
بسم الله الرحمن الرحیم

Thrombosis in Thalassemia

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Introduction

- Thrombotic disease, mostly venous, was the 5th most common complication, affecting 14% of the with β-TM and β-TI patient population
- In most cases thrombosis was spontaneous.So could be expected in otherwise healthy patients
- The median time to thrombosis following splenectomy is around eight years

OP TIMAL CARE study. Blood 2010;115(10):1886-1892.

- The incidence of thrombotic events was reported 0.9% in β-TM and 4 % β-TI from the largest study on **more than 8000 patients in Iran and Mediterranean region**
- 14% of mortalities in the whole group were attributed to thrombotic events

Thromb Haemost. 2006 Oct;96(4):488-91.

Continiue:

- TEEs could occur in every organ of the body : DVT, pulmonary embolism, portal vein thrombosis and recurrent arterial occlusions are the most important thromboembolic events in thalassemia patients patients.

  Blood Coagul Fibrinolysis. 2012 Apr;23(3):212-7.

- Silent ischemic brain lesions are more prevalent in β-TI; abnormal findings on brain MRI in 28% of patients with β-TI in a study on asymptomatic splenectomized β-TI patients

  Pediatr Hematol Oncol. 2014 Oct;31(7):583-96.

- Overt stroke is much more common in β-TM, due to risk factors such as heart failure, cardiomyopathy, arrhythmia and diabetes mellitus which are more common in β-TM

  Thromb Haemost. 2010 May;103(5):989-93.

Hemostatic Changes in Thalassemia

Chronic Platelet activation

- Detection by flow cytometry of an increased fraction of platelets carrying the activation markers CD62P (P selectin) and CD63
- Weak response of thalassemic platelets to aggregation antagonist
- Significant increase of urinary thromboxane A_2 and prostacyclin metabolites

Hemoglobin. 2010;34(1):121-2.

Abnormal Thalassemic RBCs

- Oxidation of globin subunits results in the production of hemichromes
- Binding of the hemichrome to the membrane of RBCs
  - **Hemichrome-triggered band 3 aggregation**
- Toxic **Intracellular membrane-bound free iron(MBFI)** is released due to disintegration of hem.
    - Oxidation of the membrane proteins and formation of RBCs antigens such as phosphatidylserine
- This phenomenon causes rigidity, deformation and aggregation of the RBCs
- Negatively charged phospholipids leading to thrombin generation

Hemostatic changes: primary or secondary

- **Endothelial activation**

  - increased levels of endothelial adhesion proteins (ICAM-1,ELAM-1,VCAM-1,VWF)

- **Microparticles**
  - fragments with length of 0.1 to 2 μm which are produced from the remodeling of the plasma membranes of platelets, endothelial cells and circulating RBCs in response to cell activation and apoptosis.
  - Increased in DM,sepsis,pre-eclampsia and both β-TM and β-TI

- **Monocyte activation**

  - high levels of monocyte colony-stimulating factor
  - increased monocyte phagocytic activities

