Nuovi Anticoagulanti

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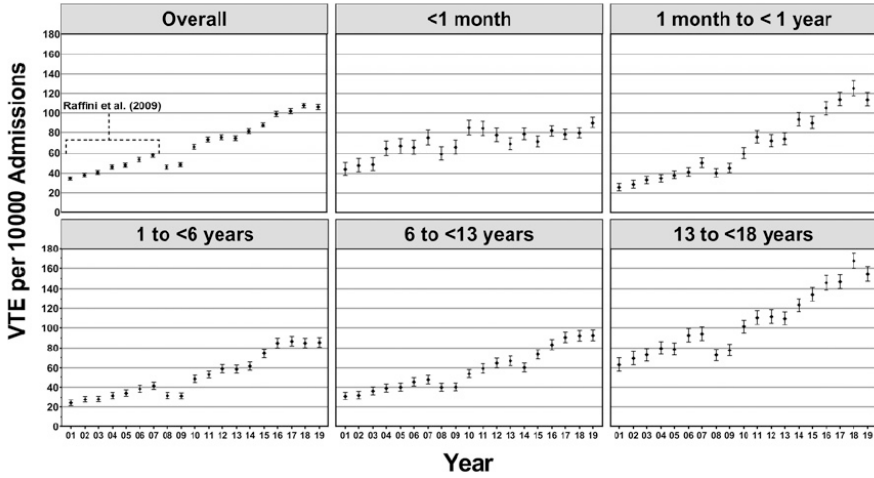
- Il tromboembolismo venoso (TEV) nei bambini e negli adolescenti è aumentato drammaticamente negli ultimi due decenni
- Il tasso di TEV nei pazienti pediatrici ricoverati continua ad aumentare, passando da un aumento del **70%** riportato dal 2001 al 2007 a un aumento del **130%** dal 2008 al 2019.

- Il rischio di TEV è diffuso in tutte le fasce d'età, ma è più elevato nei **neonati e negli adolescenti**.

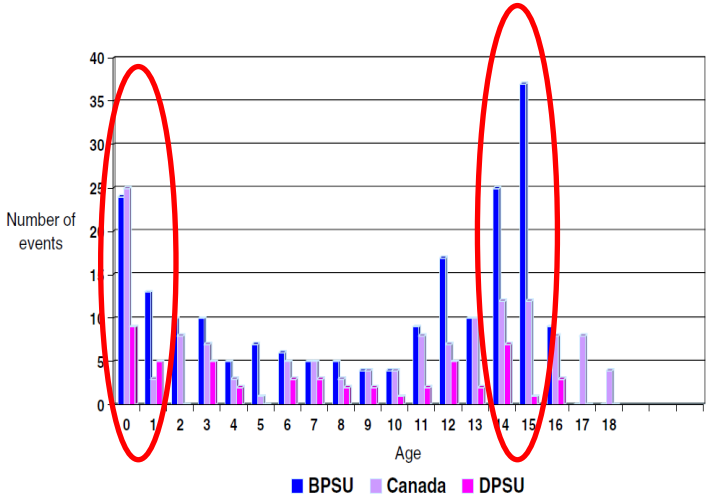
- I tassi di **morbilità e mortalità** nei bambini sono elevati (tasso di recidiva di trombosi dell'8,1%, un tasso di sindrome post-trombotica del 12,4% e un rischio di mortalità per TEV del 2,2%).

	Systemic thrombosis		Cerebral thrombosis[b]	
	Arterial	Venous	Arterial	Venous
≤28 days of life[a]	5.1/100,000 live births 2.4–6.8/1,000 NICU admissions	5.1/100,000 live births 2.4–6.8/1,000 NICU admissions	1/2,300–5,000 live births	0.6–12/10,000 live births
>28 days of life	0.2–0.3/100,000 person years	0.7–2/100,000 person years	1–2/100,000 person years	0.3–0.6/100,000 person years



PEDIATRICS Volume 149, number 3, March 2022:e2021054649

FIGURE 1
VTE rate over time (2001–2019) overall and by age group, Pediatric Health Information System.



L'aumento è dovuto principalmente a:

- **Maggiore consapevolezza e conoscenza del problema da parte degli operatori sanitari**
- **miglioramento delle metodiche per la diagnosi**
- **trattamento di pazienti critici e complessi**

La maggior parte dei casi di TEV viene diagnosticata nei bambini ospedalizzati e il 95% dei casi di TEV pediatrica è provocato:

- La presenza di un catetere venoso centrale (**CVC**) è il fattore di rischio più comune nei neonati e nei bambini
  - Circa due terzi dei casi di TEV nei bambini di età <2 anni sono associati ai CVC
  - Si stima che dal 25% al 75% dei casi di TEV nei bambini siano correlati ai CVC

- I bambini affetti **da patologie neoplastiche** e i bambini sottoposti a **chemioterapia** sono a rischio più elevato

- Anche le **comorbidità** (ad esempio infezioni/infiammazioni gravi, trombofilia, traumi o interventi chirurgici) e la sindrome da antifosfolipidi aumentano il rischio di TEV nei bambini

1. Andrew M *et al*, *Blood* 1994;83:1251–1257; 2. Chan AKC & Monagle P, *Hematology Am Soc Hematol Educ Program* 2012;1:439–443;
3. Monagle P *et al*, *Chest* 2012;141:e737S–e801S; 4. Chan A *et al*, *Thromb J* 2018;16:29; 5. Raffini L *et al*, *Pediatrics* 2011;127:e1326–e1332;
6. Sandoval JA *et al*, *J Vasc Surg* 2008;47:837–843

Hemostasis in the Pregnant Woman, the Placenta, the Fetus, and the Newborn Infant

Beth Boulden Warren, MD[1,2] Genevieve C. Moyer, MD[1,2] Marilyn J. Manco-Johnson, MD[1,2]

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DEVELOPMENTAL HEMOSTASIS

Il sistema emostatico neonatale è sia quantitativamente che qualitativamente dIverso da quello di un bambino più grande o di un adulto.

Il termine "**emostasi dello sviluppo**" è stato applicato al periodo di tempo in cui nel sistema emostatico neonatale esiste in un equilibrio in evoluzione di fattori pro e anticoagulanti.

In generale, **i neonati hanno concentrazioni più basse di molte proteine procoagulanti e anticoagulanti, il che li espone a un rischio maggiore di complicanze emorragiche e di complicanze trombotiche.**

Le differenze nel sistema emostatico sono amplificate nei neonati prematuri

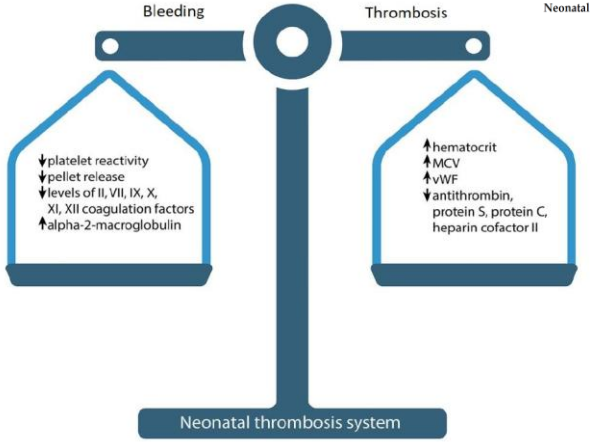
Nonostante i ridotti livelli di pro-coagulanti e i ridotti livelli di anticoagulanti, si ritiene che nel neonato sano esista un **equilibrio emostatico**, non incline all'emorragia né alla trombosi.

Tuttavia, l'equilibrio è delicato e può essere facilmente ribaltato in entrambe le direzioni

International Journal of Molecular Sciences MDPI

Review

The Hemostatic System in Newborns and the Risk of Neonatal Thrombosis



Hemostasis in the Very Young

Gili Kenet, MD[1,2] Assaf Arie Barg, MD[1,2] Ulrike Nowak-Göttl, MD, PhD[3]

Same in neonates	Reduced in neonates	Increased in neonates
Platelet count	Platelet function	Plasma levels of VWF level; VWF large multimers
Factor V	Plasma levels of vitamin K–dependent coagulation factors (II, VII, IX, X)	
Factor VIII	Fibrinogen function	
	Plasma levels of the natural anticoagulants: antithrombin, protein C and protein S	

Congeniti

- Mutazioni fattore V
- Mutazione della protrombina
- Aumento lipoproteina
- Iperomocisteinemia
- Mutazioni MTHFR
- Difetto proteina C
- Difetto proteina S
- Difetto ATIII
- Difetto cofattore eparinico II
- Drepanocitosi
- Disfibrinogenemia
- Dis/ipoplasminogenemia
- Omocistinuria
- Anomalie anatomiche
- Aumento fattore VIII
- Aumento fattore IX
- Riduzione fattore XII
- Deficit di ADAMTS 13

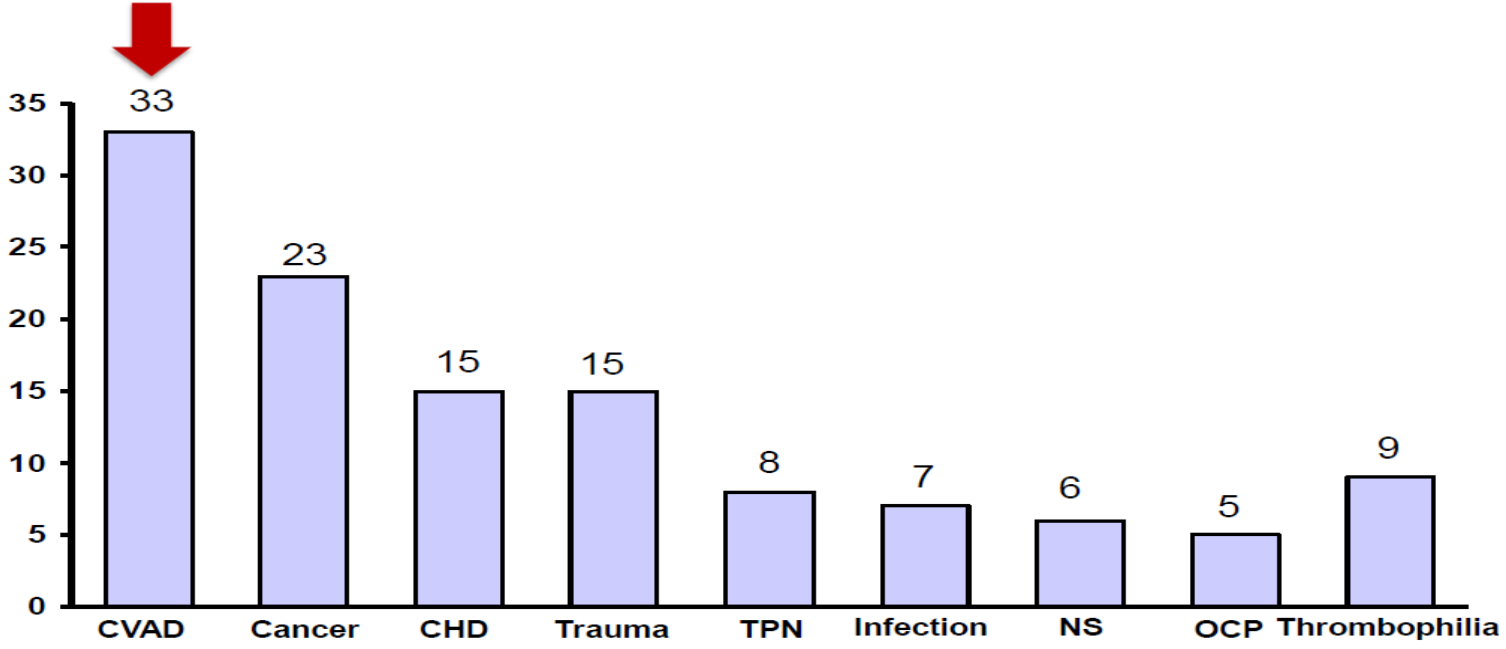
Acquisiti

- Cateteri venosi centrali
- Chirurgia, Trapianti d'organo
- Cardiopatie congenite corregibili chirurgicamente
- Immobilizzazione
- Infezioni
- Infiammazioni
- Sindrome nefrosica
- Terapia ormonale , gravidanza
- Vasculiti
- Aumento fattore VIII, IX, von Willebrand in condizioni di ipercoagulabilità
- Cardiopatie congenite
- CVC a lungo termine
- Diabete
- Lupus e Sindrome da ab antifosfolipidi
- Malformazioni vascolari
- Neoplasie
- Chemioterapia
- Trapianto di cellule staminale ematopoietiche
- Patologie renali
- Deficit di ADAMTS 13

