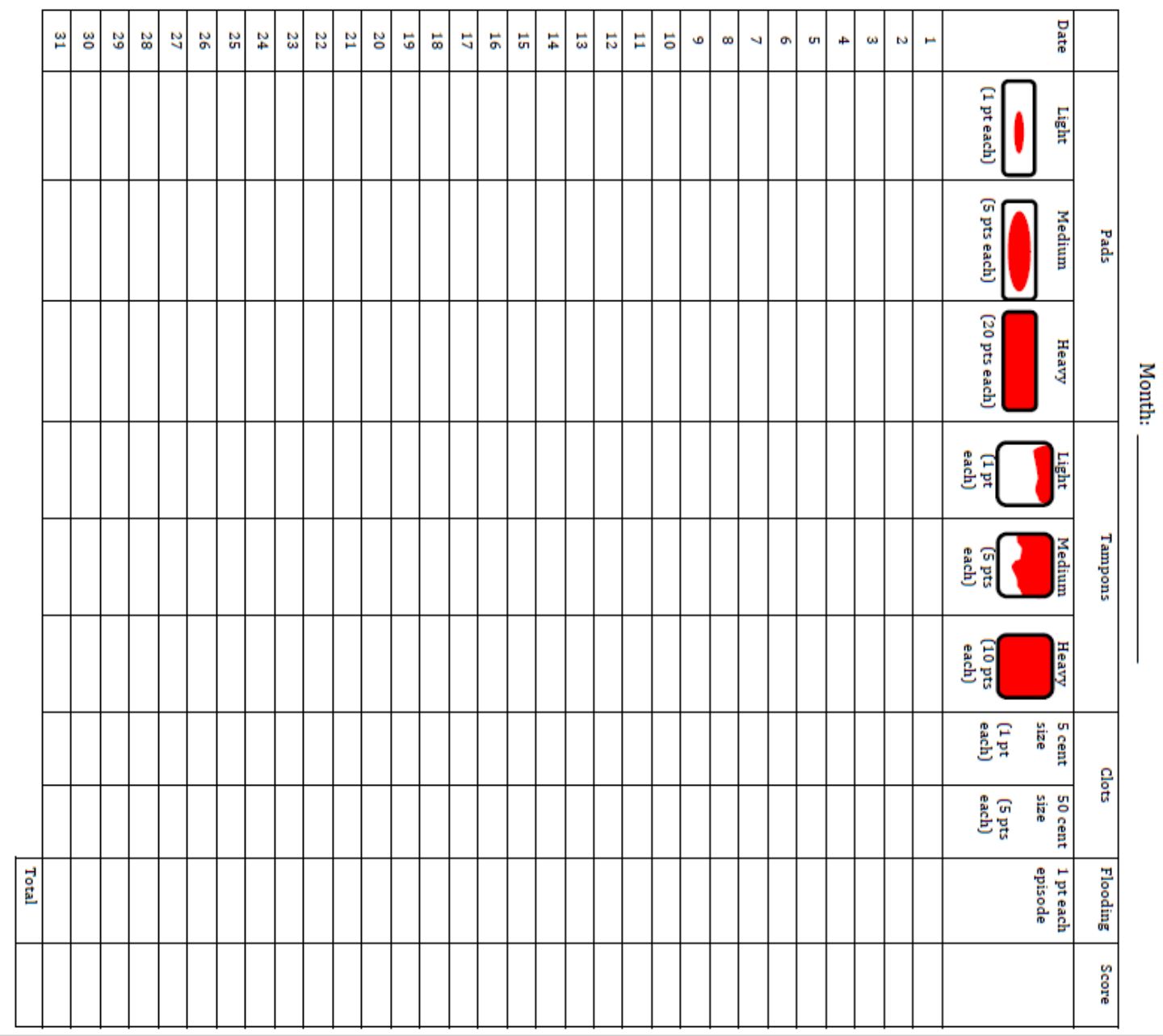
NELLE ADOLESCENTI LA DURATA DEI GIORNI DI FLUSSO PUO' ARRIVARE A 9 GIORNI SEBBENE

NON VI SIANO PARAMETRI PER ETA' (insufficienza progestinica temporanea)

ACOG Committee Opinion No. 651: Menstruation in Girls and Adolescents: Using the Menstrual Cycle as a Vital Sign. Obstet Gynecol. 2015 Dec;126(6):e143-e146.

