PREVENTION OF CENTRAL LINE-RELATED THROMBOSIS

Sarah O’Brien, MD, MSc

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**DISCLOSURES FOR SARAH O’BRIEN, MD**

<table>
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<tr>
<th>Research Support/P.I.</th>
<th>Receive salary support from Children’s Oncology Group/Bristol Myers Squibb for role as PI in ACCL1333</th>
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<tr>
<td>Employee</td>
<td>No relevant conflicts of interest to declare</td>
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<td>Major Stockholder</td>
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<td>Speakers Bureau</td>
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| Scientific Advisory Board      | Pfizer – Steering Committee
BMS – Steering Committee
GSK – Data Safety Monitoring Committee |

Presentation includes discussion of the following off-label uses of a drug or medical device: a variety of anticoagulants for the use of thromboprophylaxis in pediatric patients with central venous catheters.
Today’s Agenda

- What do we KNOW about prevention of CVL thrombosis?
- What do we THINK about prevention of CVL thrombosis?
- What is NEW in the prevention of CVL thrombosis?
WHAT DO WE KNOW ABOUT PREVENTION OF CVL THROMBOSIS?
Number of Pages Devoted to Thromboprophylaxis in 2012 ACCP Guidelines
2012 ACCP Guidelines

Long-Term Home TPN

Cardiac

+ Prophylaxis

Hemodialysis

Kawasaki

What Does Prophylaxis Even Mean?
Heparin-bonded central venous lines reduce thrombotic and infective complications in critically ill children

ARTICLE

Heparin-Bonded Central Venous Catheters Do Not Reduce Thrombosis in Infants With Congenital Heart Disease: A Blinded Randomized, Controlled Trial
PROPHYLAXIS FOR CVC-RELATED DVT
– SYSTEMATIC REVIEW

- Included 10 RCTs on thromboprophylaxis
- These RCTs tested the efficacy of:
  - Heparin-bonded CVC
  - Unfractionated heparin
  - Low molecular weight heparin
  - Warfarin
  - Antithrombin concentrate
  - Nitroglycerin
- In each study, treatment was compared with either standard of care or placebo
- All studies performed active surveillance with radiologic imaging to obtain accurate estimate of the frequency of CVC-related DVT
CVC-RELATED THROMBOSIS AND PROPHYLAXIS IN CHILDREN: A SYSTEMATIC REVIEW AND META-ANALYSIS

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<td>Unfractionated Heparin</td>
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NOTE: Weights are from random effects analysis.
Systematic Review

- Quality of the RCTs was generally adequate
- All were parallel trials except one crossover trial
- Most (6/10; 60%) were single-center trials
- Half of the trials were not powered for DVT
- Relative reductions in DVT were hypothesized to be 25-75%
Systematic Review

- Investigators were blinded in half of the trials.
- Outcome assessors were blinded in at least seven trials.
- Results of the trials, however, may have been compromised by missing data on DVT:
  - Most common reason was inability to obtain radiologic imaging.
  - On average, 10.7% of patients recruited did not have data on DVT.
  - In seven trials, outcome data were missing for at least 5% of the patients.
Only half of the trials were completed.

Four trials were terminated early for futility, and one for poor recruitment.

Futility suggests that hypothesized reduction in DVT frequency could not be achieved even if calculated sample size achieved.

Hypothesized reductions, however, were probably too large, with one trial aiming to detect a 75% relative reduction.

The magnitude of reduction in outcomes in children is more likely to be moderate at best, with a relative reduction of 25-30%.
SYSTEMATIC REVIEW

- The timing of thromboprophylaxis may partly explain the lack of efficacy
- Pierce et al. showed a significant reduction with heparin-bonded CVC when thromboprophylaxis was started upon insertion of the CVC
- With LMWH started, on average, 2.6 days after insertion of the CVC, Massicotte et al. failed to show a reduction
- The timing of thromboprophylaxis was unclear in the other RCTs that tested systemic agents
CONCLUSIONS

- An adequately powered multi-enter RCT that can detect a modest (25-30%), clinically significant reduction in the frequency of DVT is needed to determine the efficacy of thromboprophylaxis against CVC-related DVT in children.
The CATCH Trial

- Study Population: 1485 patients <16 years of age from 14 PICUs in the United Kingdom
  - 502 standard CVCs
  - 486 antibiotic-impregnated CVCs
  - 497 heparin-impregnated CVCs
- Recruited from Nov 2010 – Nov 2012
- Primary Outcome – blood stream infections
- Finding – Antibiotic-coated catheters significantly reduced risk of infection compared with standard and heparin-coated catheters
CATCH TRIAL – WHAT ABOUT DVT?

- Secondary Outcome – time to CVC thrombosis
  - 2 episodes within 5 days of difficulty flushing or drawing back blood from CVC
  - 1 episode of swollen limb
  - CVC removal due to thrombosis
  - Positive ultrasound indicating thrombosis

- Rates of Thrombosis:
  - 25% standard, 26% antibiotic, 21% heparin
  - No difference in hazard ratio for thrombosis between the three types of lines
WHAT DO WE THINK ABOUT PREVENTION OF CVL THROMBOSIS?
HTRS Survey

- Survey recipients: pediatric hematologists who have been members of HTRS for ≥5 years
- 53 out of 112 responded (47% response rate)
- 56% practice at institutions that have a pTP and/or mTP policy
- 27% would utilize prophylaxis in presence of CVL
- 31% would utilize prophylaxis in critically ill newborn with CVL
- 81% would utilize in hospitalized patient with history of CVL-related thrombosis

