
بسم الله الرحمن الرحیم

A complete hematologic test profile of hypercoaguability in children with TE:

Who, When, and What Should Be Tested?

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Thrombophilia testing: who is it good for?

F.R. Rosendaal, Leiden

Inaugural meeting of Iranian Society on Thrombosis and Haemostasis

Mofid Children Hospital

Tehran, 24 December 2015

FRR

http://pchd.sbmu.ac.ir/uploads/Tehran_Thrombophilia_testing_Rosendaal.pdf

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REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Thrombophilia Testing and Venous Thrombosis

Jean M. Connors, M.D.

ORDERING THROMBOPHILIA TESTS IS EASY; DETERMINING WHOM TO test and how to use the results is not. Although inherited and acquired thrombophilias are acknowledged to increase the risk of venous thromboembolism (VTE), the majority of patients with VTE should not be tested for thrombophilia. Data showing the clinical usefulness and benefits of testing are limited or nonexistent, as are data supporting the benefit of primary or secondary VTE prophylaxis based on thrombophilia status alone. Testing for inherited thrombophilia is controversial, with some arguing that these tests should never be performed. No validated testing guidelines have been published. The American Col-

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SickKids Handbook of Pediatric Thrombosis and Hemostasis

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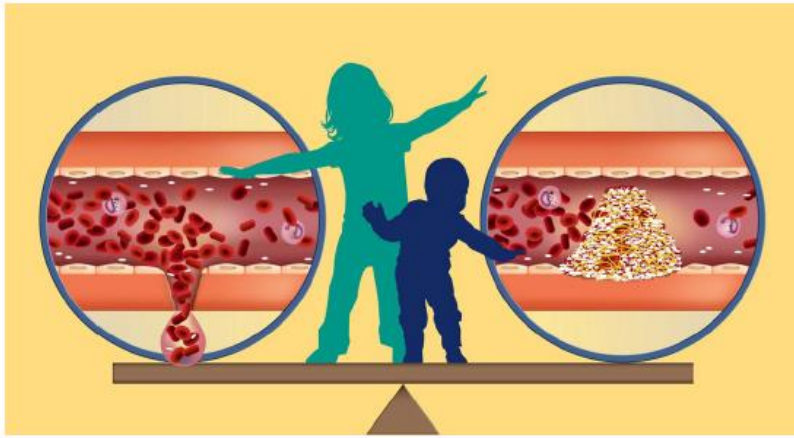
2nd, revised and extended edition



KARGER

SickKids

Thrombophilia in Children: Who to Test, How, When, and Why?

Leslie Raffini[1]

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- **Thrombophilia** refers to the propensity to develop thrombosis and can be applied :
    - Clinically to patients who develop spontaneous venous thromboembolism ,with severity out of proportion to the stimulus, recurrent thrombosis, or at a young age
    - To describe an inherited risk factor for thrombosis, which is usually identified through laboratory testing
- Individuals that demonstrate clinical “thrombophilia” do not necessarilyhave laboratory evidence of “thrombophilia,” and vice versa.

- The reported prevalence of prothrombotic conditions in pediatric stroke varies from **20% to 50%,**
- It is **common practice** to obtain a complete profile of studies for hypercoagulable states in all cases of confirmed acute AIS, **regardless of a known risk factor** such as heart disease or cervical arterial dissection.
- Inherited thrombophilias (protein C deficiency, elevated lipoprotein (a), factor V Leiden mutation and prothrombin mutation) have been associated with **an increased risk of recurrent stroke in older children**, suggesting that testing in this setting **may be useful**.

