CARDIOLOGY 2023

ANTICOAGULATION IN CHILDREN WITH HEART DISEASE

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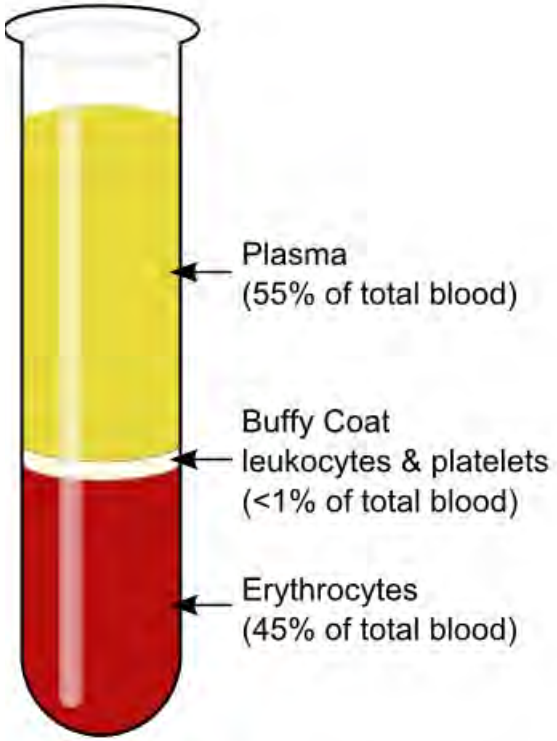
I have no disclosures

2/26/2022

WHAT IS BLOOD?

- 55% plasma
  - 90% of this is water
  - 8% soluble proteins
    - albumin, globulins, coagulation proteins
  - 1%-2% electrolytes and glucose

- 45+% formed elements
  - Cells: RBCs, WBC, and platelets



WHAT IS THE FUNCTION OF BLOOD?

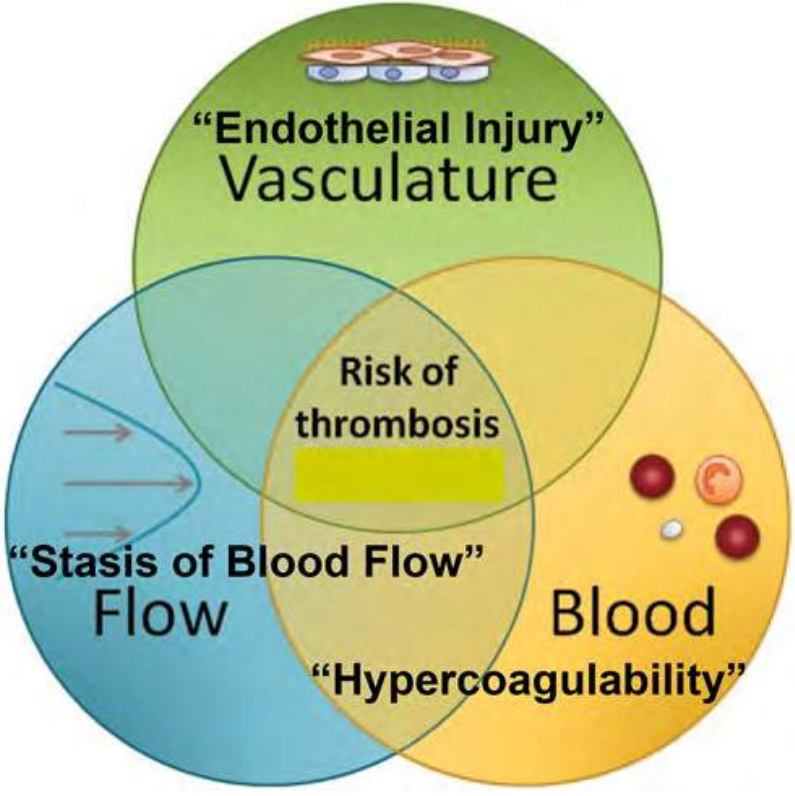
- Oxygen delivery: Delivers oxygen (RBCs/hemoglobin) and nutrients to the heart, brain, and other organs for metabolism
- Transportation: Transports electrolytes(na,ca,k,mg), nutrients (glucose), waste products (urea/nitrogen), immune cells…venous, arterial, and lymphatic vasculature connected
- Immunity: Maintains immune surveillance, protection, transportation, communication (Neutrophils, Macrophages, Lymphocytes)
- Coagulation and Anticoagulation: Blood MUST be maintained in a fluid state BUT if there is a breach in vascular integrity(injury), it must clot to repair it, and then dissolve the clot(clean up)…processes are interlinked…communication and feedback…coagulation proteins, platelets

WHY DOES BLOOD NOT CLOT?

- Despite the vast numbers of platelets and coagulation proteins, blood is a liquid that is not clotting, unless it is triggered to do so…
- Why?
  - Coagulation proteins(Factors) must be converted to active forms, at baseline they are inactive
  - Platelets must be activated to be “sticky” and form a plug
  - Endothelium is smooth, not rough, not thrombogenic, and collagen is not exposed unless there is an injury…or trigger
  - Blood flows briskly, it is not stagnant, and it carries away activated proteins and platelets

WHY DOES BLOOD CLOT?

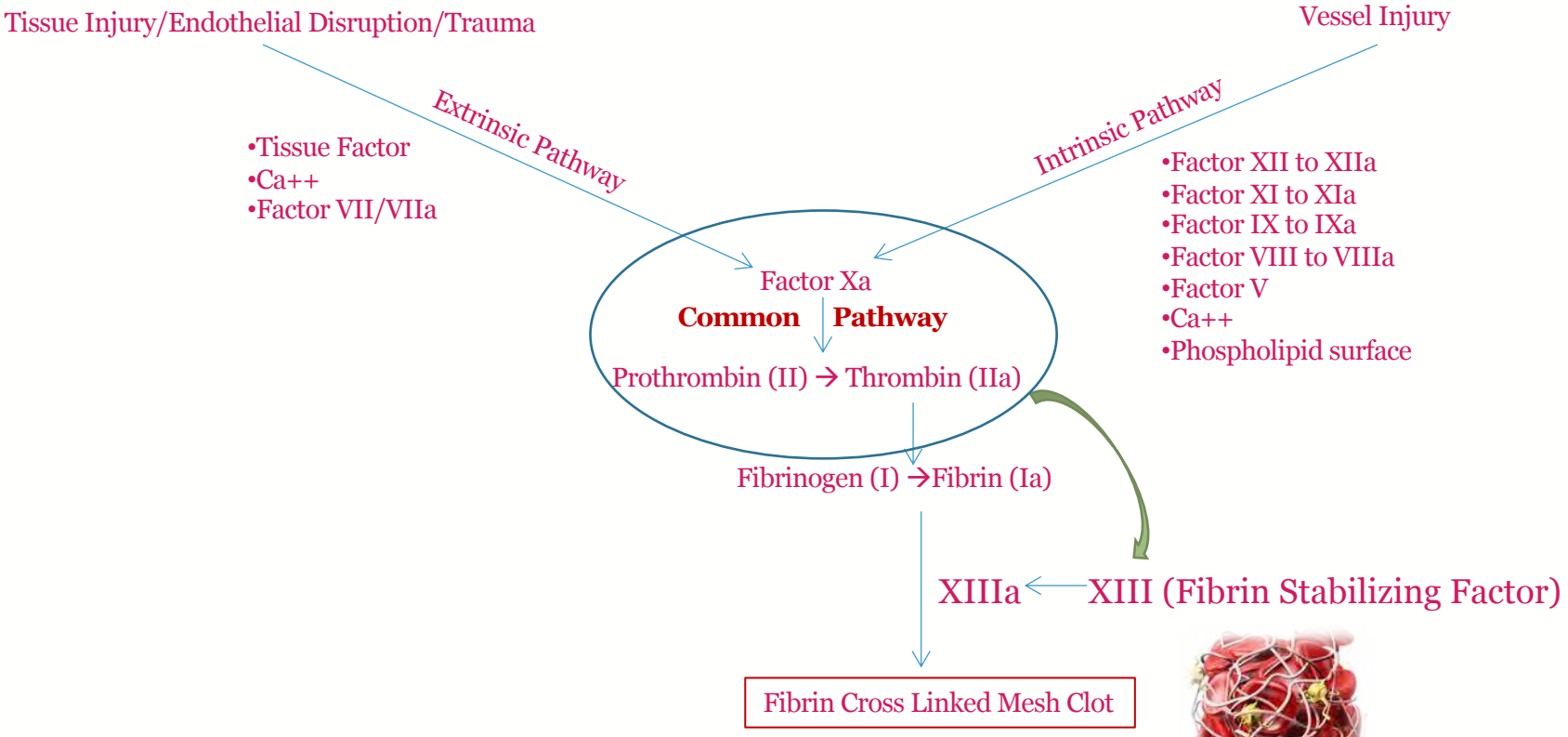
Virchow (1856) identified 3 components that promote thrombosis