Badawy et al. JPHO 2016
Multi-disciplinary expert panel (n=32)

- Strong recommendation for pharmacologic prophylaxis in injured children with a personal history of VTE (94%)

- Weak recommendation for pharmacologic prophylaxis against VTE in injured children with a CVL (91%)
PROTRACT STUDY

- Prospective multi-national cross-sectional study over four dates in 2012
- 59 PICUs, all patients <18 years of age
- 2484 patients, 87% with at least one risk factor for thrombosis (most common CVL)
- 12.4% received of all PICU patients received pharmacologic thromboprophylaxis
- Presence of a CVL was independently associated with use of prophylaxis (OR 2.32, 95% CI 1.6-3.4)
- Only 17% of patients with CVL received prophylaxis
Clinical equipoise on prophylaxis against catheter-associated thrombosis in critically ill children

Candace N. Mannarino, MD a,*, Edward Vincent S. Faustino, MD, MHS b, 1

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CLINICAL EQUIPOISE

- The largest pediatric RCT of prophylaxis was stopped early due to poor enrollment
- Only 31% of the estimated sample size was enrolled, and only 36% of the parents of eligible children consented
- An important strategy to improve enrollment for similar RCTs is to have members of the clinical care team, particularly the pediatric critical care physicians, be supportive of the RCT
- Lack of clinical equipoise or uncertainty regarding the benefit of prophylaxis can be a barrier toward successful enrollment
Clinical Equipoise

- Cross-sectional, self-administered electronic survey of pediatric critical care physicians in the United States
- Respondents were requested to answer each survey item based on their personal opinions
- Likert scales were used to determine agreement with specific statements regarding randomization and prophylaxis against DVT
- Responses from 239 physicians (out of 797 invited) were analyzed – 30% response rate
CLINICAL EQUIPOISE

- In the presence of a CVL, respondents were willing to randomize children ≥1 month old
- 90% of respondents were willing to randomize children with coagulopathy and a CVL
  - INR ≤ 2
  - PTT ≤ 50 seconds
  - Platelet count ≥50,000/mm$^3$.
- In the presence of recent surgery, 82%-94% of respondents were willing to randomize children with a CVL
  - 2 days after most types of surgery
  - 3 days after neurosurgery
What is NEW in the prevention of CVL thrombosis?
Ohio Children’s Hospitals’ Solutions for Patient Safety (OCHSPS) National Children’s Network collaborative to reduce hospital acquired conditions.

- One of 10 outcome measures is to reduce hospital-acquired Venous Thromboembolism (VTE) events.
Ohio Children's Hospitals' Solutions for Patient Safety (OCHSPS) National Network Phase I

Venous Thromboembolism Events
Network Aggregate

| Network Events | 05/11 | 06/11 | 07/11 | 08/11 | 09/11 | 10/11 | 11/11 | 12/11 | 01/12 | 02/12 | 03/12 | 04/12 | 05/12 | 06/12 | 07/12 | 08/12 | 09/12 | 10/12 | 11/12 | 12/12 | 01/13 | 02/13 | 03/13 | 04/13 | 05/13 |
|----------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
CHILDREN’S HOSPITALS ACQUIRED THROMBOSIS REGISTRY (CHAT)

- This study aims to create the first large scale, multi-institutional registry including proposed risk factors from children with confirmed HA-VTE and matched controls.
- Data from the registry will be used to define risk factors for HA-VTE in pediatric patients and to create and validate a risk assessment model and stratified scoring system.

Arash Mahajerin, MD
CHOC

Julie Jaffray, MD
CHLA

Brian Branchford, MD
Colorado
THE HOLY GRAIL

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What Else is New?
Apixaban vs. SOC for Prevention of VTE During Induction in Newly Diagnosed ALL Patients

ACCL 1333
Rationale for ACCL1333

- Catheter associated thrombosis is a commonly reported complication in pediatric ALL
- Reported incidence ranges from 5 to 50%
  - Depends on if symptomatic and asymptomatic reported
- Cerebral sinus vein thrombosis
  - 2.9% incidence in meta-analysis
- 20-30% tunneled catheters removed before end of therapy due to thrombosis or infection
- Evidence of bi-directional relationship between CVL-related thrombosis and infection
- Risk of post-thrombotic syndrome (PTS): 5.6-53%
Primary Objectives

• To compare the effect of prophylactic apixaban, a direct oral anticoagulant, versus no administration of systemic prophylactic anticoagulant during induction chemotherapy, on a composite endpoint of:
  • Adjudicated asymptomatic and symptomatic DVT, pulmonary embolism, cerebral sinus vein thrombosis, and VTE-related death
  • Adjudicated major bleeding events
• Hypothesis – Apixaban will reduce the risk of VTE (symptomatic + asymptomatic)
• 500 randomized subjects
Plasma and Genetic Biomarker Sub-study

- Objectives are to assess
  - Genetic (FVL, PT20202) and plasma (hemostatic proteins) biomarkers for VTE risk
  - Apixaban effects on surrogate efficacy and mechanistic biomarkers of hemostasis
- Hypothesis – specific or a combination of single nucleotide polymorphisms (SNPs) and hemostatic protein levels will predict the sub-population of patients at increased risk of VTE
- Plan to include 150 subjects
PARTING THOUGHTS

- We don’t know much about the efficacy of pharmacologic prophylaxis to prevent CVL-related thrombosis
- We do think there are children who could benefit from this strategy, and clinical equipoise exists
- It is important for us to retain our equipoise despite mounting external pressures and think creatively about methods to scientifically study these important questions