Should consider:

- High volume sampling in neonate and sick children
- Accuracy of coag. Based tests during treatment(VKDA,FFP,..)
- Cost
- Availabilty and affordability

- *SICKKIDS Handbook of Pediatric Thrombosis & Hemostasis 2013*
- *Raffini L. Thrombophilia in children: who to test, how, when, and why? ASH Education Program Book. 2008;2008(1):228-35.*

Why Test the Child with an Acute Thrombosis

Raffini L. Thrombophilia in children: who to test, how, when, and why? ASH Education Program Book. 2008;2008(1):228-35

- ***Acute management**:* Almost never influence the acute management of a patient with venous thrombosis except in:
  - **Purpura fulminant**: replacement therapy with plasma-derived concentrate (protein C or antithrombin) in case of sever PC,PS,AT def.
  - **APLA syndrome:** especially in catastrophic APS which needs PEX,CPM,Rituximab.
  - **SCA:**simple or exchange transfusion or erythraphresis
  - **Hyper-homocystinemia :** adding folate,B12,B6 may be helpful in clinical course and preventive *(Nathan &Oski 8th edit p.1070)*
- ***Duration of therapy** : rate of recurrence rate vs bleeding risk (for example Combined defects)*
- ***Thromboprophylaxis** (?):* history of VTE alone is enough to warrant early thromboprophylaxis ***in high-risk situations***
- ***Identification of other family members* to receive *Primary prophylaxis** in the presence of transient risk factors:* At present, there are **no studies** that demonstrate the benefit of such familial testing and counseling.
- ***Pathogenesis**:* particularly in the case of unprovoked events

Assesments required for all patients at the beginning of treatment

نام آزمایش	علت/ اندیکاسیون
CBC&PLT (نمونه در EDTA)	to establish the safety And kind of antithrombotic treatment for acute AIS
PT,INR,	
PTT	
*D-dimer	Diagnosis and monitoring the treatment
LFTs ;KFTs	To establish of antithrombotic treatment and adjusting the dosage

Past medical history ;physical exam. ; and imaging regarding to any bleeding event OR tendecy

Laboratory thrombophilia testing in the pediatric population

a Proposal for laboratory thrombophilia testing in neonates, children, and adolescents with VTEs and ATEs

Clinical scenario	Time	Testing	Tests included	Rationale
Purpura fulminans or nonsepsis DIC	Acute	Recommended	Protein C and S, antithrombin	Deficiency of protein S, protein C or antithrombin may warrant replacement therapy
Neonates/children/adolescents with unprovoked VTE	FU	Recommended	Thrombophilia workup	May help to determine the risk of recurrence, and to identify homozygous or combined defect May allow screening of family members (if positive)
Children/adolescents with recurrent (noncatheter related) VTE	FU	Recommended	Thrombophilia workup	May help to determine the risk of recurrence, and to identify homozygous or combined defect May allow screening of family members (if positive)
Children/adolescents with provoked (noncatheter related) VTE	FU	Suggest to discuss the utility with the patients/family	Thrombophilia workup	Insufficient data to recommend for or against
Neonates/children/adolescents with unprovoked, provoked (noncatheter related) or recurrent noncerebral ATE	FU	Suggest to discuss the utility with the patients/family	Thrombophilia workup	Insufficient data to recommend for or against
Neonates/children/adolescents with catheter-related VTE/ATE	FU	Not suggested	–	Does not influence treatment strategy

Laboratory thrombophilia testing in the pediatric population

b Proposal for laboratory thrombophilia testing in children and adolescents without a personal history of TE

Clinical scenario	Testing	Test included	Rationale
Children/adolescents with family history of TE and known or unknown (not yet tested) thrombophilia trait	May be considered in selected patients: – to guide thromboprophylaxis in high-risk patients – concurrent exposure to other prothrombotic conditions (e.g. oral contraceptive, CVC insertion for acute lymphoblastic leukemia therapy, major surgery) – for research purposes	Proteins C and S, antithrombin; prothrombin gene and FVL gene or test according to known familial thrombophilia trait If familial trait is unknown, consider testing the index family member with TE first	Current data suggest that one or more positive test results increase the likelihood to experience a TE in life Testing needs to be discussed with the family for each individual situation
Children/adolescents without family history for TE and/or for thrombophilia trait in the setting of presence or potential exposure to acquired prothrombotic condition(s)	Not recommended		No clinical trial demonstrating efficacy and risk/benefit of thromboprophylaxis No cost-effectiveness

Table 3. Recommendations regarding thrombophilia testing in children.