PBAC

Higham JM et al. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol*1990; 97: 734-739.



Month: _____

Date	Pads			Tampons			Clots		Flooding	Score
	Light (1 pt each)	Medium (5 pts each)	Heavy (20 pts each)	Light (1 pt each)	Medium (5 pts each)	Heavy (10 pts each)	5 cent size (1 pt each)	50 cent size (5 pts each)	1 pt each episode	
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
15										
16										
17										
18										
19										
20										
21										
22										
23										
24										
25										
26										
27										
28										
29										
30										
31										
Total										

Abnormal PBAC bleeding score (BS) ≥100, which correlates with menorrhagia, defined as >80 mL of menstrual blood loss.

ABNORMAL UTERINE BLEEDING

The International Federation of Gynecology and Obstetrics and the American Congress of Obstetricians and Gynecologists support the use of new terminology for abnormal uterine bleeding (AUB) to consistently categorize AUB by etiology (frequency, regularity, duration and volume). The term AUB can be further classified as

AUB/heavy menstrual bleeding (HMB) (replacing the term "menorrhagia") or

AUB/intermenstrual bleeding (replacing the term "metrorrhagia").

Munro MG et al. FIGO menstrual disorder Committeee. The two FIGO systems for normal and abnormal uterine bleeding symptompts and classification of causes of abnormal uterine bleeding in the reproductibve yerars: 2018 revisions. Int J Gynaecol Obstet. 2018;143(3):393-408

ABNORMAL UTERINE BLEEDING

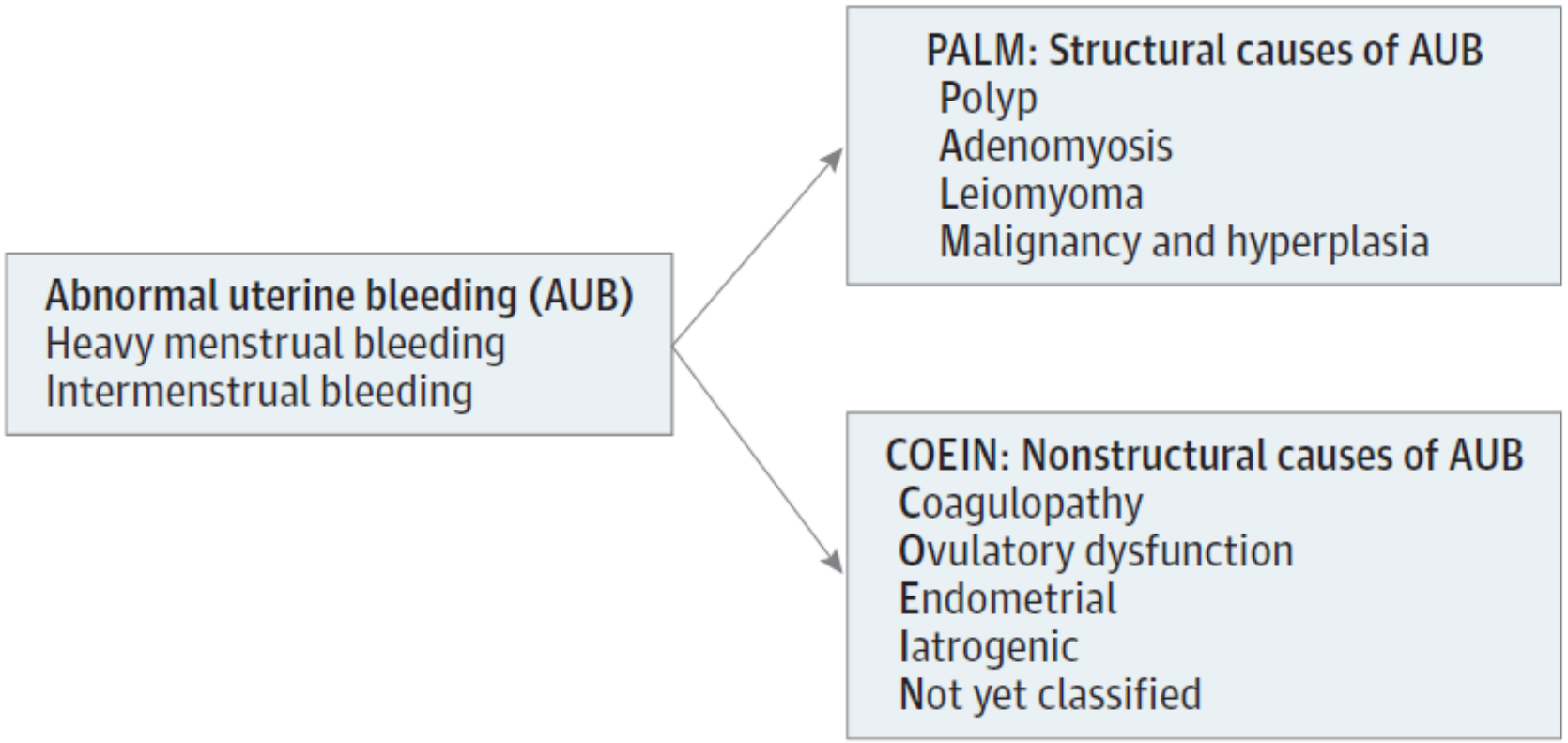
As in adults, menstrual cycles are between **21 and 34 days**, last for seven days or fewer, **with an average blood loss of 30-40 mL leading to 3-6 pads or tampon usage per day**

