Perspectives from Academia on Novel Anticoagulant Studies in Children

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Epidemiology of Thrombosis in Children

Dramatic Increase in Venous Thromboembolism in Children's Hospitals in the United States From 2001 to 2007

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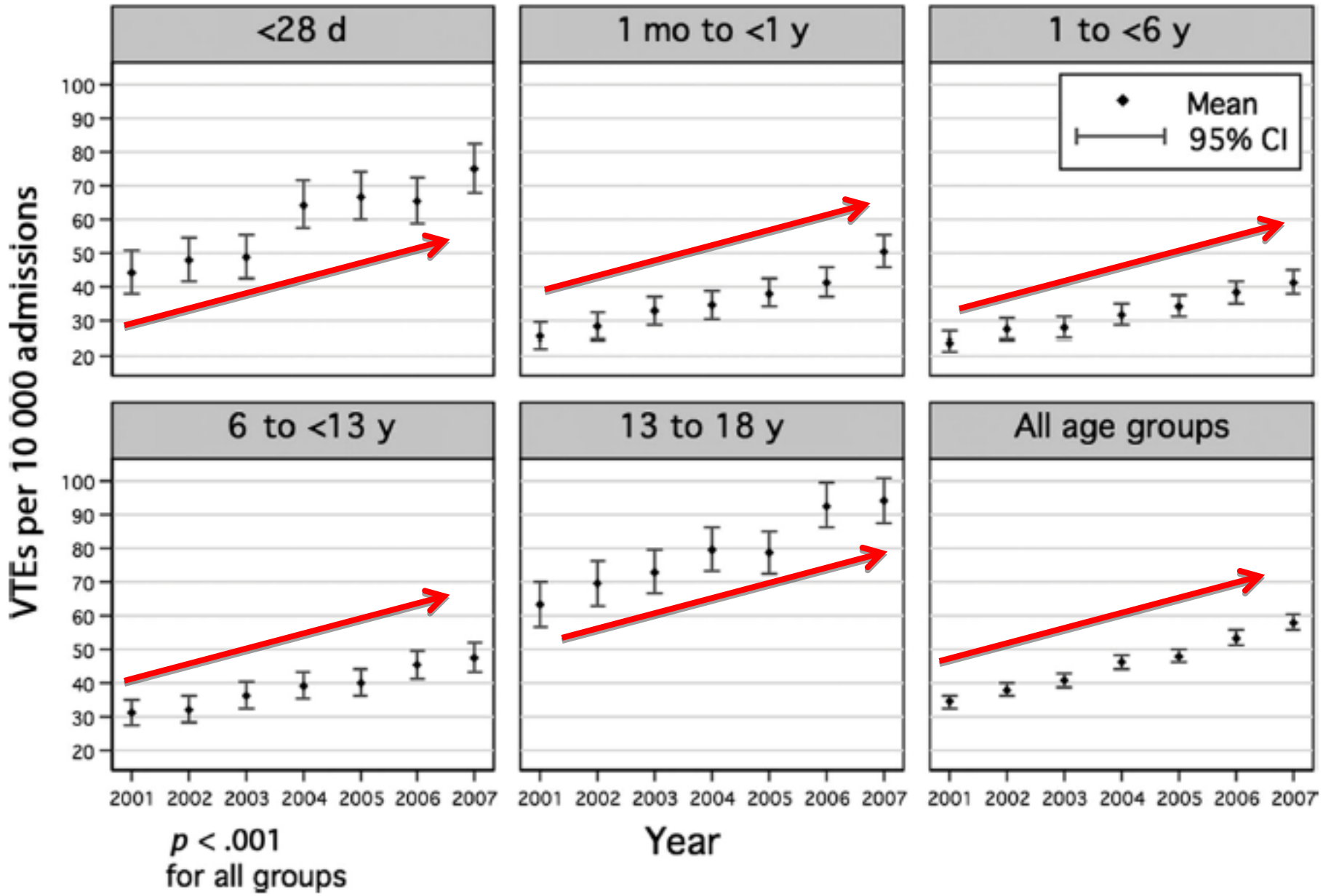
Pediatrics 2009;124:1001–1008

WHAT'S KNOWN ON THIS SUBJECT: There is no evidence demonstrating that the rate of VTE in children has changed over time, although this has been thought to be the case by pediatric hematologists.

WHAT THIS STUDY ADDS: The study demonstrates a significant increase in the rate of VTE in the United States. It is important that pediatricians are aware of this.


<28 d
1 mo to <1 y
1 to <6 y
6 to <13 y
13 to 18 y
All age groups
Mean
95% CI
VTEs per 10 000 admissions
100
90
80
70
60
50
40
30
20
2001
2002
2003
2004
2005
2006
2007
Year
p < .001
for all groups

Frequency of Anticoagulant Use

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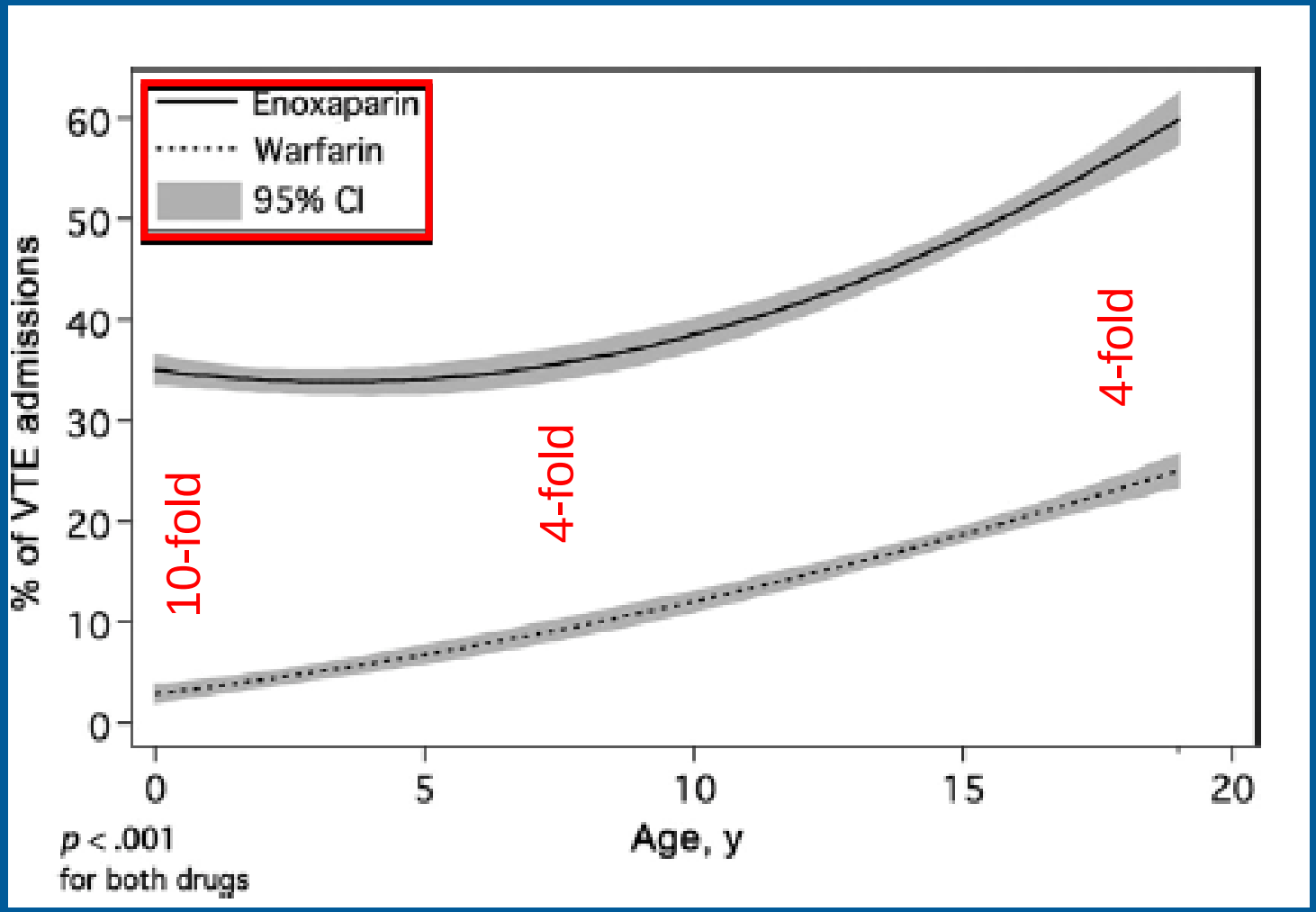

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Current Anticoagulants FDA Approved for Children

Pediatric: Argatroban clearance is decreased in seriously ill pediatric patients. Pharmacokinetic parameters of Argatroban were characterized in a population pharmacokinetic/pharmacodynamic analysis with sparse data from 15 seriously ill pediatric patients. Clearance in pediatric patients (0.16 L/hr/kg) was 50% lower compared to healthy adults (0.31 L/hr/kg). Four pediatric patients with elevated bilirubin (secondary to cardiac complications or hepatic impairment) had, on average, 80% lower clearance (0.03 L/hr/kg) when compared to pediatric patients with normal bilirubin levels. (See PRECAUTIONS, Pediatric Use.)

What anticoagulants are being prescribed to children?