Who	Recommendation	Why	Comments
Adolescents with spontaneous thrombosis	Testing should be strongly considered	Identify combined defects Counsel regarding risk of recurrence Counsel/test other family members	This group has the highest prevalence of inherited thrombophilia
Neonates/children with non-catheter related venous thrombosis or stroke	Testing should be considered	Identify combined defects Counsel regarding risk of recurrence Counsel/test other family members	—
Neonates/children with symptomatic catheter-related thrombosis	Not enough data to make a recommendation	Reports vary regarding the role of thrombophilia in catheter-related thrombosis	—
Neonates/children with asymptomatic catheter-related thrombosis	Testing is not recommended	Thrombosis in the setting of catheter-related thrombosis is extremely common No data to suggest thrombophilia is increased	Consider testing if there are recurrent events
Asymptomatic children with a positive family history	Decision to test should be made on an individual basis only after counseling	Counsel adolescent females on risk of estrogen Thromboprophylaxis in high-risk situations	Be careful about false reassurance Test parent first, if possible Encourage waiting until child is older
Asymptomatic children-routine screening (prior to catheter placement, leukemia therapy or oral contraceptives)	Testing is not recommended	Not cost effective Many patients with risk factor will not have an event Catheter-related thrombosis not necessarily increased with inherited thrombophilia and there is no effective prophylaxis	—
Neonates/children participating in thrombosis research	Testing is recommended	More data on long term outcomes are needed to definitively determine the role of genetic risk factors and optimal therapies	—

Table 1. Most common thrombophilias and diagnostic laboratory studies.

An initial screen usually done during the acute stage:
Protein C, Protein S, Antithrombin, Antiphospholipid antibody screening , Hb electrophoresis*

	Prothrombin 20210 mutation	Polymerase chain reaction

Additional tests can be done acutely or, for small infants to preserve blood volume, at any time up to 3–6 months after the stroke:
activated protein C-resistance, factor V Leiden mutation, prothrombin gene mutation, lipoprotein (a), homocysteine, and factor VIII

	Elevated lipoprotein (a)	ELISA

- **Myeloproliferative neoplasms (MPN) and PNH are associated with significantly increased thrombotic risk, particularly arterial events.**
- Appropriate testing should be pursued in patients with blood count abnormalities (cytopenias, cytoses) or evidence of hemolysis.

Level II Testing*	Dysfibrinogenemia	Clotting assay (Clauss method), immunologic assay, thrombin time
	Elevated factor IX, XI	One-stage clotting assay

*if thrombophilic defect strongly suspected and level I testing is normal

Conditions associated with acquired thrombophilic laboratory abnormalities

- **Acute thrombosis**
  - Low protein S
  - Low protein C
  - Low antithrombin
- **Infection**
  - Antiphospholipid antibodies
- **Inflammation**
  - Elevated factor VIII
  - Low free protein S
  - Elevated Lp(a)
- **Nephrotic syndrome**
  - Low protein C
  - Low protein S
  - Elevated Lp(a)
- **Complex congenital heart disease (single ventricle)**
  - Low protein S
  - Low protein C
  - Low antithrombin
- **Asparaginase (acute lymphoblastic leukemia)**
  - Low antithrombin
- **Liver disease**
  - Low protein S
  - Low protein C
  - Low antithrombin
- **Warfarin therapy**
  - Low protein S
  - Low protein C
- **Heparin therapy**
  - Low antithrombin
- **Nutritional deficiency**
  - Elevated homocysteine
- **Pregnancy**
  - Low protein S

Table 3. Prevalence and impact (expressed as pooled odds ratio) of laboratory thrombophilia in childhood TEs

