Antithrombotic Therapy and Novel Approaches Through and Beyond Fontan Completion

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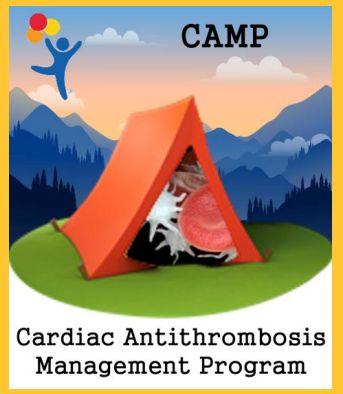
Associate Professor of Pediatrics, University of Colorado



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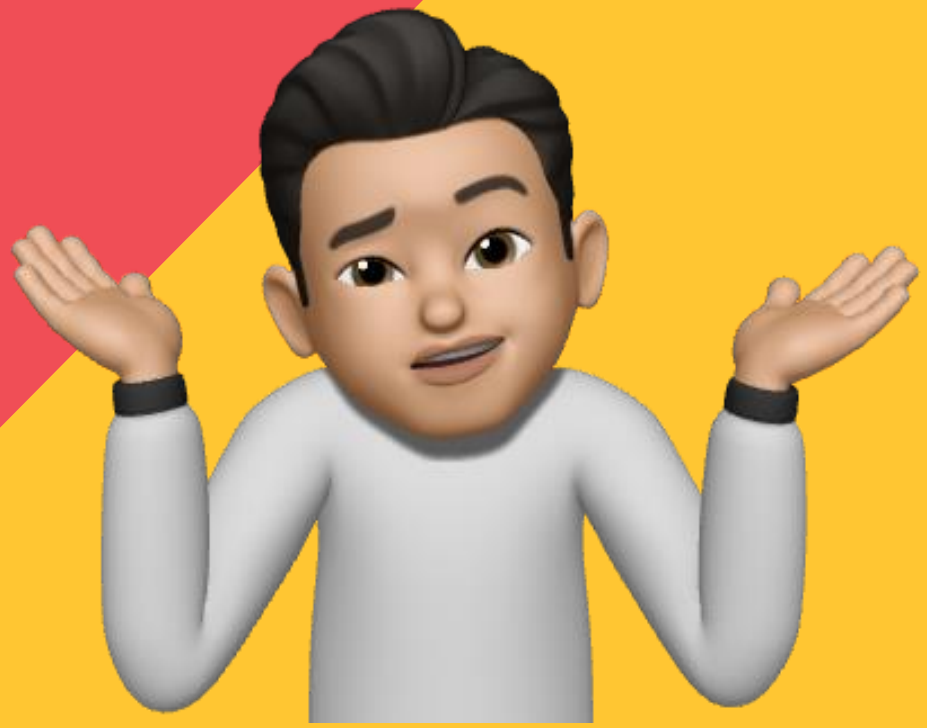
National Pediatric Cardiology
Quality Improvement Collaborative

FONTAN
OUTCOMES NETWORK

What's the big deal, anyway?

…"Just give the kid aspirin, right?"



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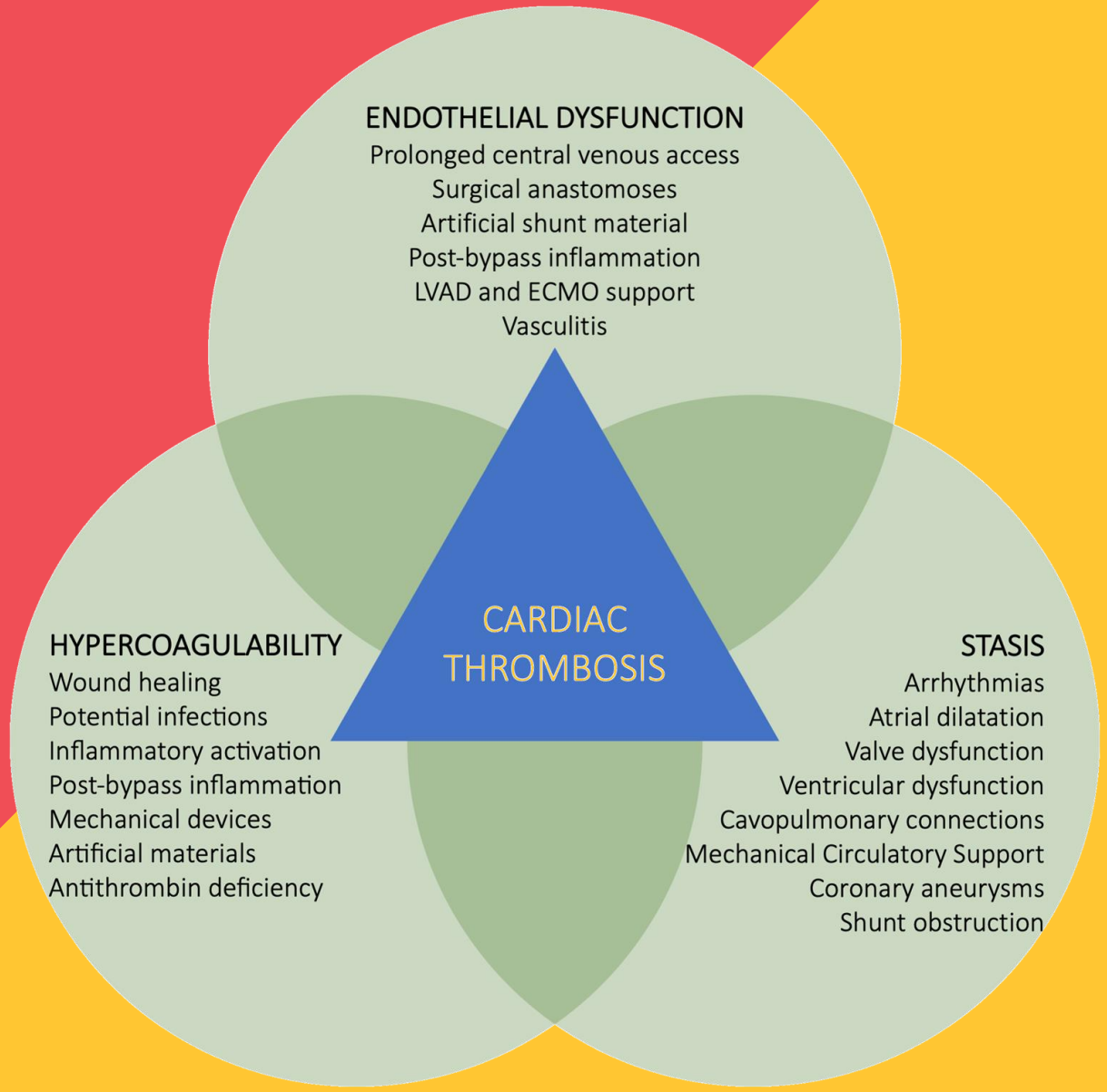

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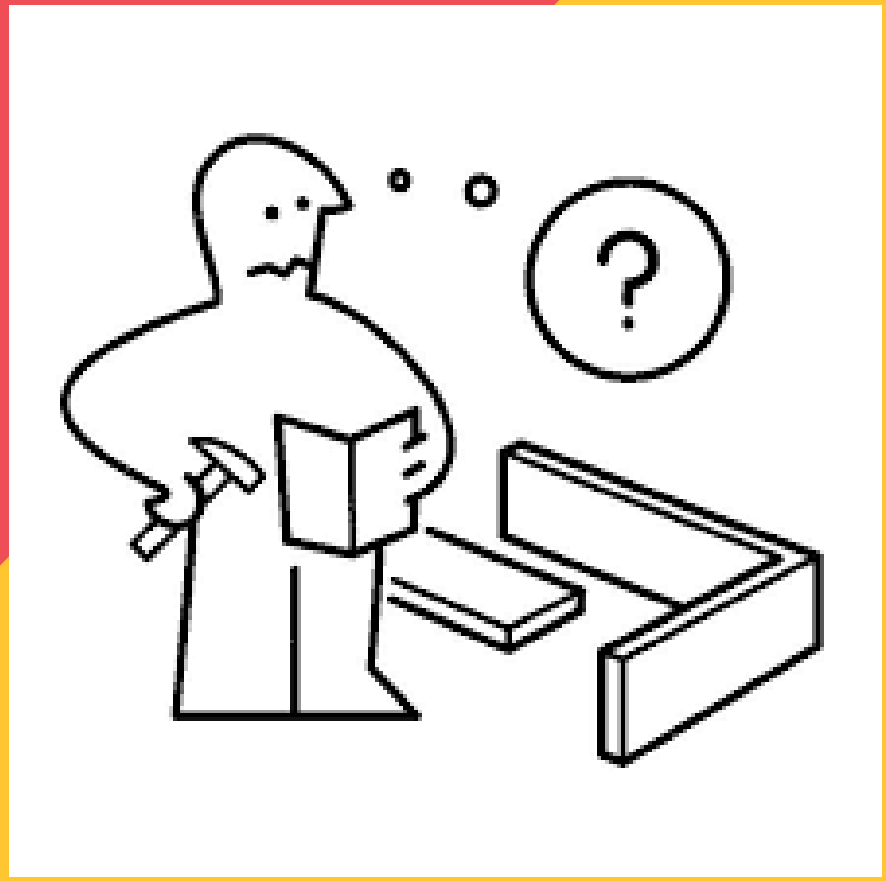