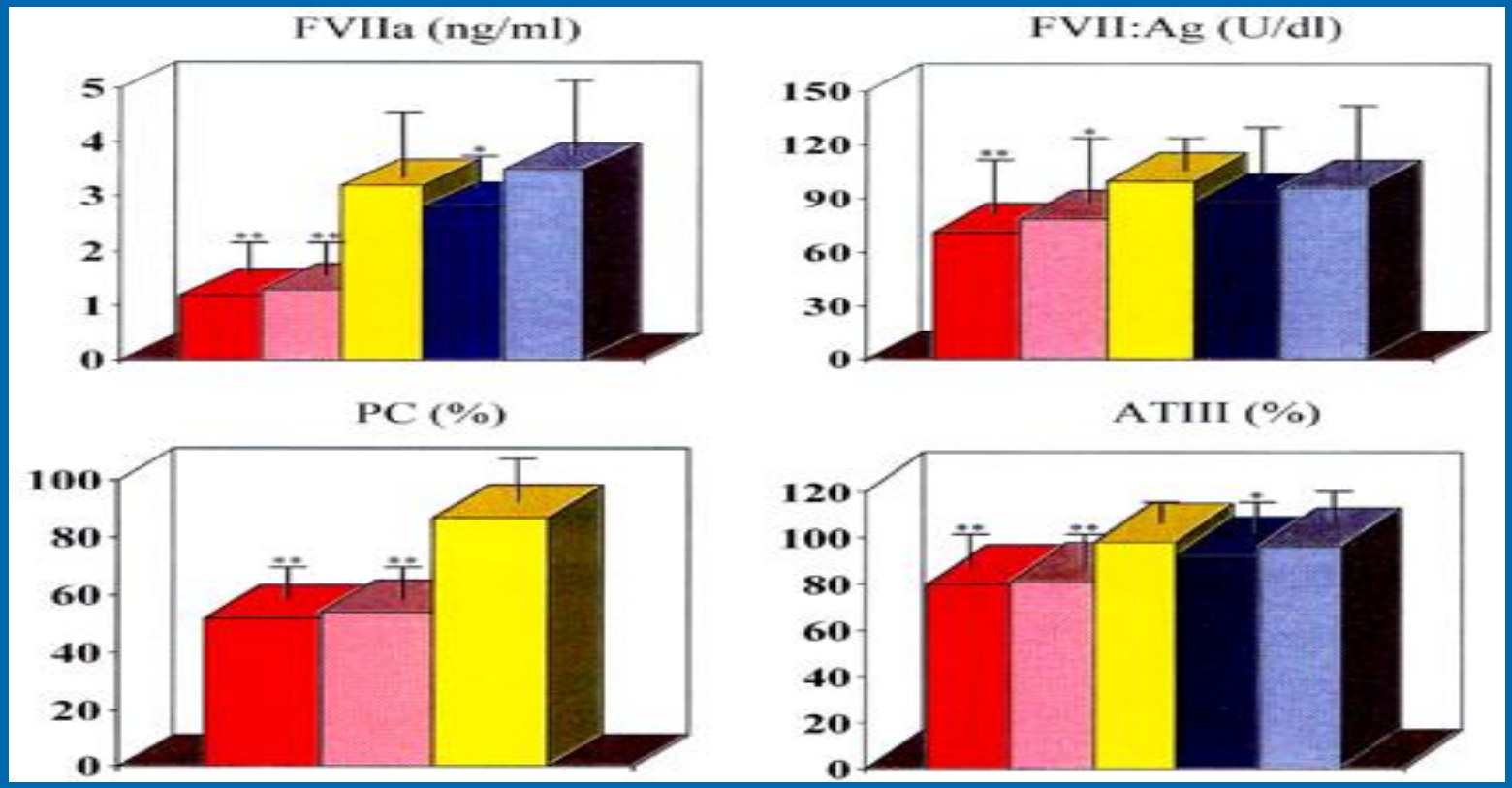
- **Granulocyte activation**

  - increased granulocyte phagocytic function

Coagulation Factors

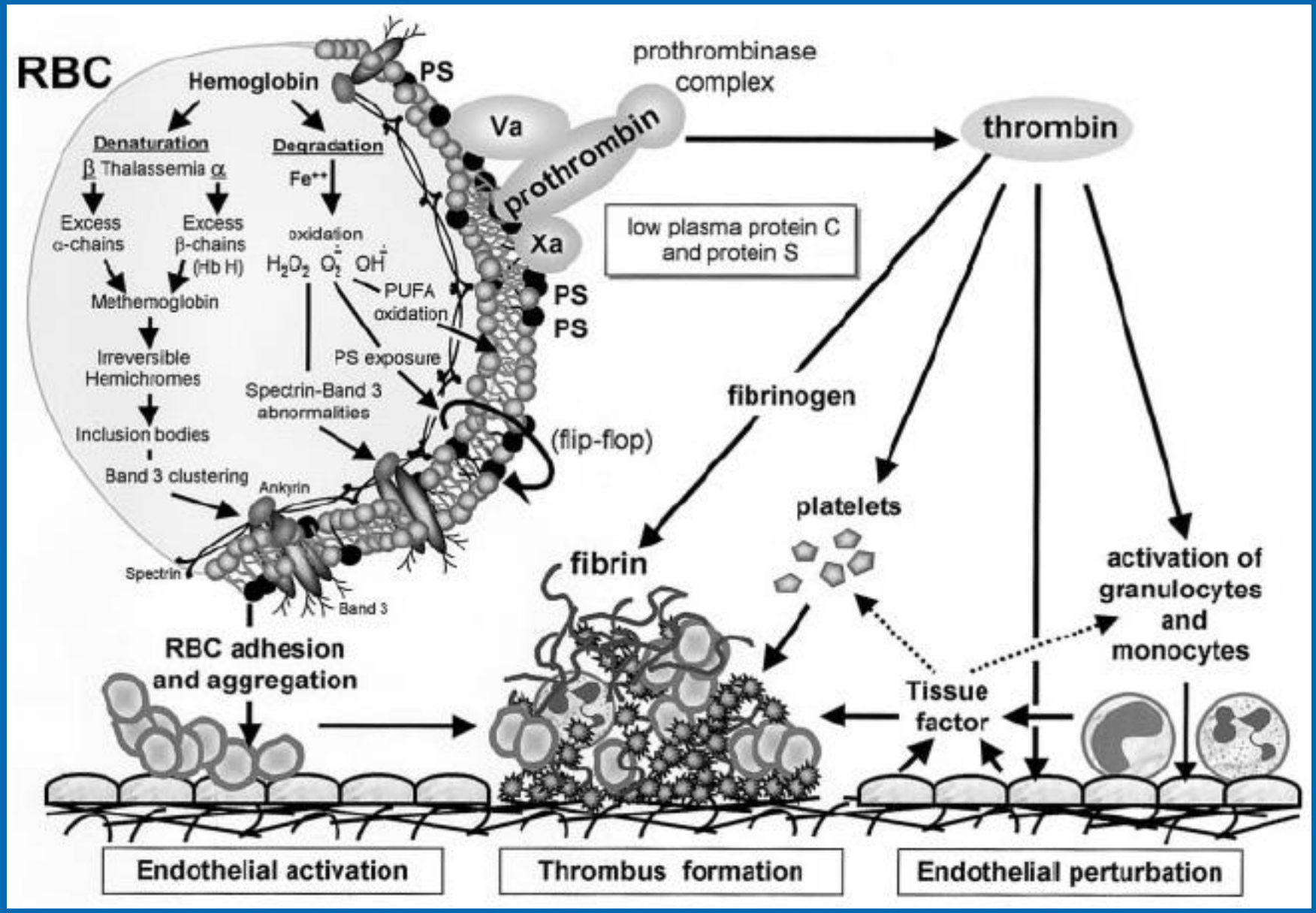
- Increased plasma Prothrombin fragment 1.2
- Decreased levels of coagulation inhibitors (protein C and protein S):
  - Protein C and S are very sensitive to even mild degrees of impairment in liver synthetic functions.
  - High affinity binding of protein C to phosphatidylserine and other negatively charged phospholipids
- Low levels of antithrombin III
- Plasma homocysteine level is elevated in patients with β-TM
- Due to lower level of TAFI (specially in TM) a low grade consumptive coagulopathy with continuous thrombin generation and exaggerated fibrinolysis might be observed

NTDT vs TDT & Splenectomized vs Non-splenectomized



TI splenectomized
TI non splenectomized
Controls
TM splenectomized
TM non splenectomized