- Heparin

Basically…All of them

- Argatroban
- Bivalirudin
- Lepirudin
- Tissue plasminogen activator

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History of anticoagulation in children

	Discovery	First clinical use	First use in children	First prospective study
Heparin	1916	1937	1954[1]	1994[6]
Warfarin	1929	1954	1976[2] (1962)	1994[7]
LMWH	1970s	1980s	1993[3]	1996[8]
DTIs	1884	1997	1999[4]	2007[9]
Fondaparinux	1985	2001	2004[5]	2009[10]
Rivaroxaban	2005	2010	?	Underway

[1]Bartolozzi G. Riv Clin Pediatr 1954; 54:429-39.
[2]Carpentieri. Arch Dis Child 1976; 51:445-8.
[3]Fijnvandraat K. Thromb Haemost 1993; 69:649.
[4]Ranze O. Eur J Pediatr 1999; 158 (suppl 3):S130-3.
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[6]Andrew M. Pediatr Res 1994; 35:78-83.
[7]Andrew M. Thromb Haemost 1994; 71:265-269.
[8]Massicotte P. J Pediatr 1996 128:313-8.
[9]Young G. J Thromb Haemost 2007; 5:1654-1659.
[10]Young G. Pediatr Blood Cancer 2011 57: 1049-1054.

What about the new oral anticoagulants

- None reported so far…
  but, it is just a matter of time

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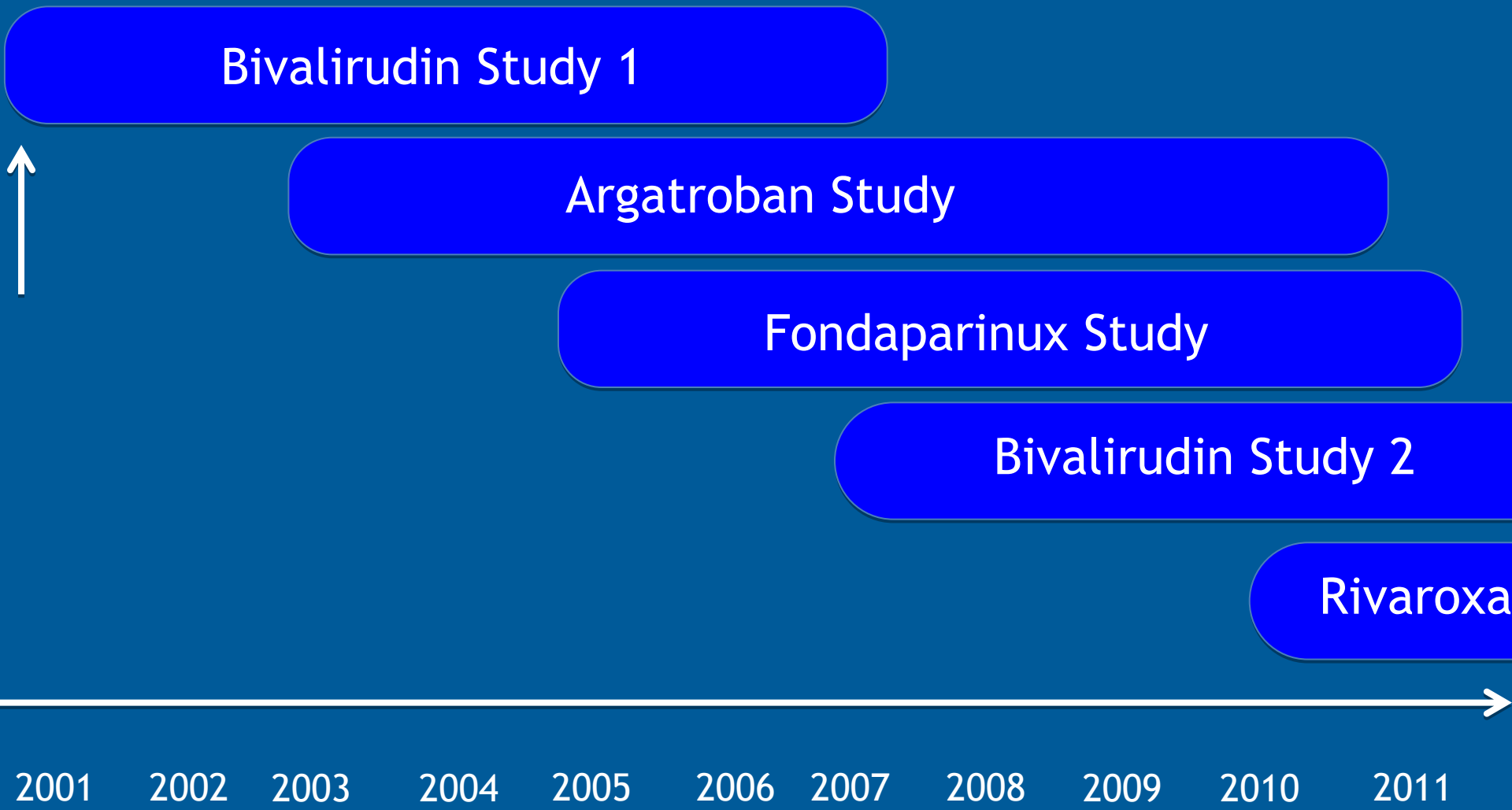

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Bivalirudin Study 1

- Investigator-initiated, industry sponsored (The Medicines Company) under company IND
- Protocol development initiated in 2001
- Only included patients <6 months of age
- Patient enrollment 2002-2005 (16 patients over 3 years)
- Study published in 2007

2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011

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Bivalirudin Study 1

- Study challenges
  - Enrollment very slow
    - Limited funding—only 2 participating sites
    - Families reluctant to enroll their children
  - Pharmacokinetics not done (pharmacodynamics only)
  - No support for follow up study for older children so data not generalizable

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Bivalirudin Study 1

- Study positives
  - First completed study of new anticoagulant in over 10 years
  - The Medicines Company was the only company at that time that was willing to support me to study their anticoagulant
  - The Medicines Company built a good relationship with me and I in turn supported their cardiac catheterization study recently published

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Argatroban Study

- Industry initiated/sponsored (GlaxoSmithKline) under company IND
- Protocol development initiated in 1999?
- For patients with confirmed heparin-induced thrombocytopenia (HIT)
- Patient enrollment 2000-2003 was 0
- In 2003, I was asked to become the PI (along with Lyn Boshkov)
- Study protocol significantly revised and new centers added
- Study resumed in 2004 and accrued 18 patients over ~3 years
- Two papers published in 2011 [a clinical manuscript and PK (PD) manuscript published collaboratively with FDA]

2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011

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Argatroban Study

- Study Challenges
  - Company did not know the experts in the field—selected a PI that was not a hematologist and not an expert in HIT
    - Poor study design (almost impossible to recruit subjects)
    - Poor choice of participating centers
    - This led to more than 3 years of work for 0 subjects
  - Study redesign and new centers led to completion of study though with significant delay
  - Collaboration with FDA for PK was fruitful but delayed publication of results by ~2 years

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Argatroban Study

- Study Positives
  - GSK formed a new steering committee and followed the recommendations made leading to successful study completion
    - Study redesign
    - New participating sites
  - Collaboration with FDA led to a robust PK analysis despite a sparse number of samples from a small number of subjects
    - Led to a separate PK publication
  - This is the first and still only anticoagulant with pediatric labeling

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Fondaparinux Study

- Investigator initiated under an investigator IND
- Funded by FDA OPD grant
- For children with DVT but only older than 1 year (IND condition)
- Patient enrollment 2007-2009 (24 subjects—full enrollment)
- Study was just published

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Fondaparinux Study

- Study Challenges
  - I originally approached industry in 2004 (Sanofi then GSK) for support to conduct the study, but they were not interested
  - GSK requested a waiver from FDA to conduct a pediatric study which was not granted
  - GSK later approached me to conduct the study but by then I was over half way through and had all the funding I needed
  - Ultimately, GSK was licensed the study data from me and my institution
  - Study did not include children <1 year due to an IND restriction
  - Study had short follow up period

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Fondaparinux Study

- Study Positives
  - FDA funded the study through OPD
  - Study completed relatively quickly with 4 participating sites
  - As a result of the relationship developed with GSK for fondaparinux data, we are collaborating on obtaining additional follow up data
  - We are also working together along with the FDA to ensure all post-marketing obligations are met

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Bivalirudin Study 2

- Investigator initiated under an investigator IND
- Funded by an NIH R01 grant
- For children with DVT who were not included in the original study (children between 6 months-18 years)
- Study accrued 18 of 30 planned patients
- Data analysis has just begun

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Bivalirudin Study 2

- Study Challenges
  - Funding was limited which hampered several aspects of study development and planning
  - Several sites did not recruit any subjects in 3 years
  - Slow recruitment
    - Continuous infusion drug and PK requirement led to losing many potential subjects

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Bivalirudin Study 2

- Study Positives
  - NIH funded study
  - Study generated over 200 matched PK (bivalirudin levels) and PD (aPTT) pairs which should provide a robust analysis
    - This is a first for a pediatric study
    - Will be able to assess limitations of aPTT
  - The Medicines Company provided study drug reducing the cost to the Federal Government
  - I was able to learn which US sites are best at recruiting subjects for such clinical trials

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Rivaroxa

- Industry-initiated and funded by Bayer
- First phase of 3 phase development plan under way
- Goal is to complete all 3 phases by 2017

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Rivaroxa

- Study Challenges
  - Slow recruitment into first phase
    - Select patient population

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Rivaroxa

- Study Positives
  - Bayer early on formed an Advisory Board of international experts and held several meetings over 2 years
  - EMA regulations required development of a detailed pediatric investigational plan
  - Bayer and the Advisory Board designed a 3 phase development plan accepted by EMA and FDA
  - Bayer accepted and continues to accept the input from the Advisory Board (now Steering Committee)

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Other new anticoagulants

- There is a pediatric development plan for apixaban and dabigtran
  - I am not involved so I don't have any specifics

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What have I learned over the past 10 years?