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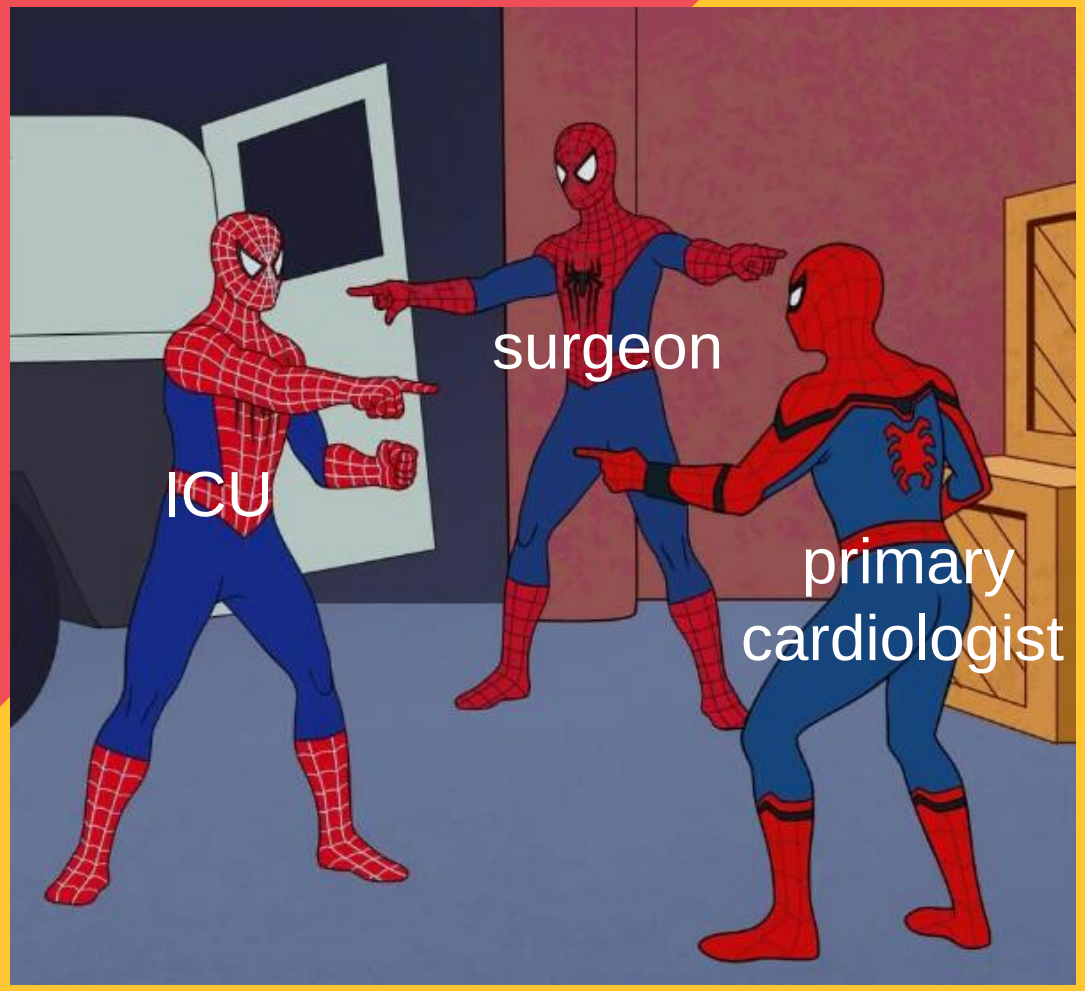
- Everyone does/wants something different…
  ….consistency is hard to achieve, patterns hard to observe, experience hard to gather



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- Each patient is unique and deserves/requires specified patient-centric care

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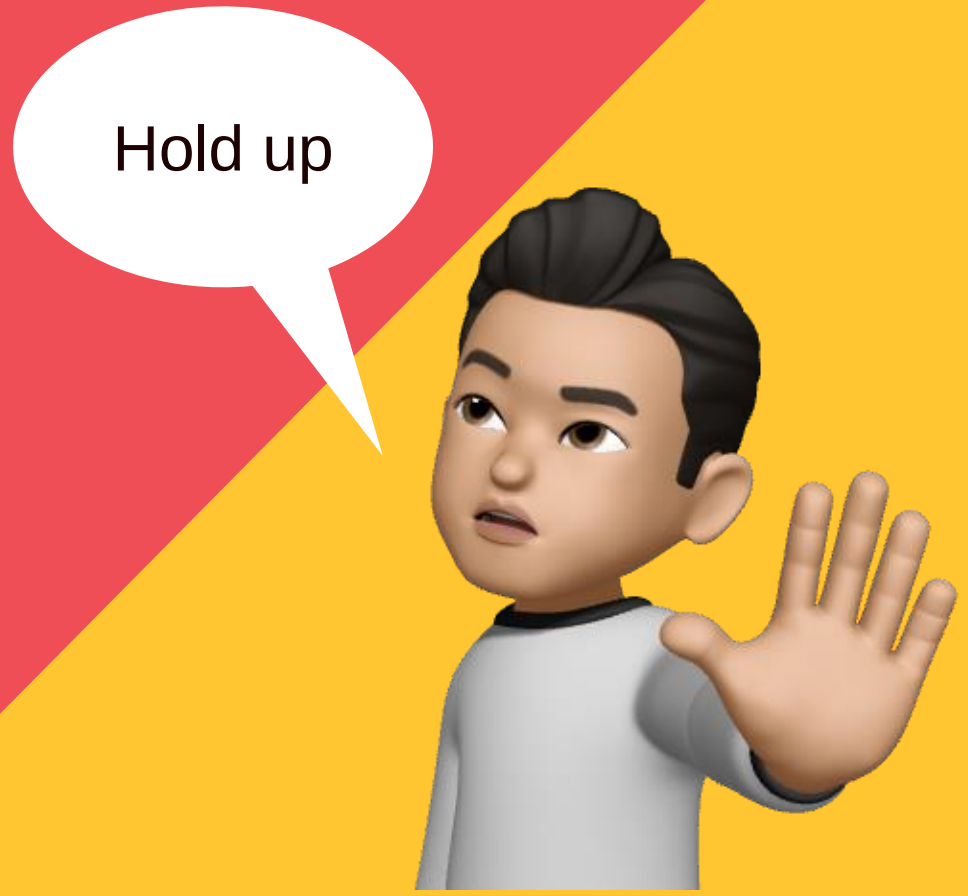
- Lastly…

  We cardiologists *love* to deal with anticoagulation



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Poll Question

Do single ventricle patients at your center remain on aspirin lifelong?

a. Lifelong

b. Stop after some time post-surgery (any stage)

Poll Question

Are single ventricle patients at your center maintained on thromboprophylaxis **more than aspirin** as a routine (excluding treatment for thrombosis)? *Select all that apply.*

a. Stage 1 always
b. Stage 1 sometimes
c. Stage 2 always
d. Stage 2 sometimes
e. Fontan always
f. Fontan sometimes

How to best approach antithrombotic management in single ventricle patients

Collaborative decision making based on care pathways and protocols:

- Protocols written in an evidence- AND *experience-based* multidisciplinary manner
- Find the middle ground that surgeons, primary cardiologists, and ICU can agree upon.

Champions for consistent, yet patient-centric, management:

- Collaboration with invested colleagues in hematology
- Collective learning (cardiologists learn from hematologists, hematologists learn from cardiologists)
- *This will be the hardest piece to achieve*

Multidisciplinary outpatient care:

- Interstage programs, single ventricle care programs, Fontan multidisciplinary care teams
- Includes care for thrombosis and thrombosis prevention

~~How to best approach antithrombotic management in single ventricle patients~~

BUILD RELATIONSHIPS

Collaborative decision making based on care pathways and protocols:

- Single ventricle-specific protocols for thromboprophylaxis, both long-term and post-operative
- Take into account the experience of your center (evidence-based protocols are great, but great evidence does not exist)

Champions for consistent, yet patient-centric, management:

- Make a friend in hematology and foster a mutually beneficial relationship between disciplines.
- Identify a pharmacist champion who understands SV patients and anticoagulation (or willing to learn)
- Will need to learn/identify patients that require more-specified management (off protocol).
- Single ventricle patients require patient-centric management of new thrombosis events

Multidisciplinary outpatient care:

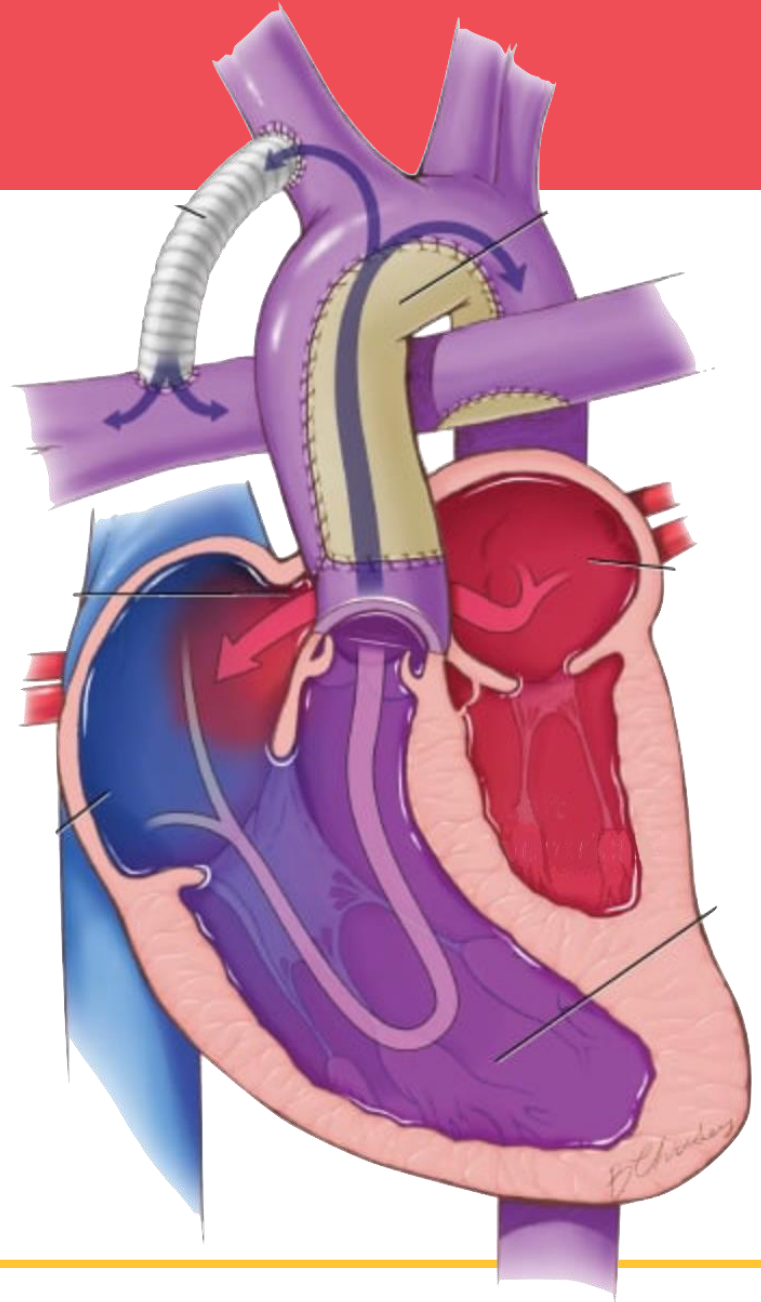
- If outpatient anticoagulation management services exist, try to integrate cardiology.
- Integrate these services with your multidisciplinary teams at each stage of palliation.

I acknowledge: these things are WAY easier said than done!

Sensitive Material

The content that is about to be shared might be considered sensitive for some members of the community.

Please feel free to take a break or step away, if needed.