Catheter-Associated Risk Factors for Neonatal Thrombosis	Risk Factors Associated with the Neonatal Condition	Risk Factors Associated with Maternal Condition
1. Central venous catheter 2. Parenteral nutrition 3. Blood transfusion 4. Intravenous medication administration 5. Catheter-associated infections 6. Femoral venous catheter	1. Lung Ventilation 2. Systemic viral infections and complications 3. Gestational age 4. ICU length of stay 5. Congenital heart defects 6. Sepsis 7. Emergency C-section 8. Preterm birth 9. Low Apgar score 10. Malignant neoplasms in the neonate 11. Male sex 12. Acute respiratory distress syndrome	1. Preeclampsia 2. Placental Insufficiency 3. Systemic inflammatory disorders 4. Gestational diabetes mellitus 5. Hereditary or acquired thrombophilia 6. Hypertension 7. Thrombocytopenia 8. Low ADAMTS-13 activity 9. High vWF level

Fenomeno multifattoriale

Fattori di rischio



Andrew M. et al. Blood; 1994

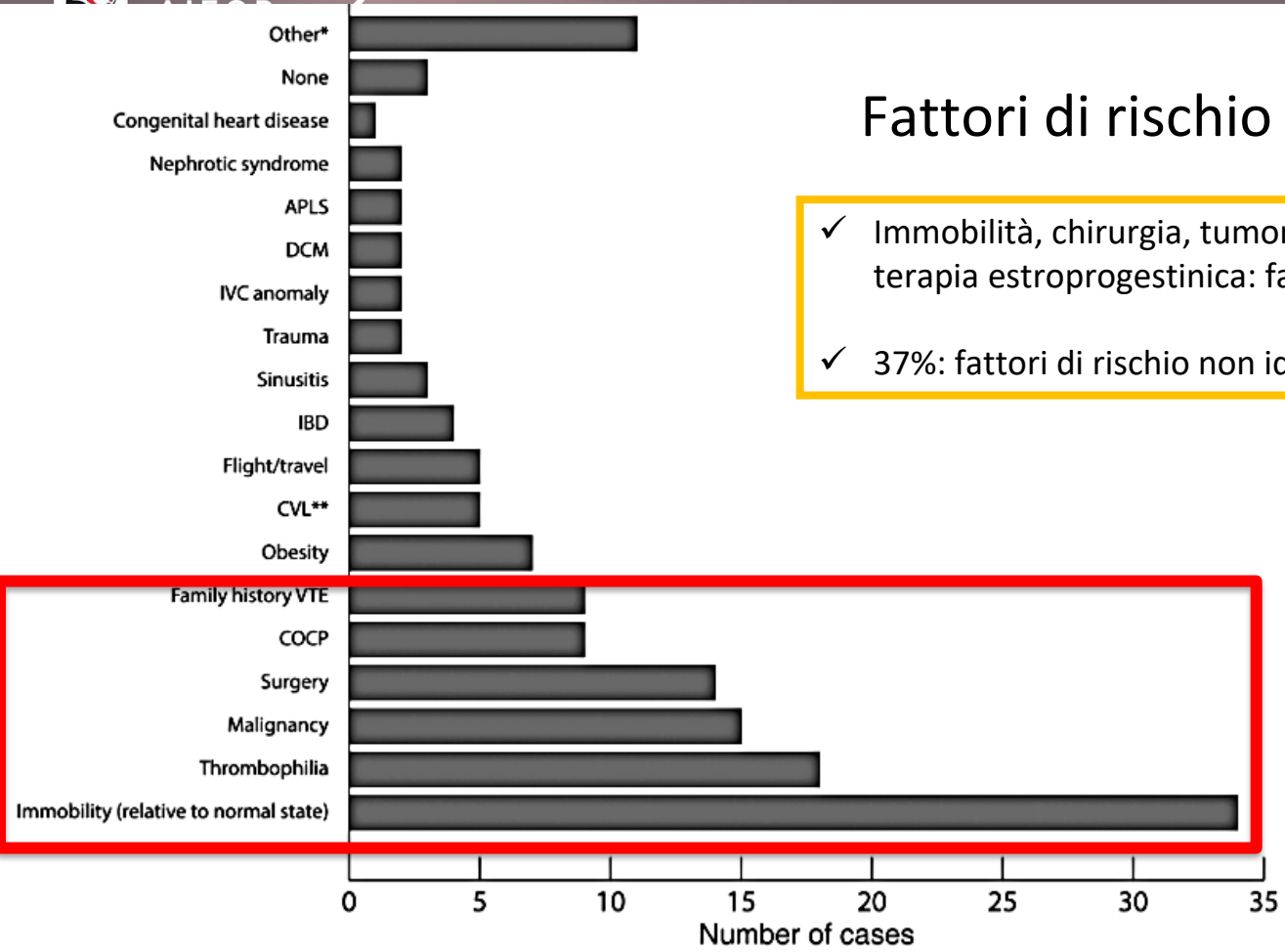
"High risk" groups

- CVC e neoplasia (incidenza 1-15%)
- CVC, ricovero in UTI e NPT (incidenza 18.3-26%)
- CVC in sede ombelicale nei neonati
- TVP nel contesto di trapianto di organi (fegato e rene)

Chalmers E, Thrombosis Research 2006

Fattori di rischio nell'adolescenza

- ✓ Immobilità, chirurgia, tumori, obesità, storia familiare, terapia estroprogestinica: fattori di rischio frequenti
- ✓ 37%: fattori di rischio non identificati



Biss , Arch Dis Child 2016

Le opzioni di trattamento per il TEV pediatrico includono

- **l'osservazione**

- la **terapia anticoagulante/antiaggregante** con eparina non frazionata (UFH), eparina a basso peso molecolare (LMWH), gli anticoagulanti orali , ASA, Clopidogrel.

- la **trombolisi** (farmacologica, farmacomeccanica o chirurgica).

A causa della scarsità di studi randomizzati e controllati condotti sui bambini con questi agenti, il dosaggio e la durata dell'anticoagulazione sono estrapolati dalle linee guida per gli adulti; non sono disponibili formulazioni pediatriche specifiche per l'età e tutti i farmaci della terapia standard sono utilizzati off-label.

Studi clinici standard of care

Randomised trials of anticoagulation in children for treatment of prevention of venous thrombosis.

Study title (therapeutic agents)	Study purpose	Centres involved	Total number children recruited/ target recruitment	Study outcome
REVIVE (Reviparin)	Primary prophylaxis CVL	36 centres over 2 years	78/352 patients (20%)	Closed early due to slow recruitment
Protekt (Reviparin)	VTE treatment	20 centres over < 2 years	186/600 patients (31%)	Closed early due to slow recruitment
Fontan (UFH/warfarin vs aspirin)	Primary prophylaxis post Fontan surgery	6 centres over 5 years	111/222 (50%) ? Power calculations NB 242 surgeries	Closed due to slow recruitment
PAARKA (antithrombin)	Primary prophylaxis in ALL CVAD and Asparaginase	10 centres over 2 years	109	Not powered for efficacy
KidsDott (LMWH/warfarin or fondaparinux)	6 vs 12 weeks treatment for secondary VTE in children	> 10 years. Up to 45 centres now	300 patients of target 850	

Monagle, Thromb Res 2019 Jan;173:186-90

Table 5
Treatment with alternative anticoagulants in pediatric practice

	Medical Condition	Medication Options	Pros	Cons
Required	Heparin-induced thrombocytopenia	Argatroban Bivalirudin Fondaparinux	Pediatric and adult clinical trial data available	Limited familiarity No antidotes
Recommended	Extensive VTE	Bivalirudin	Rapid clot resolution No need for laboratory monitoring	Limited familiarity
	Typical VTE	Fondaparinux	Once-daily dosing No risk for heparin-induced thrombocytopenia No impact on bone mineralization	Limited familiarity No antidote
Suggested	Typical VTE in hospitalized patients	Bivalirudin	Rapid clot resolution No need for laboratory monitoring	Limited familiarity
Not recommended	All situations	Direct oral anticoagulants	N/A	No pediatric data on safety/efficacy

Abbreviations: N/A, not applicable; VTE, venous thromboembolism.

"the only clear indication for the use of one of these anticoagulants is the presence or suspicion of HIT, which requires avoidance of heparin and LMWH and for which VKA is not appropriate at least for acute management. The only agent studied in children specifically for this indication is argatroban and it is thus the agent of choice for children with HIT."