Requirements for success

- Funding
  - Although I was successful in obtaining Federal funding for two studies, it is not easy and very time-consuming
  - With new regulations (particularly EMA), funding to study new drugs is available
  - Funding should not come **ONLY** from industry
    - Industry's agenda may not be in line with academic pursuits

Requirements for success

- Collaboration between academia and industry
  - Industry sponsors need to know who the experts are
    - Argatroban versus Rivaroxaban, for example
  - Industry-sponsors should form Advisory Boards/Steering Committees early in the process
  - Academics/Clinicians whether on the Advisory Boards/Steering Committees or not need to work to open and recruit patients on to studies

Requirements for success

- Collaboration with regulatory authorities by both academia and industry
  - Bad example: For fondaparinux, FDA restricted the investigator-initiated IND to children >1 year of age…but now is requiring GSK to study this drug in children <1 year of age
  - Good example: Argatroban PK(PD) analysis with academia, industry (GSK) and FDA
    - PK manuscript has co-authorship with FDA, GSK, and me
    - This resulted in pediatric labeling for argatroban

What should not happen!

- The Enoxaparin example
- Despite being the most commonly prescribed anticoagulant in children, there is:
  - No industry funding for ongoing research
  - No FDA approval and nothing planned
  - No prospective data on safety/efficacy since 1996
  - Yet, there are concerns for adverse effects from long-term use (osteopenia) not to mention lack of data on efficacy and bleeding

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Journal of Thrombosis and Haemostasis, **5**: 1654–1659

ORIGINAL ARTICLE

Pilot dose-finding and safety study of bivalirudin in infants <6 months of age with thrombosis

G. YOUNG,* M. D. TARANTINO,† J. WOHRLEY,† L. C. WEBER,† M. BELVEDERE* and D. J. NUGENT*
*Children's Hospital of Orange County, Los Angeles, CA; and †Comprehensive Bleeding Disorders Center, University of Illinois College of Medicine-Peoria, Peoria, IL, USA

Pharmacokinetic and Pharmacodynamic Basis for Effective Argatroban Dosing in Pediatrics

Journal of Clinical Pharmacology, 2011;51:19-28

Rajanikanth Madabushi, PhD, Donna S. Cox, PhD, Mohammad Hossain, PhD, Duane A. Boyle, PharmD, Bela R. Patel, PhD, Guy Young, MD, Young-Moon Choi, PhD, and Jogarao V. S. Gobburu, PhD

Pediatr Blood Cancer 2011;56:1103–1109

Argatroban Therapy in Pediatric Patients Requiring Nonheparin Anticoagulation: An Open-Label, Safety, Efficacy, and Pharmacokinetic Study

G. Young, MD,[1]* L.K. Boshkov, MD,[2] J.E. Sullivan, MD,[3] L.J. Raffini, MD,[4] D.S. Cox, PhD,[5] D.A. Boyle, PharmD,[5] H. Kallender, PhD,[5] E.A. Tarka, MD,[5] J. Soffer, MD,[5] and M.J. Hursting, PhD,[6]

Pediatr Blood Cancer 2011;57:1049–1054

FondaKIDS: A Prospective Pharmacokinetic and Safety Study of Fondaparinux in Children Between 1 and 18 Years of Age

Guy Young, MD,[1]* Donald L. Yee, MD,[2] Sarah H. O'Brien, MD,[3] Rachna Khanna, MPH,[1] April Barbour, PhD,[4] and Diane J. Nugent, MD[5]

Perspectives on Thrombosis Associated with Congenital Heart Disease and Pediatric Cardiac Surgery

Michael Artman, MD

November 2, 2011

Joyce C. Hall Distinguished Professor
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University of Missouri-Kansas City School of Medicine
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Conflict Disclosure

There are no conflicts to disclose

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Background

- Congenital cardiac defects are common
  - Approximately 1 of every 120 live births in the US
- Currently estimated to be about 800,000 children and over 1,000,000 adults with congenital heart disease in the US
- Advances in surgical and medical care result in increasing survival rates
  - Adult CHD population projected to grow 5% annually

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Background

- Thrombosis related to congenital heart disease and cardiac surgery in children has been considered to be a rare event
- Manlhiot et al recently reviewed 1542 surgical cases over 3 years at a single institution and reported a prevalence of ***11%*** (3% had multiple clots)
- Multitude of thrombotic complications
- Several risk factors including younger age, ECMO, heart transplant, cyanosis, previous thrombosis

Manlhiot et al. *Circulation* 2011; 124:1511-1519

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Surgery for Congenital Cardiovascular Defects

Patients are at risk for venous and arterial thrombosis due to:

- Turbulent blood flow (e.g. shunts)
- Disruption of blood flow during surgery
- Platelet dysfunction and activation
- Inflammation
- Hypercoagulability (due developmental differences and disease states)

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Thrombosis is Associated with Poorer Outcomes

	No Thrombosis (n=1371)	Thrombosis (n=171)	*P*	Estimate (95% CI)*	OR (95% CI)*	*P*
Total intensive care unit stay, d	3 (1–17)	11 (2–86)	<0.001	+10.0 (9.4–10.7)		<0.001
Total hospital stay, d	7 (3–43)	25 (7–159)	<0.001	+15.2 (14.3–16.0)		<0.001
Cardiac arrest, n (%)	24 (1.8)	30 (18)	<0.001		4.9 (2.3–10.2)	<0.001
Early catheter reintervention, n (%)	34 (2.5)	21 (12)	<0.001		3.3 (1.6–6.9)	0.002
Early reoperation, n (%)	52 (3.8)	26 (15)	<0.001		2.5 (1.4–4.4)	0.003
In-hospital mortality, n (%)	23 (1.7)	27 (16)	<0.001		5.1 (2.3–11.3)	<0.001

CI indicates confidence interval; OR, odds ratio.

*All models adjusted for age at surgery, stage 1 single-ventricle palliation, heart transplantation, oxygen saturation <85%, Aristotle score, total cardiopulmonary bypass time, use of deep hypothermic circulatory arrest, and use of ventricular assist device/extracorporeal membrane oxygenation.

Manlhiot et al. *Circulation* 2011; 124:1511-1519

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Who is at Risk for Thombosis?

<u>Congenital Cardiovascular Defects</u>

- Prosthetic valves
- Systemic-to-pulmonary artery shunts
- Abnormal flow patterns (e.g., post-Fontan procedure)

<u>Acquired Heart Disease</u>

- Coronary artery aneurysms in Kawasaki disease
- Severe dilated cardiomyopathy

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Example: Fontan Patients

- First performed by Dr. Francis Fontan in 1968
- Since the original procedures, several surgical modifications have been described
  - Regardless of the technical approach, systemic venous flow enters directly into the pulmonary arterial bed
  - Result is sluggish blood flow
- Utilized for complex congenital heart defects (such as hypoplastic left heart syndrome and other forms of single ventricle)

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Thromboembolism in Fontan Patients

- Accounts for significant morbidity and mortality
- Poor survival after thromboembolic complications
  - Mortality up to 25% in pediatrics and up to 38% in adults
- Thromboembolism rates from 3% to 33%
  - About half occur early
  - Likely the true rate is underestimated
  - No anticoagulation therapy confers substantial risk for thromboembolic death (hazard ratio > 90)

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Anticoagulation Post-Fontan

- Monagle et al. randomized 111 patients to **ASA** (5 mg/kg/day; 57 patients) or **warfarin** (target INR 2-3; 54 patients) after a heparin lead-in
  - Followed for 2 years
- No significant difference between therapies
  - Thrombosis rate suboptimal for both treatments (21% ASA; 24% warfarin)
  - 1 major bleeding event in a warfarin patient (INR 11.9)
  - 33% on warfarin had at least one minor bleeding episode vs. 14% on ASA (p=0.03)

Monagle et al. *J Am Coll Cardiol* 2011; 58:645-651

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Lessons from Fontan Patients

- Most thromboemboli are clinically silent
- Invasive monitoring (TEE) is challenging in children
- Use of warfarin is challenging in children
  - Mean INR 2.2 at the time of clot detection
  - Only 45% of observations were within therapeutic range
  - Nearly 20% of patients stopped drug before the end of study
  - Implications for quality of life for kids due to increased bleeding
- Adequate anticoagulation may not be accomplished with a single agent
- Clinical trials are especially difficult in this population

Canter *J Am Coll Cardiol* 2011; 58:652-653
Monagle et al. *J Am Coll Cardiol* 2011; 58:645-651

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Current Status: Post-Fontan

- No consensus as to the optimal type or duration of antithrombotic therapy
- Aspirin (1 - 5 mg/kg/d) or unfractionated heparin followed by vitamin K antagonists to achieve a target INR of 2 - 3) is currently recommended
  - Optimal dose of aspirin and the target INR for this population remains unproven
- Use of antiplatelet and anticoagulation therapy for 6 to 12 months followed by lifelong antiplatelet therapy appears to be the most commonly used strategy

Marrone et al., *Pediatr Cardiol* 2011; 32:32–39

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CHD Patients: Acute Therapy

- Unfractionated heparin is the mainstay of treatment, but not without problems
- Low molecular weight heparin - labeling information exists, but no RCTs in pediatric cardiac patients
- Argatroban - pediatric labeling exists, but indicated only for anticoagulation after HIT or suspected HIT
  - "The safety and effectiveness of Argatroban, including the appropriate anticoagulation goals and duration of therapy, have not been established among pediatric patients."
- Bivalirudin - "safety and effectiveness in pediatric patients have not been established

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CHD Patients: Chronic Therapy

- Warfarin: mainstay of treatment but far from ideal
  - Drug interactions
  - Infants less than 1 year of age need increased dosage to achieve the target INR
  - Infants and younger children have more significant fluctuations of vitamin K intake
  - Sparse data in children regarding the risks
  - Fontan patients required 25% decreased dosage as compared with other congenital heart disease patients
  - Children on corticosteroids had less INRs in target range
  - Patients receiving enteral nutrition require higher dosage

Cheung YF, Leung MP.*J Paediatr Child Health* 1998, 34:563–567
Reller MD*. Curr Cardiol Rep* 2001, 3:90–95

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Characteristics of the “Ideal” Drug

- Oral formulation (age appropriate)
- No known long-term adverse events
- Minimal drug-drug/drug-environment interactions
- Favorable safety-toxicity profile
- Measurable pharmacokinetics with good pharmacodynamic measures
  - Feasible randomized controlled trial that can provide information for labeling

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Summary: Issues and Challenges

- The population of children and adults surviving with CHD is growing
- Long-term anticoagulation is often required
- Challenges include:
  - Few randomized controlled trials in children
  - Indications are different than in adults
  - Small patient population (compared to adults)
  - Difficulty in detecting thromboses in children
  - Major problems accruing patients for clinical trials

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Future Directions

- RCT's will require closer collaboration among hematologists, cardiologists, cardiac surgeons
- Develop and/or exploit pharmacokinetic data and surrogate biomarkers to evaluate pharmacodynamics
- Essential to study drugs in the CHD and cardiac surgery populations
  - Different pathophysiology than other populations
  - Life-long need for safe and effective therapy
  - Coordinate with NHLBI Pediatric Heart Network?