Stage 1

Antithrombotic management after Stage 1

What do the guidelines say?

What are the most recent guidelines?

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Prevention and Treatment of Thrombosis in Pediatric and Congenital Heart Disease: A Scientific Statement From the American Heart Association

Therese M. Giglia, M. Patricia Massicotte, James S. Tweddell, Robyn J. Barst, Mary Bauman, Christopher C. Erickson, Timothy F. Feltes, Elyse Foster, Kathleen Hinoki, Rebecca N. Ichord, Jacqueline Kreutzer, Brian W. McCrindle, Jane W. Newburger, Sarah Tabbutt, Jane L. Todd and Catherine L. Webb

Circulation. 2013;128:2622-2703; originally published online November 13, 2013;
doi: 10.1161/01.cir.0000436140.77832.7a

Yes, our *most-recent* guidelines for thrombosis prevention after stage 1 are from **2013**

Antithrombotic management after Stage 1

What are the risk factors? What do we know?

Obstruction in Modified Blalock Shunts: A Quantitative Analysis With Clinical Correlation

Winfield J. Wells, MD, R. James Yu, BS, Anjan S. Batra, MD, Hector Monforte, MD, Colleen Sintek, MD, and Vaughn A. Starnes, MD

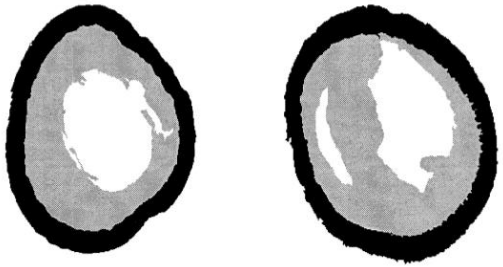
Childrens Hospital Los Angeles, Los Angeles, California

(Ann Thorac Surg 2005;79:2072–6)

Evaluation of 155 infants/children who had takedown of mBTT shunt (all patients prescribed aspirin)

Histopathologic analysis:

23% with >50% narrowing



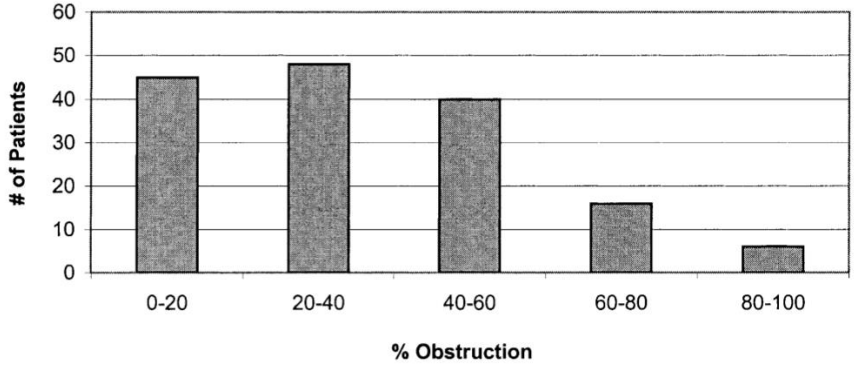


Fig 2. Distribution of percent of obstruction.

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Grouped RVPA and AP shunts together

Risk factors for thrombosis of shunts:

- Heterotaxy
- Other congenital anomaly
- Smaller BTT shunt size
- Infection

Emphasis on historic reports of luminal narrowing of PTFE shunts being caused by organized thrombus or fibrotic proliferation

Antithrombotic management after Stage 1
Okay, so what do we do?

What are the other details?

- Reasonable to give low-dose heparin after shunt
- *Probably recommend* treatment dose heparin if risk factors for thrombosis, CA-VTE, or stented shunt
- *May consider* LMWH+ASA (or clopidogrel) if high risk for thrombosis

Wait, what about clopidogrel?

- PICOLO trial (2008) randomized patients to receive clopidogrel vs. placebo (88% on concomitant ASA)
- No difference in mortality or shunt thrombosis
- No difference in bleeding

DAPT is generally not recommended for shunts

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In the absence of increased risk of bleeding, long-term use of low-dose aspirin is recommended therapy for the prevention of long-term polytetrafluoroethylene systemic to pulmonary shunt thrombosis in infants and children (*Class I; Level of Evidence B*).

Antithrombotic management after Stage 1

What have we learned over 10 years?

Most studies have evaluated "aspirin resistance"

Platelet testing to guide aspirin dose adjustment in pediatric patients after cardiac surgery

The Journal of Thoracic and Cardiovascular Surgery · Volume 154, Number 5

Sirisha Emani, PhD,[a] David Zurakowski, PhD,[b] Michelle Mulone, BS,[c] James A. DiNardo, MD,[b] Cameron C. Trenor III, MD, MMSc,[d] and Sitaram M. Emani, MD[a]

VERIFY NOW

Aspirin Resistance in Single-Ventricle Physiology: Aspirin Prophylaxis Is Not Adequate to Inhibit Platelets in the Immediate Postoperative Period

(Ann Thorac Surg 2015;99:2158–65)

Arshid Mir, MD, Summer Frank, MPH, Janna Journeycake, MD, Joshua Wolovits, MD, Kristine Guleserian, MD, Lisa Heistein, MD, and Matthew Lem[illegible], MD

TEG

Aspirin resistance in infants with shunt-dependent congenital heart disease

Cardiology in the Young **32**: 705–710. doi: 10.1017/S1047951121002973

Wonshill Koh[1,2], Megan Rodts[1], Ashley Nebbia[3], Jaclyn Sawyer[3], Brandon Henry[1] and David S. Cooper[1,2]

VERIFY NOW

Antiplatelet Effect of Ketorolac in Children After Congenital Cardiac Surgery

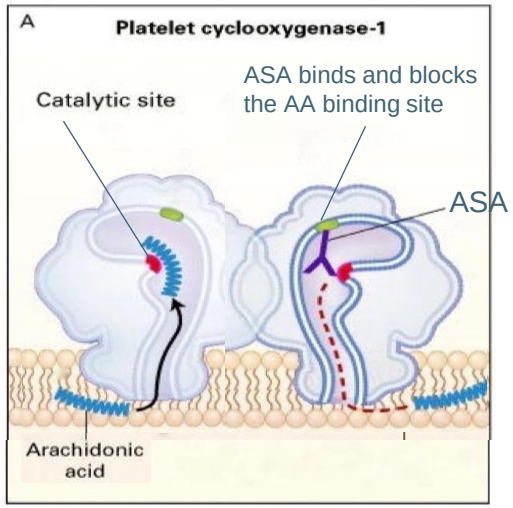
World Journal for Pediatric and Congenital Heart Surgery 2018, Vol. 9(6) [illegible]-658

John S. Kim, MD, MS[1], Jon Kaufman, MD[1], Sonali S. Patel, MD, PhD[1], Marilyn Manco-Johnson, MD[2], Jorge Di Paola, MD[2], and Eduardo M. da Cruz, MD[1]

TEG

- Aspirin binds and permanently blocks the binding site for AA on the COX-1 enzyme
- However, ASA has a circulating half-life of **20 min**
- Any platelets generated after aspirin is cleared, will not be inhibited
- Aspirin does not *last for 7 days*, rather, its effect lasts for the life of the platelet (well, the platelets in circulation for the 20 min after aspirin is given)

…more on this later



Antithrombotic management after Stage 1

What have we learned over 10 years?

Most studies have evaluated "aspirin resistance"

Aspirin unresponsiveness predicts thrombosis in high-risk pediatric patients after cardiac surgery

The Journal of Thoracic and Cardiovascular Surgery • Volume 148, Number 3

Sirisha Emani, PhD, Bethany Trainor, RN, David Zurakowski, PhD, Christopher W. Baird, MD, Francis E. Fynn-Thompson, MD, Frank A. Pigula, MD, and Sitaram M. Emani, MD

*study of all patients <18 requiring heart surgery

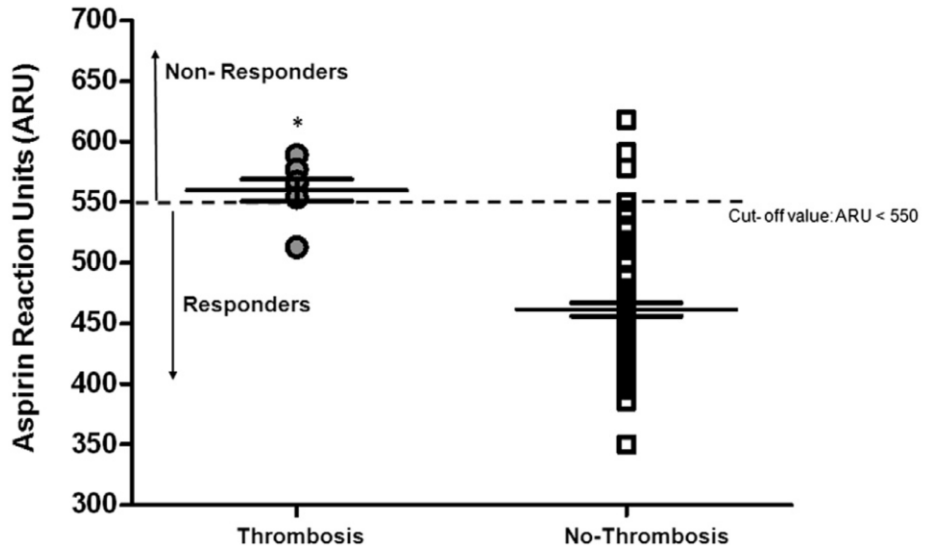


FIGURE 1. Association between aspirin unresponsiveness and thrombosis: *Circles* represent patients with thrombosis and *squares* represent patients without thrombosis. *Dashed line* indicates the cut-off value for aspirin unresponsiveness (≥550 aspirin reaction units [*ARU*]). *Significant difference in aspirin unresponsiveness between patients with thrombosis compared with those without thrombosis.

Okay, so aspirin is probably good
and
we probably should test/titrate it…

… but there still is no concensus.
Do we use VerifyNow?
Do we use TEG?
What about ROTEM?

*And **still** no specific evidence or guidance for stage 1 single ventricle patients*

RVPA (Sano) shunts:

- Aspirin only
- Aggressive treatment with LMWH if concomitant thrombosis (most-commonly CA-VTE)
- Strict adherence to guidelines recommending 6-12 weeks of treatment for CA-VTE

…mBTT (and central) shunts are a different story

Children's Hospital Colorado aortopulmonary shunt thromboprevention protocol:

- Start Bivalirudin infusion 2-6 hours after surgery (once bleeding risk is deemed reduced)
- Target aPTT 50-70 for shunt prophylaxis and maintain for minimum 5 days post-op
- Start aspirin 5-10 mg/kg/dose BID once enteral access is achieved
- Convert bivalirudin to enoxaparin (target anti-Xa 0.5-1) until stage 2

But why *bivalirudin*?!?