Thrombophilia	Prevalence	First VTE odds ratio (95% CI)	Recurrent VTE odds ratio (95% CI)	First CSVT odds ratio (95% CI)	First AIS odds ratio (95% CI)
FVL G1691A[1]	~1:20	3.8 (3–4.8)	0.6 (0.4–1.2)	2.7 (1.7–4.3)	3.7 (2.8–4.9)
Prothrombin G20210A[1]	~1:50	2.6 (1.6–4.4)	1.9 (1.0–3.5)	2.0 (0.9–4.1)	2.6 (1.7–4.1)
Protein					23.6)
Protein					.9) (R)
Antithrombin deficiency[1]	~1:50,000	9.4 (3.3–26.7)	3.0 (1.4–6.3)	18.4 (3.3–104.3)	3.3 (0.7–15.5)
Lp(a)[1]	NA	4.5 (3.3–6.2)	0.8 (0.5–1.4)	NA	6.5 (4.5–9.6)
≥2 genetic traits[2]	NA	9.5 (4.9–18.4)	4.5 (2.9–6.9)	6.1 (0.9–43.1)	18.8 (6.5–54.1)
LAC/APLA	variable	4.9 (2.2–10.9)	NA	NA	7.0 (3.7–13.1)
FVIII:C	NA	5.5 (2.0–15.1)	NA	NA	NA
FVIII:Ag	NA	4.3 (1.5–12.1)	NA	NA	NA

- The studies are limited by sample heterogeneity.
- The prevalence and impact of thrombophilia in noncerebral ATE are even less clear

Adapted from references [13–16]. FVIII:C = Activity (>90th percentiles); FVIII:Ag = antigen (>90th percentile); NA = not applicable; R = random effect model. [1] Heterozygote trait. [2] Including FVL, Prothrombin G20210A mutation, Lp(a) (>30 mg/dl), antithrombin deficiency, protein C deficiency, and/or protein S deficiency.

Decreased Natural Inhibitors of Coagulation Factors

protein C, protein S, and antithrombin

Table 5. Age-related reference ranges for coagulation inhibitors performed on an STA® analyzer

Coagulation inhibitors, % (reagent used)	Age						
	day 1	day 3	1 month to 1 year	1–5 years	6–10 years	11–16 years	adults
Antithrombin (Stachrom ATIII)	76* (58–90) n = 18 (9 F/12 M)	74* (60–89) n = 22 (10 F/12 M)	109* (72–134) n = 41 (8 F/33 M)	116* (101–131) n = 49 (26 F/23 M)	114* (95–134) n = 59 (25 F/34 M)	111* (96–126) n = 26 (8 F/18 M)	96 (66–124) n = 43
Protein C chromogenic (Chromogenic-Stachrom Protein C)	36* (24–44) n = 22 (9 F/13 M)	44* (28–54) n = 21 (10 F/11 M)	71* (31–112) n = 25 (5 F/20 M)	96* (65–127) n = 42 (21 F/21 M)	100 (71–129) n = 53 (21 F/32 M)	94* (66–118) n = 25 (8 F/17 M)	104 (74–164) n = 42
Protein C clotting (Clotting-Staclot Protein C)	32* (24–40) n = 20 (9 F/11 M)	33* (24–51) n = 22 (11 F/11 M)	77* (28–124) n = 24 (4 F/20 M)	94* (50–134) n = 39 (16 F/23 M)	94* (64–125) n = 50 (17 F/33 M)	88* (59–112) n = 20 (6 F/14 M)	103 (54–166) n = 44
Protein S clotting (Clotting (functional)-Staclot Protein S)	36* (28–47) n = 22 (13 F/9 M)	49* (33–67) n = 24 (11 F/13 M)	102* (29–162) n = 41 (8 F/33 M)	101* (67–136) n = 49 (26 F/23 M)	109* (64–154) n = 59 (25 F/34 M)	103* (65–140) n = 27 (9 F/18 M)	75 (54–103) n = 44

For each reagent the first two rows show the mean and boundaries including 95% of the population. The last two rows show the number of individual samples and the ratio of females (F) to males (M) for each group. * Denotes values that are significantly different from adult values ($p < 0.05$). Modified from Monagle et al. [6].