Cappellini et al.2000

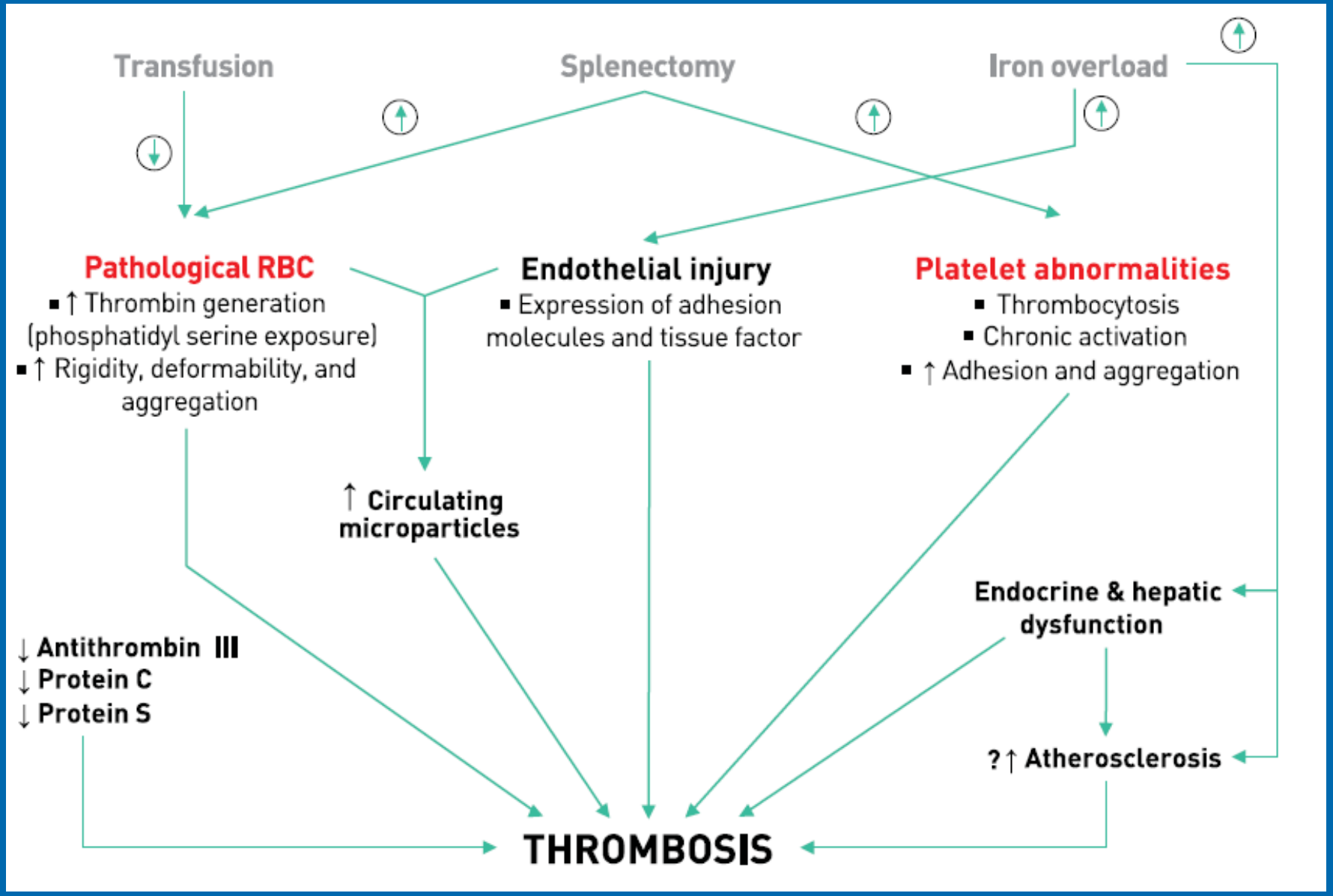


Eldor & Rachmilewitz, Blood 2002

Hemostasis and splenectomy

- Thrombocytosis
- Decreased protein C and S levels
- Decreased level of TAFI
- Increased D-Dimer
- Higher thrombin generation due to higher number of negatively charged pathological red blood cells and higher levels of procoagulant microparticles

J Pediatr Hematol Oncol. 2016 Nov;38(8):636-641
Hematol Oncol Stem Cell Ther. 2010;3(2):60-5.
Thromb Res. 2007;120(6):805- 10.
Am J Hematol. 2007 Nov;82(11):1001-4.
Pak J Biol Sci 2010;13:448e51.