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Questions?

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Development of Novel Oral Anticoagulants (NOAC) for Pediatric Use

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Group Director
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Innovative Medical Science for Children

Advancing the Development of Medicines for Children

Properties of an Ideal Anticoagulant

Effective Safe Convenient

- Wide therapeutic index
- Predictable, consistent response
- Effects thrombosis without substantially affecting hemostasis
- No need for monitoring or dose titration
- Minimal intra- and inter-subject variability
- Rapid onset of action; rapid offset of action
- Oral, but with other dosage forms available
- No off target effects
- Half-life suitable for once or twice daily administration
- No interactions with food or other drugs
- Available reversing agent without risk of thrombosis
- Does not bind PF4 (no HIT); no need for ATIII

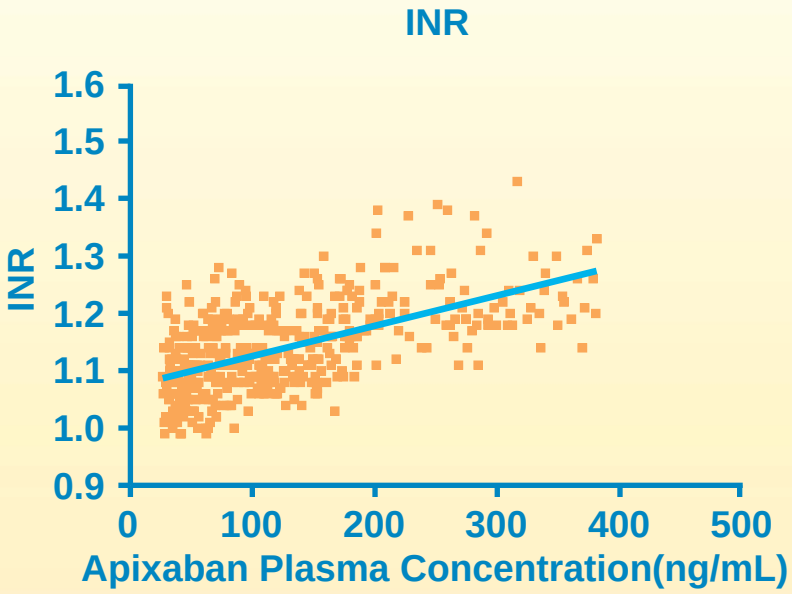
Important Characteristics: Dabigatran, Rivaroxaban, Apixaban

	Dabigatran ***Pradaxa***	**Rivaroxaban** ***Xarelto***	**Apixaban** ***Eliquis***
Primary affinity	IIa K_i = 4.5 nM	Xa K_i = 0.4 nM	Xa K_i = 0.08 nM
Selectivity	700-10,000 fold	> 10,000 fold	> 30,000 fold
Oral bioavailability*	6.5% (tartaric acid)	80%	50%
T_{max}*	1.25–3 hr	2-4 hr	2-4 hr
Elimination	Biphasic	Monophasic	Monophasic
Half-life*	12-17 hr	5-9 hr	12 hr
Renal clearance*	~80%	~50% total ~33% unchanged	~25%
Metabolism*	Conjugation to active glucoronide	~ 2/3 of dose; CYP3A4,CYP2C8 + non-CYP	< 1/3 of dose; CYP3A4+ non-CYP
P-GP interaction	yes	yes	yes
Volume of distribution*	60-70 L	50 L	~20 L

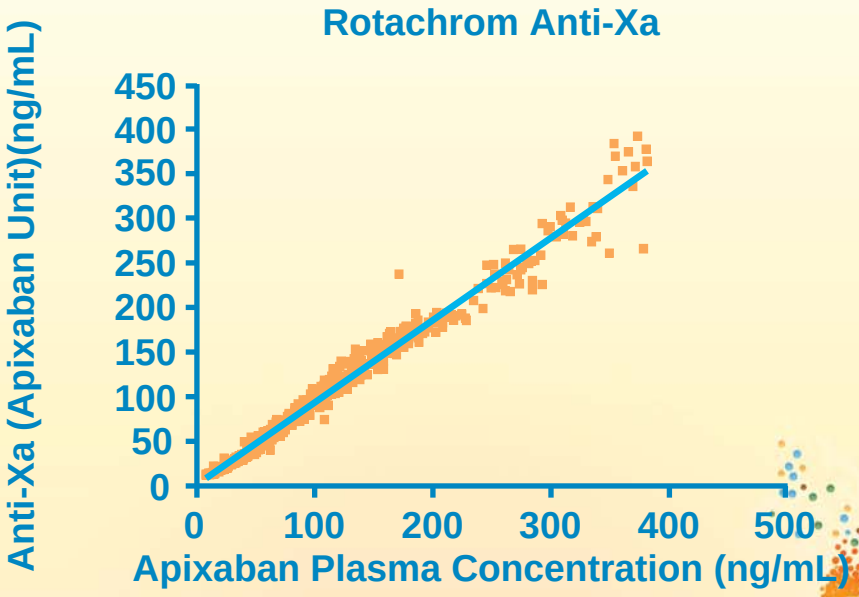
Edoxaban data not included

Anti-Xa Assay Show Strong Concordance With Pharmacokinetics

- Commercial PT/INR assays may not be appropriate for assessing factor Xa inhibitors as they are highly variable and inconsistent
- In clinical samples, chromogenic anti-FXa assays showed a strong positive correlation with apixaban plasma concentrations



r^2=0.3347



r^2=0.9786

* ~500 samples of a Phase I Apixaban clinical trial.
Wang Z. et al. Presented at WCCPT 2008; Poster T2TH071.

Comparison of NOAC Efficacy and Bleeding

		Dabigatran	Rivaroxaban	Apixaban
VTEp orthopedics (TKR, THR)	Efficacy	Similar to enoxaparin	Superior to enoxaparin	Similar or superior to enoxaparin
	Bleeding	Less or equal bleeding	Greater bleeding	Less or equal bleeding
VTE Treatment (acute; short and long term recurrence prevention)	Efficacy	Equal to VKA efficacy	Equal to LMWH/ VKA for acute and superior to placebo for continued treatment	Phase 2 Equal efficacy to LMWH/VKA (Phase 3 in progress)
	Bleeding	Equal bleeding	Equal bleeding for acute; greater for continued	Equal bleeding
Stroke prevention in atrial fibrillation	Efficacy	Higher dose superior to warfarin (open label)	Non-inferior to warfarin	Superior to warfarin
	Bleeding	Similar bleeding	Similar bleeding	Less bleeding
ACS	Studies in progress			

In order to avoid monitoring, clinical effect and adverse events are correlated to dose and not drug level or PD marker.

Pediatric Drug Development Bottom Lines

- The final responsibility to improve children's health should be shared in partnership by industry, regulatory agencies, health professionals and society as a whole
- Requirements: every drug/biologic compound developed into the clinical space must have a pediatric plan

- Pediatric drug development requires consideration for all of components of full drug development and include:
  - Academic consultation early in process
  - Age appropriate indication
  - juvenile toxicology
  - Age appropriate formulation(s) development
    - Bioequivalence, food effects, acceptability, taste, swallowability, tube compatability, texture, stability, need for water or refrigeration, excipients
  - Biomarker studies/End point determination
  - Dose selection (pharmacometrics)
  - Safety and Efficacy studies (?acceptable for extrapolation)
  - Long term safety/epidemiology
  - Transparency
  - Cycle again if new indication, dose, ROA, active ingredient, formulation

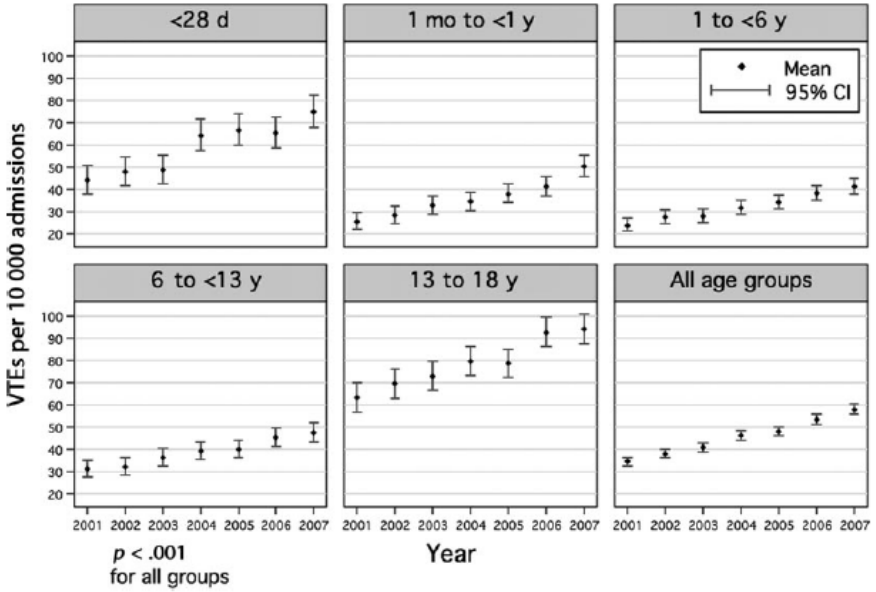
Pediatric Health Information System Reviews