- Acquired PC and PS deficiency:
  - Increased consumption in : sepsis- and non-sepsis associated DIC, acute TE settings, infections (typically varicella for protein S) or
  - Decreased production such as by vitamin K deficiency, liver disorders, or medications (e.g. VKAs, oral contraceptives, asparaginase chemotherapy)
    - laboratory testing to investigate protein C and/or S circulating levels should occur at least 2 weeks after VKA discontinuation.
- Acquired AT deficiency can occur in association with :
  - Large protein losses (e.g. nephrotic syndrome), liver disease, sepsis, and treatment with asparaginase chemotherapy
- Patients with antithrombin deficiency may be heparin resistant

Resistance to Natural Inhibitor of Coagulation:

- **FVL Mutation :**the most common genetic disorder associated with thrombosis in adults and in children, 5% carrier rate in Caucasian
- Heterozygous mutation is associated with a low-to-mild risk and Homozygous mutation with greater risk of VTE and stroke in children
- **Acquired APCR** : may occur in the setting of oral contraceptive use or in association with high concentrations of coagulation FVIII
- **Tests:**
  - Activated Protein C Resistance (Blood Collected into Citrate)
  - FVL Mutation (Blood Collected into **EDTA)**

Biochemical Mediators of Endothelial Damage:
1- APLA

- APLA include:
  - *Lupus Anticoagulant (LAC) : (Blood Collected into Citrate).*three sequential laboratory steps :
    - (1) demonstration of an abnormal phospholipid-dependent coagulation screening test (using diluted Russell viper venom test and/or a lupus-sensitive aPTT),
    - (2) a mixing study
    - (3) a confirmatory test, which incorporates the addition of exogenous phospholipids to prove that the abnormality is phospholipid dependent.
  - ACLA and β 2 -GPI Abs Both IgG and IgM are measured by immunoassay (ELISA): *(Blood Collected into Clotted Blood Tube)*
- Positivity for **one** APLA carries a lower risk of thrombosis or pregnancy complications compared to those with **multiple (particularly triple**) positivity
- *May be transient due to* acute infection, inflammation, malignancy, and medications ,also in newborn infants with a positive maternal history for APS
- Assessment for the presence of an LAC may be helpful **prior to initiation of anticoagulation (including warfarin, heparins, and the direct oral anticoagulants)** since anticoagulation may affect the interpretation of LAC screens
- Children presenting with an unprovoked TE should be assessed for the presence of APLA.

Biochemical Mediators of Endothelial Damage:
2- Homocysteine

- *Homocysteine assay: (Fasting Blood Collected into Heparin)*
- Significance:
  - Polymorphisms in the MTHFR gene, such as MTHFR C677T mutation. Even in homozygotes, causes ONLY a mild elevation of the homocysteine level, which is usually ONLY in the presence of a subtherapeutic level of folic acid; therefore:

    MTHFR polymorphism independent of homocysteinemia does not increase the risk of TE

    (i.e. MTHFR genetic testing is likely not recommended).

- Homocystinuria is a genetic metabolic disorder leading to very high serum homocysteine levels (typically > 100 mmol/L), a high risk of arterial thromboembolism, and characteristic manifestations (Marfanoid) in children and young adults.