AUB might also be classified as acute or chronic. Acute AUB refers to an episode of heavy bleeding which is sufficient in quantity to require immediate intervention to prevent further blood loss. Abnormalities in quantity, regularity and/or timing in the last six months may all be defined as chronic AUB. **Usually, chronic menstrual bleeding that exceeds 80 mL will result in anemia.**

Bennett AR, Gray SH. What to do when she's bleeding through: the recognition, evaluation and management of abnormal uterine bleeding in adolescents. Curr Opin Pediatr 2014;26:413-419.

American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 557: Management of acute abnormal uterine bleeding in nonpregnant reproductive-aged women. Obstet Gynecol 2013;121:891-896.

Figure 2. Federation of International Gynecology and Obstetrics Classification for Causes of Abnormal Uterine Bleeding: PALM-COEIN[a]



Munro MG, Critchley HO, Broder MS, Fraser IS; FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet. 2011 Apr;113(1):3-13.

FOCUS

HEAVY MENSTRUAL BLEEDING (HMB) PROBLEMATICA COMUNE A MOLTE ADOLESCENTI

MOTIVO DI VISITA DAL: MEDICO DI MEDICINA GENERALE/PEDIATRA, GINECOLOGO/ENDOCRINOLOGO, EMATOLOGO

PREVALENZA HMB IN ADOLESCENZA 34%-37%

Friberg B, Ornö AK, Lindgren A, Lethagen S. Bleeding disorders among young women: a population-based prevalence study. Acta Obstet Gynecol Scand. 2006;85(2):200-6.

FOCUS

IMPATTO ENORME SULLA QUALITA' DELLA VITA CON DIVERSI GIORNI "PERSI":

- SCUOLA

- ATTIVITA' SPORTIVE/RICREATIVE

E NECESSITA' DI PROLUNGATI PERIODI DI RIPOSO O TERAPIE FARMACOLOGICHE

TALORA ACCESSO IN PRONTO SOCCORSO CON RICOVERO E TRASFUSIONE DI EMODERIVATI

Friberg B, Ornö AK, Lindgren A, Lethagen S. Bleeding disorders among young women: a population-based prevalence study. Acta Obstet Gynecol Scand. 2006;85(2):200-6.

IL CAMBIO DI DEFINIZIONE O DI PARADIGMA?

> 80 ml sangue/periodo

Fraser IS et al. Fertil Steril (2007)

"excessive menstrual blood loss, which interferes with the woman's physical, emotional, social and material QOL, and which can occur alone or in combination with other symptoms."