- E. Neufeld and J. Newburger report for BMS (3 yr review (2005-7))
  - ~40,000 unique inpatient admissions in 30 children's hospitals with administration of an anti-thrombotic medications
    - 30,000 ASA
    - 10,000 enoxaparin
    - 6,000 warfarin
    - 1200 clopidogrel
    - 200 bivalirudin
    - <100 others
  - 20 of top 25 diagnoses requiring anticoagulants or antiplatelet drugs were congenital heart disease related

Dramatic Increase in Venous Thromboembolism in Children's Hospitals in the United States From 2001 to 2007

Leslie Raffini, Yuan-Shung Huang, Char Witmer and Chris Feudtner

Pediatrics 2009;124;1001; originally published online September 7, 2009; DOI: 10.1542/peds.2009-0768



70% increase in VTE From 2001-7 in 35-45 PHIS Hospitals

VTE at The Children's Hospital Boston (4 yrs)

RISK FACTOR BY TYPE	N (%)
Genetic	
Factor V Leiden heterozygote	12 (6)
Factor V Leiden homozygote	2 (1)
Antithrombin deficiency	1 (0.5)
Protein C deficiency	1 (0.5)
Protein S deficiency	
Mechanical risk factors	
Indwelling catheters/lines This is a severe underestimate of prevalence in our hospital because catheter-associated thrombosis in ICUs does not necessarily generate a thrombosis service consult.	57(29)
Paget-Schroetter syndrome	4(2)
May Thurner syndrome	3 (1.6)
Trauma/Dissection	4 (2)
Trauma alone	6 (3)
Pathophysiologic risk factors	
Infection	7(3.6)
Lupus	6 (3)
Malignancy/L-asparaginase (many line related)	22 (11.4)
Vascular malformations	4 (2)
Oral contraceptives	12(6)
High dose estrogen	
Heparin induced thrombocytopenia with thrombosis (HITT)	2(1)
Antiphospholipid antibody, lupus anticoagulant	18 (9.3)
Lipoprotein (a)	3 (1.55)
Elevated homocysteine	5 (2.6)
Lifestyle risk factors	
Obesity	4 (2)
Smoking	2(1)

Need for NOACs in Pediatrics

- Prevention
  - Central venous catheter related thrombosis
  - Congenital heart disease
    - Acquired heart disease
  - Sickle cell disease
  - Genetic thrombophilia
  - Acquired thrombophilia
    - Oncology
    - Lupus anticoagulant
  - Secondary prevention
- Treatment

Expert Consultation

- United States
- Keith Hoots
- Ellis Neufeld
- Jane Newberger (cardiology)*
- Jon Tyson (neonatology)
- Robert Arceci
- Peter Gustav Steinherz
- Thomas Wells (nephrology)
- Donald L. Yee*
- Lia Gore*
- Leslie Raffini
- Jennifer Li (cardiology)*
- Anthony Chan**
- Neil Goldenberg**

- Europe
- Elizabeth Chalmers*
- Ulrike Nowak-Göttl
- M Peters*
- Christoph Male *
- Heleen van Ommen
- Chrisitian Lowe

- Canada
- Patti Massicotte
- Lesley Mitchell**
- Michelle Lisa Noga (radiology)
- Ravi Bhargava (radiology)
- Brian McCrindle (cardiology)*

* Member of committee ** chair of committee (ESC, DMC, adjudication)

NOAC Pediatric PK/PD Studies

Dabigatran PIP	Apixaban PIP	Rivaroxaban PIP	Edoxaban PIP
1. Open-label PK &safety study - Age: **8 PTS**: 12 years - <18 years -Treatment Duration 3 days at the end of Std anticoagulant 2. Open-label PK safety study - Age: **16 PTS**: successive groups 2y -<12y, 1y-<2y -Treatment: 3 days after Std anticoagulant	1. Multiple dose PK, PD &Tolerability -Age: 0<27d; 28d-<2y;2y-<6y;6y-<12y,12y-<18y with CVC - N. 60 subjects -Duration: 35 days	1. Safety, tolerability, PK/PD study - Age: 6 months - <18 yrs -Treatment: pre-treated for >3m with LMWH and/or VKA for VTE; - Duration: single dose 2. Open-label, safety, PK/PD - Age: 6 years - <18 years -Treatment: pre-treated for >2m with LMWH and/or VKA for VTE Duration: 4weeks 3. Open-label, multiple dose safety, PK/PD - Age: 6 months - <6 yrs -Treatment: Pre-treated for >2m with LMWH and/or VKA for VTE (oral formulation) - Duration: 4 weeks	4. Open-label, sequential design PK/PD Age: from birth to <18 y with deep vein thrombosis treated initially with standard of care
3. Open-label, PK/PD & safety – Age: 12y - <18y, 2y-<12y, 1y-<2 years – Treatment: Dabi vs enoxaparin – Duration: 20 days 4. Open-label, PK/PD &safety - Age: < 1year -Treatment: Dabi vs enoxaparin -Duration: 20 days			
	VTEtx	VTEp	Cardiac

NOAC Pediatric Clinical Studies in PIPs

Dabigatran PIP	Apixaban PIP	Rivaroxaban PIP	Edoxaban PIP
	VTEtx	VTEp	cardiac
1. Open-label, NI study -Age: 0y -<18 years -*Treatment*: Dabi vs enoxaparin - *Duration:* 3 months -complete thrombus resolution, recurrence of a venous thrombotic event, development of the pro-thrombotic syndrome 2. Open-label, single-arm safety study - Age: 0y -<18 years - extended secondary prevention of venous thrombosis	1. Double-blind, placebo-ctrl, safety & efficacy in VTEp (DVT or PE and all cause death) - Age: Newborn - <18 years (10%<28d) - N. 530 subjects with CVC - Duration: For the time of catheter placement or 1 year (whichever shorter) 2. Prospective, open label, safety trial vs VKAs - PK/PD - Age: neonates-<27d; 28d-<2y;2y-<12y,12y-<18 years - N. 150 cardiac patients requiring chronic anticoagulation - Duration: 1 year of treatment / until anticoag no longer needed (whichever shorter)	2. Open-label, multiple dose, safety -Age: birth - <18 years -with acute VTE -Duration: 3 months -oral formulation and tablets	1. Open-label, safety and efficacy -parallel-group , observational trial - Age: from 36 weeks gestational age to <18y - with cardiac diseases at risk of thrombotic events. 2. Open-label, active controlled, Efficacy -LMWH/UFH + edoxaban vs LMWH/UFH + VKA or LMWH / UFH only - Age: 38 weeks gestational age to <18 y - with confirmed venous thromboembolic diseases