The "Thrombus/Clot Team"

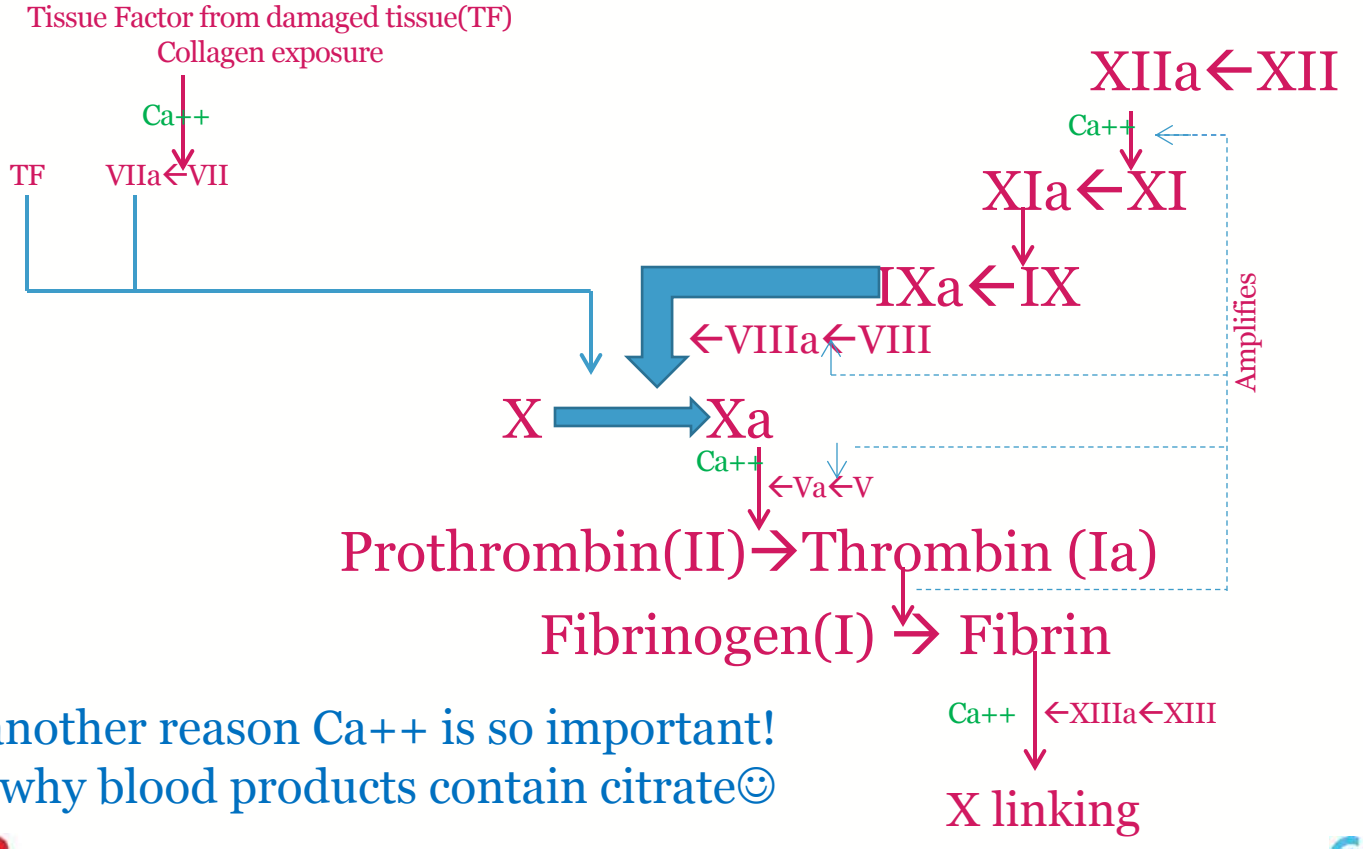
- Platelets
- Calcium
- Coagulation Proteins
- Phospholipid membrane
- Vitamin K
- Endothelium of blood vessels
- Liver makes the coagulation proteins

HOW DOES BLOOD CLOT?



EXTRINSIC PATHWAY

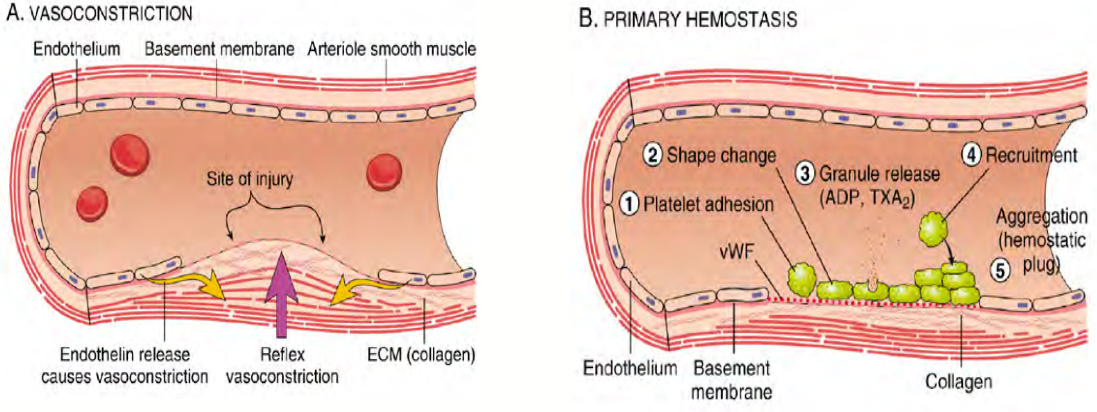
INTRINSIC PATHWAY



Yet another reason Ca++ is so important!
And why blood products contain citrate☺

HEMOSTASIS: PLATELET PHASE

1. Smooth, non thrombogenic endothelial surface is injured
2. Basement membrane exposed, collagen is exposed
3. Vasoconstriction

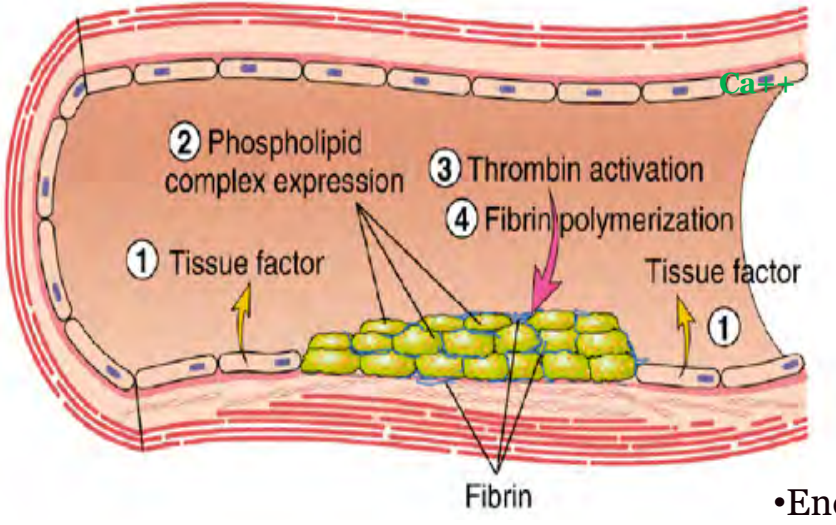


Aspirin is a cox inhibitor ;
it inhibits Thrombaxane A2 (TXA2)
and platelets are not able to "stick