FIGO/UK NICE Munro MG et al. Int J Gynaecol Obstet (2018)

GENDER EQUITY

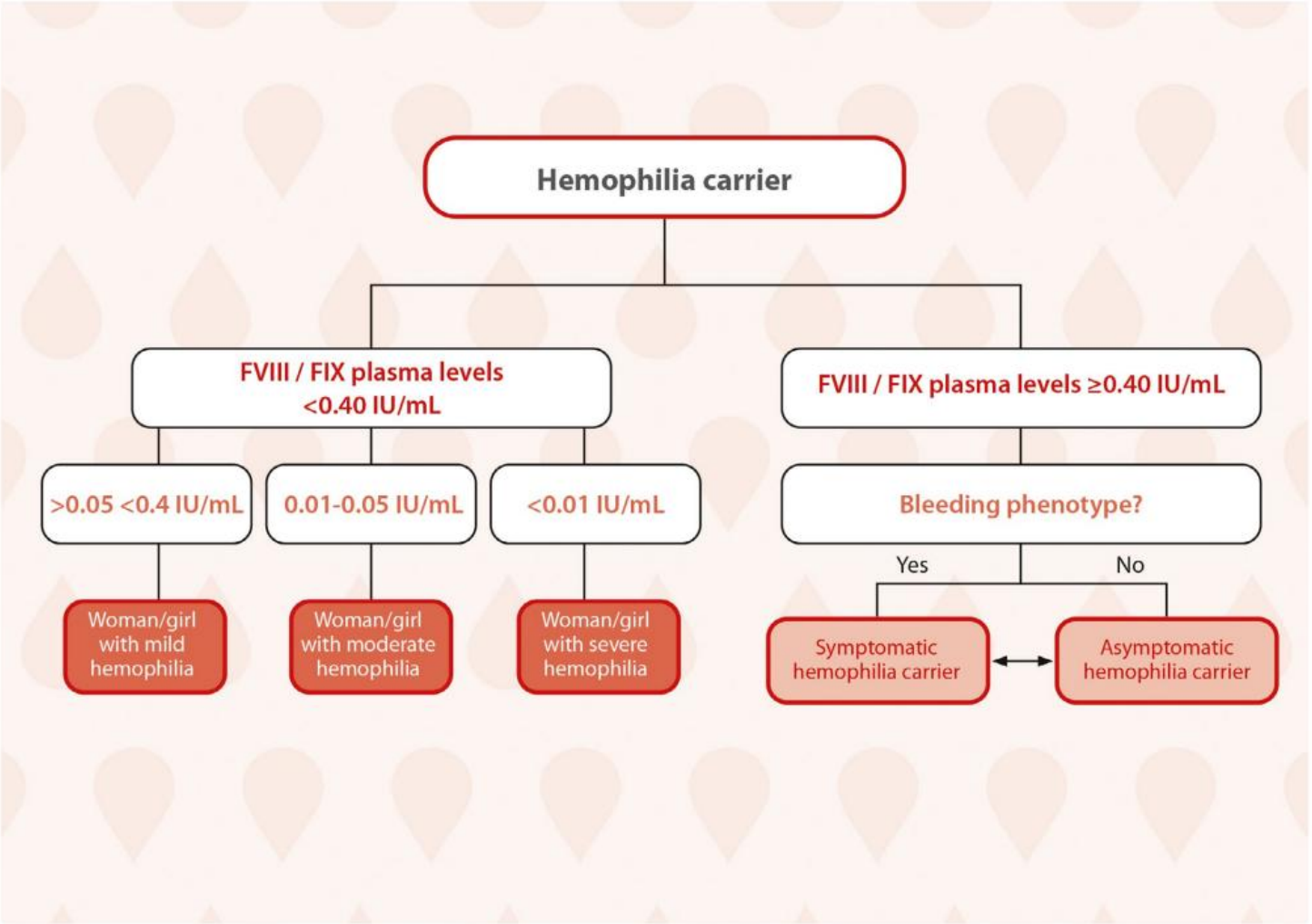


FIGURE 1 New nomenclature for hemophilia carriers and women and girls with hemophilia. The term "asymptomatic hemophilia carrier" solely reflects the bleeding phenotype, not the actual burden of being a hemophilia carrier. FVIII/FIX, factor VIII/IX; IU/ml, international units per milliliter