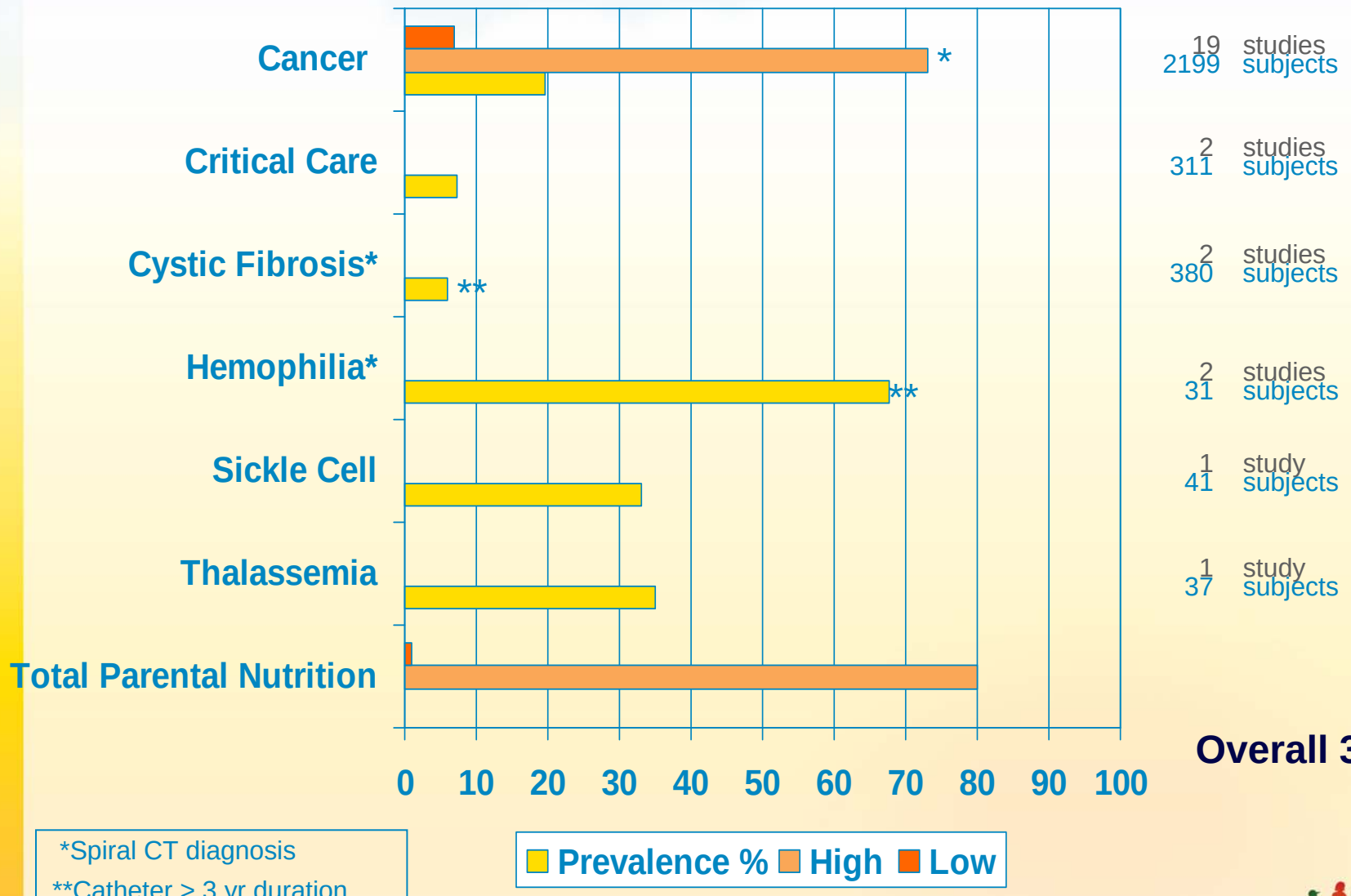
Unmet Pediatric Need for VTEp

- Adequately-powered, randomized controlled intervention studies of anticoagulants in children have not been performed
  - There are no approved anticoagulant drugs for children
- Most common association of VTE in children is presence of CVC
- Symptomatic VTE in 5.3/10000 hospitalizations—60% related to a CVC[1]
- As many as 73% of children with acute lymphoblastic leukemia (ALL) have catheter-associated DVT following induction chemotherapy[2]
  - only 3-6% have symptomatic DVT (10% PARKA)
  - Prevalence seems dependent on radiographic technique
- Asymptomatic VTE uniquely important in children[1,2,3]
  - 6-25X as frequent as symptomatic VTE
  - Leads to
    - Loss of central venous access
      - Life-threatening for children needing intravenous chemotherapy
    - Pulmonary embolism
    - Superior vena cava syndrome
    - Post-thrombotic syndrome
- No effective therapy for CVC-VTE prevention

[1]Massicotte MP et al., J Pediatr 1998;133:770-776
[2]Farinasso L, et al., Leukemia 2007;21:552-6
[3]Mitchell LG and the PARKAA Group, Cancer 2003;97:508-16

Catheter Related Thrombosis in Children

Modified Meta-Analysis



Overall 35%

*Spiral CT diagnosis

**Catheter > 3 yr duration

Definition of clinical efficacy and safety outcomes for clinical trials of paediatric venous thromboembolism

L. MITCHELL*, N.A. GOLDENBERG†, C. MALE¶, G. KENET‡, P. MONAGLE§, and U. NOWAK-GÖTTL**, ON BEHALF OF THE PERINATAL AND PAEDIATRIC HAEMOSTASIS SUBCOMMITTEE OF THE SCIENTIFIC AND STANDARDIZATION COMMITTEE OF THE INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEMOSTASIS

TREATMENT STUDIES:

- ***Primary Outcome***
- *Composite of:*
- All recurrent VTE (defined as either contiguous progression or non-contiguous new thrombus)
- VTE-related mortality
- ***Secondary Outcomes***
- Individual components of primary outcome
  - All recurrent VTE
  - VTE-related mortality
- All-cause mortality
- New symptomatic PE
- New symptomatic DVT (including DVT progression)
- New asymptomatic DVT (including DVT progression)
- Post-thrombotic syndrome

- ***PROPHYLAXIS STUDIES:***
- ***Primary Outcome***
- *Composite of:*
- All incident VTE
- VTE-related mortality
- ***Secondary outcomes***
- Individual components of primary outcome
- All incident VTE
- VTE-related mortality
- All-cause mortality
- Incident symptomatic PE
- Incident symptomatic DVT
- Incident asymptomatic DVT
- Post-thrombotic syndrome

BLEEDING OUTCOMES FOR TREATMENT AND PROPHYLAXIS STUDIES

- ***Primary outcome: MAJOR BLEEDING***
- ***Composite of:***
- **(1) Fatal bleeding**
- **(2) Clinically overt bleeding associated with a decrease in Hgb of at least 20 g/L (i.e., 2 g/dL) in a 24 hour period**
- **(3) Bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system**
- **(4) Bleeding that requires surgical intervention in an operating suite.**
- ***Secondary Outcomes:***
- ***CLINICALLY RELEVANT NON MAJOR BLEEDING***
- ***Composite of:***
- **Overt bleeding for which blood product is administered and not directly attributable the patient's underlying medical condition;**
- **Bleeding that requires medical or surgical intervention to restore hemostasis, other than in an operating suite**
- ***MINOR BLEEDING***
- **Any overt or macroscopic evidence of bleeding that does not fulfill the above criteria for either major bleeding or clinically-relevant, non-major bleeding**

Examples of use of anticoagulants in cardiac disease

- Single ventricular disease (pre or post Fontan)
- Systemic to pulmonary artery shunts
- Kawasaki's disease
- Arrhythmias
- Cardiomyopathy
- Cardiac valvular abnormalities
- Pulmonary hypertension
- Thrombosis related to cardiac catheterization

Multicenter, Randomized Trial of ASA vs Heparin/Warfarin for VTEp for 2 years after Fontan Procedure.

Monagle et al J Am Coll Cardiol 2011;58:645–51

- Patients randomized to receive either
  - ASA (5 mg/kg/day, no heparin phase)
  - Warfarin (started <24 h of heparin lead-in; target international normalized ratio: 2.0 to 3.0).
- Primary adjudicated endpoint: thrombosis, intracardiac or embolic
- At 3 months and 2 years after the Fontan procedure, transthoracic and transesophageal echocardiograms.
- Major bleeding and death were primary adverse outcomes.
- 111 eligible patients were randomized (57 to ASA, 54 to heparin/warfarin).
- Baseline characteristics for each group were similar.
- There were 2 deaths unrelated to thrombosis or bleeding.
- 13 thromboses in the heparin/ warfarin group (3 clinical, 10 routine echo) 12 thromboses in the ASA group (4 clinical, 8 routine echo).
- Overall thrombosis 2 years after Fontan surgery was 19%, despite thrombosis prophylaxis.
- Cumulative risk of thrombosis was persistent but varying and similar for both groups (p 0.45). Major bleeding occurred in 1 patient in each group.

AESOP: Apixaban Efficacy & Safety for thrOmbosis Prevention

- **Range finding and toxicity study in juvenile rats**
- **In vitro validation of level of apixaban in relation to FXa levels in serum from children birth to 17 yo study**
- **Formulation/Palatability (adult and children)/stability**
- **Bioequivalence**
- **NG tube recovery with and without formula**
- **Feasibility study of radiographic tests to determine presence of catheter related thrombosis (MRA, U/S)**
- **PK/PD (MAD) → (SAD with modeling)**
- **CVC-VTE prevention study**
- **Prevention of VTE in congenital heart disease**
- **VTE treatment program (extrapolation of efficacy with open label safety study and dose confirmation)**

Conclusions

- NOACs may prove to be one of the most significant innovations in clinical practice in the last 60 years
- Both thrombin inhibitors and direct factor Xa inhibitors allow physicians to use these medications
  - without monitoring
  - with a broad therapeutic window
  - with less regard for food intake
  - with limited drug-drug interactions
- Comprehensive pediatric drug development programs are in progress

Challenges

- Harmonization of FDA with EU; not scientifically but in timing of consideration so that global, adequately powered studies can be done
- Phase 1 studies in prevention: initial insistence of PDCO for MAD trial for 10 days not feasible
  - Strategy of sparse sampling of off-label treated subjects
  - Phase 1 trial of treated patients reasonable
- Determination of end points
- Operations will be challenging
  - Recruitment of patients especially with competing trials will challenge the success of any of them
- Do we need randomized, controlled trials to determine efficacy of anti-coagulant medications? We clearly need safety trials.
- How do we determine dose? Adult studies efficacy/safety based; not level based.
- Off label use huge hurdle: It is a race between getting the science done and wide use of the medication without appropriate data

NHLBI Resources to Support Pediatric Anticoagulation Trials

Dr. Donna Di Michele
Deputy Director
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute, NIH

FDA-ODAC
November 2, 2011

National Heart Lung and Blood Institute

NHLBI Resources: Pediatric AC Trials

Resources

- *Clinical Trial Planning / Funding Options*
- *Research Infrastructure for Clinical Trials*
- *Ancillary Clinical Trials Support*

NHLBI Resources: Pediatric AC Trials

DBDR Resources:

Clinical Trial Planning / Funding Support

- *RFA / R01 grant mechanisms*
- *R34 pilot award program*
- *RFA: U34 / U24 planning grants*

DBDR: Thrombosis and Hemostasis Branch

Supports research related to the causes, prevention, diagnosis, and treatment of thrombotic and hemostatic disorders

- *Basic and translational research*
- *Clinical investigations and trials*
- *Observational studies*
- *Technology development*
- *Training and career development*

NHLBI Resources: Grant Mechanisms (R01)

Deep Vein Thrombosis and Venous Disease (R01)

- *Explore mechanisms of VTE initiation progression & recurrence*
- *Initiate clinical &translational studies to improve diagnosis and therapy**
- *Encourage collaborative studies and resource sharing*
- *Interact with CDC to further increase resources*

Supports 8 R01 grants, funding period from 9/2008 to 8/2013

National Heart Lung and Blood Institute

NHLBI Resources: Grant Mechanisms
Clinical Trial Pilot Studies (R34) PAR-10-005

The NHLBI invites applications proposing pilot studies to obtain data that is critical for the design of robust clinical trials

- ***Feasibility****: Must demonstrate that the proposed pilot studies are both necessary and sufficient to permit the design of the full-scale clinical trial that would be proposed following the R34 award period, its significance and potential public health impact*

- ***PAR*** *mechanism: no set-aside funds, special review panel*

- ***Direct costs*** *are limited to $450,000 over a three-year period*

- ***Application Due Dates****: February 16, June 16, October 16*

National Heart Lung and Blood Institute

Recommendations

- *Increase # of well-designed Phase II &III clinical trials that could lead to improved clinical care for hemostatic and thrombotic disorders*
- *Establish processes to assist planning, timely initiation and successful completion of investigator -initiated clinical trials*
- *Develop programs to encourage clinical trials for rare bleeding and clotting diseases and for studies in pediatric populations, include processes for planning, initiation and successful completion of trials that meet the special needs of the selected population*
- *Identify new pathways to stimulate the development and conduct of clinical trials with the emphasis on personalized medicine and comparative effectiveness research that would not be supported by industry*