- Specific, potent, and reversible inhibitor of thrombin
- Binds circulating and clot-bound thrombin
- Inhibits thrombin-mediated platelet activation and aggregation
- Immediate onset of action and very short half life (20 min, protease degradation)

So, what do we do at Children's Hospital Colorado?

Children's Hospital Colorado
Here, it's different.™

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…(yes, BID aspirin, we will come back to this)

We maintain all our AP shunt patients on BID aspirin and enoxaparin through the interstage

- Current experience of 13 consecutive patients on this protocol
- Bridged with bival for any other surgeries (g-tube), shunt/PA stent, or NPO (NEC)
- No shunt thrombosis (nor other thrombosis)
- No bleeding
- All patients make it to stage 2

So, what do we do at Children's Hospital Colorado?

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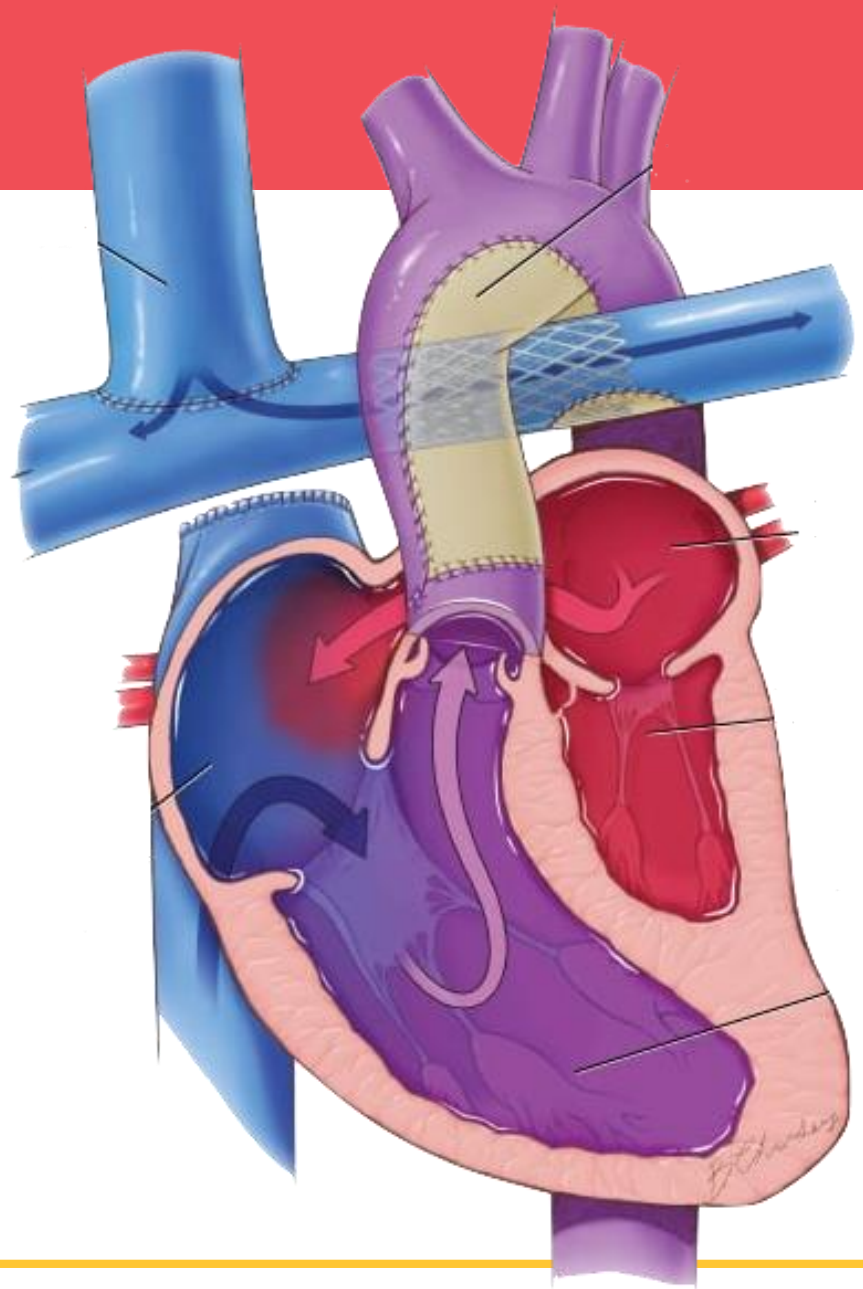


Stage 2

Antithrombotic management after Stage 2
Phew, you made it to the Glenn

Incidence and Timing of Thrombosis After the Norwood Procedure in the Single-Ventricle Reconstruction Trial

J Am Heart Assoc. 2020;9:e015882. DOI: 10.1161/JAHA.120.015882

Michael H. White, MD, MSc; Michael Kelleman, MS, MSPH; Robert F. Sidonio Jr, MD, MSc; Lazaros Kochilas, MD, MSc; Kavita N. Patel, MD, MSc

Secondary analysis of PHN SVR trial data

57 of 549 infants with thrombosis (21.2%)

Table 2. Timing and Number of Thromboembolic Events From Stage I Through Stage II Hospital Discharge in the SVR Trial

	Stage I Hospitalization	Interstage I	Stage II Hospitalization
Total first-time thromboembolic events	35	7	15

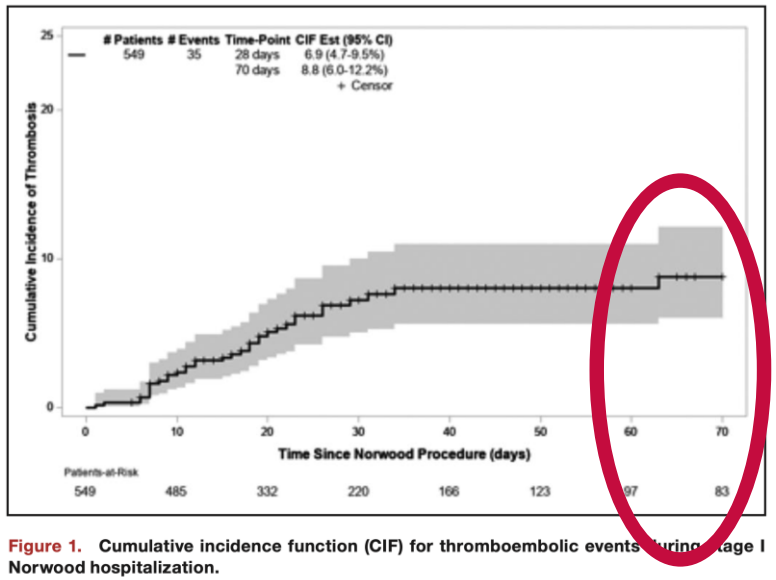
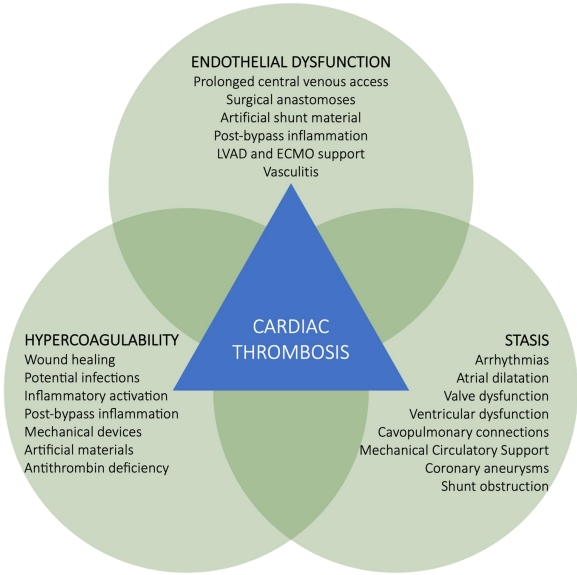


Figure 1. Cumulative incidence function (CIF) for thromboembolic events during Stage I Norwood hospitalization.

<u>No longer at risk for shunt thrombosis or related complications:</u>

However, now with passive venous blood flow via cavopulmonary connection



Antithrombotic management after Stage 2

What do the guidelines say?

Okay, so there is a chylothorax,

what do we do?

Review > Cardiol Young. 2022 Aug;32(8):1202-1209. doi: 10.1017/S1047951122001871. Epub 2022 Jul 6.

Development of consensus recommendations for the management of post-operative chylothorax in paediatric CHD

Richard P Lion [1], Melissa M Winder [2], Rambod Amirnovin [3], Kristi Fogg [4], Rebecca Bertrandt [5], Priya Bhaskar [6], Cameron Kasmai [5], Kathryn W Holmes [7], Rohin Moza [2], Piyagarnt Vichayavilas [8], Erin E Gordon [9], Amiee Trauth [10], Megan Horsley [10], Deborah U Frank [11], Arabela Stock [12], Greg Adamson [13], Alissa Lyman [7], Tia Raymond [14], Isaura Diaz [15], Alicia DeMarco [16], Parthak Prodhan [17], Michael Fundora [18], Alaa Aljiffry [18], Aaron G Dewitt [19], Benjamin W Kozyak [19], Lawrence Greiten [20], Carly Scahill [21], Jason Buckley [4], David K Bailly [22]; PC4 Chylothorax Work Group

Recommendations for workup looking for VTE (both as cause and consequence of chylothorax) and provide prophylactic anticoagulation

but with what?…

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<u>No longer at risk for shunt thrombosis or related complications:</u>

However, now with passive venous blood flow via cavopulmonary connection

<u>Emphasis on chylothorax as a risk factor for thrombosis:</u>

- Loss of endogenous anticoagulant proteins (Protein C, S, and AT) …results in relative hypercoagulable state
- In addition to cavopulm/PA thrombosis risk, now at increased risk for cerebral sinus venous thrombosis (and associated stroke)

General recommendation is the same: *aspirin for all*…

However, if patient has draining chylothorax, recommendation is to monitor coagulation status (clotting studies, antithrombin, and anti-Xa level)

Antithrombotic management after Stage 2

Okay, so there is a chylothorax,

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Recommendations for workup looking for VTE (both as cause and consequence of chylothorax) and provide prophylactic anticoagulation

but with what?…

Some recommend fairly aggressive anticoagulation with enoxaparin:

Post-operative Anticoagulation Strategy Following Comprehensive Stage 2 Procedure for Single Ventricle Physiology