Table 2. Common anticoagulant therapies for use in pediatric VTE[1,14,15]

Drug name	Mechanism of action	Pharmacokinetic properties and dosing	Therapeutic monitoring (based on adult ranges)
UFH	Binds to AT and potentiates anticoagulant activity. The heparin-AT complex inactivates factors IIa (thrombin), Xa, XIa, and XIIa.	Half-life 0.5-2.5 h Route: Continuous infusion Initial dose: Age <12 mo: bolus 75 U/kg followed by 28 U/kg/h Age >1-<12 y: bolus 75 U/kg followed by 20 U/kg/h Age >12 y: bolus 80 U/kg followed by 18 U/kg/h	Target range: aPTT: 1.5-2.5 times control OR UFH anti-Xa level: 0.3-0.7 U/mL
Enoxaparin (LMWH)	Binds to AT and potentiates anticoagulant activity. Has a reduced inhibitory activity against factor IIa (thrombin) relative to factor Xa.	Half-life 3-6 h, renal clearance Route: Subcutaneous injection Initial dose: Age <2 mo: 1.5-1.7 mg/kg q12 h Age >2 mo: 1 mg/kg q12 h	Target range: Enoxaparin anti-Xa peak: 0.5-1 U/mL (drawn 3-4 h after third dose)
Dalteparin (LMWH)	Similar to enoxaparin.	Half-life 3-6 h, renal clearance Route: Subcutaneous injection Initial dose: Age 1 mo-<2 y: 150 IU/kg q12 h Age 2-<8 y: 125 IU/kg q12 h Age 8-<17 y: 100 IU/kg q12 h	Target range: Dalteparin anti-Xa peak: 0.5-1 U/mL (drawn 3-4 h after third dose)
Fondaparinux	Synthetic pentasaccharide that binds AT and enhances inactivation of factor Xa. No inhibitory activity against factor IIa.	Half-life 17 h Route: Subcutaneous injection Initial dose: Age >1 y: 0.1 mg/kg q24 h	Target range: Fondaparinux anti-Xa 0.5-1 mg/L (drawn 3-4 h after third dose)
Warfarin	Interferes with the cyclic conversion of vitamin K through the inhibition of vitamin K epoxide reductase. Resultant decrease in the posttranslational γ-carboxylation of vitamin K–dependent clotting factors II, VII, IX, and X and anticoagulants protein C and S.	Half-life 20-60 h Route: Oral Loading dose: 0.2 mg/kg × 1 (if INR <1.3) (maximum, 10 mg) Check INR daily (days 2-4) and if the INR is: 1.1-1.3: Repeat loading dose 1.4-1.9: 50% of loading dose 2.0-3.0: 50% of loading dose 3.1-3.5: 25% of loading dose >3.5: Hold until INR <3.5, restart at 50% loading dose	Target range: INR: 2-3

Anticoagulanti tradizionali

- PK e PD poco prevedibile (ENF)
- dipendenza dai livelli di ATIII (eparine)
- Avvio attività ritardata e lunga persistenza (AVK)
- Necessità del monitoraggio ± costante (AVK)
- Mancanza di studi e autorizzazione per l'età pediatrica

- Somministrazione parenterale (Eparina)
- **Rischio di tossicità epatica e di deterioramento osseo nei bambini in terapia a lungo termine con LMWH.**
- **AVK disponibili solo in pillole**
- **Numerose interazioni con farmaci ed alimenti (AVK)**

Anticoagulante ideale

1. **PK e PD prevedibile**
2. **Indipendenza dalla ATIII**
3. **Somministrazione orale**
4. **Efficacia e sicurezza comparabili o superiore**
5. **Poche interazioni con farmaci ed alimenti, induttori/ inibitori dell'isoenzima CYP3A4 o della glicoproteina P (P-gp).**
6. **Ampia finestra terapeutica**
7. **No monitoraggio (idealmente)**
8. **Studi Pediatrici (Pediatric Investigation Plan)**

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Direct Oral Anticoagulants: Overcoming the Challenges of Managing Venous Thromboembolism in Children

Christoph Male, MD[1], Paul Monagle, MD[2,3], Manuela Albisetti, MD[4], Leonardo R. Brandão, MD[5,6], and Guy Young, MD[7]

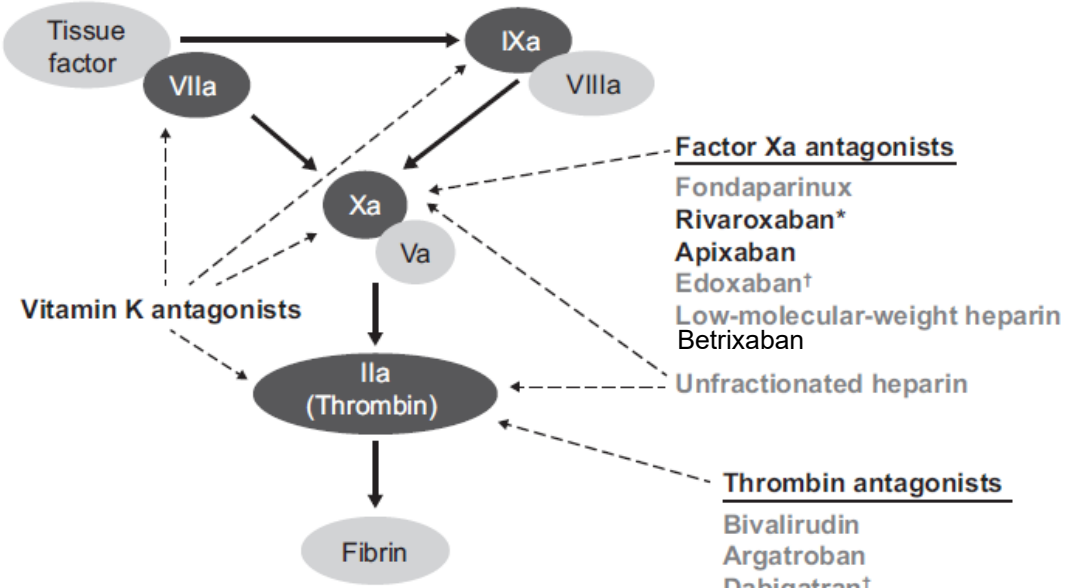


Figure 2. Anticoagulant drug targets. *Requires ≥5 days of parenteral anticoagulant administration before initial use (pediatric patients only). †Requires ≥5 days of parenteral anticoagulant administration before initial use. Continuous lines denote activation; dashed lines denote inhibition. *Gray text* denotes parenteral administration.

Table 1. Completed DOAC phase 2b/3 pediatric thrombosis trials

Trial/phase	Indication	Age group	Comparator/SOC agent	Initial treatment	No. of children treated	Outcomes	Key observations
Rivaroxaban*							
Einstein Jr phase 3[16] (NCT02234843)	VTE treatment and prevention of recurrent VTE	From birth to age <18 y	SOC (UFH, LMWH, fondaparinux, and VKA)	≥5 d of SOC anticoagulant	500	Rivaroxaban vs SOC anticoagulant Efficacy: symptomatic recurrent VTE: 4 (1%) vs 5 (3%); HR, 0.4; 95% CI, 0.11-1.41. Safety: major bleeding/CRNMB: 10 (3%) (all nonmajor) vs 3 (2%) (1 nonmajor and 1 CRNMB); HR, 1.58; 95% CI, 0.51-6.27.	Patients received SOC anticoagulant for 5-9 d before starting rivaroxaban. CVC-provoked VTE represented 25% of study population. Infants and younger children were underrepresented (37 of 335 [11%]). Subanalysis of special populations reported: CVC, infection-related CSVT, and cancer.
UNIVERSE phase 3[17] (NCT02846532)	Thromboprophylaxis for children after Fontan procedure	2-8 y	Part A: none Part B: aspirin	NA	112	Part B: rivaroxaban vs aspirin Efficacy: event rate, 2 (3%) vs 3 (9%) Safety: major bleeding, 1 (2%) in rivaroxaban CRNMB: 4 (6%) vs 3 (9%)	Shorter duration between Fontan surgery and the first study drug dose in the aspirin group (mean, 37 d) than in the rivaroxaban group (mean, 45 d). Not powered to test a formal hypothesis for efficacy.
Apixaban							
PREVAPIX-ALL phase 3[18,19] (NCT02369653)	Thromboprophylaxis during induction chemotherapy for ALL/LL	1-18 y	None	NA	512	Apixaban vs SOC anticoagulant† Efficacy: VTE occurrence, 31 (12.1%) vs 45 (17.6%); RR, 0.69 (0.45-1.05); 1-sided $P = .04$ Safety: major bleeding, 2 in each arm; CRNMB, 11 vs 3 events	Apixaban was not shown to be efficacious in the primary analysis but decreased VTE risk for patients with obesity The study design was powered to demonstrate the benefit of anticoagulant prophylaxis of CVL-associated thrombosis for children with ALL/LL.
SAXOPHONE phase 2[20] (NCT03395639)	Thromboprophylaxis for cardiac disease	From 29 d to <18 y of age	SOC anticoagulant (LMWH or VKA)	NA	192	Apixaban vs SOC anticoagulant† Efficacy: no thromboembolic (TE) events in either arm. Safety: 1 had 2 primary safety events (IR, 1.8/100 P-Y) vs 3 with 4 events (IR, 6.8/100 P-Y).	Bone density and quality of life were measured for 12 mo but not reported.
Edoxaban							
ENOBLE phase 3[21] NCT02798471	Thromboprophylaxis in cardiac disease	38 wk to <18 y	SOC (UFH, LMWH, VKA)	NA	168	Edoxaban vs SOC anticoagulant Efficacy: none vs 2 TE events in SOC (1.7%) Safety: major, none; CRNMB, 1 in each group. Extension arm (n = 147, all on edoxaban) Efficacy: 4 TE (2.8%; 2 strokes and 2 coronary artery thrombosis or myocardial infarction) Safety: major, none; CRNMB, 1 (0.7%).	Compliance with investigational drug was measured and was 94% in the edoxaban group in the main treatment period but reduced to 55% in the extension study.
HOKUSAI-Jr phase 3[14] (NCT02798471)	VTE treatment	From 38 wk to <18 y of age	SOC (UFH, LMWH, fondaparinux, and VKA)	≥5 d of parenteral treatment	290	Not available	Study completed; study results not published.
Dabigatran*							
DIVERSITY phase 2b/3[22] (NCT01895777)	VTE treatment and prevention of recurrent VTE	From birth to age 17 y	SOC anticoagulant (LMWH, VKA, or fondaparinux)	≥5 d of parenteral treatment	260	Dabigatran vs SOC anticoagulant Efficacy: Composite outcome: 81 (46%) vs 38 (42%); $P = .001$ Safety: on treatment bleeding, 38/176 (22%) vs 22/90 (24%); HR, 1·15; 95% CI, 0·68-1·94; $P = .61$ Major bleeding: 4/176 (2%) vs 2/90 (2%); HR, 0·94; 95% CI, 0·17-5·16; $P = .95$	Patients received 5-21 d of SOC anticoagulant before starting dabigatran. Dabigatran drug levels were monitored to determine appropriate dose. 17 of 176 (~10%) of the population prematurely discontinued dabigatran because of failure to achieve target dabigatran plasma concentration after 1 dose adjustment allowed per protocol. Infants and younger children were underrepresented (22/176 [12.5%]). Subanalysis of special populations: CVC, CSVT, and thrombophilia from birth to <2 y of age.
DIVERSITY phase 3[6] NCT 02197416	VTE secondary prevention (single arm)	From birth to <18 y of age	NA	NA	203	Efficacy: 1% (2/203) recurrence Safety: major bleeding, 1.5% (3/203). CRNMB, 1% (2/203).	Study reported development of posthrombotic syndrome in 2 of 162 participants (1.2%) with DVT- or CVC-related thrombosis.

New Anticoagulants in Neonates, Children Adolescents

Susan Halimeh[1] Christoph Male[2] Ulrike Nowak-Goettl[3]

Hamostaseologie 2022;42:123–130.

Thrombotic events are an increasing challenge in pediatrics. Standard-of-care anticoagulants for pediatric thrombosis have several disadvantages which could be overcome by using direct oral anticoagulants (DOACs). Until recently, there was not enough evidence from clinical trials to recommend for or against the use of any of the four DOACs in children with thrombosis. In this literature review, we looked at the latest clinical trials in this field. On clinicaltrials.gov, we found **13 current studies with published results**.