- **Von Willebrand Factor** binds to site
- Glycoprotein Ib
- Platelets activated→ADP & ThromboxaneA2→Recruitment/Aggregation/"Sticky"
- Platelet Plug…but it is not stable

Thrombus

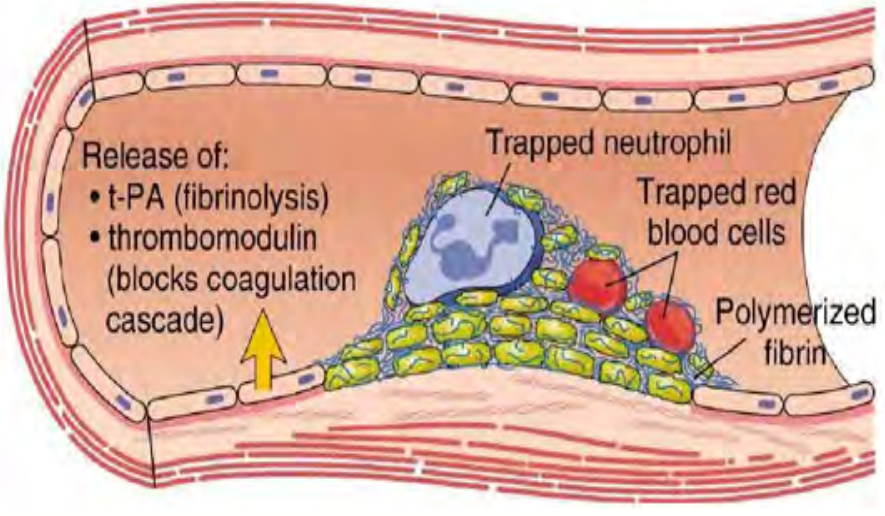
INTRINSIC or EXTRINSIC PATHWAYs
Fibrin →Fibrin Mesh/Thrombus



UFH and LMWH potentiate Antithrombin IIIa inhibiting Thrombin and Xa

"Natural" Anticoagulation

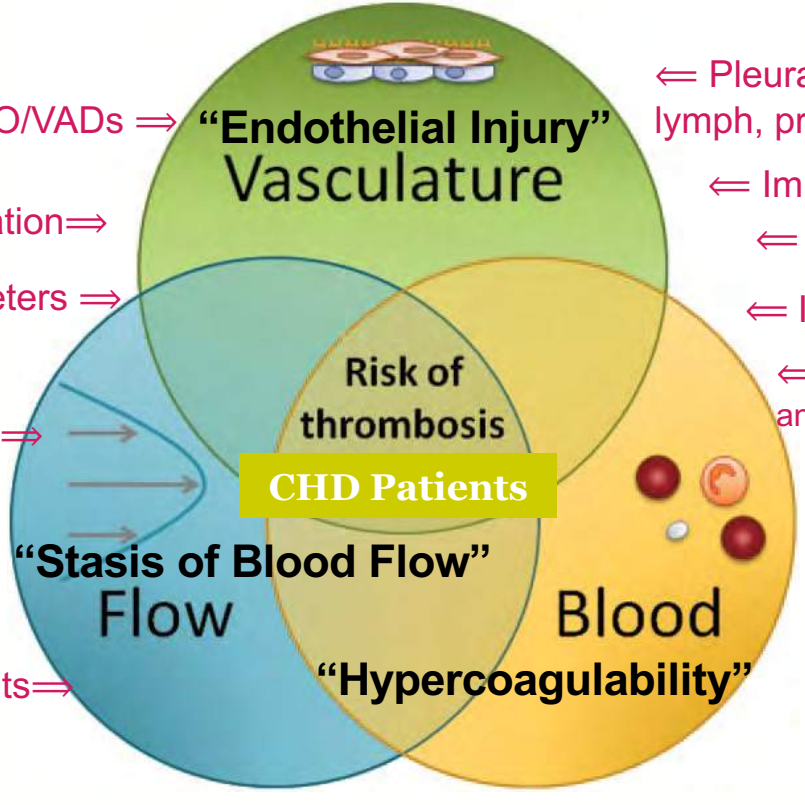
Anticoagulation Triggered



•Endogenous Antithrombin IIIa inhibits Thrombin and Xa
•tPA triggers Plasmin which begins to degrade the fibrin mesh

Can administer IV tPA to dissolve clots

WHY ARE CHD PATIENTS AT RISK FOR THROMBUS?



CPB/ECMO/VADs ⟹

Cardiac Catheterization⟹

Central venous catheters ⟹

PICC lines⟹

Arterial catheters⟹

Intracardiac lines ⟹

Prosthetic valves⟹

Stents and shunts and conduits⟹

⟸ Pleural/Chylous effusions with loss of lymph, proteins(coagulation proteins)

⟸ Immobility (older children)

⟸ Sedation/Paralysis

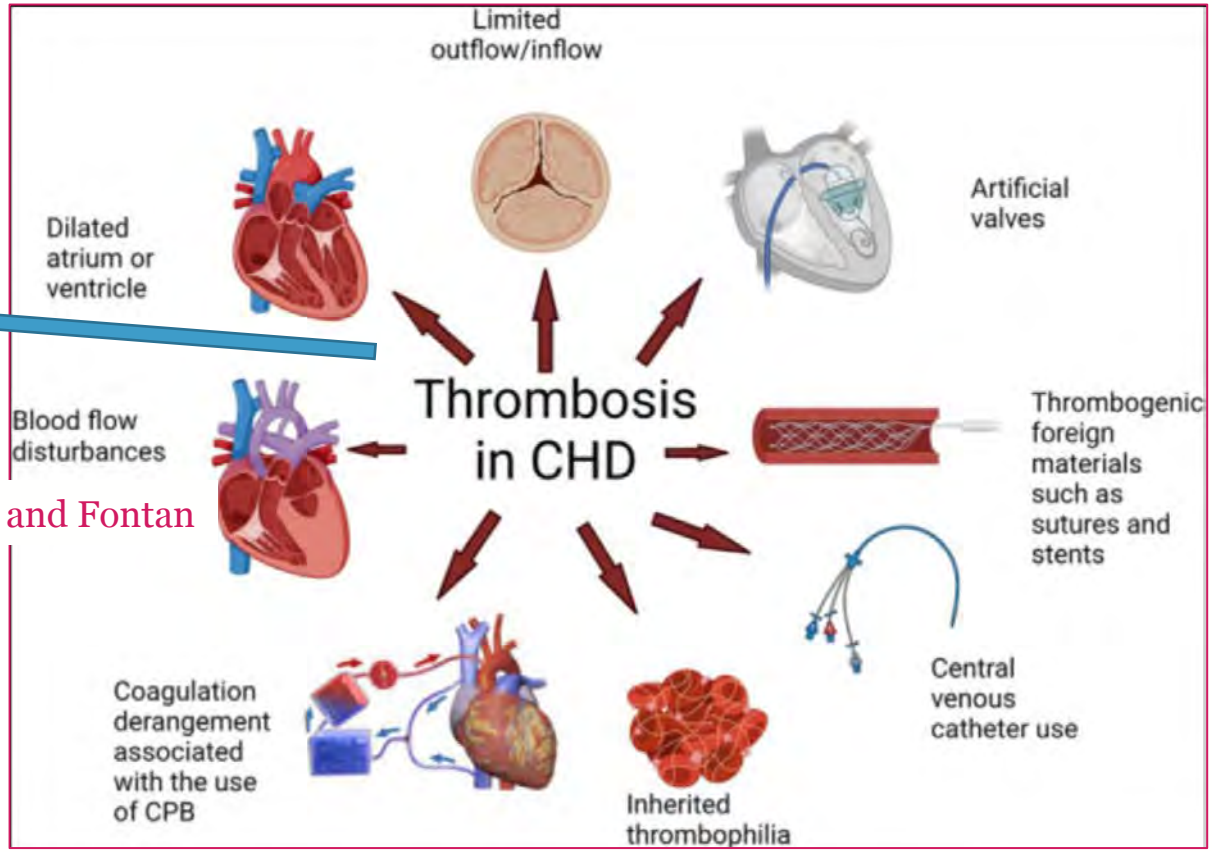
⟸ Inflammation/infection

⟸ Age~neonates have less antithrombin III

- Single Ventricle
- Kawasaki Disease
  - Coronary Aneurysms
- Cardiomyopathy/Myocarditis
- VADS
- Prosthetic Valves