Pediatric Cardiology (2022) 43:1517–1521

Colleen Cloyd[1] · Emma L. Wysocki[2] · Hunter Johnson[1] · Julie C. Miller[3] · Joann Davis[4] · Mark Galantowicz[5] · Andrew R. Yates[6]

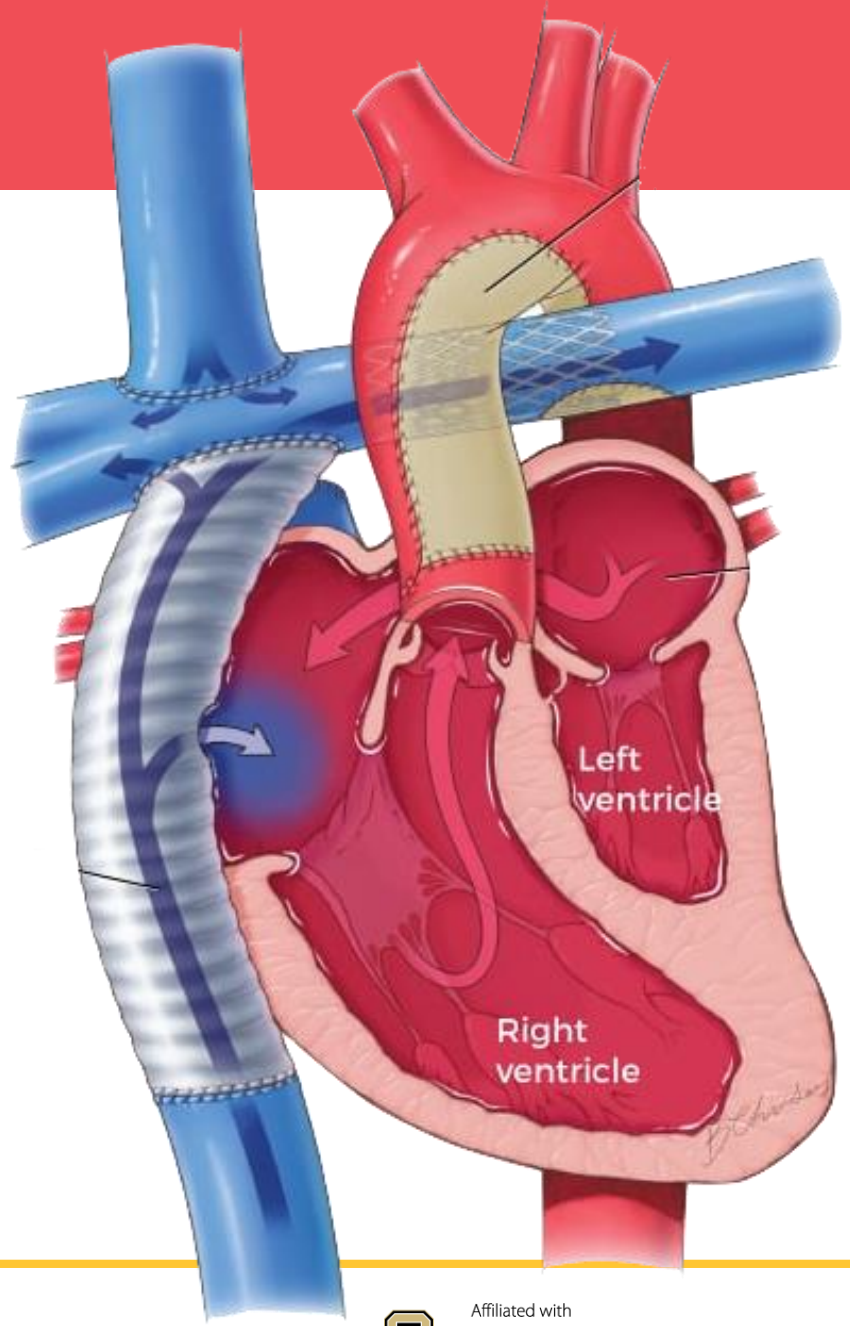
Single institutional protocol:

Therapeutic anticoagulation with enoxaparin for 6 weeks after Stage 2

- *71 infants studied*
- *4 with thrombosis*
- *3 with clinically significant bleeding*

But are there other anticoagulant options?

Hold that thought!



Stage 3

Antithrombotic management after Stage 3
What is so special about the Fontan?

Prophylaxis with warfarin/LMWH *may be reasonable* for 3-12 months after the Fontan.

Long-term therapy with warfarin/LMWH *may be reasonable* if anatomic or hemodynamic risk factors.

Prophylaxis after the Fontan *may be reasonable* in adolescence/adulthood.

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Post-operative thromboprevention recommendations are not different

(again, aspirin for all)

…No, *just aspirin* may be not be *good enough*

Canadian Journal of Cardiology 38 (2022) 1024–1035

Review

Coagulation and Anticoagulation in Fontan Patients

Josephine F. Heidendael, MD,[a] Leo J. Engele, MD,[a] Berto J. Bouma, MD, PhD,[a] Anne I. Dipchand, MD, PhD,[b] Sara A. Thorne, MBBS, MD,[c] Brian W. McCrindle, MD, PhD,[b] and Barbara J.M. Mulder, MD, PhD[a]

The difference:

We are now looking to the future*…*

adolescence, adulthood, complications

Canadian Journal of Cardiology 38 (2022) 1024–1035

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Josephine F. Heidendael, MD,[a] Leo J. Engele, MD,[a] Berto J. Bouma, MD, PhD,[a] Anne I. Dipchand, MD, PhD,[b] Sara A. Thorne, MBBS, MD,[c] Brian W. McCrindle, MD, PhD,[b] and Barbara J.M. Mulder, MD, PhD[a]

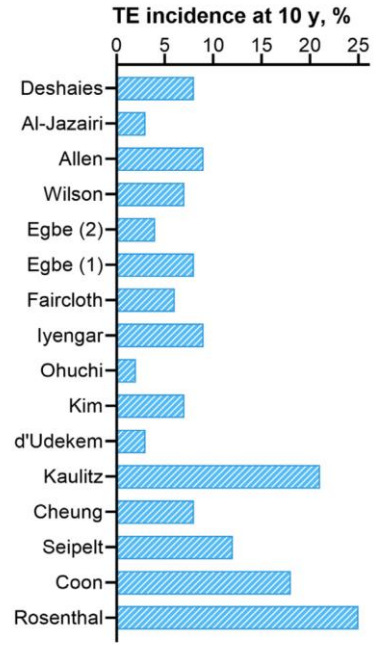


Figure 1. Display of reported thromboembolic event (TE) incidence at 10 years in Fontan patients.

Randomized Controlled Trial > J Am Coll Cardiol. 2013 Jan 22;61(3):346-53.
doi: 10.1016/j.jacc.2012.08.1023. Epub 2012 Dec 12.

Factors associated with thrombotic complications after the Fontan procedure: a secondary analysis of a multicenter, randomized trial of primary thromboprophylaxis for 2 years after the Fontan procedure

Brian W McCrindle [1], Cedric Manlhiot, Andrew Cochrane, Robin Roberts, Marina Hughes, Barbara Szechtman, Robert Weintraub, Maureen Andrew, Paul Monagle; Fontan Anticoagulation Study Group

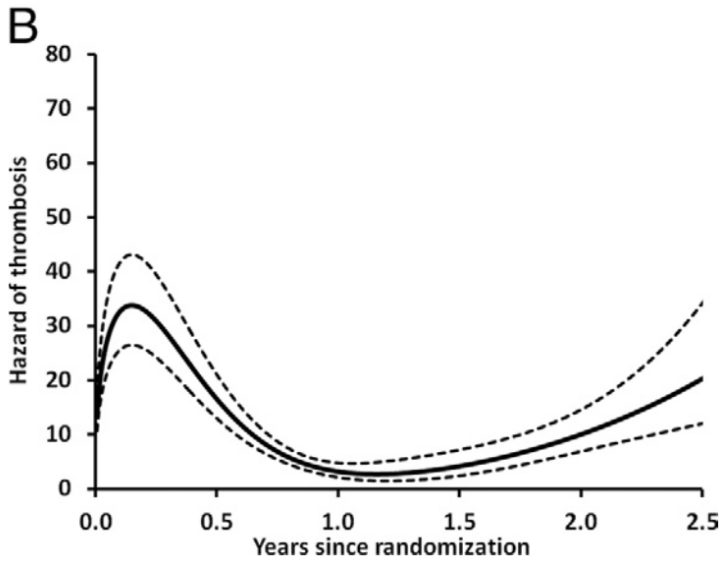


Figure 1 Freedom From and Hazard of Thrombosis Over Time in Patients After Fontan Surgery

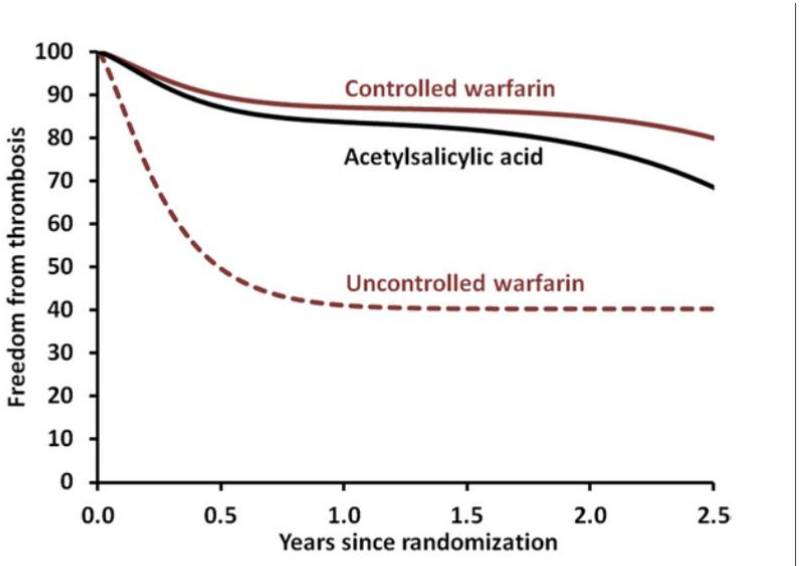


Figure 2 Freedom From Thrombosis Over Time Stratified by Thromboprophylaxis Choice and Effectiveness

Canadian Journal of Cardiology 38 (2022) 1024–1035

Review

Coagulation and Anticoagulation in Fontan Patients

Josephine F. Heidendael, MD,[a] Leo J. Engele, MD,[a] Berto J. Bouma, MD, PhD,[a] Anne I. Dipchand, MD, PhD,[b] Sara A. Thorne, MBBS, MD,[c] Brian W. McCrindle, MD, PhD,[b] and Barbara J.M. Mulder, MD, PhD[a]

So, is aspirin good enough or what?!?