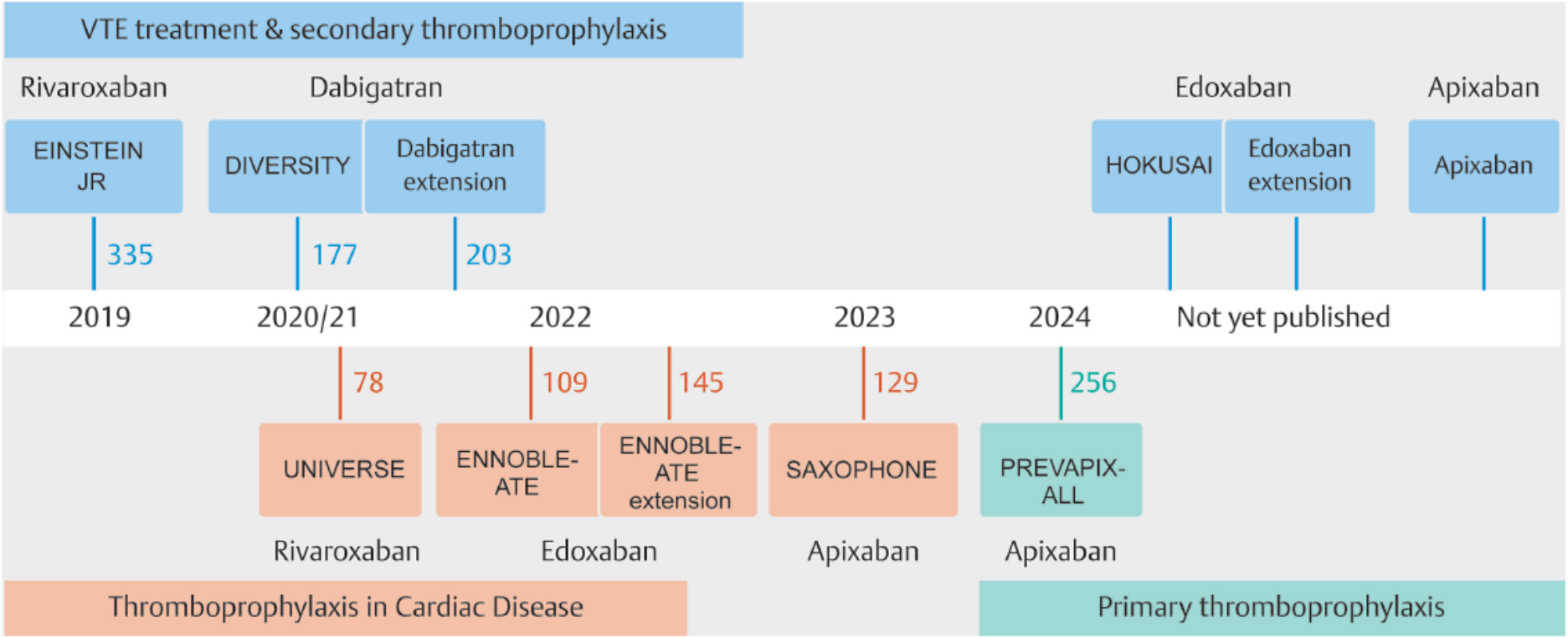
For two of the four DOACs, namely dabigatran and rivaroxaban, we found successful phase III studies which led to the approval for the use in children. The results of these pivotal phase III studies allow to finally recommend rivaroxaban and dabigatran for the prophylaxis and treatment of thrombotic events in children.

Dabigatran etexilate for the treatment of acute venous thromboembolism in children (DIVERSITY): a randomised, controlled, open-label, phase 2b/3, non-inferiority trial

Jacqueline Halton, Leonardo R Brandão, Matteo Luciani, Lisa Bomgaars, Elizabeth Chalmers, Lesley G Mitchell, Ildar Nurmeev, Anjali Sharathkumar, Pavel Svirin, Kirill Gorbatikov, Igor Tartakovsky, Monika Simetzberger, Fenglei Huang, Zhichao Sun, Jörg Kreuzer, Savion Gropper, Paul Reilly, Martina Brueckmann, Manuela Albisetti on behalf of the DIVERSITY Trial Investigators*

Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial

Christoph Male, Anthonie W A Lensing, Joseph S Palumbo, Riten Kumar, Ildar Nurmeev, Kerry Hege, Damien Bonnet, Philip Connor, Hélène L Hooimeijer, Marcela Torres, Anthony K C Chan, Gili Kenet, Susanne Holzhauer, Amparo Santamaría, Pascal Amedro, Elizabeth Chalmers, Paolo Simioni, Rukhmi V Bhat, Donald L Yee, Olga Lvova, Jan Beyer-Westendorf, Tina T Biss, Ida Martinelli, Paola Saracco, Marjolein Peters, Krisztián Kállay, Cynthia A Gauger, M Patricia Massicotte, Guy Young, Akos F Pap, Madhurima Majumder, William T Smith, Jürgen F Heubach*, Scott D Berkowitz, Kirstin Thelen, Dagmar Kubitza, Mark Crowther, Martin H Prins, Paul Monagle, for the EINSTEIN-Jr Phase 3 Investigators†


VTE treatment & secondary thromboprophylaxis
Rivaroxaban
Dabigatran
Edoxaban
Apixaban
EINSTEIN JR
DIVERSITY
Dabigatran extension
HOKUSAI
Edoxaban extension
Apixaban
335
177
203
2019
2020/21
2022
2023
2024
Not yet published
78
109
145
129
256
UNIVERSE
ENNOBLE-ATE
ENNOBLE-ATE extension
SAXOPHONE
PREVAPIX-ALL
Rivaroxaban
Edoxaban
Apixaban
Apixaban
Thromboprophylaxis in Cardiac Disease
Primary thromboprophylaxis

Pharmacologic properties of DOAC agents

Variable	Dabigatran etexilate	Rivaroxaban	Apixaban*	Edoxaban*
Prodrug	Yes	No	No	No
Mechanism of action	Direct IIa inhibitor; inhibits clot-bound and free thrombin	Direct Xa inhibitor; inhibits clot-bound and free Xa	Direct Xa inhibitor; inhibits clot-bound and free Xa	Direct Xa inhibitor; inhibits clot-bound and free Xa
Time to onset of action and peak concentration	22 min-4.5 h	1-3 h	1-2 h	1-2 h
Oral bioavailability	3%-7%	66% (fasting); 80%-100% (with food)	50%; prolonged absorption	62%
Half-life	12-17 h	5-9 h	8-12 h	10-14 h
Plasma protein binding	92%-95%	87%	99%	55%
Metabolism	Conjugation, prodrug is P-gp substrate	CYP3A4/5, CYP2J2, hydrolysis, and P-gp substrate	CYP3A4 (major), CYP1A2, 2C8, 2C19, 2J2 (all minor), and P-gp substrate	Conjugation, hydrolysis, CYP3A4 (all minor), and P-gp substrate
Elimination	Renal (80%)	Renal (66%), fecal (7%), and unchanged (36%)	Renal (27%), fecal (56%), and biliary (minimal)	Renal (50%), metabolism and biliary/intestinal excretion (50%)
Absorption	Lower gastric region and duodenum	Primarily proximal small intestine and some gastric absorption	Primarily proximal small intestine and some gastric absorption	Primarily proximal small intestine and some gastric absorption
Antidote	Idarucizumab*	Andexanet-α*	Andexanet-α*	Andexanet-α*
Other options for overdose	Hemodialysis and gastric lavage with charcoal (within 2 h of consumption)	PCC (3 or 4 factor)	PCC (3 or 4 factor)	PCC (3 or 4 factor) and TXA
Food interaction	None	None	None	None
Drug interactions that increase drug levels	Amiodarone, quinidine, azole antifungals (eg, ketoconazole), and ritonavir proton pump inhibitor	Azole antifungals (eg, ketoconazole), all HIV protease inhibitors (eg, ritonavir), and clarithromycin	Azole antifungals (eg, ketoconazole), all HIV protease inhibitors (eg, ritonavir), and clarithromycin	Azole antifungals (eg, ketoconazole), all HIV protease inhibitors (eg, ritonavir), and clarithromycin
Drug interactions that decrease drug levels	Rifampin, phenytoin, carbamazepine, and St. John's wort	Anticonvulsants (eg, phenytoin and carbamazepine), and rifampin	Anticonvulsants (phenytoin and carbamazepine), and rifampin	Anticonvulsants (phenytoin and carbamazepine), and rifampin
Laboratory measurement to assess anticoagulant effect†	aPTT, TCT, and dilute TCT	PT/INR and anti–factor Xa assay (for Xa inhibitor)	PT/INR [minimal effect] and anti–factor Xa assay (for Xa inhibitor)	Anti–factor Xa assay (for Xa inhibitor)
Available formulations	Capsules, pellets (sprinkles), and oral solution‡	Tablet and oral solution	Tablet and oral solution	Tablet and oral solution

Table 3. Published rivaroxaban dosing strategy in Einstein Jr and UNIVERSE clinical trials

Einstein Jr phase 3 (VTE treatment) Body weight–adjusted rivaroxaban regimens in a 20-mg equivalent dose			UNIVERSE phase 3 (post-Fontan thromboprophylaxis) Body weight–adjusted rivaroxaban regimens in a 10-mg equivalent dose (mg or mL*)		
Body weight	**Dose**	**Total**	**Body weight**	**Dose**	**Total**
2.6 to <3 kg	0.8 mg per dose TID	2.4 mg	7 to <8 kg	1.1 mg per dose BID	2.2 mg
3 to <4 kg	0.9 mg per dose TID	2.7 mg	8 to <10 kg	1.6 mg per dose BID	3.2 mg
4 to <5 kg	1.4 mg per dose TID	4.2 mg	10 to <12 kg	1.7 mg per dose BID	3.4 mg
5 to <7 kg	1.6 mg per dose TID	4.8 mg	12 to <20 kg	2 mg per dose BID	4.0 mg
7 to <8 kg	1.8 mg per dose TID	5.4 mg	20 to <30 kg	2.5 mg per dose BID	5.0 mg
8 to <9 kg	2.4 mg per dose TID	7.2 mg			
9 to <10 kg	2.8 mg per dose TID	8.4 mg			
10 to <12 kg	3 mg per dose TID	9 mg			
12 to <30 kg	5 mg per dose BID	10 mg			
30 to <50 kg	15 mg per dose OD	15 mg			
≥50 kg	20 mg per dose OD	20 mg			

Dosing nomogram (starting doses)

A — Dabigatran etexilate capsules - 50, 75, 110 and 150 mg

Initial dose	Single Dose [mg]		Weight [kg]												
	Age [completed years]	Age [completed months]	9 to <11	11 to <13	13 to <16	16 to <21	21 to <26	26 to <31	31 to <41	41 to <51	51 to <61	61 to <71	71 to <81	81 to <91	≥ 91
	8	96		100	100	125	150	150	185	220	260	300	300		
	9	108			100	125	150	150	185	220	260	300	300		
	10	120			100	125	150	150	185	220	260	300	300	330	330
	11	132				125	150	150	185	220	260	300	300	330	330
	12	144				125	150	150	185	220	260	300	300	330	330
	13	156				125	150	150	185	220	260	300	300	330	330
	14	168					150	150	185	220	260	300	300	330	330
	15	180					150	150	185	220	260	300	300	330	330
	16	192						150	185	220	260	300	300	330	330
	17	204						150	185	220	260	300	300	330	330