Transfusion
Splenectomy
Iron overload
Pathological RBC
▪ ↑ Thrombin generation (phosphatidyl serine exposure)
▪ ↑ Rigidity, deformability, and aggregation
Endothelial injury
▪ Expression of adhesion molecules and tissue factor
Platelet abnormalities
▪ Thrombocytosis
▪ Chronic activation
▪ ↑ Adhesion and aggregation
↑ Circulating microparticles
↓ Antithrombin III
↓ Protein C
↓ Protein S
Endocrine & hepatic dysfunction
? ↑ Atherosclerosis
THROMBOSIS

Risk factors

- NTDT
  - Hb <9 g/dl
- Ineffective erythropoiesis:
  - NRBC ≥300/100 WBC
- Never or previously minimally transfused patients
- Splenectomy
- Age >20 years >35 years
- Iron Overload: Serum ferritin ≥1000 ng/ml OR liver iron concentration ≥5 mg Fe/g dry weight or serum ferritin level ≥800 ng/ml
- personal or family history of thrombotic events
- Pregnant patients
- Thrombocytosis
  - platelet count ≥500×109 /ul,
- Evidence of pulmonary hypertension

J Thromb Haemost. 2010 Oct;8(10):2152-8.

J Thromb Haemost 2006;96(4):488-491.

OP TIMAL CARE study. Blood 2010;115(10):1886-1892.

Blood 2012;120(21):1021.

Other acquired risk factors

- CV line
- CHD
- Trauma
- Surgery
- Immobilization
- TPN
- Pregnancy, puerperium
- Drug (OCP)
- Infection
- Liver failure
- Splenectomy (thrombocytosis)
- DM
- Hypothyroidism

Cerebrovascular disease

- Assessment with brain or cerebrovascular imaging for high-risk patients may be considered:
  - MRI
  - MRA
  - PET-CT
- In a multivariate analysis, increasing age and transfusion naivety were associated with a higher incidence of ischemic lesions in MRI
- The vast majority of patients (94%) had evidence of small to medium (<1.5 cm) lesions

J Thromb Haemost. 2010 Jan;8(1):54-9.

- Routine assessment or management of positive findings in asymptomatic patients cannot yet be recommended unless deemed necessary by the treating physician

Pulmonary hypertension

- Patients with NTDT should undergo routine echocardiographic assessment (annually) for the assessment of TRV
- Echocardiographic TRV values should be interpreted as follows:
  - > TRV >2.5 m/s, asymptomatic: 'possible' to have pulmonary hypertension
  - > TRV >2.5 m/s, symptomatic or with other echocardiographic criteria suggestive of pulmonary hypertension: 'likely' to have pulmonary hypertension
  - > TRV >3.2 m/s: 'likely' to have pulmonary hypertension
- Patients 'likely' to have pulmonary hypertension on echocardiography should undergo right heart catheterization to confirm the diagnosis. Ventilation/perfusion lung scan testing is also recommended to rule out pulmonary thromboembolic disease
- Patients with confirmed pulmonary hypertension should be referred to a cardiologist and managed as per standard local or international guidelines for the treatment of pulmonary hypertension
- Patients with 'possible', 'likely', or confirmed pulmonary hypertension may benefit from the following interventions
  - > Blood transfusion
  - > hydroxyurea
  - > Sildeanfil citrate
  - > Adequate control of iron overload status
  - > Anticoagulant therapy

Prophylactic intervention

- high-risk patients
- Aspirin therapy should be considered in:
  - Splenectomized NTDT patients with elevated platelet counts (≥500 x 109/l)
  - After the first episode of TEE
- The use of transfusion therapy for the primary or secondary prevention of thrombotic or cerebrovascular disease in high-risk NTDT patients
- There is no sufficient evidence to recommend iron chelation or hydroxyurea therapy for the primary or secondary prevention of thrombotic or cerebrovascular disease

Treatment

1. Superficial thrombophlebitis
    a. Anti-inflammatory agents
    b. Hot compress
    C. Rest and elevation of the affected extremity
2. Deep. Vein thrombosis
    a. Heparin full dose 7-10 days
    b. Warfarin therapy
3. Pulmonary embolism
    a. Thrombolytic therapy
    b. Embolectomy indicated if medical management fails to improve patient's clinical status within a few hours