NHLBI Resources: Grant Mechanisms
Clinical Trials Planning Grants (U34 / U24)

- *Program to specifically support the **planning**, not pilot, phase of multicenter investigator-initiated clinical trials focused either on rare hemostatic and thrombotic disorders, or on more common hemostatic and thrombotic disorders that occur rarely in special patient populations*

- *U34 similar to general R34 in duration of support and level of funding, but:*
  - focused on rare thrombotic and hemostatic disorders
  - built-in assistance of U24 Clinical Trials Development Resource for Hematologic Disorders (clinical trial design & methodology expertise)

- *Clinical Trial Planning Grant Program is not designed for the collection of preliminary data or the conduct of pilot studies to support the rationale for a clinical trial.*

RFA-HL-12-023 - Clinical Trials Planning Studies for Rare Thrombotic and Hemostatic Disorders (U34)

- ***U34 Planning Grants****: set-aside funds to support up to 10 applications; special review panel*

- ***Application Due Dates****: Single submission date for early Fall 2011, 2012, 2013*

http://grants1.nih.gov/grants/guide/rfa-files/RFA-HL-12023.html

RFA-HL-12-016 - Clinical Trials Development Resource for Hematologic Disorders (U24)

Resource of expert consultants to assist investigators in the development of multi-site clinical trials for hematologic disorders supported by

- *Clinical Trials Planning Studies for Rare Thrombotic and Hemostatic Disorders (U34) (RFA-HL-12-023) and*
- *NHLBI Clinical Trial Pilot Studies (R34) (PAR-10-005) awards.*

Application Due Date: Single submission date - October 2011

http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-12-016.html

Academic institutions, School of Public Health & commercial organizations have submitted applications with pending review

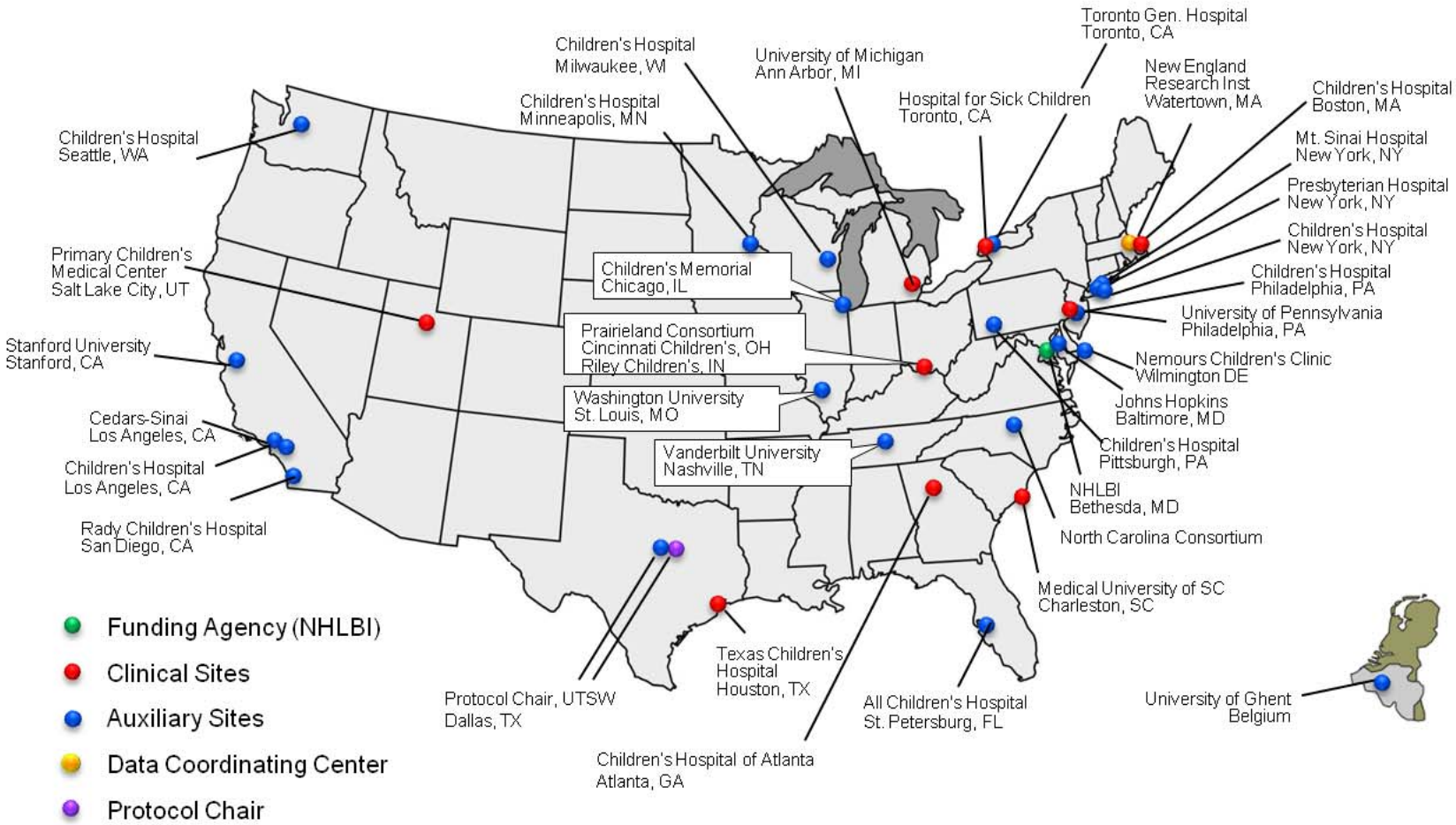
NHLBI Resources: Pediatric AC Trials

Resources

Research Infrastructure for Clinical Trials

- *NHLBI-based research networks*
- *Potential trans-Institute collaborations*

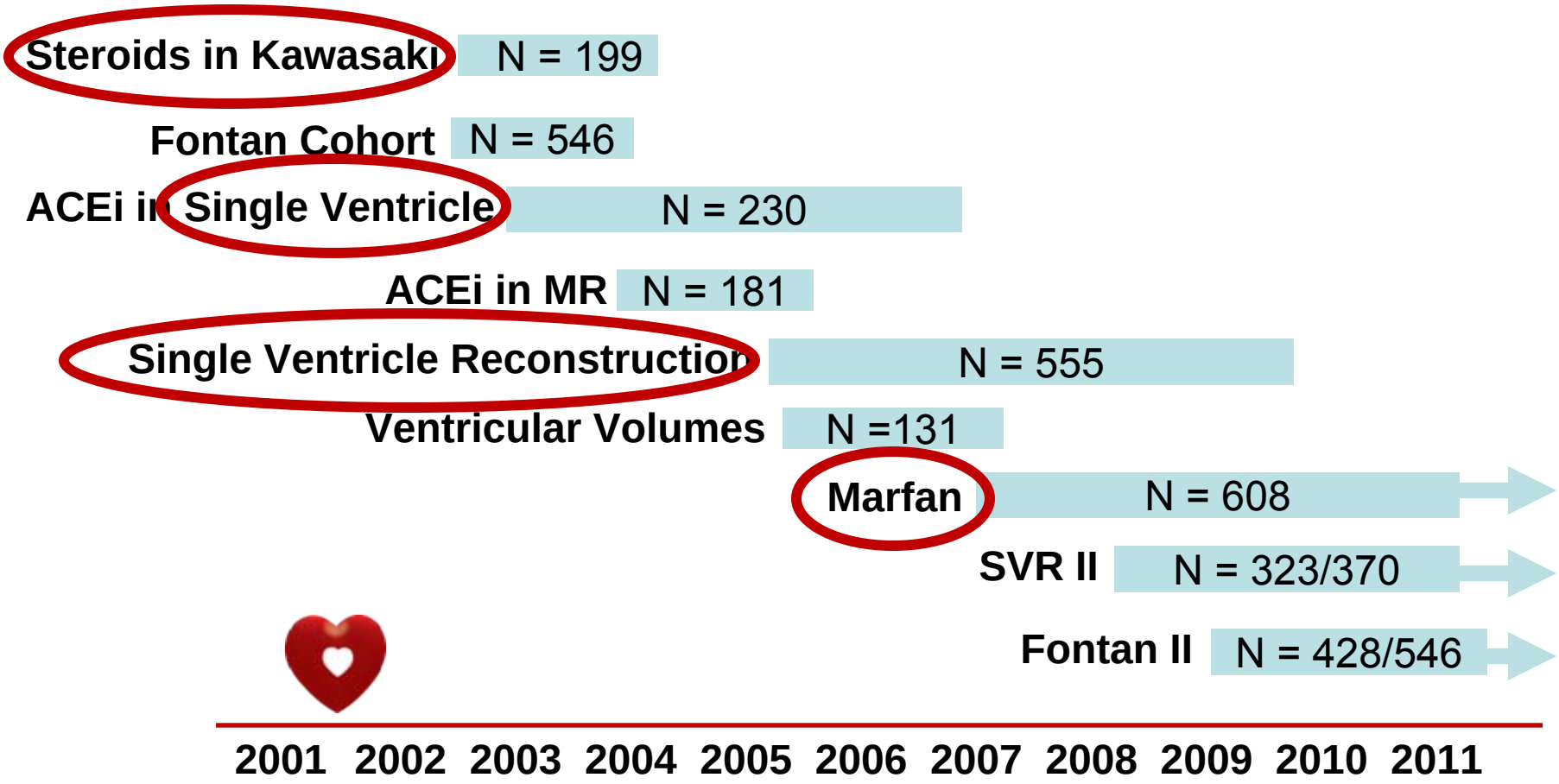
Pediatric Heart Network 2011



National Heart Lung and Blood Institute
People Science Health

PEDIATRIC HEART NETWORK

Pediatric Heart Network Studies



National Heart Lung and Blood Institute

8 Centers, 7 Sites, 2nd Cycle of Funding (5 yrs each):

- Children's Hospital of LA, UCLA (combined as 1 site)
- Children's Hospital of Pittsburgh
- Children's Hospital of Philadelphia
- DC Children's
- Phoenix Children's Hospital
- University of Michigan (Mott Children's Hospital)
- Children's Hospital of Michigan (Detroit)