Virchow's Triad: Factors that Predispose to Thrombosis (1856)

- ECMO
- VAD
- Stent in duct
- Shunt
- Kawasaki Disease
- Rhythm issues

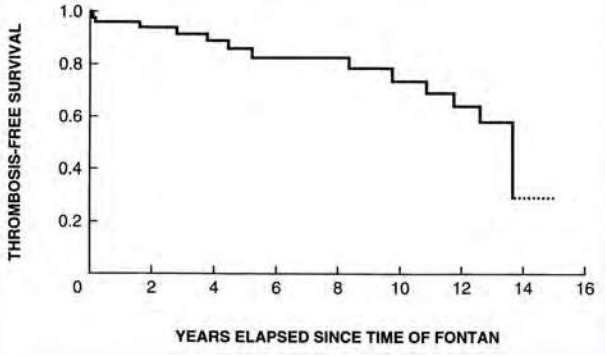


SV and Fontan

- Abdelghani E, Cua CL, Giver J, Rodriguez V. Thrombosis Prevention and Anticoagulation Management in the Pediatric Patient with Congenital Heart Disease. Cardiol Ther. 2021 Dec;10(2):325-348. doi: 10.1007/s40119-021-00228-4. Epub 2021 Jun 29. PMID: 34184214; PMCID: PMC8555036.

CHD and Thrombosis

- Children with one or more of “Virchow’s factors” are a ***clot waiting to happen***
- Patient individual risk may change over time as factors are added or subtracted
  - Neonates and “sick” children have low endogenous antithrombin
  - Risk increases with hospitalizations (venous lines, inflammation, sepsis, surgical procedures requiring usual anticoagulation to be paused)
  - Kawasaki Disease: presence and size of the coronary aneurysm determines the level of anticoagulation recommended *(McCrindle et.al.,Circulation.2017;135.)*
  - Fontan: thrombosis risk is higher first year post-op and then again 6+ years later after the Fontan *(Rosenthal, et.al. Circulation. 1995;92:287–293)*



	Population	Incidence	Significant Risk Factors	Notes
Manlhoit 2011	Pediatric n= 1542	11% (60% symptomatic)	age < 31d, sat <85%, previous thrombosis, transplant, DHTA, ECMO, longer time w CVL	Thrombosis associated w longer ICU/hosp stay, higher OR arrest, cath intervention, reoperation, mortality
Hanson 2012	Pediatric n=1070	3.8% (VTE only)	SV physiology, longer time w CVL	
Emani 2014	Neonatal n=100	20%	SV physiology	All pts w CVL and prosthetic material received UFH at 10 U/kg/hr. Mortality signif higher for those w thrombosis
Silvey 2018	Pediatric n= 91909 PHIS database	2.9% within 12m of OR	Highest prevalence in neonates, BTS and septostomy	"Thrombosis rate is increasing" 1.7% 2004 to 4.4% 2012. Thrombosis associated w longer LOS, cost, bacteremia and mortality

WHO SHOULD BE ANTICOAGULATED?
Prevention(Thromboprophylaxis) & Treatment

Thrombosis	Prevention	Treatment
Venous	• Central venous catheter • Critically ill • Trauma • Perioperative prophylaxis	• Deep vein thrombosis and pulmonary embolism • Cerebral sinovenous thrombosis
Both	• Cardiac catheterization • Shunts (e.g., Fontan); stents • Hemodialysis • Extracorporal membrane oxygenation • Cardiopulmonary bypass surgery • Ventricular assist devices	• Cardiac thrombosis
Arterial	• Central arterial catheter • Mechanical heart valves • Dilated cardiomyopathy • Kawasaki's syndrome	• Arterial thrombosis • Arterial ischemic stroke

Male C. Anticoagulation in Pediatric Patients. Hamostaseologie. 2022 Feb;42(1):46-53. doi: 10.1055/a-1703-0821. Epub 2022 Jan 18. PMID: 35042258.

WHAT ARE THE OPTIONS? 3 CATEGORIES

- **Anticoagulants**
  - Unfractionated Heparin (UFH)
  - Low Molecular Weight Heparin (LMWH)
  - Fondaparinux
  - Warfarin
  - Direct Thrombin Inhibitors (IV)
    - Bivalirudin
    - Lepirudin
    - Argatroban
  - Direct Oral Anticoagulants (DOAC's)
    - Direct Anti –Xa Inhibitors
      - Rivaroxaban (Xarelto)
      - Apixaban (Eliquis)
      - Edoxaban (Lixiana)
    - Direct Thrombin Inhibitor
      - Dabigatran (Pradaxa)

Antiplatelet Agents

Aspirin
Clopidogrel (Plavix)
Dipyridamole (Persantine)

Thrombolytic Agents

Tissue Plasminogen Activator (tPA)

ADMINISTRATION/RATIONALE IMPACT CHOICE

IV

- UFH
- Bivalirudin
- tPA

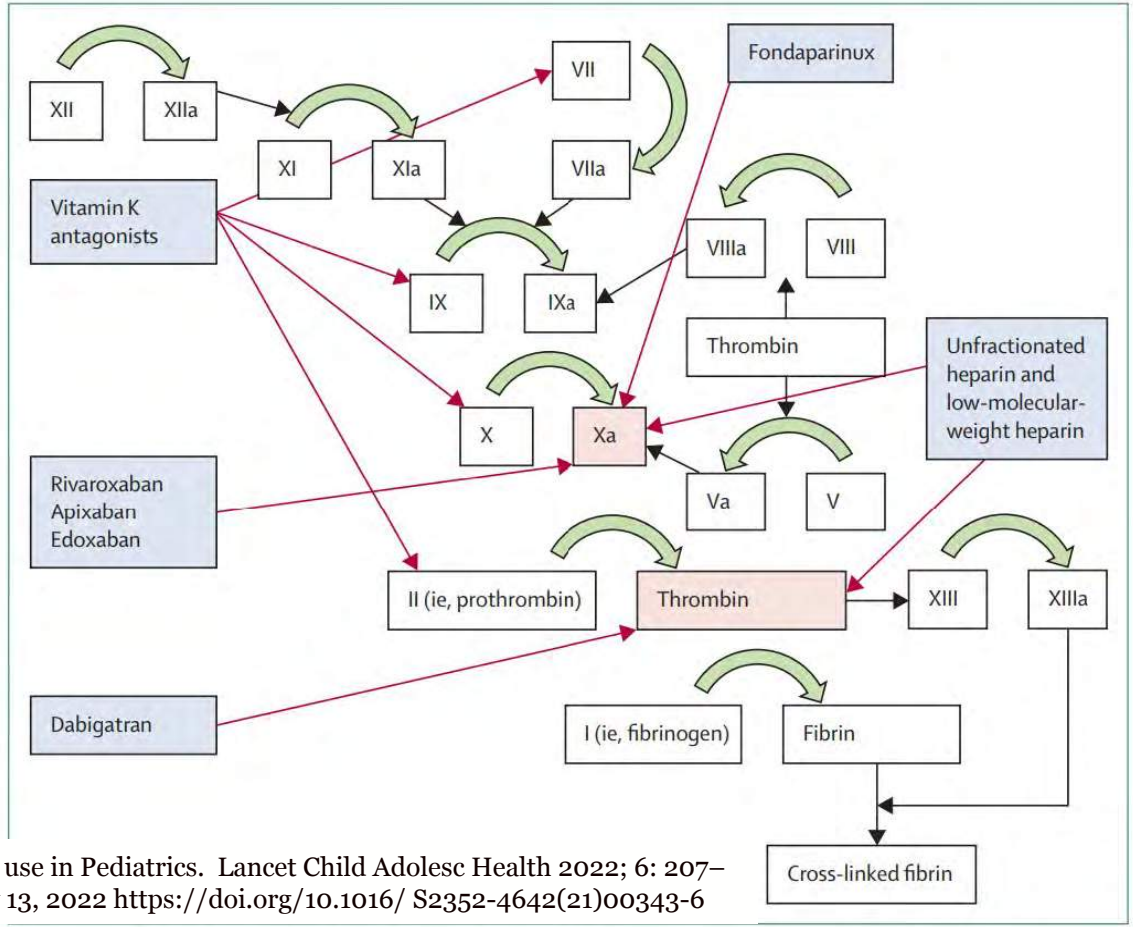
SubQ

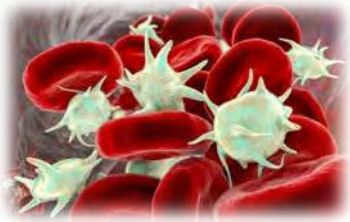
- LMWH
- Fondaparinux

Oral

- Platelet inhibitors (ASA)
- Warfarin
- DOACs

HOW DO THEY WORK?