Doses > 330 mg BID capped to 330 mg BID

100 2×50mg capsules
125 50mg + 75mg capsules
150 150mg or 2×75mg capsules
185 75mg + 110mg capsules
220 2×110mg capsules
260 110+150mg or 110+2×75mg capsules
300 2×150mg or 4x75mg capsules
330 3×110mg capsules

Age- and weight-adjusted starting doses using capsules

B — Dabigatran etexilate pellets

Initial dose	Single Dose [mg]		Weight [kg]																
	Age [completed years]	Age [completed months]	2.5 to < 3	3 to < 4	4 to < 5	5 to < 7	7 to < 9	9 to < 11	11 to < 13	13 to < 16	16 to < 21	21 to < 26	26 to < 31	31 to < 41	41 to < 51	51 to < 61	61 to < 71	71 to < 81	81 to < 91	≥ 91
	<0.08	<1				20														
	0.08	1			20	20														
	0.17	2			20	20														
	0.25	3		20	20	30	30													
	0.33	4	20	20	20	30	40													
	0.42	5		20	20	30	40	40												
	0.50	6			30	30	40	50												
	0.58	7			30	30	40	50												
	0.67	8			30	40	40	50	60											
	0.75	9			30	40	50	50	60											
	0.83	10				40	50	50	70	70										
	0.92	11				40	50	60	70	80										
	1	12				40	50	60	70	80	90									
	1.5	18				50	50	70	80	90	90	110								
	2	24					60	70	80	100	100	140								
	2.5	30					60	70	90	100	110	140	150	160						
	3	36					60	70	90	100	110	140	150	160						
	4	48						80	90	100	110	140	150	160	220					
	5	60						80	90	100	110	140	150	160	220	260				
	6	72						80	90	100	110	140	150	160	220	260	300			
	7	84							90	100	110	150	150	160	220	260	300	300		
	8	96							90	100	110	150	150	160	220	260	300	300		
	9	108								100	110	150	150	160	220	260	300	300		
	10	120								100	110	150	150	160	220	260	300	300	330	330
	11	132									110	150	150	160	220	260	300	300	330	330

Doses > 330 mg BID capped to 330 mg BID

20 20 mg stick pack
30 30 mg stick pack
40 40 mg stick pack
50 50 mg stick pack
60 2×30 mg stick packs
70 30+40 mg stick packs
80 2×40 mg stick packs
90 40+50 mg stick packs
100 2×50 mg stick pack
110 110 mg stick pack
140 30+110 mg stick packs
150 150 mg stick packs
160 110+50 mg stick pack
220 2×110 mg stick packs
260 110+150 mg stick pack
300 150+150 mg stick pack
330 3×110 mg stick pack

Age- and weight-adjusted starting doses using pellets

C — Dabigatran etexilate OLF - 6.25 mg per mL

Initial dose	Single Dose [mg]		Weight [kg]										
	Age [completed years]	Age [completed months]	2.5 <3	3 to <4	4 to <5	5 to <7	7 to <9	9 to <11	11 to <13	13 to <16	16 to <21	21 to <26	26 to <31
	<0.08	<1	12.50	12.50	12.50	18.75							
	0.08	1	12.50	12.50	18.75	18.75							
	0.17	2	12.50	18.75	18.75	25.00							
	0.25	3	12.50	18.75	25.00	25.00	31.25						
	0.33	4	18.75	18.75	25.00	31.25	37.50						
	0.42	5		18.75	25.00	31.25	37.50	43.75					
	0.50	6			25.00	31.25	43.75	43.75					
	0.58	7			25.00	31.25	43.75	50.00					
	0.67	8			31.25	37.50	43.75	50.00	62.50				
	0.75	9			31.25	37.50	43.75	56.25	62.50				
	0.83	10				37.50	50.00	56.25	62.50	75.00			
	0.92	11				43.75	50.00	56.25	68.75	75.00			

12.50 2 mL
18.75 3 mL
25.00 4 mL
31.25 5 mL
37.50 6 mL
43.75 7 mL
50.00 8 mL
56.25 9 mL
62.50 10 mL
68.75 11 mL
75.00 12 mL

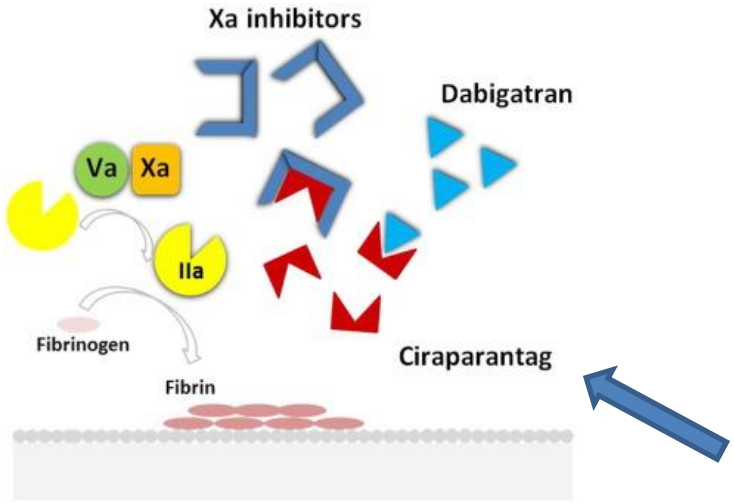
Age- and weight-adjusted starting doses using OLF

Review Article

Current status of oral anticoagulant reversal strategies: a review

Aranyak Rawal[1], Devarshi Ardeshna[2], Sheharyar Minhas[3], Brandon Cave[4], Uzoma Ibeguogu[5], Rami Khouzam[5]

Ann Transl Med 2019;7(17):411



Conclusions

Since the emergence of DOACs and the significant increase in their use, there has become a greater need for management of bleeding attributed to their use. For direct thrombin inhibitors reversal and management of acute bleeding is clear. **Idarucizumab** provides a targeted and effective reversal of anticoagulation and allows for rapid return to hemostasis.

The management of factor Xa inhibitors, however, is not as straightforward due to the emergence of routine off-label use of PCC.

Andexanet alfa is a decoy receptor that prevents native factor Xa from binding to factor Xa inhibitors and is the recommended first line therapy for management of factor Xa inhibitor related bleeding. However, its broad utilization may be limited by its cost and the lack of comparator data with PCC.

PCCs are recommended when andexanet alfa are not available and may be an effective modality for many patients; however, they do not provide uniform reversal of bleeding.

Factor VIIa and aPCCs show promising *in-vitro* data but more clinical data is needed, and they remain recommended only when PCCs fail to control bleeding.

Ciraparantag is a new molecular agent for factor Xa inhibitors and dabigatran that is undergoing further trials and may lead to more promising and clear directions in the future.

A review of the perioperative management of direct oral anticoagulants for pediatric anesthesiologists

Kara Furman[1] | Andrew Giustini[2] | Joshua Branstetter[3] | Gary Woods[4] | Laura A. Downey[5]

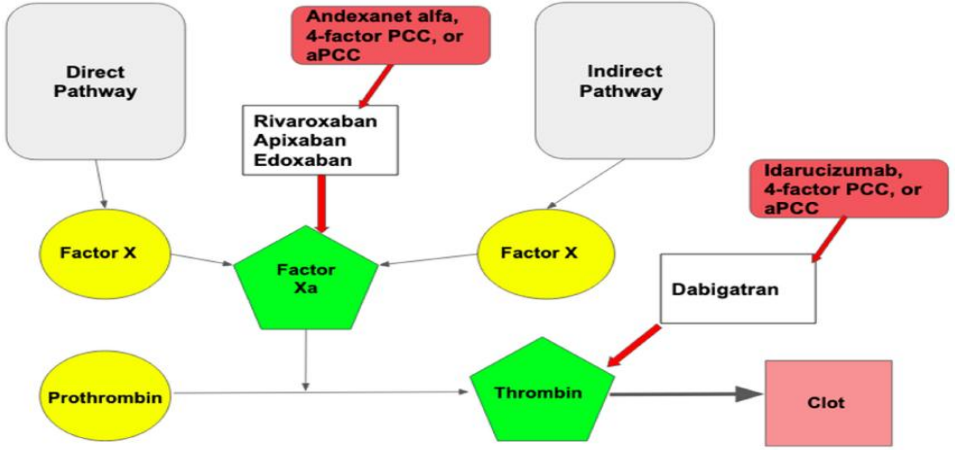
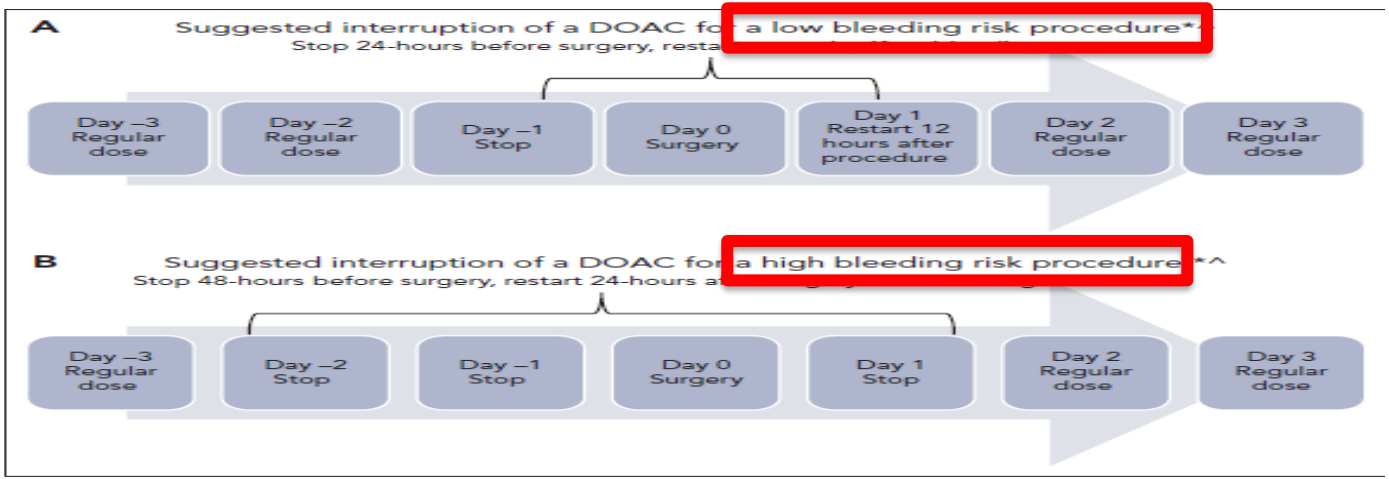


FIGURE 1 Mechanisms of action of direct oral anticoagulants used in pediatrics. Red arrows denote inhibition.