Elevated Procoagulant Factors

- *Prothrombin (II) G20210A Mutation (Blood Collected into EDTA)*

- *Elevated FVIII (Blood Collected into Citrate):*
  - >90th percentiles for their respective age-appropriate value)
  - One stage method
  - **Persistent elevated plasma FVIII level**, potentially reflecting a genetic trait, appears to be of more relevance as a risk factor for VTE than does an acute transient elevation of FVIII level (**acute phase reaction**):
    - measurement of FVIII is suggested usually 3–6 months after the acute phase of the event
    - measurement of FVIII plasma levels in the parents may be helpful

Decreased Antifibrinolytic Activity:

- Apolipoprotein A [Lp(a)] assay: **(Blood Collected into EDTA)**
- Competetive antagonism with Plasminogen and TPA; inducing secretion of the plasminogen; Athgerosclerosis because of LDL.
- The association between elevated Lp(a) and the risk for VTE or ATE in children is not clear

Table 1. Antithrombotic agents used to treat arterial thrombosis in children

Treatment modality	Mode of action	Route	Half-life	Antidote
Anticoagulation				
Heparin	Thrombin and FXa inhibitor (AT-dependent)	i.v.	30 min.	Protamine
LMWH	FXa inhibitor (AT-dependent)	s.c	6 hours*	Protamine (partial)
Bivalirudin	Direct thrombin inhibitor	i.v.	25 min.	None
Argatroban	Direct thrombin inhibitor	i.v.	40 min.	None
Vitamin K-antagonist	γ-carboxylation Inhibitor	p.o.	10-90 hours**	Vitamin K
Antiplatelet				
Aspirin	Cyclooxygenase activity inhibitor	p.o.	5-7 days***	Platelet transfusion
Dipyridamole	Phosphodiesterase and adenosine deaminase	p.o.	12-24 hors***	Platelet transfusion
Clopidogrel	Irreversible binding to the P_2Y_{12}-ADP receptor	p.o.	7-14 days***	Platelet transfusion
Fibrinolysis				
rtPA (Alteplase)	Conversion of plasminogen to plasmin	i.v.	5 min.	None

Treatment of arterial thrombosis in children: Methods and mechanisms. *Thrombosis Research,* 18 June 2018

Table 3. Published guidelines for the treatment of acute ischemic stroke (AIS) in children.

Type of arterial thrombosis	Source	Recommendation	Duration of therapy	Comments
Neonates				
General (first event)	Chest 2012[21]	No treatment	NA	
	UK 2005[57, 58]	NA	NA	
	AHA 2008[44]	UFH or LMWH	NA	Only when severe thrombophilia or embolization is present
Cardioembolic	Chest 2012[21], expert opinion[59]	UFH or LMWH	3-6 months	ASA if cardiac defect persist
	UK 2005[57, 58]	NA	NA	
	AHA 2008[44]	UFH or LMWH	NA	Only when severe thrombophilia or embolization is present
Recurrent	Chest 2012[21]	UFH or LMWH or ASA	Indefinite time	
	UK 2005[57, 58]	NA		
	AHA 2008[44]	UFH or LMWH	NA	
Non-neonates				
General	Chest 2012[21]	UFH or LMWH or ASA	2 years (ASA)	Consider initial UFH for 5 to 7 days until cardioembolic and dissection excluded.
	UK 2005[57, 58]	ASA	NA	
	AHA 2008[44]	UFH or LMWH	1 week	1 week after an ischemic stroke pending further evaluation to determine the cause of the stroke
Cardioembolic	Chest 2012[21], expert	UFH or LMWH or VKA	3-6 months or longer if risk	

Antithrombotic Recommendations for Children (Non-Neonate) with Arterial Ischemic Stroke

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- Begin antithrombotic therapy promptly provided that initial imaging shows no ICH, with or without confirming the presence of thrombophilia:
  - Initial therapy may be with UFH, LMWH, or ASA (1–5 mg/kg)
- Once dissection and cardioembolic causes are excluded ,daily ASA prophylaxis is recommended.
- The duration of therapy : continue daily ASA prophylaxis therapy for a minimum of 2 years
- Recurrent AIS while on ASA therapy:it is reasonable to change to clopidogrel [0.2–1 mg/kg/day, rounded to one-quarter or one-half tablets (75 mg tablets)] or to anticoagulant therapy with LMWH or VKA
- AIS secondary to a cardioembolic cause, anticoagulation with LMWH or VKA is recommended for at least 3 months
- Hold anticoagulation If there is : hemorrhagic conversion; severely hypertensive ; risks for bleeding, anticoagulation treatment
  - A close follow-up brain imaging (CT or MRI) is recommended
- Postpone beginning anticoagulation later than 48–72 h after stroke onset in hopes of minimizing the risk if there is large territorial infarctions (e.g. >2/3 of the MCA territory)
  - A close follow-up brain imaging (CT or MRI) is recommended