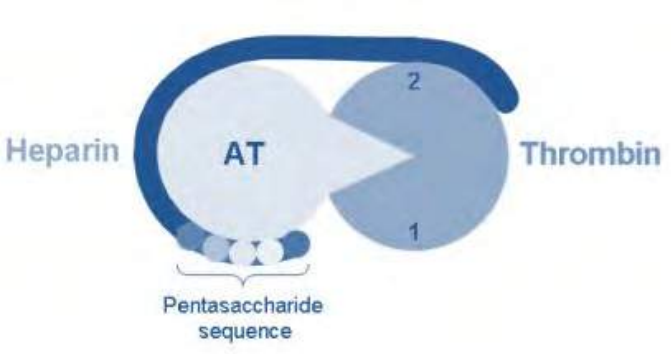
Platelet Inhibition
- Aspirin
- Plavix
- Dipyridamole

Direct Oral Anticoagulant for use in Pediatrics. Lancet Child Adolesc Health 2022; 6: 207–14. Published Online January 13, 2022 https://doi.org/10.1016/ S2352-4642(21)00343-6

UNFRACTIONATED HEPARIN (UFH)

- UFH binds to the enzyme inhibitor antithrombin III and activates it by increasing the flexibility of its reactive site loop
- Activated ATIII/Heparin complex binds with and inactivates thrombin
- Heparin/ATIII also inactivates Factor Xa
- Called “Unfractionated Heparin” or UFH to distinguish it from the LMWHs; however, in general it is simply referred to as heparin
- Derived from porcine intestine
- Antidote is protamine

Protamine is positively charged molecule that binds to the negatively charged Heparin molecule and neutralizes it



UNFRACTIONATED HEPARIN (UFH)~HEPARIN

- Prevents the formation of clots and extension of existing clots…but does not break down clots that have already formed
- No renal/hepatic adjustments needed
- Heparin is degraded in the stomach, cannot be given orally, only parentally
- Half life of 1.5 hours, so needs to be given IV and as a continuous infusion
- Does not cross the placenta
- Drug of choice of short-term anticoagulation, surgery/cath lab/etc, but more are exploring bivalirudin for this
- Availability of an immediate antidote (protamine sulfate) if there is bleeding
- Usual choice to initiate anticoagulation…and can then bridge to something oral
- Short half-life makes it useful in critically ill patients where there is concerning for bleeding as well as clotting or the need for procedures where anticoagulation needs to be stopped (4-6 hr off time)
- Follow aPTT and/or Anti Xa levels

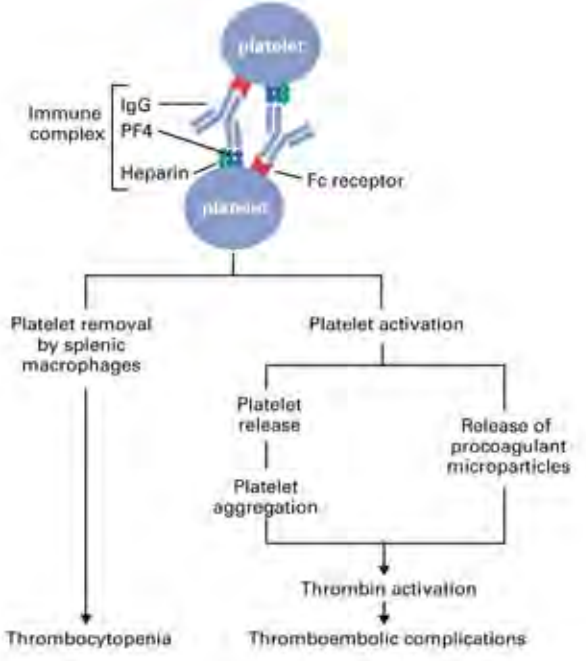
UFH LIMITATIONS

- Laboratory monitoring of heparin challenging!!
    1. Different assays used for therapeutic drug monitoring (the activated partial thromboplastin time [aPTT], the anti-factor Xa level, and the activated clotting time), all of which have their own limitations
    2. Degree to which these assays accurately reflect the degree of " real time" anticoagulation is not entirely clear, and several studies have demonstrated discrepancies between the aPTT and the anti-Xa assay, and it is not entirely clear which laboratory test reflects reality
- High degree of patient variability in the pharmacokinetics of heparin further complicating management
- Heparin therapy can result in heparin-induced thrombocytopenia (HIT), a serious adverse effect that can go unrecognized in children owing to its rarity
- Heparin is a biologic compound (pig intestines and bovine lungs) and, therefore, subject to potential contamination, which has in the past led to severe complications
- Despite these limitations, heparin is widely used in children, and is still considered the first-line therapy for the prevention of thrombosis in patients undergoing cardiac catheterization and cardiopulmonary bypass surgery, and for anticoagulation of extracorporeal circuits (many now prefer bivalirudin)

Of note, only 2 prospective studies of heparin in children… 65 and 38 patients treated both prophylactically and for prevention of thrombosis in patients with congenital heart disease but many of us have a history and a level of comfort with heparin despite the concerns

HEPARIN INDUCED THROMBOCYTOPENIA (HIT)

- "Usually" Heparin prevents clotting but does not impact platelets
- But the immune system, in response to heparin, can cause thrombocytopenia or HIT
- 2 types: Nonimmune and Immune-mediated HIT
  - Nonimmune HIT, which occurs most frequently, is characterized by a mild decrease in the platelet count and is not harmful
  - Immune-mediated HIT is dangerous
    - An immune complex forms between heparin and a specific blood factor (platelet factor 4, or "PF4") that is released by platelets
    - The body views this "heparin-PF4" complex as a foreign substance and antibody is formed against the heparin-PF4 complex
    - The antibody binds to this complex and the platelets are destroyed but it also activates other proteins as well as the coagulation pathway and thrombin production
  - Platelets fall, your patient is at risk for clotting and bleeding
- The treatment for HIT is to stop Heparin



LOW-MOLECULAR-WEIGHT HEPARIN (LMWH)

- Derived from heparin but shorter polysaccharide chains
- Inhibits Factor Xa, thus prevents the prothrombin to thrombin split
- More stable, longer half life
- More predictable dose response and able to be used in outpatient setting
- Anticoagulated immediately
- NO food or drug interactions
- Measure AntiXa levels, but more predictable, so less measuring needed
- Over past 20 years many consider LMWHs to be first line for treatment/prevention of VTEs
- In pediatrics, twice daily dosing (injections)
- Neonates who cannot take a warfarin pill
- Bridging patients from warfarin or to warfarin, in many situations has replaced heparin as a bridging option
- Can still see HIT, but less so
- BUT…This is a SQ Injection only!