Van Galen K et al. A new hemophilia carrier nomenclature to define hemophilia in women and girls. J Thromb Haemost. 2021;19:1883–1887

HEMATOLOGICAL TREATMENT

Antifibrinolytic agents act by decreasing fibrinolysis and promoting clot formation, reducing menstrual blood loss significantly (40% - 50%). Tranexamic acid is as effective as COC in reducing menstrual bleeding and should be prescribed 10 mg/kg intra-venous (IV) every to eight hours or 1300 mg orally three times per day (CIRCA (25 mg/kg x 3/die), up to five days.

Desmopressin acetate, a synthetic analogue of the antidiuretic hormone vasopressin, has been used to treat abnormal uterine bleeding in women with coagulation disorders, especially those with von Willebrand disease and mild haemophilia A.It stimulates release of vWD and factor VIII from the endothelium and increases platelet adhesiveness. It is typically prescribed and managed by hematologists.

rFVIIa 15-30 mcg/Kg ogni 4-6 ore

Mitan LAP, Slap GB. Dysfunctional uterine bleeding. In: Neinstein LS, Gordon CM, Katzman DK, Rosen DS, Woods ER, eds. Adolescent Health Care: A Practical Guide. 5° ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2007.

Box. Medication Regimens Used to Control Acute Heavy Menstrual Bleeding

Intravenous Regimens

- Conjugated equine estrogen: 25 mg every 4-6 h for 24 h
- Tranexamic acid: 10 mg/kg: (max 600 mg) every 8 h for 2-8 d
- Aminocaproic acid: 100-200 mg/kg (max 30 g/d) every 4-6 h

Oral Regimens

- Combined oral contraceptive containing 30-50 µg EE
  - Three times per d for 7 d, then taper to daily dosing
- Medroxyprogesterone acetate: 20 mg three times per d for 7 d, then taper to daily dosing
- Norethindrone acetate: 10 mg three times per d for 7 d, then taper to daily dosing
- Tranexamic acid: 1300 mg three times per d for 5 d
- Aminocaproic acid: 100-200 mg/kg (max 30 g/d) every 4-6 h

Adapted from ACOG Committee Opinion No. 557,[62] Moon et al,[66] and Haamid et al.[67]

3 volte al giorno per 7 giorni e poi dose giornaliera

Borzutzky C, Jaffray J. Diagnosis and Management of Heavy Menstrual Bleeding and Bleeding Disorders in Adolescents. JAMA Pediatr. 2020 Feb 1;174(2):186-194.

AIEOP ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

AMBRA STUDY

1

ANEMIA MICROCITICA FERROCARENZIALE

FERROCARENZIALE

ANEMIA NORMOCITICA O MICROCITICA SANGUINAMENTO UTERINO ATTIVO

2

PBAC > 100 BAT SCORE > 3

3

EMOCROMO, RETICOLOCITI, EMOGRUPPO
SIDERMIA, TRANSFERRINA, FERRITINA
PT, PTT, FBG, FVIII, FXIII, VWF Ag, VWF Attività
PFA 100 (TEMPO DI CHIUSURA), AGGREGAZIONE PIASTRINICA

TSH, FT4, TPO AB, TG AB
FSH, LH, 17 BETA ESTRADIOLO, PROGESTERONE, INIBINA B
ORMONE ANTIMULLERIANO, PROLATTINA
ECO PELVI
ECO TIROIDE