… perhaps, warfarin monotherapy is as good as aspirin…

… however, we have all taken care of Fontan patients who have thrombosis while on aspirin alone (whether immediate post-op or years later)

Are we back to warfarin or are we still doing aspirin?

"Maybe Fontans need more than aspirin, but I can't subject them to lovenox or warfarin for the rest of their lives!"

"If only there was something easier, then I would choose more than aspirin."

Randomized Controlled Trial > J Am Coll Cardiol. 2013 Jan 22;61(3):346-53.
doi: 10.1016/j.jacc.2012.08.1023. Epub 2012 Dec 12.

Factors associated with thrombotic complications after the Fontan procedure: a secondary analysis of a multicenter, randomized trial of primary thromboprophylaxis for 2 years after the Fontan procedure

Brian W McCrindle [1], Cedric Manlhiot, Andrew Cochrane, Robin Roberts, Marina Hughes, Barbara Szechtman, Robert Weintraub, Maureen Andrew, Paul Monagle; Fontan Anticoagulation Study Group

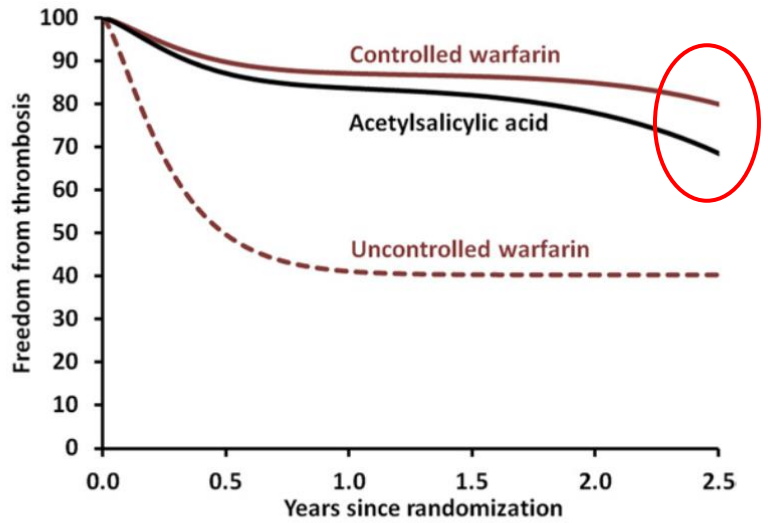


Figure 2 Freedom From Thrombosis Over Time Stratified by Thromboprophylaxis Choice and Effectiveness

Antithrombotic management after Stage 3

Here come the DOACs!

#DisforDirect

*(the artists formerly known as the **Novel** Oral AntiCoagulants, NOACs)*

Dabiga**T**ran (direct thrombin inhibitor)	*Pradaxa*
Rivaro**X**aban (Xa inhibitor)	*Xarelto*
Api**X**aban (Xa inhibitor)	*Eliquis*
Edo**X**aban (Xa inhibitor)	*Savaysa*
Betri**X**aban (Xa inhibitor)	*Bevyxxa*

First DOAC was FDA approved in 2010:

- Dabigatran was approved for stroke prevention in adults with atrial fibrillation (2010)
- Followed by Rivaroxaban (2011), Apixaban (2012), and Edoxaban (2015) for atrial fib
- Eventually, all approved for treatment of adult VTE (*betrixaban in 2017 for prophy only*)

DOACs in adults

Randomized Controlled Trial > N Engl J Med. 2009 Sep 17;361(12):1139-51.
doi: 10.1056/NEJMoa0905561. Epub 2009 Aug 30.

Dabigatran versus warfarin in patients with atrial fibrillation

Randomized Controlled Trial > N Engl J Med. 2011 Sep 8;365(10):883-91.
doi: 10.1056/NEJMoa1009638. Epub 2011 Aug 10.

Rivaroxaban versus warfarin in nonvalvular atrial fibrillation

Randomized Controlled Trial > N Engl J Med. 2011 Mar 3;364(9):806-17.
doi: 10.1056/NEJMoa1007432. Epub 2011 Feb 10.

Apixaban in patients with atrial fibrillation

Randomized Controlled Trial > N Engl J Med. 2013 Nov 28;369(22):2093-104.
doi: 10.1056/NEJMoa1310907. Epub 2013 Nov 19.

Edoxaban versus warfarin in patients with atrial fibrillation

Randomized Controlled Trial > N Engl J Med. 2009 Dec 10;361(24):2342-52.
doi: 10.1056/NEJMoa0906598.

Dabigatran versus warfarin in the treatment of acute venous thromboembolism

Randomized Controlled Trial > N Engl J Med. 2010 Dec 23;363(26):2499-510.
doi: 10.1056/NEJMoa1007903. Epub 2010 Dec 3.

Oral rivaroxaban for symptomatic venous thromboembolism

Randomized Controlled Trial > N Engl J Med. 2013 Aug 29;369(9):799-808.
doi: 10.1056/NEJMoa1302507. Epub 2013 Jul 1.

Oral apixaban for the treatment of acute venous thromboembolism

Randomized Controlled Trial > N Engl J Med. 2013 Oct 10;369(15):1406-15.
doi: 10.1056/NEJMoa1306638. Epub 2013 Aug 31.

Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism

Initial clinical trials in AF and VTE:

Equally or more effective than VKA and similar or lower risk of bleeding than VKA

The *How* of DOACs

Two mechanisms of DOAC action:

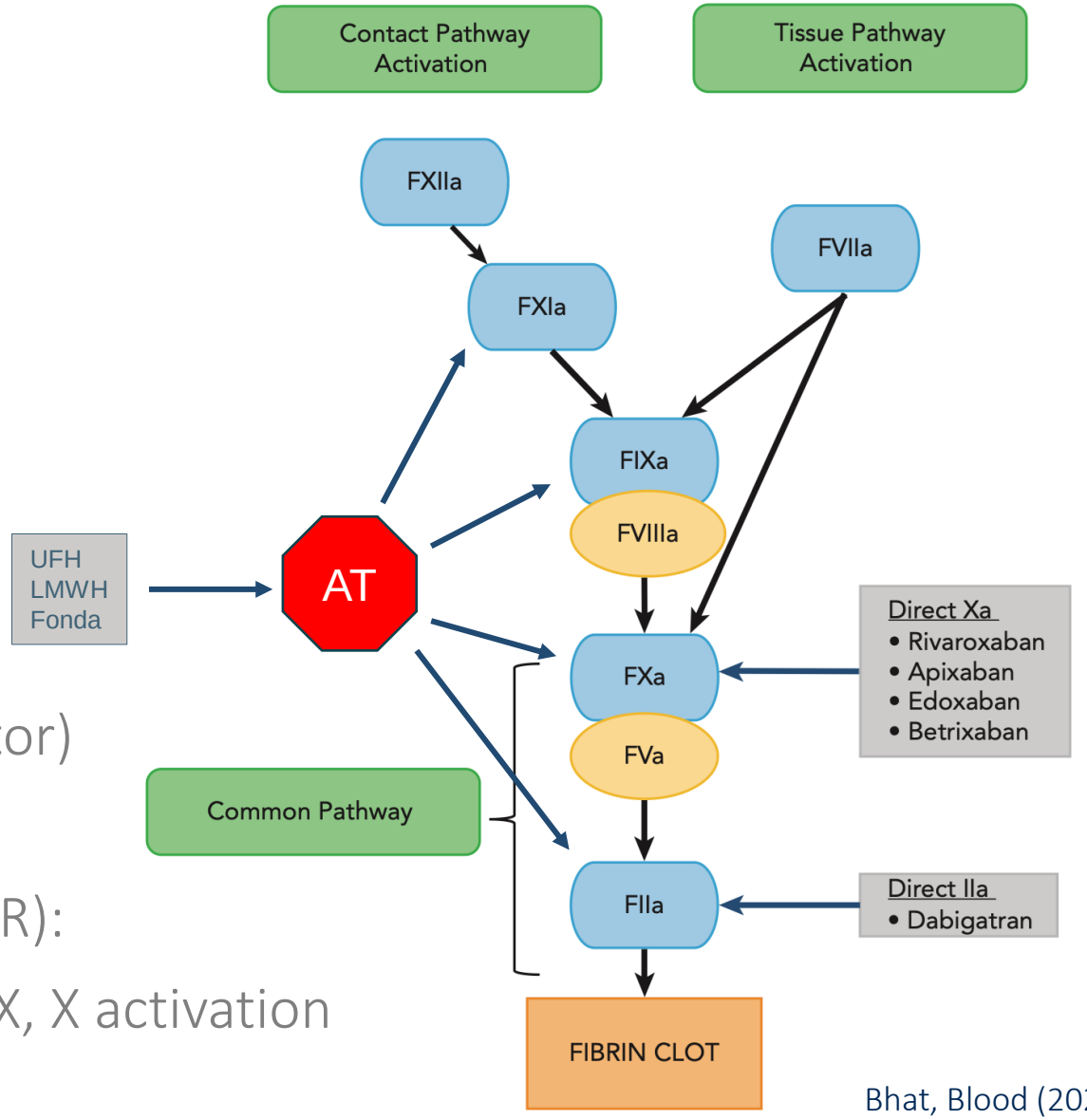
- Xa inhibition (direct)
- Thrombin (IIa) inhibition (direct)

The heparins (UFH, LMWH, fondaparinux):

- Xa inhibition (indirect, antithrombin as a cofactor)

Warfarin inhibits Vitamin K oxide reductase (VKOR):

- Impairs vitamin K activation → reduces II, VII, IX, X activation



Bhat, Blood (2024)