LMWH Dosing

- Prophylaxis vs Treatment dosing
- 0.5mg/kg vs 1mg/kg BID or 1.5mg/kg daily
- Half life of 4 hours
- AntiXa therapeutic range 0.5-1.2 unit/ml
- Measure levels 4 hours after dose
- Hold 12-24h for procedures
- Bridging options to and from heparin and to and from warfarin
- Antidote is protamine, but it is less effective with LMWH

- Clinical practice pathway for post-cath pulse loss in infants → 89% resolution w 12 wks of Rx

  (Glatz, et al. Catheter Cardiovasc Interv. 2015 Jan 1;85(1):111-7)
- Clinical practice guideline for catheter-associated VTE in infants → 70.7% complete or partial resolution w 12wks of Rx *(Linder et.al. J Am Coll Cardiol. 2019 Mar, 73 (9_Supplement_1) 628)*
- Renal excretion so EXTREME CAUTION or do not use with renal failure
- Long term use associated with osteoporosis!
- Sub Q injections ☹

FONDAPARINUX

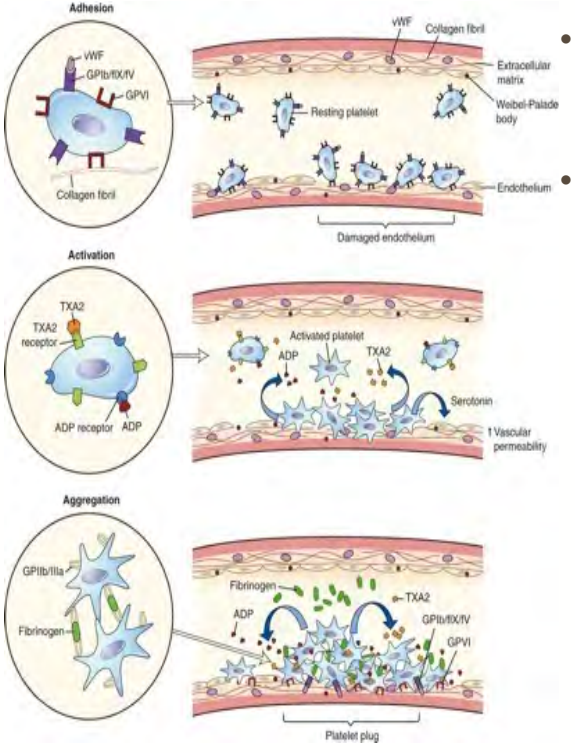
- Synthetic antithrombin dependent inhibitor of factor Xa
- By selectively binding to AT, fondaparinux potentiates the neutralization of factor Xa …neutralizes it…but it does not inactivate thrombin
- Daily Sub Q injection (0.1 mg/kg), longer half life than LMWH, but like LMWH clearance is renal
- Monitor with anti-Xa
- No reversal agent…and a long half life
- Pediatric studies suggest may be an option instead of LMWH but in patients who are stable with LOW risk for bleeding

DIRECT THROMBIN INHIBITOR (IV ONLY): BIVALIRUDIN

- Bivalirudin is a Direct Thrombin Inhibitor that binds directly to both circulating AND clot bound Thrombin
- Used for UFH failures and in patients with suspected or confirmed HIT
- 20% is renally cleared, and so doses should be reduced in patients with renal insufficiency
- Half life is 25 minutes
- Impacts the PTT, ACT, PT, INR and the Diluted Thrombin Time (DTT)
- Lab monitoring is with PTT (early on) and DTT with DTT more sensitive
- Relatively easy to reach and maintain therapeutic levels (DTI 60-90)
- No antidote; treat by stopping (short half life), consider recombinant Factor VIIa, continuous renal replacement therapy, plasmapheresis
- With ASA, a game changer in Berlin Heart anticoagulation: incidence of stroke was reduced by 44% *(J Heart Lung Transplant 2021;40:251–259)*
- Used in some institutions as cath lab procedural anticoagulant in neonates/infants with superior results to UFH (CHOP QI: dec rate of thrombosis and dec time on enoxaparin for clots that formed)
- Neonates have low endogenous antithrombin levels making UFH dosing difficult, Bivalirudin not dependent on antithrombin levels…so some consider Bivalirudin a better choice for neonates needing ECMO, VADs
- Growing interest in using Bivalirudin over UFH…efficacy, safety…it is more $$ but many argue that given it is more predictable with dosing and monitoring that the cost evens out
- VTE studies in pediatrics show it is safe, clot resolution

Argatroban an approved option as well but not as well studied

ANTIPLATELET AGENTS: ASPIRIN



- There are various steps in platelet activation: adhesion, spreading, shape change, aggregation, release reaction, exposure of a procoagulant surface, and clot retraction
- The rapid progression of these different capacities causes the activated platelets to form a hemostatic plug that occludes the site of injury to prevent blood loss
  - Vascular injury causes generation of a phospholipase that synthesizes arachidonic acid (AA)
  - AA activates COX enzyme
  - COX converts AA to thromboxane 2 (TXA2)
  - TXA2 promotes platelet aggregation, shape changes, and degranulation
  - Aspirin irreversibly inactivates COX enzyme and stops TXA2 production & inhibits platelet function
  - Continues to inactivate platelet until it “dies” ~7-10 days
  - Producing new platelets every day (bone marrow)

ASPIRIN

- Antiplatelet dose is 2-5 mg/kg/day
- No half life; it irreversibly binds as long as platelets live (~7 -10 days)
- Too much aspirin?
  - Perform bleeding time test
  - Not specific, but sensitive – shows there is a bleeding issue but could be due to various issues
  - New Platelet Function Testing (PFTs) now available ~VerifyNow
- Reversal Agent: None, but give platelets if patient is bleeding
- Has been the mainstay for thromboprophylaxis for BT shunts, SV patients, stents
- Easiest and cheapest, but…may not be enough for some patients

ASPIRIN EVIDENCE

- Prevents thrombosis in BTTS *(Li et al,, Circulation. 2007;116:293-297)*
- Rx of choice to prevent thrombosis in stented PDAs (sometimes w clopidogrel)
- Early after Fontan: ASA comparable to warfarin *(Jacobs et al.Ann Thorac Surg2002 Jan;73(1):64-8. Monagle et al., JACC Vol. 58, No. 6, 2011)*
- Meta-Analyses Fontan: no difference between ASA and warfarin in overall risk of TE

  *(Marrone et al.*Pediatr Cardiol (2011) 32:32–39; *Alsaied et al.Heart 2015 Nov;101(21):1731-7)*
- Rx of choice in Kawasaki Disease with coronary aneurysms ± clopidogrel or warfarin)

  (McCrindle et.al.Circulation. 2017;135:e927–e999)
- Adjunct therapy to warfarin in mechanical heart valve thromboprophylaxis *(Otto, et al. Circulation.2021;143)*

ANTIPLATELET AGENTS: CLOPIDOGREL (Plavix)

- Inhibits platelet activation and aggregation but differently from Aspirin
  - Irreversible binding of is active metabolite to the P2Y12 class of ADP receptors on platelets
- Used alone or with aspirin
- Clarinet study: clopidogrel did not reduce all-cause mortality or shunt-related morbidity in infants < 3 months also receiving ASA *(Wessel et.al. N Engl J Med 2013 Jun 20;368(25):2377-84)*
- "May be considered" in Kawasaki Disease in conjunction with ASA in small+ coronary aneurysms as an alternative to anticoagulation *(McCrindle et. al.Circulation. 2017;135:e927–e999)*
- Used as prophylaxis with ASA when drug eluding stents are used (stented PDAs when this is the only source of PBF, stented pulmonary veins)
- Used instead if an Aspirin allergy

ANTIPLATELET AGENTS: DIPYRIDAMOLE (Persantine)

- Inhibits platelet aggregation
- IV and oral forms
- As an adjunct to other antiplatelet of anticoagulation medications

PLATELET FUNCTION TESTING

- Monitoring of antiplatelet therapy is becoming increasingly important for the identification of hypo- or hyper-responder patients at risk of both thrombosis or hemorrhage
- The development of new, simpler instruments for assessing platelet function at the point-of-care (POC) or bedside has led to better prospects of using PFT not only in specialized clinical or research laboratories, but also in general laboratories and in different clinical settings
- Point-of-care testing (POCT) dedicated to platelet function has now become available
- PFT POCT includes new methodologies which may be used in critical clinical settings and in general laboratories because they are rapid and easy to use, employing whole blood without the necessity of sample processing.
- Platelet function testing for monitoring antiplatelet therapies are spreading and the study of platelet function is strengthening…outpatient use is spreading as well