CLINICAL GUIDELINES

blood advances

American Society of Hematology/International Society on Thrombosis and Haemostasis 2024 updated guidelines for treatment of venous thromboembolism in pediatric patients

Direct Oral Anticoagulants

Recommendations comparing use of DOACS *(Dabigatran or Rivaroxaban)* to standard of care anticoagulants *(LMWH, VKA, UFH, Fondaparinux)* for pediatric patients with VTE.

Patient groups/factors in which a DOAC should **NOT** be used or used **with great caution**:

- gut absorption issues, chronic or temporary
- recent surgery
- liver disease
- kidney disease (GFR < 30 mL/min) severe enough to cause a coagulopathy
- anti-phospholipid syndrome
- pre-term neonates
- active cancer

DOAC: *Direct Oral Anticoagulants* ***LMHW:*** *Low molecular weight heparin* ***VKA:*** *Vitamin K Antagonist* ***UFH:*** *Unfractionated heparin*

Thrombosis Research 195 (2020) 243–249

Contents lists available at ScienceDirect

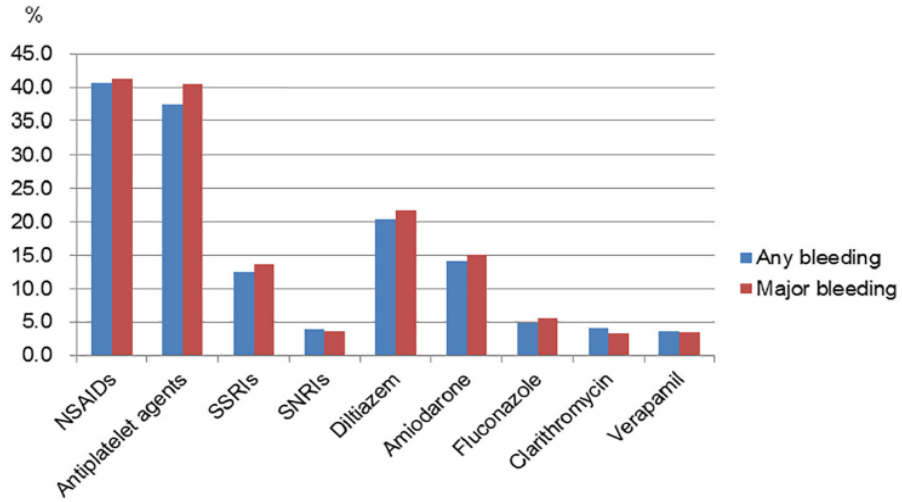
Thrombosis Research

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

Full Length Article

The increased risk of bleeding due to drug-drug interactions in patients administered direct oral anticoagulants

Ji Yun Lee[a], Il-Young Oh[a], Ju-Hyeon Lee[a], Sang-Young Kim[b], Seong So Hyeon-Jong Yang[d], Yang-Ki Kim[c,*], Soo-Mee Bang[a,*]



NSAIDs, non-steroidal anti-inflammatory drugs ; SSRIs, selective serotonin reuptake inhibitors; SNRIs serotonin-norepinephrine reuptake inhibitors

Fig. 1. The proportions of patients exposed to interactive drugs to direct oral anticoagulants in any or major bleeding events.

Table 1 Approved and Targeted Indications of Direct-Acting Oral Anticoagulants in Pediatric Patients

Medication	VTE treatment and secondary prevention	VTE prevention	Cardiac/arterial TE prevention
Dabigatran	NCT00844415, NCT01083732, NCT02223260[13-15]	NA	NA
	DIVERSITY: NCT01895777[16,17]		
	NCT02197416[18,19]		
Rivaroxaban	EINSTEIN-Jr: NCT01145859[20,21]	NA	UNIVERSE (following Fontan procedure): NCT02846532[29,30]
	NCT01684423, NCT02309411, NCT02564718[22]		
	NCT02234843[23-25]		
	EINSTEIN-Jr CVT: NCT02234843[27]		
	EINSTEIN-Jr CVC-VTE: NCT02234843[28]		
Apixaban	NCT02464969[31,a]	PREVAPIX-ALL (ALL/lymphoblastic lymphoma, CVC): NCT02369653[32,33,a]	SAXOPHONE (various congenital and acquired cardiac diseases): NCT02981472[34,35,a]
Edoxaban	NCT02303431[36,a]	NA	ENNOBLE-ATE (various cardiac diseases): NCT03395639[38,39,a]
	Hokusai: NCT02798471[37,a]		
Betrixaban	NA	Risk for VTE recurrence or presence of CVAD: NCT03346083[40,a]	NA
		Preterm/term neonates with UVC or UAC: EMEA-001834-PIP02-16[41,a]	

Abbreviations: ALL, acute lymphoblastic leukemia; CVAD, central venous access device; CVC, central venous catheter; NA, not applicable; TE, thromboembolism; UAC, umbilical arterial catheter; UVC, umbilical venous catheter; VTE, venous thromboembolism.
[a]Ongoing clinical trial.

IL PERCORSO AUTORIZZATIVO IN ITALIA

FARMACO	EMA	AIFA (Cnn)	GU (Cnn)	INDICAZIONI	ANTIDOTO
DABIGATRAN	13/11/2020	30/03/2021	12/04/2021	Trattamento di episodi tromboembolici venosi (TEV) e prevenzione di TEV ricorrente in pazienti pediatrici dalla nascita a meno di 18 anni di età.	SI[1]
RIVAROXABAN	13/11/2020	30/03/2021	12/04/2021	Trattamento del tromboembolismo venoso (TEV) e prevenzione delle recidive di TEV nei neonati a termine, nei lattanti e bambini piccoli, nei bambini e negli adolescenti di eta' inferiore a diciotto anni dopo almeno cinque giorni di trattamento anticoagulante parenterale iniziale.	SI[2]

ANTIDOTI

	EMA	AIFA C(nn)	GU C(nn)	AIFA (H)	GU (H)
1: IDARUCIZUMAB:	25/09/2015	15/12/2016	23/02/2016	10/02/2017	10/02/2017
2: ANDEXANET	26/04/2019	20/06/2019	8/07/2019		

GAZZETTA UFFICIALE
DELLA REPUBBLICA ITALIANA
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Serie Generale n. 223 del 23-9-2022

Le nuove indicazioni terapeutiche del medicinale rivaroxaban (rivaroxaban):

rivaroxaban" 15 mg compresse:

trattamento del tromboembolismo venoso (TEV) e prevenzione delle recidive di TEV nei bambini e negli adolescenti di eta' inferiore a diciotto anni e peso compreso tra 30 kg e 50 kg dopo almeno cinque giorni di trattamento anticoagulante parenterale iniziale;

rivaroxaban" 20 mg compresse:

trattamento del tromboembolismo venoso (TEV) e prevenzione delle recidive di TEV nei bambini e negli adolescenti di eta' inferiore a diciotto anni e peso superiore a 50 kg dopo almeno cinque giorni di trattamento anticoagulante parenterale iniziale;

rivaroxaban" 1 mg/mL granuli per sospensione orale:

trattamento del tromboembolismo venoso (TEV) e prevenzione delle recidive di TEV nei neonati a termine, nei lattanti e bambini piccoli, nei bambini e negli adolescenti di eta' inferiore a diciotto anni dopo almeno cinque giorni di trattamento anticoagulante parenterale iniziale»,

«dopo almeno cinque giorni di trattamento anticoagulante»

AGENZIA ITALIANA DEL FARMACO

Istituzione della Nota AIFA 101 relativa alle indicazioni terapeutiche TVP, EP e TEV

13 Ottobre 2023

Gli effetti della Nota 101 sono sospesi fino all'8 gennaio 2024 come da determina DG AIFA n. 394/2023 del 13/10/2023, pubblicata in GU il 17/10/2023.

Nota 101

Farmaci a carico SSN inclusi nella Nota 101:

- **Anticoagulanti orali inibitori della vitamina K (AVK)**: warfarin - acenocumarolo
- **Inibitori diretti della trombina o del fattore Xa (NAO/DOAC)**: dabigatran - apixaban - edoxaban - rivaroxaban

Attualmente, il Rivaroxaban è l'unico DOAC rimborsato dal SSN per l'uso in età pediatrica

Bambino Gesù
OSPEDALE PEDIATRICO

- Cardiopatie
- Neoplasie
- Otomastoiditi
- IBD
- LA e Linfomi
- Nefropatie
- Terapia intensiva/ subintensiva neonatale
- Profilassi post trapianto (fegato , reni)
- Malformazioni vascolari (MAV)

J Thromb Thrombolysis (2014) 38:121–123
DOI 10.1007/s11239-013-1024-7

Rivaroxaban for the treatment of consumptive coagulopathy associated with a vascular malformation

Christophe Vandenbriele · Thomas Vanassche · Marijke Peetermans · Peter Verhamme · Kathelijne Peerlinck

LYMPHATIC RESEARCH AND BIOLOGY
Volume 16, Number 3, 2018
© Mary Ann Liebert, Inc.
DOI: 10.1089/lrb.2017.0029

Effectiveness and Safety of Treatment with Direct Oral Anticoagulant Rivaroxaban in Patients with Slow-Flow Vascular Malformations: A Case Series

Joana M. Mack, MD[1,2] Gresham T. Richter, MD[2,3] and Shelley E. Crary, MD, MS[1,2]

Thrombosis Research 213 (2022) 30–33

Is there a place for prophylaxis with DOACs in Klip
and other low-flow vascular malformations with i
coagulopathy and thromboembolic events?

Carine J.M. van der Vleuten [a,b,*], Lilly G.J.M. Zwerink [a,b], Edith
J. de Jong [a], D. Maroeska W.M. te Loo [b,d]

Thrombosis Research 168 (2018) 114–120

ment of localized intravascular
nous malformations

Hermans*
ersitaires Saint-Luc, Université catholique de Louvain, 1200 Brussels, Belgium

What about DOACs' use in vascular malformations?