VTE description	Treatment recommendation	Comments
Asymptomatic DVT or PE	• Anticoagulation **OR** observation	• Natural history is not well known; • Decision is likely to vary based on thrombus location and patient

Symptomatic DVT or PE	• Anticoagulation
	  • Provoked VTE: **treat ≥3 mo** (if provoking factor is resolved)
	  • Unprovoked VTE: **treat 6-12 mo**; consider longer duration based on patient's preferences
	• Avoid thrombolysis (unless life- or limb threatening OR iliac and common femoral veins (higher risk for more severe post-thrombotic syndrome [PTS] *)
	• Avoid IVC filter (unless absolute contraindication to anticoagulation)
		• Observation may be necessary or reasonable **for premature neonates or critically ill children at high risk of bleeding**

Massive PE with hemodynamic compromise	• **Thrombolysis** followed by anticoagulation	
Submassive PE (no hemodynamic instability)	• Anticoagulation alone unless **low risk for bleeding** OR at high risk for decompensation due to **concomitant cardiopulmonary disease***	Submassive PE :with echocardiography and/or biomarkers compatible with right ventricular dysfunction but without hemodynamic compromise

**ORTEL et al ,Blood.13 October 2020 X Volume 4, Number 19*

VTE description	Treatment recommendation	Comments
CVAD thrombosis	• Anticoagulation **OR** observation	• Natural history is not well known; • Decision is likely to vary based on thrombus location and patient
RVT	• Unilateral: anticoagulation alone • Bilateral: consider thrombolysis for bilateral RVT (life-threatening)	• Observation may be necessary or reasonable **for premature neonates or critically ill children at high risk of bleeding**
Portal vein thrombosis	• Occlusive: anticoagulation • Nonocclusive: observation (close radiologic follow-up)	
Cerebral sinovenous thrombosis	• Anticoagulation alone	Decision in patients with **intracranial haemorrhage** needs to be individualized, but some patients **may benefit from anticoagulation**

**ORTEL et al ,Blood.13 October 2020 X Volume 4, Number 19*

Common anticoagulant therapies for use in pediatric VTE

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)

- LMWH is preffered
- UFH because of its short half-life, reversibility (with protamine), and nonrenal clearance is usually reserved for:
  - patients at highest risk of bleeding
  - in renal failure
- If multidose vial is used,1 unit on an insulin syringe is equivalent to 1 mg of enoxaparin.(100mg/ml OR 10000U/ml)
- Whole milligram dosing of enoxaparin, rather than decimal dosing, appears to be safe and effective in children

Drug name	Mechanism of action	Pharmacokinetic properties and dosing	Therapeutic monitoring (based on adult ranges)
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

Pediatric concerns include:

- Developmental changes in vitamin K–dependent proteins,
- Age-related dietary differences (ie, high vitamin K in formula), and
- No liquid formulation: warfarin pills are commonly crushed and dissolved in water

- The loading period is approximately 3-5 days for most patients before a stable maintenance phase is achieved.
  - Warfarin should be started on day 1 or day 2 of heparin therapy. Heparin should be continued for a minimum of 5 days duration.
  - For extensive DVT with or without PE, warfarin should be started on day 5 of heparin therapy.
- Children with mechanical heart valves require an INR between 2.5 and 3.5.

DOAC

- DOACs approved for adult VTE include the direct factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban) and direct thrombin inhibitor, dabigatran.
- BENEFITS:lack of interaction with diet, fewer drug interactions, no need for monitoring
- The 2018 ASH guidelines for pediatric VTE recommend that DOACs not be used in children until completion of clinical trials

- **Rivaroxaban for treatment of pediatric VTE (Einstein-Jr study):**
  - 335 children (aged 0-17 years) , different ethnicity were enroleed
  - Children were required to have completed at least 5 days of initial heparinization before start of treatment with rivaroxaban.
  - Pediatric rivaroxaban treatment regimens with **tablets in dose strengths of 5, 10, 15, or 20 mg or newly-developed fruit-flavored oral suspension formulation (was provided as granules in a bottle that had to be filled with water to achieve a concentration of 1 mg/mL)** had an exposure within the adult range.