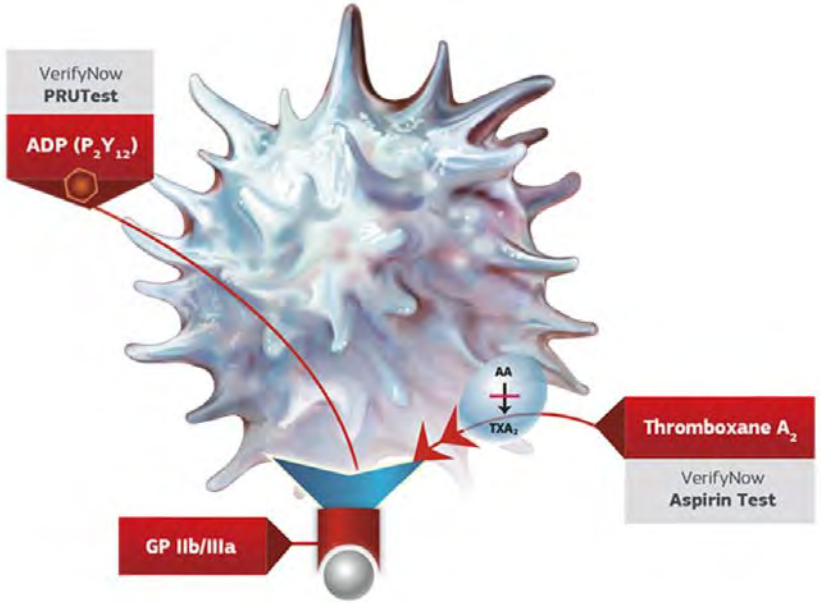
PLATELET FUNCTION TESTING: VerifyNow

- Understanding a patient's unique response to antiplatelet medications is essential to effective treatment decisions
- VerifyNow system offers platelet reactivity results in minutes, providing antiplatelet therapy guidance in many clinical settings
- VerifyNow testing can measure antiplatelet effect and identify risk for a related bleeding, thrombotic or major cardiac event, as well as non-adherence
- Analyzer and specialized tubes
- Inpatient POC testing, moving into outpatient settings/labs
- Reported in Aspirin Reaction Units (ARUs)
  - 350-549 ARUs therapeutic range for platelet function <550
  - 550-700 ARUs non therapeutic.

VerifyNow: 2 Products

VerifyNow Aspirin Test
Aids in the assessment of Aspirin's affect on platelets, allowing rapid, informed treatment decisions

VerifyNow PRUTest*
Measures the level of platelet P2Y12-receptor blockade to help identify patient response to antiplatelet therapy, including clopidogrel (Plavix), prasugrel (Effient) and ticagrelor (Brilinta)



THROM

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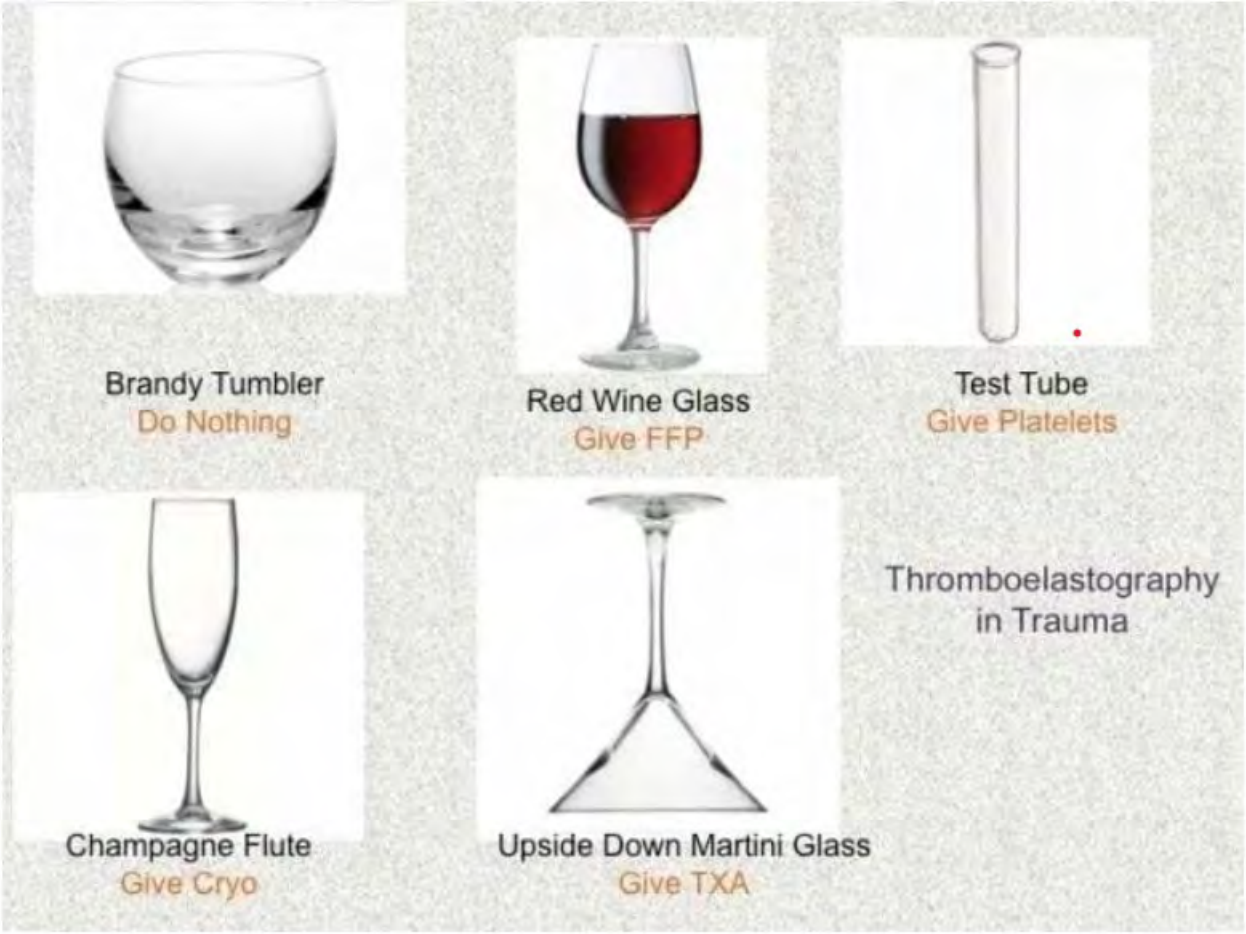
- Does not … t count (which ar…
- R values, …



VITAMIN K ANTAGONISTS: WARFARIN

- Pesticide for rats and mice
- Vitamin K antagonist: inhibits vitamin K reductase enzyme
- Vitamin K is a cofactor in making Factors II, VII, IX, X (fat soluble factors)
- Thus, coumadin impacts the formation of factors: II, VII, IX, X
- For decades, has been the mainstay of outpatient anticoagulation

WARFARIN/COUMADIN

- Several issues with foods(VitK), medications (antibiotics, amiodarone, etc), vitamins, baby formulas
- Problematic to use in infants with Vitamin K in formulas, changing diets/Vitamin K consumptions
- Genetic factors can impact warfarin sensitivity
- Not safely compounded as a liquid, tablet only
- Very long half life(29-45 hours)
- Takes a few days to reach therapeutic levels…5 days
- Follow PT/INR frequently; going to lab or POC testing at home
- Know the target range:
  - 2-2.5
  - 2.5-3
- Can give with aspirin for antiplatelet effect
- Long term use associated with osteoporosis
- Studies show, maintaining a targeted INR is inconsistent in children
  - (Streif et al, Analysis of warfarin therapy in pediatric patients: a prospective cohort study of 319 patients)
- Major Risk: Bleeding! If INR >8, consider reversal agent!
  - Immediate reversal = FFP or KCentra
  - Vitamin K can take hours to work

