CARDIOLOGY 2024

Oral Anticoagulation and CHD: What's New?

Kathryn M. Dodds, CRNP

Clinical Program Manager Fontan FORWARD Program Children's Hospital of Philadelphia

Faculty, Lecturer Pediatric Acute Care NP Program Critical Care Concentration University of Pennsylvania School of Nursing 2/16/2024



15-year-old with HLHS (MS, AA) surgically palliated to a fenestrated ECC Fontan. His only medication is Aspirin, 81 mg daily. But he admits, he misses doses...





2024

What Should We Do?





Why Did This Happen?

Virchow (1856) identified 3 components that promote thrombosis...



CARDIOLOGY 2024

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



How Does Blood Clot?

∞024





Hemostasis: Platelet Phase

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



B. PRIMARY HEMOSTASIS



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

lardiad Center

•Von Willebrand Factor binds to site

•Glycoprotein Ib

CARDIOLOGY

2024

•Platelets activated \rightarrow ADP & ThromboxaneA2 \rightarrow Recruitment/Aggregation/"Sticky"

•Platelet Plug...but it is not stable

Q

Thrombus

"Natural" Anticoagulation

INTRINSIC or EXTRINSIC PATHWAYS Anticoagulation Triggered Fibrin \rightarrow Fibrin Mesh/Thrombus Trapped neutrophil Release of: (2) Phospholipid Trapped red (3) Thrombin activation t-PA (fibrinolysis) complex expression blood cells thrombomodulin 4 Fibrin polymerization (blocks coagulation 1) Tissue factor Tissue factor cascade) 1 Fibrin

UFH and LMWH potentiate Antithrombin IIIa inhibiting Thrombin and Xa

•Endogenous Antithrombin IIIa inhibits Thrombin and Xa •tPA triggers Plasmin which begins to degrade the fibrin mesh *Can administer IV tPA to dissolve clots*



Polymerized

fibrin

Why Are CHD Patients at Risk?



CARDIOLOGY 2024



 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*
- 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)





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

CARDIOLOGY

©024

- 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 dictate choice

IV

- UFH
- Bivalirudin
- tPA

SubQ

- LMWH
- Fondaparinux

Oral

- Platelet inhibitors (ASA)
- Warfarin
- DOACs





Antiplatelet Agents: Aspirin



- Vascular injury generates 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, many argue safest, 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

CARDIOLOGY

2024

• As an adjunct to other antiplatelet of anticoagulation medications



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; go 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

Direct Oral Anticoagulants (DOACS)

Anti Xa Inhibitors

• Rivaroxaban

- Direct Thrombin Inhibitor
- Dabigatran (Pradaxa)

- Apixaban
- Edoxaban
- 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 VALVES



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-multinational-randomized-trial-of-apixaban-versus-standard-of-care-anticoagulation-forthromboprophylaxis-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 Fontan females
- No lab monitoring
- Less GI bleeding than seen with Xarelto
- 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?



15-year-old with HLHS (MS, AA) surgically palliated to a fenestrated ECC Fontan. His only medication is Aspirin, 81 mg daily. But he admits, he misses doses...



Children's Hospital of Philadelphia Cardiac Center

What Should We Do?

- A. Restart Aspirin
- B. Restart Aspirin with Plavix
- C. Start Enoxaparin and bridge to Warfarin/Start Warfarin
- D. Admit for tPA
- E. Start Xarelto



We Started Xarelto (15 mg daily) with Aspirin

6 months later...

1 year later...







The FUTURE of DOACs for CHD?

- Rivaroxaban and Dabigatran authorized in EU, Canada, and US with pediatric formulations
- Apixaban studies concluded as well, now available
- 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

CARDIOLOGY

• New group, Factor IX and Factor XII inhibitors may have the promise of anticoagulation but a decreased risk for bleeding.



Summary: All about balance

- 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
 - Valves
- 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 ALL 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?