AIEOP ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

AMBRA STUDY

PREVALENZA DELLA PROBLEMATICA

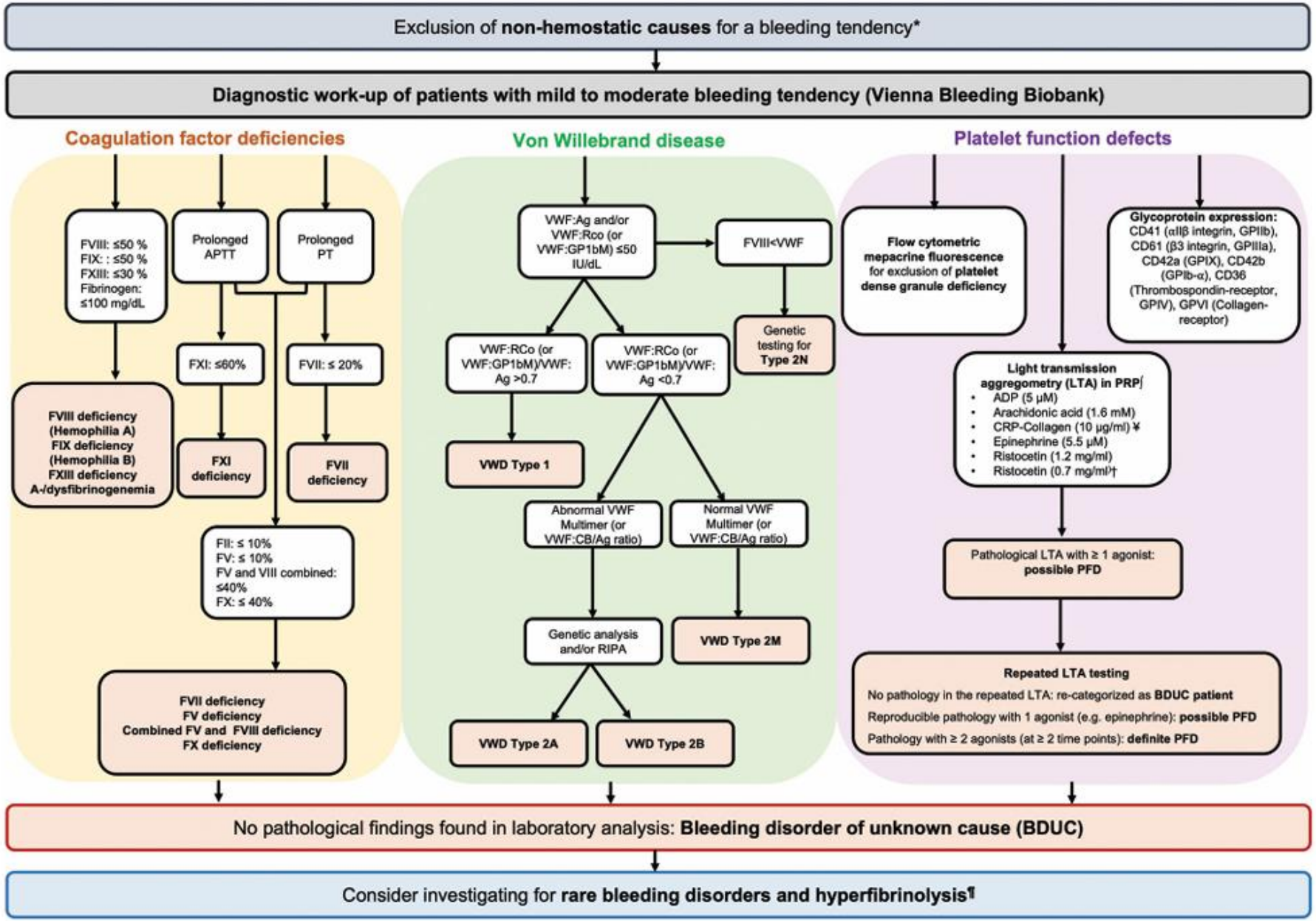
GESTIONE CLINICA

DIAGNOSI DI MALATTIA EMATOLOGICA O ENDROCRINOLOGICA/GINECOLOGICA

BLEEDING DISORDER OF UNKNOWN CAUSE (BDUC)

TERAPIE EMOSTATICHE (efficacia, eventi avversi)

TERAPIE ORMONALI (efficacia, eventi avversi)



Mehic D, Gebhart J, Pabinger I. Bleeding Disorder of Unknown Cause: A Diagnosis of Exclusion. Hamostaseologie. 2024 Aug;44(4):287-297.

GRAZIE PER L'ATTENZIONE

UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

European Reference Network | Hematological Diseases (ERN EuroBloodNet)