Dabigatran etexilate versus low-molecular weight heparin to control consumptive coagulopathy secondary to diffuse venous vascular malformations

Laurent Ardillon[a], Catherine Lambert[b], Stéphane Eeckhoudt[c], Laurence M. Boon[d] and Cedric Hermans[b]

Diffuse venous malformations can be associated with a consumptive coagulopathy characterized by a reduction of fibrinogen level, platelet count and elevated D-dimer level. We report a case of a patient with extensive venous malformations, hemorrhagic symptoms and biological signs of intravascular coagulopathy. She was initially treated effectively with low-molecular weight heparin (LMWH) (enoxaparin 1 mg/kg, bid) and switched to low-dose dabigatran etexilate (110 mg bid) for more than 2 years. Both treatments showed a similar clinical efficacy with the absence of bleeding or thrombotic complications. Compared with LMWH, dabigatran etexilate provided a similar correction of the fibrinogen level and platelet count but was less effective to reduce the D-dimer level. Although dabigatran etexilate can be safely used to control the consumptive coagulopathy secondary to venous malformation and provides a practical alternative to LMWH, its efficacy *in vivo* at a low dose to reduce the D-dimer level was lower than that of LMWH. *Blood Coagul Fibrinolysis* **27:216–219 Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.**

Blood Coagulation and Fibrinolysis 2016, **27**:216–219

Keywords: chronic intravascular coagulopathy, dabigatran etexilate, D-dimer level, oral anticoagulation, sclerotherapy, venous malformation

[a]Haematology–Haemostasis Unit, University Hospital, Tours, France, [b]Haemostasis and Thrombosis Unit, Haemophilia Clinic, Division of Haematology, [c]Haemostasis Laboratory, Department of Biological Chemistry and [d]Division of Plastic and Reconstructive Surgery, Center for Vascular Anomalies, Clinic of the Saint-Luc University Hospital, Catholic University of Leuven, Brussels, Belgium

Correspondence to Professor Cedric Hermans, MD, FRCP (Lon, Edin), PhD, Haemostasis and Thrombosis Unit, Division of Haematology, Haemophilia Clinic, St-Luc University Hospital, Avenue Hippocrate 10, 1200 Brussels, Belgium
Tel: +32 2 764 17 85; fax: +32 2 764 89 59;
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Received 19 May 2015 **Revised** 22 July 2015
Accepted 4 August 2015

Successful treatment with dabigatran for consumptive coagulopathy associated with extensive vascular malformations

Atsushi Yasumoto[a], Ryohei Ishiura[b], Mitsunaga Narushima[b] and Yutaka Yatomi[a]

Vascular malformation is occasionally complicated by consumptive coagulopathy, known as localized intravascular coagulopathy (LIC), which is characterized by a reduced fibrinogen level, an elevated D-dimer level and a normal platelet count. We report the case of a 17-year-old Japanese girl who presented with LIC secondary to extensive vascular malformations, whose condition had progressed to disseminated intravascular coagulation (DIC). She suddenly presented with severe anaemia, despite the absence of obvious bleeding, and she began to require regular red blood cell (RBC) transfusions. As she was suffering from paroxysmal atrial fibrillation, we treated her with dabigatran, after obtaining informed consent. Immediately after the administration of dabigatran, the results of clotting tests improved dramatically. Seven months later, she has not required any RBC transfusions, and the dabigatran treatment has been well tolerated. The present case report suggests that dabigatran may be a useful treatment option for patients with DIC associated with vascular malformations. *Blood Coagul Fibrinolysis* **28:670–674 Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc.**

Blood Coagulation and Fibrinolysis 2017, **28**:670–674

Keywords: dabigatran, disseminated intravascular coagulation, local intravascular coagulopathy, vascular malformation

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Received 21 March 2017 **Revised** 31 August 2017
Accepted 12 September 2017

Il flusso di sangue attraverso le MAV è interrotto, turbolento e a volte stagnante. La lesione e la flogosi della parete vasale attivano le cellule endoteliali e la coagulazione, con produzione di trombina e fibrina e sviluppo di coagulopatia

Le **MV extra-tronculari**, la varietà più frequente, sono sottese nel 40% dei casi una coagulopatia causata dalla stasi venosa e dall'attivazione del processo coagulativo, con tendenza alla formazione di trombi endoluminali e allo sviluppo di un quadro patologico definito **"coagulazione intravascolare localizzata" (LIC)**

La calcificazione dei trombi endovasali può condurre alla formazione di noduli di consistenza dura noti come **"fleboliti",** spesso palpabili, dolorosi, facilmente identificabili con l'imaging e possono notevolmente compromettere la funzionalità e la qualità di vita.

TITOLO DELLO STUDIO	**Utilizzo del rivaroxaban nelle malformazioni venose pediatriche complicate da trombosi: un'analisi retrospettiva monocentrica**
CODICE DEL PROTOCOLLO (Assegnato dal Promotore)	RIVMAV
SPONSOR/PROMOTORE	Nessuno
FINANZIATORE/SUPPLIER:	Nessuno
CENTRO COORDINATORE	Centro Emostasi e Trombosi U.O.C. OncoEmatologia Ospedale Pediatrico Bambino Gesù, Roma

Follow-up clinico → 3 → 6 → 12 mesi

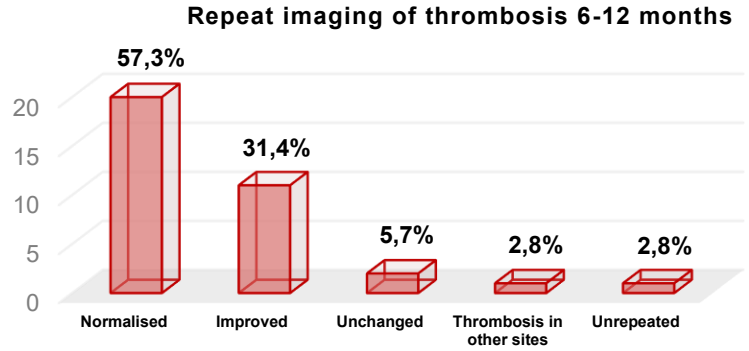
Obiettivo primario

- Valutare il miglioramento, la risoluzione o la progressione della trombosi venosa nei pazienti trattati con rivaroxaban.

- 90% pazienti trattati con rivaroxaban, rivalutati a 3 e 6 mesi, hanno riportato una regressione completa del dolore dovuto alla trombosi.
- Di questi, il 71% era stato precedentemente trattato con acido acetilsalicilico, senza alcun miglioramento clinico e con recidiva trombotica.
- Due pazienti hanno riferito dolore occasionale e un paziente persistenza di dolore.

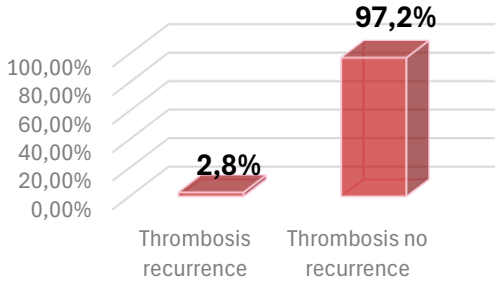
Pazienti arruolati = 35

Giugno 2025
MAV 60 pz
Non Mav 47 pz

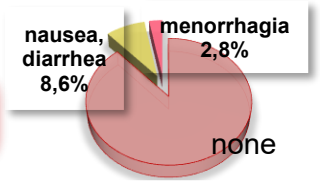


Obiettivo secondario

- Valutare le recidive sintomatiche nei pazienti sottoposti a profilassi secondaria.



Effetti collaterali



Bambino Gesù
OSPEDALE PEDIATRICO

Titolo: Utilizzo degli Anticoagulanti Orali Diretti (DOACs)
in età pediatrica: un'analisi retrospettiva multicentrica
Codice dello studio: DOAC-PED
Protocollo: versione 1.0 del 30/05/2025

Bambino Gesù
OSPEDALE PEDIATRICO

PROTOCOLLO

Titolo dello Studio:	Utilizzo degli Anticoagulanti Orali Diretti (DOACs) in età pediatrica: un'analisi retrospettiva multicentrica
Codice dello Studio o del Protocollo:	DOAC-PED
Versione del Protocollo:	Versione 1.0
Data:	30 Maggio 2025
Promotore:	Ospedale Pediatrico Bambino Gesù, IRCCS Piazza Sant'Onofrio, 4 - Roma
Principal Investigator:	Dott. Matteo Luciani
Co-Principal Investigator:	Dott.ssa Paola Giordano (Bari) Dott. Angelo Claudio Molinari (Genova) Dott. Giovanni Del Borrello (Torino)
Altri Sperimentatori:	Dott.ssa Giovina Di Felice (Roma) Dott.ssa Ariela Smigliani (Roma)

Titolo: Utilizzo degli Anticoagulanti Orali Diretti (DOACs)
in età pediatrica: un'analisi retrospettiva multicentrica
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Lista Centri versione 1.0 del 30/05/2025

Bambino Gesù
OSPEDALE PEDIATRICO

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Centro	Principal Investigator
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Bari	Dott.ssa Giordano
Bari Oncoematologia pediatrica	Dott. Grassi
Bologna	Dott. Prete (Co-PI dott. Facchini)
Bolzano	Dott. Boscarol
Brescia	Dott. Gorio
Cagliari	Dott. Montecchiari
Genova	Dott. Molinari
Lecce	Dott.ssa Tornesello
Napoli	Dott. Schiavulli
Roma Gemelli	Dott.ssa Lazzareschi
San Giovanni Rotondo	Dott. Maggio
Taranto	Dott.ssa Brescia
Torino	Dott. Del Borrello
Trento	Dott. Petrone
Trieste	Dott. Verzegnassi
Varese	Dott. Marinoni
Verona	Dott. Esposto

Assessing Direct Oral Anticoagulants in the Clinical Laboratory

Robert C. Gosselin, CLS[a,*], Adam Cuker, MD, MS[b]

KEY POINTS

- Traditional screening tests such as the prothrombin time and activated partial thromboplastin time are insufficient for detecting "*on-therapy*" concentration of direct oral anticoagulants (DOACs).
- Thrombin clotting time and heparin calibrated anti-Xa assays are sensitive to screen for significant concentration (≥30 ng/mL) of dabigatran and oral factor Xa inhibitors, respectively.
- Drug calibrated dilute thrombin time, ecarin-based assays, and chromogenic factor anti-IIa are rapid assays that can be used to quantify dabigatran.
- Heparin or a DOAC calibrated anti-Xa test is a rapid method that can be used to estimate or quantify factor Xa DOACs, respectively.
- At the time of writing, there are limited Food and Drug Administration-cleared methods for screening, quantifying, or neutralizing DOACs.

Clin Lab Med 44 (2024) 551–562

SUMMARY

DOACs have revolutionized the prevention and treatment of thrombotic disorders such as VTE and atrial fibrillation. Unlike older anticoagulants such as UFH and VKAs, **they do not require routine laboratory monitoring.**

Nevertheless, there are special clinical situations in which DOAC measurement may be important for guiding clinical management, particularly emergency situations such as major bleeding, acute stroke, or need for an urgent invasive procedure.

Current standards to initiate DOACs in children

- **Diagnosis of VTE**
  - Limited experience of DOACs for arterial thrombotic events, stroke
- **Age**
  - Neonates>37 gestational weeks and >2.6 kg or >3rd weight percentile
  - More experience with children aged >2 years
- **Clinically stable patient & low bleeding risk**
  - No immediate procedures planned, no intracranial haemorrhage within 30 days, no severe thrombocytopenia, not post operative, no recent severe trauma
  - Re-evaluate continuously according to patient"s evolving clinical presentation
- **No severe renal dysfunction**
  - GFR >30 mL/min/1,73 m² for apixaban
  - GFR >50 mL/min/1,73 m² for rivaroxaban
- **No severe hepatic dysfunction**
  - AST/ALT<3-5xULN, no coagulopathy based on liver dysfunction
- **Adequate oral intake**
  - Oral or nasogastric tube feeding for at least 48h
  - Naso-jejunal tube not optimal due to absorption site of DOACs (generally distal stomach and proximal duodenum)
- **Initial parenteral or subcutaneous anticoagulation for at least 5 days**
- **No relevant drug-drug interactions**
  - Strong inducers or inhibitors of CYP3A4 and/or P-glycoprotein (e.g. Azole antifungals, anticonvulsants, others)
- **Available drug formulations**
  - Able to swallow pills/ liquid/ pellets
- **Dosing regimens from published trials**
  - Age specific dosing regimens based on PK (increased clearance at younger ages)
  - Adapt dosing to body weight regularly
- **No triple positive antiphospholipid-syndrome (limited paediatric data)**
- **No mechanical heart valve (limited paediatric data)**

What did we learn (and did not learn) from the pediatric direct oral anticoagulant trials, and how might we better design pediatric anticoagulant trials in the future?