Antithrombotic Recommendations for Neonate with Arterial Ischemic Stroke

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- The importance of inherited thrombophilia in the pathophysiology and long-term outcomes of peri natal stroke is not yet proven : **NO evidence to support routine extensive thrombophilia screening**
- Fewer than 5% of neonates with noncardiogenic AIS have recurrent systemic or cerebral thrombosis :**Anticoagulation or ASA is NOT recom mended anticoagulation should be considered**
- Neonates with cardioembolic AIS have a 14% risk of recurrent AIS : **Anticoagulation with either UFH or LMWH for 3–6 months, followed by ASA (if the cardiac defect has not been fully repaired)**

- Moyamoya related AIS :
  - ASA may be useful in preventing moyamoya
  - Anticoagulants are rarely recommended because of the perceived risk of ICH
- SCA related ASI:
  - The use of antithrombotic therapy in primary and secondary AIS prevention in patients with SCD is controversial: the perceived increased risk of hemorrhage in patients with moyamoya-type vasculopathy.
  - The basic principle for SCD stroke treatment is to improve oxygen delivery to the brain

Thrombolysis in Hyperacute AIS

- As per the American Heart Association guidelines and others, t-PA is not recommended for stroke in children outside of a study setting
- However, in young adults (adolescents, teenagers), no consensus against its use has been established.

Roach ES, Golomb MR, Adams R, Biller J, Daniels S, Deveber G, et al: Management of stroke in infants and children: a scientific statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young. Stroke 2008; 39: 2644–2691.

Management guideline for CSVT in neonates:

- **2.17. For neonates with cerebral sinovenous thrombosis (CSVT) without significant intracranial hemorrhage, we suggest :**
  - **anticoagulation, initially with UFH or LMWH and subsequently with LMWH, for a total therapy duration between 6 weeks and 3 months rather than shorter or longer treatment duration** (Grade 2C) **.**
- **For neonates with CSVT with significant hemorrhage, we suggest :**
  - **either (1) anticoagulation**
  - **or (2) supportive care with radiologic monitoring of the thrombosis at 5 to 7 days and anticoagulation if thrombus extension is noted as compared with no therapy** (Grade 2C) **.**

Antithrombotic Therapy in Neonates and Children, CHEST / 141 / 2 / FEBRUARY, 2012 SUPPLEMENT

Management guideline for CSVT in children:

- **2.51. For children with CSVT without significant intracranial hemorrhage, we recommend :**
  - **anticoagulation initially with UFH or LMWH and subsequently with LMWH or VKA for a minimum of 3 months relative to no anticoagulation** (Grade 1B) **. In children who after 3 months of therapy still experience occlusion of CSVT or ongoing symptoms, we suggest administration of a further 3 months of anticoagulation** (Grade 2C) **.**
- **For children with CSVT with significant hemorrhage, we suggest:**
  - **initial anticoagulation as for children without hemorrhage OR**
  - **radiologic monitoring of the thrombosis at 5 to7 days and anticoagulation if thrombus extension is noted at that time** (Grade 2C) **.**
- **In children with CSVT and potentially recurrent risk factors (for example, nephrotic syndrome, asparaginase therapy), we suggest prophylactic anticoagulation at times of risk factor recurrence** (Grade 2C) **.**
- **We suggest thrombolysis, thrombectomy, or surgical decompression only in children with severe CSVT in whom there is no improvement with initial UFH therapy** (Grade 2C) **.**