  - Low or high values of pharmacokinetic parameters were not linked to efficacy, bleeding, or adverse event outcomes.
  - Bodyweight-adjusted pediatric rivaroxaban regimens are validated and provide for appropriate treatment of children with VTE.

Rivaroxaban for treatment of pediatric VTE (Einstein-Jr study)

Bodyweight, kg		Rivaroxaban dose (mg) regimens used in phase 3	
		Total daily dose	Regimen
		2.4	0.8 TID
3	<4	2.7	0.9 TID
4	<5	4.2	1.4 TID
5	<7	4.8	1.6 TID
7	<8	5.4	1.8 TID
8	<9	7.2	2.4 TID
9	<10	8.4	2.8 TID
10	<12	9.0	3.0 TID
12	<30	10.0	5.0 BID
30	<50	15.0	15.0 OD
≥ 50		20.0	20.0 OD

Young et al. JTH Volume18, Issue7 July 2020Pages 1672-1685

DOACs NOTES AND COMMENTS

- All of the DOACs are renally excreted. Rates of bleeding are higher in adults with chronic renal disease
- Gastrointestinal considerations:
  - DOACs are absorbed in stomach and proximal intestine
  - No food interactions
  - Rivaroxaban and dabigatran **should be taken with meals**
- Do not use in patients with antiphospholipid antibody syndrome. DOACs interfere with the lupus anticoagulant assay (false positive)
- **Hold for elective procedures:**
  - Low bleeding risk procedure,normal renal function: 24 h
  - High bleeding risk procedure,normal renal function: 48-72 h
- Reversal for life-threatening bleeding or urgent surgery
  - Idarucizumab (Mono clonal Ab against Dabigatran): reversal agent for dabigatran
  - Andexanet a (modified inactive form of factor Xa that binds to and sequesters Xa inhibitors): reversal agent for factor Xa inhibitors

THROMBOLYTICS

- limb-, life-, or organ-threatening VTE indications:
  - Bilateral renal vein thrombosis,
  - Superior vena cava (SVC) syndrome,
  - Cerebral sinovenous thrombosis(CSVT) with neurologic decline,
  - “Phlegmasi alba dolens”(extremity deep vein thrombosis [DVT]with pending limb ischemia)
  - Intracardiac thrombi causing cardiovascular instability
  - Massive pulmonary embolism
- Catheter directed thrombolysis (CDT) may reduce the severity of PTS
- Alteplase:
  - Short half-life (3-5 minutes)
  - Administered systemically or at the site of thrombosis
    - “low-dose” infusions (0.01-0.06 mg/kg/h) for 6 to 72 hours or “high-dose” infusion (0.1-0.6 mg/kg/h) for 2 to 6 hours, repeated if needed
  - Use of adjuvant UFH during systemic thrombolysis
  - Site-directed endovascular rtPA requires an experienced pediatric interventionalist (radiologist or cardiologist), but may be preferred
  - Monitoring :
    - No “therapeutic range” for thrombolysis,
    - laboratory monitoring (complete blood count, prothrombin time, partial thromboplastin time, fibrinogen, D-dimer) every 6 to 12 hours during systemic thrombolysis is recommended to assess for risk of bleeding
    - In neonates, baseline and follow-up head ultrasound should be performed

Bleeding complications

- Rate of bleeding complications in children:
  - UFH:1.5% to 24%
  - LMWH:0.8% to 5.6%
  - Warfarin:0.5% to 12.2%
- Protamine:
- The duration of protamine is approximately 2 hours, and a heparin rebound effect may occur
- Only partially reverses the anticoagulation effect of LMWH, and a repeat dose, based on anti-Xa levels, may be required secondary to the long half-life of LMWH
- Warfarin:
- Mild bleeding: Vit K
- urgent reversal of warfarin : 4 factor PCC (if not available ,FFP should be used)

Physical activity

- It is reasonable to recommend a gradual return to a **non-contact activity** starting after 3 weeks (highest risk for embolization)
- Full participation as soon as 6 weeks
- Any activity that precipitates return of symptoms should be discontinued