- No “liquid” formulation
- Osteoporosis
- Diet/Food challenges
- Narrow therapeutic margin and
- Need for frequent blood testing
- Interactions with multiple other medications
- Long half life
- ONLY “Oral” OPTION FOR MECHANICAL VALVE

Kcentra: Prothrombin Complex Concentrate (Human) [(Factors II, VII, IX, X), Protein C, and Protein S

- Urgent reversal of acquired coagulation factor deficiency induced by warfarin, rivaroxaban, or apixaban therapy in patients with acute major bleeding
- Urgent reversal of acquired coagulation factor deficiency induced by warfarin, rivaroxaban, or apixaban therapy in patients with a need for an URGENT surgery/invasive procedure
- Prothrombin Complex Concentrate (Kcentra®) shown to be faster and more effective than FFP
- Patients should also receive Vitamin K 1 mg IV but discuss use of Vitamin K with cardiology for patients with prosthetic valves.
- The optimal route and dose of vitamin K for reversal in children is dependent on patient condition. The IV route is recommended in urgent situations given the more predictable absorption but must be given slowly (over 30-60 min.) because of the risk of anaphylactic shock. Oral administration is the preferred route in young children. Subcutaneous dosing can be used but is not established as superior to oral dosing. IM injections are never indicated. The effectiveness of administered Vitamin K can be monitored by INR. The effect has been seen at 4-6 hours after IV administration.
- Additional short-term anticoagulation with heparin should be considered. Note also that the half-life of warfarin is 36-42 hours and that it is metabolized via the liver.

THROMBOLYTIC AGENTS: tPA (Alteplase)

After vessel has healed, t-PA is released →tPA converts plasminogen →plasmin

- plasmin is an enzyme that removes fibrin and dissolves clots
- plasmin digests fibrin and fibrinogen, and factors 5, 8, 12, & prothrombin

- Only available as IV
- Can be aerosolized for Plastic Bronchitis
- Fast onset of action, half life is 5min
- NO TEST TO MEASURE
- NO REVERSAL AGENT
- Hypertension can cause bleeding
- High dose and low dose options
- Rapid thrombus resolution but with RISK

- Major vascular thromboses that need immediate resolution to regain perfusion receive systemic tPA
- Acute ischemic strokes
- Mechanical heart valve leaflet thrombi
- Line clots
- Arterial thrombosis
- Plastic Bronchitis(aerosolized)

DIRECT ORAL ANTICOAGULANTS (DOACS)

Anti Xa Inhibitors

- Rivaroxaban
- Apixaban
- Edoxaban

Direct Thrombin Inhibitor

- Dabigatran (Pradaxa)

- Oral administration
- Predictable pharmacokinetics
- No antithrombin dependence
- Little food interactions but best taken with food
- Few drug interactions
- Wider therapeutic windows
- No monitoring requirements
- ALL with completed or ongoing PEDIATRIC studies

Rivaroxaban (Xarelto)

- First to be approved in pediatrics
  - EINSTEIN-Junior trial: rivaroxaban vs. SOC *(Connor et.al. Blood Adv. 2020 Dec 22;4(24):6250-6258*
    - Rates of recurrent VTE and bleeding in children were similarly low in both groups
  - UNIVERSE study *(McCrindle et.al. J Am Heart Assoc. 2021 Nov 16; 10(22): e021765)* RCT comparing rivaroxaban to aspirin for thromboprophylaxis in children within 4 months after a Fontan procedure for a study period of 12 months. Rivaroxaban was shown to be non-inferior to ASA in thrombosis prevention with low rates of bleeding in both groups
- Treatment and prevention of VTE, stroke, Fontan thromboprophylaxis, atrial arrythmia prophylaxis
- **NOT APPROVED FOR USE WITH MECHANICAL VALVES**
- Do not use if antiphospholipid antibody syndrome
- Consider carefully if renal, hepatic, malabsorption
- Oral suspension available (1mg/ml), sweet and creamy or tablets (2.5, 10, 15, 20 mg tabs)
- Can crush, can give in GT, but not JT
- Should be given with food!
- Prior labs: CBC, Renal function, PT/INR
- No food interactions or restrictions
- No routine monitoring of labs
- It does impact the INR
- Reversal is with Andexanet alfa, FDA approved IF uncontrolled bleeding…not approved if not bleeding
- Fast becoming drug of choice instead of warfarin for outpatient anticoagulation but again WARFARIN ONLY FOR MECHANCIAL VALVE

Apixaban (Eliquis)

- Dissolvable minitablet and oral solutions under study
- Pediatric studies, still on going, with wide spectrum of indications
  - Acute lymphoblastic leukemia central venous catheter
  - RCT in congenital and acquired heart disease (SAXOPHONE)
  - SAXOPHONE study https://abstracts.isth.org/abstract/the-saxophone-study-a-multi-center-multi-national-randomized-trial-of-apixaban-versus-standard-of-care-anticoagulation-for-thromboprophylaxis-in-children-with-congenital-or-acquired-heart-disease/.
    - Prospective, randomized, open label phase II multi-national clinical trial of apixaban 2:1 in children and infants with congenital and acquired heart disease (including KD) compared to SOC VKA or LMWH over 4 years. (overall >70% SV and 66.7 post-Fontan)
    - Thromboprophylaxis w apixaban was found to be safe and well tolerated in children w heart disease w no difference in major bleeding. No thrombotic events in either group
  - CANINES trial in acute VTEs in pediatric patients
- Dosing is twice daily and currently, only tablets available
- Less of a renal concern
- May be a better option for menstruating females
- No lab monitoring
- Case series reports effective use of apixaban in treatment of intracardiac thrombosis in CHD (RA, Fontan, LV in HLHS/MS) (*Esch, et.al. Interactive CardioVascular and Thoracic Surgery 30 (2020) 950–951)*

Edoxaban

- Oral suspension under study in pediatric patients
- RCT study looking at use for thromboprophylaxis in children with cardiac disease ENNOBLE-ATE
  - Prospective, phase 3, open-label, randomized controlled trial to evaluate and compare the safety and efficacy of edoxaban against SOC VKA or LMWH in children with cardiac diseases (including KD)
- Study completed 1/18/2022 presented at AHA 2022 as the 2022 Outstanding Research Award in Pediatric Cardiology

DOAC: Dabigatran (Pradaxa)

- Oral Direct Thrombin Inhibitor
- Coated granules, suspension, capsules
- Studied in pediatrics completed, FDA approved
- DIVERSITY trial: dabigatran vs. LMWH and warfarin
  - (Halton et.al. Lancet Haematol. 2021 Jan;8(1):e22-e33) dabigatran was non-inferior to SOC
  - RCT for safety and efficacy (compared to LMWH and VKA) in children 0-18 years of age
  - Thrombus resolution/freedom from reoccurrence 46 % compared to 42% and bleeding events similar
  - But in prevention arm, 12.3% had to stop in that they did not reach target concentration so at this point not “monitoring”, but may be an issue?

The FUTURE of DOACs for CHD?

- Rivaroxaban and Dabigatran authorized in EU, Canada, and US with pediatric formulations
- Apixaban studies concluding as well
- BUT should only be initiated after at least 5 days of parental anticoagulation
- Clinically stable children who need long term anticoagulation
- Great studies, but small numbers, and no premature infants or children with severe comorbidities involved
- NOT for use with mechanical valves (adult studies stopped early for bleeding and valve issues)
- But these drugs are the future, and others are in trial
- New group, Factor IX and Factor XII inhibitors may have the promise of anticoagulation but a decreased risk for bleeding.

SUMMARY

- Children and adolescents with heart disease are a setup for thrombosis, especially
  - Neonates
  - Single ventricle patients at all stages of palliation
  - Kawasaki Disease with coronary aneurysms
  - Cardiomyopathy/Myocarditis
  - VADs
- The risk is not fixed and may change over time as new risk factors are acquired
  - Careful, sequential reassessment is essential
  - Be proactive instead of reactive
- An understanding of available agents is important
- “An ounce of prevention is worth a pound of cure”
- DOACs warrant further investigation as oral therapy for thrombosis prevention (and treatment) in our high-risk CHD populations …”cautious” optimism?