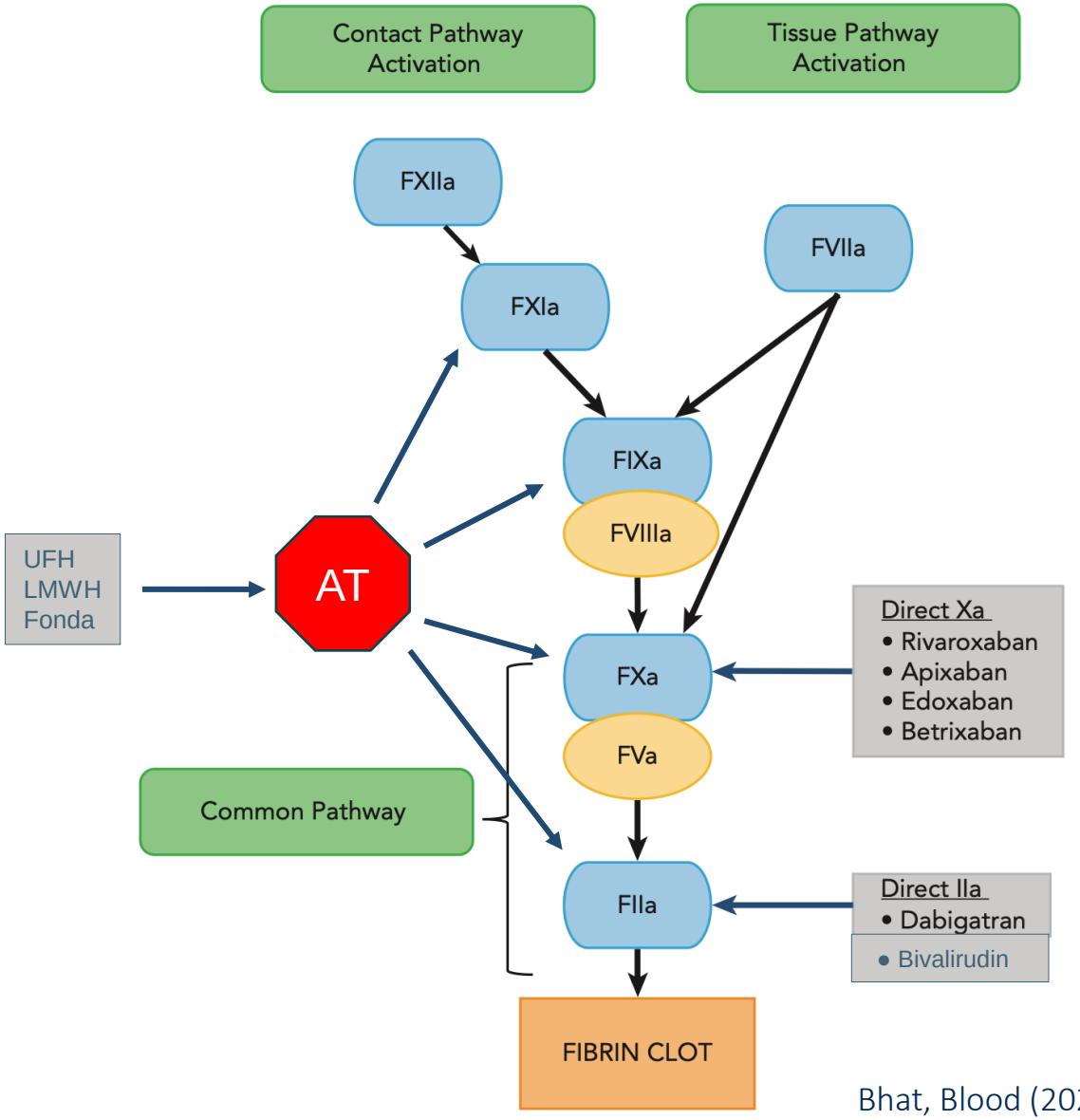
The *How* of DOACs

Two mechanisms of DOAC action:

- Xa inhibition (direct)
- Thrombin (IIa) inhibition (direct)

  Similar mechanism to bivalirudin (parenteral DTI)

  **binds circulating and clot-bound thrombin (? thrombolytic effect)*



Bhat, Blood (2024)

Clinical Trial > Lancet Haematol. 2020 Jan;7(1):e18-e27.
doi: 10.1016/S2352-3026(19)30219-4. Epub 2019 Nov 5.

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

Christoph Male [1], EINSTEIN-Jr Phase 3 Investigators

Clinical Trial > Lancet Haematol. 2021 Jan;8(1):e22-e33.
doi: 10.1016/S2352-3026(20)30368-9. Epub 2020 Dec 5.

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

Jacqueline Halton [1], DIVERSITY Trial Investigators

Clinical Trial > Lancet Haematol. 2024 Jan;11(1):e27-e37.
doi: 10.1016/S2352-3026(23)00314-9. Epub 2023 Nov 16.

Apixaban versus no anticoagulation for the prevention of venous thromboembolism in children with newly diagnosed acute lymphoblastic leukaemia or lymphoma (PREVAPIX-ALL): a phase 3, open-label, randomised, controlled trial

Sarah H O'Brien [1], PREVAPIX-ALL investigators

The *who/what/when/where/why* of DOACs in children (without CHD)

Rivaroxaban, Dabigatran, Apixaban…

… first to be studied in children (non-CHD)

EINSTEIN-Jr (rivaroxaban) and DIVERSITY (dabigatran) trials

- Non-inferior treatment (compared to heparins or VKA)
- Equivalent safety profile without serious bleeding
- Both FDA approved for VTE in children (2021)

PREVAPIX-ALL (apixaban) trial:

- Compared DOAC vs no anticoagulation for prevention of VTE in ALL patients at high risk
- No significant treatment benefit, but secondary analysis demonstrated reduced VTE in obese patients with ALL
- Major bleeding infrequent (both groups), but more epistaxis

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Randomized Controlled Trial > J Am Heart Assoc. 2021 Nov 16;10(22):e021765.
doi: 10.1161/JAHA.120.021765. Epub 2021 Sep 24.

Thromboprophylaxis for Children Post-Fontan Procedure: Insights From the UNIVERSE Study

Brian W McCrindle [1], Alan D Michelson [2], Andrew H Van Bergen [3], Estela Suzana Horowitz [4], Juan Pablo Sandoval [5], Henri Justino [6], Kevin C Harris [7], John L Jefferies [8], Liza Miriam Pina [9], Colleen Peluso [9], Kimberly Nessel [9], Wentao Lu [9], Jennifer S Li [10]; UNIVERSE Study Investigators *

Clinical Trial > J Am Coll Cardiol. 2022 Dec 13;80(24):2301-2310.
doi: 10.1016/j.jacc.2022.09.031. Epub 2022 Oct 31.

Edoxaban for Thromboembolism Prevention in Pediatric Patients With Cardiac Disease

Michael A Portman [1], Jeffrey P Jacobs [2], Jane W Newburger [3], Felix Berger [4], Michael A Grosso [5], Anil Duggal [5], Ben Tao [5], Neil A Goldenberg [6]; ENNOBLE-ATE Trial Investigators

Randomized Controlled Trial > J Am Coll Cardiol. 2023 Dec 12;82(24):2296-2309.
doi: 10.1016/j.jacc.2023.10.010.

Apixaban for Prevention of Thromboembolism in Pediatric Heart Disease

R Mark Payne [1], Kristin M Burns [2], Andrew C Glatz [3], Christoph Male [4], Andrea Donti [5], Leonardo R Brandão [6], Gunter Balling [7], Christina J VanderPluym [8], Frances Bu'Lock [9], Lazaros K Kochilas [10], Brigitte Stiller [11], James F Cnota 2nd [12], Otto Rahkonen [13], Asra Khan [14], Rachele Adorisio [15], Serban Stoica [16], Lindsay May [17], Jane C Burns [18], Jose Francisco K Saraiva [19], Kimberly E McHugh [20], John S Kim [21], Agustin Rubio [22], Nadia G Chía-Vazquez [23], Marcie R Meador [14], Joshua L Dyme [24], Alison M Reedy [24], Toni Ajavon-Hartmann [24], Praneeth Jarugula [24], Lauren E Carlson-Taneja [24], Donna Mills [24], Olivia Wheaton [25], Paul Monagle [26]

UNIVERSE Study:

Multicenter RCT, 2-part, open-label study of rivaroxaban vs. ASA

112 pts randomized 2:1, over 35 sites (10 countries)

All Fontan patients

Similar safety and fewer thrombotic events

FDA Approved for Fontan prophy (2021)

ENNOBLE-ATE Trial:

Multicenter RCT, open-label, phase 3 study of edoxaban vs. SOC AC

168 patients randomized 2:1, over 48 sites (14 countries)

44% pts after Fontan, 22% KD, 4% pts with heart failure, 30% other

Lower rate of clinically-relevant bleeding and thrombotic events

SAXOPHONE Study:

Multicenter RCT, open-label, phase 2 study of apixaban vs. SOC AC

192 patients randomized 2:1, over 33 sites (12 countries)

74% single ventricle pts, 14% KD, 12% other cardiac disease

Lower rate of bleeding (there were no thrombotic events)

children with congenital heart disease

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Antithrombotic management after Stage 3
Real-world experience with DOACs

J Thromb Haemost. 2023 Jun;21(6):1601-1609. doi: 10.1016/j.jtha.2023.03.005. Epub 2023 Mar 14.

Real-world use of apixaban for the treatment and prevention of thrombosis in children with cardiac disease

Christina VanderPluym [1], Paul Esteso [2], Ashish Ankola [3], Amy Hellinger [4], Courtney Ventresco [4], Beth Hawkins [4], Ryan L Kobayashi [2], Ryan Williams [2], Maria A Cetatoiu [4], Kimberlee Gauvreau [2], Jesse J Esch [2]

- 219 children, median age 6.8 years (0.3-19)
- 79% prophylaxis and 21% treatment
- Dose was adjusted to apixaban levels in 25% of the pts
- 4 bleeding safety events (3 CRNM; 1 major, hemoptysis)
- 95% effective (37/39 patients with follow-up imaging)

Pediatr Cardiol. 2023 Jan 21. doi: 10.1007/s00246-022-03094-6. Online ahead of print.

Use of Rivaroxaban in Children with Congenital Heart Disease: A Single-Center Case Series

Silvestre Duran [1], Christina Gerber [2], Shannon Bilsky [2], Sarah Plummer [2], Martin Bocks [2]

- 27 children, range 4 months to 15 years
- 70% of patients were single ventricle
- 15 pts for prophylaxis and 12 pts for treatment
- No new VTE, 10 of 12 treatment pts had improvement
- 2 CRNM bleeding events

Remember I promised to mention other drugs for prophylaxis after the Glenn?

Apixaban and Rivaroxaban can be prescribed at doses appropriate for infants

Before we talk about DOACs, back to aspirin for a minute:

… remember? we said we would come back to this

- Aspirin binds irreversibly to circulating platelets, but the half-life is 20 minutes
- Studies report highly variable rates of ”aspirin resistance”
- But are we performing/timing the tests appropriately?

Randomized Controlled Trial > Thromb Haemost. 2011 Sep;106(3):491-9.
doi: 10.1160/TH11-04-0216. Epub 2011 Jul 28.

Twice daily dosing of aspirin improves platelet inhibition in whole blood in patients with type 2 diabetes mellitus and micro- or macrovascular complications

Galia Spectre [1], Lisa Arnetz, Claes-Göran Östenson, Kerstin Brismar, Nailin Li, Paul Hjemdahl

Randomized Controlled Trial > J Thromb Haemost. 2012 Jul;10(7):1220-30.
doi: 10.1111/j.1538-7836.2012.04723.x.