TABLE 4 DOAC pediatric investigational programs limitations, gaps in knowledge and potential solutions.

Missing information	Solvable by RCT	Possible solution
Patient populations • Including neonates, premature infants, patients with arterial thrombosis, and arterial stroke, among others	Possible but not feasible	Well-designed and well-resourced cooperative registries (eg, IPTN's ThrombPeds)
Optimal therapeutic range • Including which populations may benefit from drug level monitoring	Possible but not feasible	
Real-world bleeding rates	No	
Efficacy • Adequately powered trials to show superiority or noninferiority	Possible but not feasible	
Immediate DOAC therapy • Can DOACs be safely and effectively started upon the diagnosis of VTE	Possible	
Importance of oral feeding • Duration of stability on oral feeds before DOAC therapy can be initiated	No	
Threshold renal/liver disease Impact of concurrent therapies	Possible but studies need different design	
Off-target impacts • Including any impact on growth and/or development	Possible if RCT rolls into long-term follow-up cohorts	
Strategies for interruption/reversal • Including data on periprocedural management: what type of procedures and for how long to be withheld	No	
Quality of life • Strategies for interruption of therapy that will permit the safe participation in activities with high risk of traumatic injury (ie, contact sports)	Possible but studies need different design	
Compliance • How does efficacy and safety are compromised with missing doses periodically during long-term treatment or secondary prophylaxis	Possible but methods important	
Reversal strategies • When and in whom to use reversal agents	No	

Res Pract Thromb Haemost. 2023;7:e100140

- Paediatric systemic thrombo thromboembolism)
- Paediatric systemic thromboembolism)
- Neonatal systemic
- Paediatric cerebral venous)
- The new Registry

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SPECIALTY SECTION
This article was submitted to Pediatric

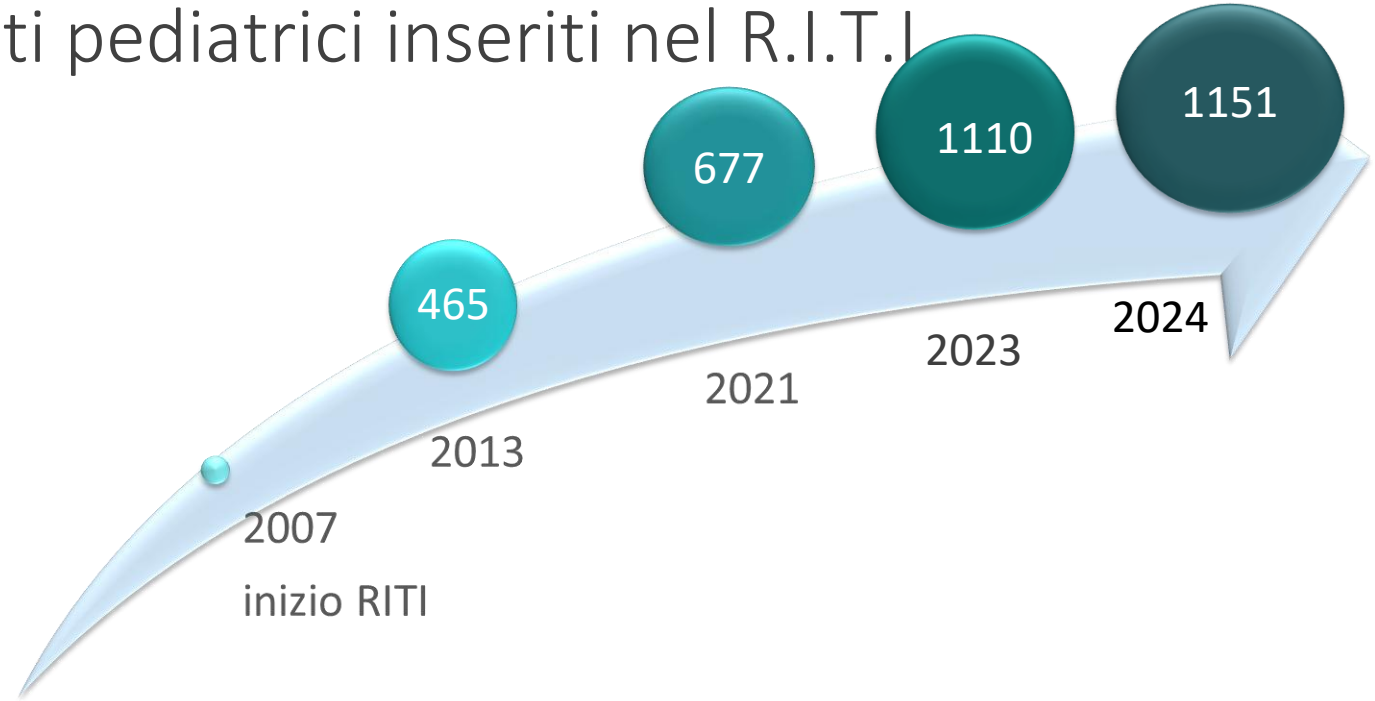
The new Italian registry of infantile thrombosis (RITI): A reflection on its journey, challenges and pitfalls

Maria Federica Pelizza[1,2†], Matteo Martinato[3,4†], Anna Rosati[5], Margherita Nosadini[1], Paola Saracco[6], Paola Giordano[7], Matteo Luciani[8], Laura Ilardi[9], Donatella Lasagni[10], Angelo Claudio Molinari[11], Rossana Bagna[12], Antonella Palmieri[13], Luca Antonio Ramenghi[14], Massimo Grassi[7], Mariella Magarotto[15], Federica Magnetti[12], Andrea Francavilla[3], Giuseppe Indolfi[16], Agnese Suppiej[17], Chiara Gentilomo[18], Roberta Restelli[9], Antonella Tufano[19], Daniela Tormene[20], Jacopo Norberto Pin[1], Clarissa Tona[1], Davide Meneghesso[21], Lidia Rota[22], Marta Conti[23], Giovanna Russo[24], Giulia Lorenzoni[3], Dario Gregori[3], Stefano Sartori[1,2*‡], Paolo Simioni[20*‡] and Collaborators of the R.I.T.I. (Italian Registry of Infantile Thrombosis)

I numeri del Registro

Pazienti pediatrici inseriti nel R.I.T.I

Timeline

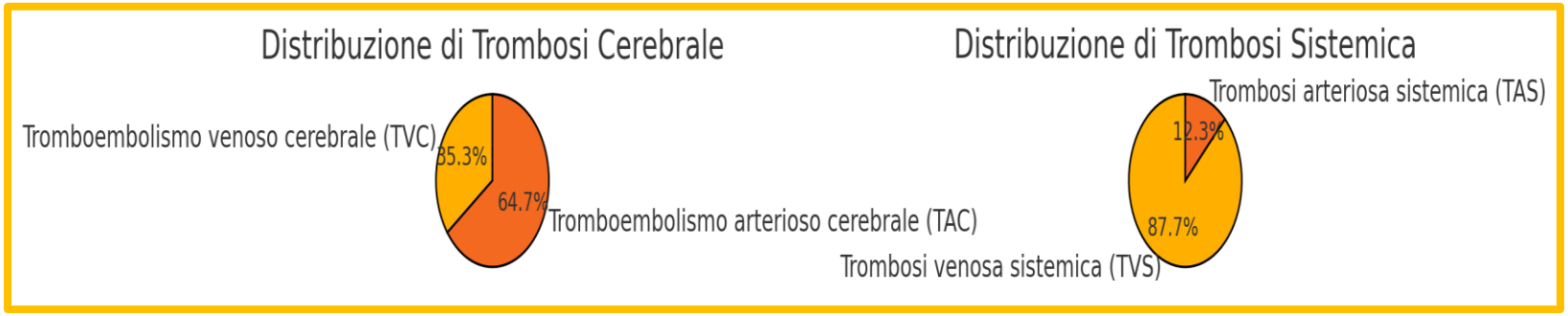


RITI Contributors and Patients' Distribution

R.I.T.I
REGISTRO ITALIANO TROMBOSI INFANTILE

- 85 Enrolling Physicians
- 51 Centres
- 16/20 Italian Regions involved

1151 patients (November 2024)



Direct oral anticoagulants: unresolved issues/unmet needs

- Accesso ai DOAC
- Informazione dei Pediatri di base
- Durata ottimale del trattamento del TEV
- Utilizzo per la profilassi (anomalie vascolari)
- Efficacia comparativa tra i DOAC disponibili (personalizzazione?)
- Setting specifico dei pazienti (Arteriose, renali, Portali, anomalie vascolari, Stroke, COVID, Neonati ex prematuri Protesi valvolari, Sindrome da Antifosfolipidi)
- Necessità del monitoraggio terapeutico dei farmaci
- Efficacia e disponibilità (costi) degli antidoti
- Gestione della chirurgia (definizione di protocolli ad hoc)
- Problemi di assorbimento
- Pochi bambini sotto i due anni negli studi.
- Metrorragie nelle adolescenti.
- Interferenze con farmaci. Vietati dronedarone, itraconazolo, ketoconazolo, CyA e tacrolimus
- Necessario raccogliere i dati sulla trombosi pediatrica e neonatale in registri nazionali ed internazionali

Table 4. Key age and disease specific management issues and areas of future study of DOACs

Special population	Clinical challenges and future research needs
Age groups	
Neonates	PK and PD in gestational age <37 wk Safety in the presence of comorbidities • Critically ill or on mechanical ventilation • Absorption with naso-jejunum tube feeding • Presence of arterial central lines • Sepsis Access to liquid formulation or sprinkles Management surrounding invasive procedures and surgeries Impact on growth and development, immune function, and bone health
Toddler/young child	Availability of a liquid formulation or pellets Safety with noncontact activities; eg, in school or on the playground
Teenager	Safety for athletes playing contact sports Management of menstrual bleeding (in young women) Impact on quality of life Safety in the presence of high-risk behavior Optimal contraceptive options Safety with use of concomitant antifibrinolytics
Medical comorbidities	
Cancer	Safety with chemotherapy induced toxicity affecting different organ systems, for example, liver, kidney, and GI, thrombocytopenia, concomitant medications, and sepsis Periprocedural management
Renal/liver dysfunction, GI malabsorption, or short gut	Use in mild or moderate renal and liver dysfunction PK/PD in GI malabsorption and short gut Key safety considerations

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GRAZIE A
TUTTI PER
L'ATTENZIONE

Recommendations for the management and prevention of pediatric thrombosis

- Early and routine screening for at risk populations
- Personalized anticoagulation therapy
- Multidisciplinary team approach
- Timely and accurate diagnosis
- Balancing the risk of bleeding
- Psychosocial support for children and families
- Regular follow-up and monitoring
- Research and development of pediatric-specific guidelines