The recovery of platelet cyclooxygenase activity explains interindividual variability in responsiveness to low-dose aspirin in patients with and without diabetes

B Rocca [1], F Santilli, D Pitocco, L Mucci, G Petrucci, E Vitacolonna, S Lattanzio, D Mattoscio, F Zaccardi, R Liani, N Vazzana, A Del Ponte, E Ferrante, F Martini, C Cardillo, R Morosetti, M Mirabella, G Ghirlanda, G Davì, C Patrono

Unpublished data in patients at Colorado receiving aspirin after Fontan:

- *With “Peak” and “trough” TEG platelet mapping testing*
- *87% (46/53) had waning antiplatelet effect at 24 hrs after 81 mg ASA (prior to a next dose)*

(Effective arachidonic acid inhibition on 81 mg confirmed with “peak” aspirin testing)

Our patients after Fontan are now routinely discharged on aspirin 81 mg BID

So, what do we do at Children’s Hospital Colorado?

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Our patients after Fontan are now routinely discharged on aspirin 81 mg BID

Back to the DOACs after Fontan…

- We maintain aggressive treatment of thrombosis (eg. CA-VTE), initially with *standard of care* anticoagulation (warfarin or LMWH)
- After discharge, Fontan patients with thrombosis will follow up in outpatient Cardiac Thrombosis Clinic for consideration of conversion to DOAC for continued therapy
- At-risk patients will discharge after Fontan on DOAC therapy (with BID aspirin)

Answer in the Zoom chat:
At your centers, what are some criteria to identify at-risk or high-risk Fontan patients?

How do we identify at-risk patients?

AMERICAN COLLEGE of CARDIOLOGY®

Anticoagulation Algorithm For Fontan Patients

Apr 05, 2023 | Tarek Alsaied, MD, FACC; Mathias Possner, MD; Jef Van den Eynde, MD, BSc(Med); Jacqueline Kreutzer, MD, FACC

Expert Analysis

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How do we identify at-risk patients?

Anticoagulation Algorithm For Fontan Patients

Apr 05, 2023 | Tarek Alsaied, MD, FACC; Mathias Possner, MD; Jef Van den Eynde, MD, BSc(Med); Jacqueline Kreutzer, MD, FACC

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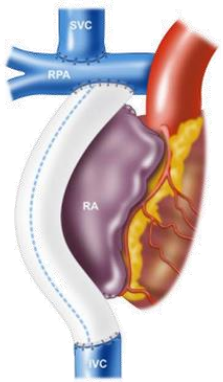

High Risk

- Recent thromboembolic event or stent
- Multiple risk factors (e.g. previous thromboembolic event, recurrent atrial arrhythmias not controlled or within 6 months of control, prior thrombosis on bioprosthetic valves, recent thrombosis in the Fontan pathway, mechanical valve)

Warfarin OR NOAC

(Therapeutic dose)

Intermediate Risk

- Single risk factor (e.g. atrial arrhythmias under control (≥6 months), history of remote stroke and an open fenestration, advanced heart failure/severe ventricular dysfunction/Fontan circulatory failure, protein-losing enteropathy with albumin consistently below 3 g/dl or total protein < 6 g/dL, presence of pulmonary artery stump, prior thrombosis on bioprosthetic valve in the immediate post-operative period, remote prior thrombosis in the Fontan pathway, atriopulmonary Fontan, genetic prothrombotic predisposition)

Aspirin OR

Warfarin OR NOAC

(Prophylactic dose)

Low Risk

- No known risk factors

Aspirin only

We take it one step further:

… THE RULE …

"One strike and you're out"

Any complication after Fontan commits patient to lifelong DOAC prophylaxis

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- At-risk patients will discharge after Fontan on DOAC therapy (with BID aspirin)
- Any Fontan patient with thrombosis converts to DOAC prophylaxis after treatment

But how do we, at Colorado, make this all happen?

So, what do we do at Children's Hospital Colorado?

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How to best approach antithrombotic management in single ventricle patients

BUILD RELATIONSHIPS

Collaborative decision making based on care pathways and protocols:

- Single ventricle-specific protocols for thromboprophylaxis, both long-term and post-operative
- Take into account the experience of your center (evidence-based protocols are great, but great evidence does not exist)

Champions for consistent, yet patient-centric, management:

- Make a friend in hematology and foster a mutually beneficial relationship between disciplines.
- Identify a pharmacist champion who understands SV patients and anticoagulation (or willing to learn)
- Will need to learn/identify patients that require more-specified management (off protocol).
- Single ventricle patients require patient-centric management of new thrombosis events

Multidisciplinary outpatient care:

- If outpatient anticoagulation management services exist, try to integrate cardiology.
- Integrate these services with your multidisciplinary teams at each stage of palliation.

Remember this slide?

Our patients after Fontan are now routinely discharged on aspirin 81 mg BID

Back to the DOACs after Fontan…

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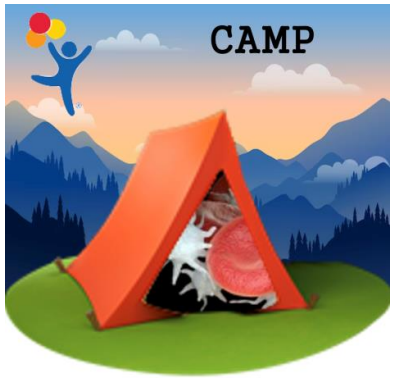

Cardiac Antithrombosis Management Program

Cardiac Antithrombosis Management Program

- Multidisciplinary consult service for the inpatient Heart Institute
- We provide consultation for:
  - Anticoagulant selection
  - Duration of anticoagulation
  - Aspirin responsiveness testing
  - Timing of repeat vascular imaging
  - Outpatient follow up plan

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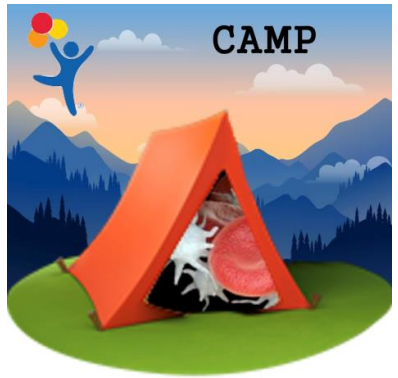

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- We provide consultation for:
  - Anticoagulant selection
  - Duration of anticoagulation
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  - Timing of repeat vascular imaging
  - Outpatient follow up plan
- CAMP consult is requested via 3 possible routes:
  - CAMP Consult Order (Epic EHR)
  - CAMP Secure Chat Group (Epic EHR)
  - Contact any CAMP team member directly
- Consult notes in EHR within 24 hours
- CAMP Rounds (every 2 wks):
  - Review of active consult inpatients
  - Review of patients with new thromboses and/or requiring AC
  - Follow up consult notes as needed

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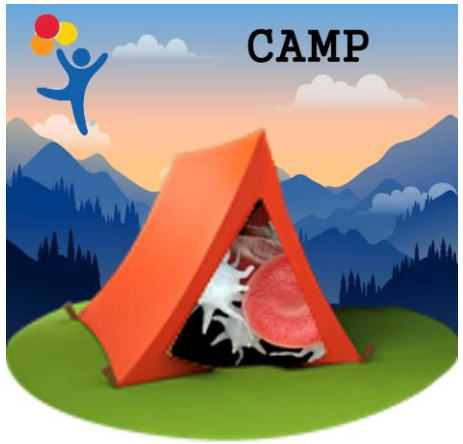

Cardiac Antithrombosis Management Program

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FONTAN OUTCOMES NETWORK

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But how do we, at Colorado, make this all happen?

Cardiac Thrombosis Clinic

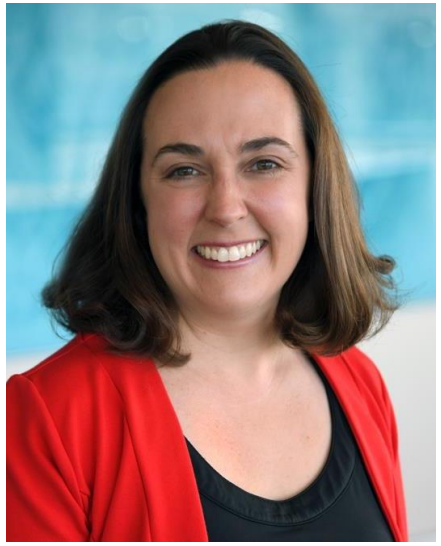
Joint ***outpatient clinic*** with hematology at the Hemophilia and Thrombosis Center

HTC Medical Director: Michael Wang, MD

Co-Directors, Cardiac Thrombosis Clinic:

- John Kim, MD
- Beth Warren, MD

HTC Pharmacist: Tim Schardt, PharmD



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Cardiac Thrombosis Clinic

- Scheduled monthly (most visits via telehealth)

- Frequent referral questions:
  - Thrombophilia evaluation and follow up
  - Duration of anticoagulation
  - Alternatives to LMWH/VKA and conversion to DOAC
  - Infant mechanical valve anticoagulation

- I stay away from and avoid addressing cardiology management issues, rather, I incorporate the physiologic/surgical considerations into thrombosis decisions.

Importantly, Beth has learned a lot of cardiology, while I have learned a lot of hematology!

How to best approach antithrombotic management in single ventricle patients

SUMMARY

Collaborative decision making based on care pathways and protocols:

- Consistency with protocols (that everyone can agree on) will build experience and expertise
- We don't have great evidence, but we have lots of experience… it's okay to trust your experience

Champions for consistent, yet patient-centric, management:

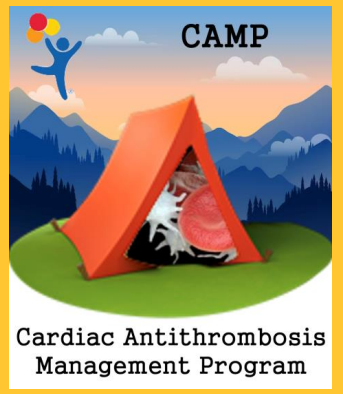
- Build a multidisciplinary team that includes a pharmacist willing to learn anticoagulation in SV patients
- Learn when to go off protocol and provide patient- and situation-specific managements

Multidisciplinary outpatient care:

- Integrate hematology with cardiology outpatient services
- Integrate outpatient thrombosis care with other multidisciplinary single ventricle program

Thank you!

John.Kim@childrenscolorado.org
CAMP-Cardiology@childrenscolorado.org



contact me

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Heart Institute

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