Over 17,000 pediatric ICU patients per year

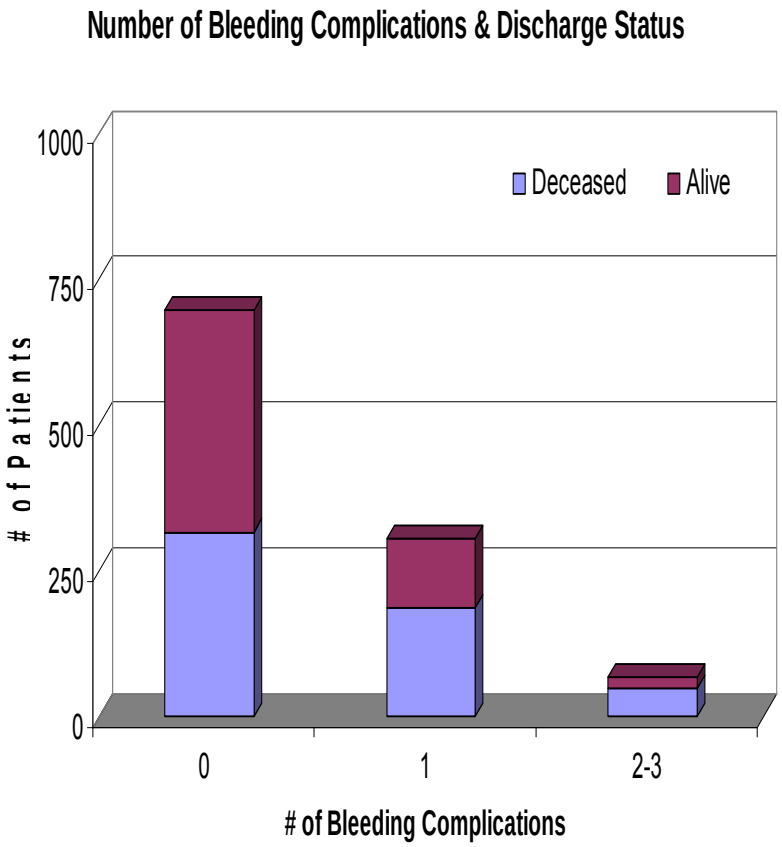
Diverse ethnic backgrounds and geographic distribution

Diverse interest and expertise

- Cardiology, Respiratory, Extracorporeal Support, Health Outcomes Research, Cardiac Arrest, Sepsis, Genomics and Proteomics

Initial look at thrombosis as complication of ECMO:

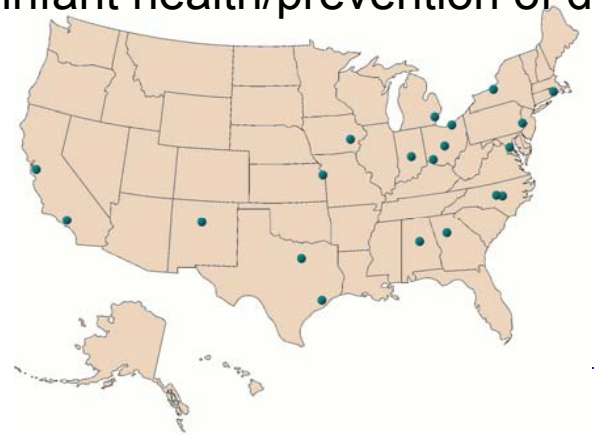
- 789 ECMO pts over 5 yrs from CPCCRN sites (1215 incl NICU)
- Correlated with data from ELSO registry for thrombosis
  - CNS 15%
  - Mechanical 33%
- Variable anticoagulation regimens
- Effects of new technology unknown



NICHD NEONATAL RESEARCH NETWORK (NRN)

NRN Aims

- Identify priority issues for research
- Observational and interventional studies
- Evaluate interventions, including efficacy, safety, and cost-effectiveness
- Includes: translational research, genetics, evaluation of new technologies in the promotion of infant health/prevention of disease



NRN Population

Number of births –150,749

NICU admissions –33,276

Infants < 29 weeks –3,885

Infants < 1000 grams –3,027

NRN Organization:

Steering Committee

- 18 Center PIs
- Data Center PI
- NICHD Program Officer

Data Coordinating Center – RTI

International

Advisory Board

Data Safety Monitoring Committee

National Heart Lung and Blood Institute

NICHD Pediatric Trials Network for Best Pharmaceuticals for Children Act

Need for infrastructure for all aspects of pediatric clinical trials performance

- *Management*
- *Clinical trials performance*
- *Formulations development for clinical trials*
- *Clinical pharmacology study design and analysis*
- *Device development (validation)*

Awarded September 28, 2010: Duke University

https://www.fbo.gov/index?s=opportunity&mode=form&id=cf49c1b60b546914941b266295b24c84&tab=core&_cview=1

National Heart Lung and Blood Institute

NHLBI Resources: Pediatric AC Trials

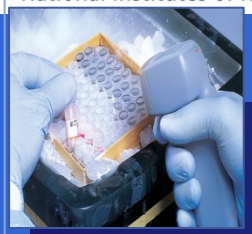
Resources

Ancillary Support

- *NHLBI BioLINCC- Biorepository*
- *Technology Development- SBIR Program*
- *Training Pediatric Hematology Clinician-Scientists*

U.S. Department of Health and Human Services
National Institutes of Health

National Heart Lung and Blood Institute



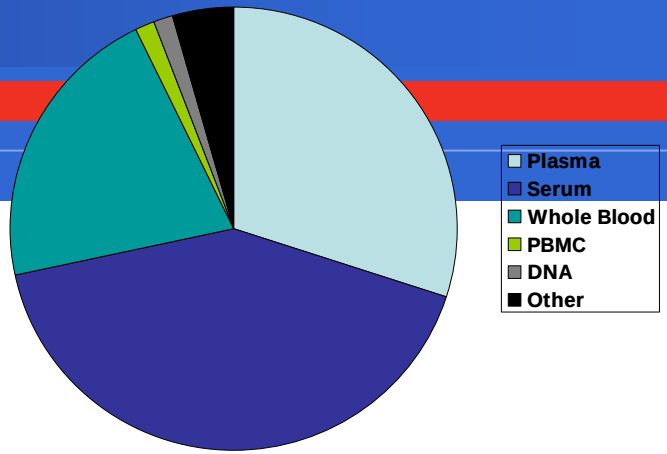
The Repository currently includes about 4 million plasma, serum, cellular or tissue specimens

- Managed since the mid-1970s by the Division of Blood Diseases and Resources, Transfusion Medicine and Cellular Therapeutics Branch, NHLBI.
- Currently resides at SeraCare Bioservices in Gaithersburg, MD.
- Information on the NHLBI Repository can be viewed at http://www.nhlbi.nih.gov/resources/medres/reposit/reposit.htm.

Implementation of a Biorepository and Limited Access Data Information Coordinating Center (BioLINCC) that will:

1. **Develop and maintain an interactive web-based platform with inventory search engine, application system, and information kiosk.**
2. **Store biospecimen data sets and documents.**
3. **Assist with biospecimen selection.**
4. **Maintain & coordinate central data warehouse to include the Limited Access Data Sets (LADS).**
5. **Coordinate acquisition and distribution requests.**
6. **Coordinate Allocation Committee activities.**
7. **Provide IRB review, as needed.**
8. **Track and prepare reports on repository activities.**

Types of Stored Biospecimens



67 Collections from 51 Programs

The category "Other" includes urine, RBC, lymphocytes, immunoglobulins, cord blood units, buffy coats, tissue.

NHLBI Resources: Pediatric AC Trials

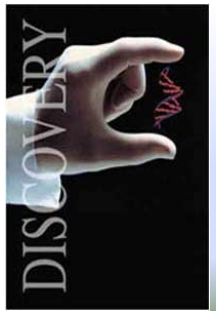
BioLINCC / Biorepository

www.biolincc.nhlbi.nih.gov

RFA-HL-12-004, Maximizing the Scientific Value of the NHLBI Biologic Specimen Repository: Scientific Opportunities (R21)

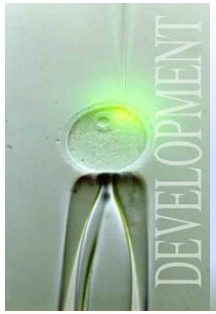
http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-12-004.html .

NHLBI Resources: Three Phase SBIR & STTR Program



PHASE I – R41, R43

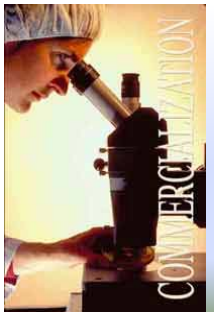
- **Feasibility Study**
- **$150K and 6-month (SBIR) ***
- ***or* 12-month (STTR) Award**



PHASE II – R42, R44

- **Full Research/R&D**
- **$1M and 2-year Award (SBIR & STTR) ***
- **Commercialization plan required**

SBIR Bridge Award



PHASE III

- **Commercialization Stage**
- **Use of non-SBIR/STTR Funds**

* Note: Actual funding levels may differ by topic.

SBIR Bridge Award Program
Key Elements

Provide $1 million/year for 3 years to incentivize partnerships between SBIR Phase II awardees and third party investors/strategic partners

Require non-federal matching funds at least equal to the federal investment

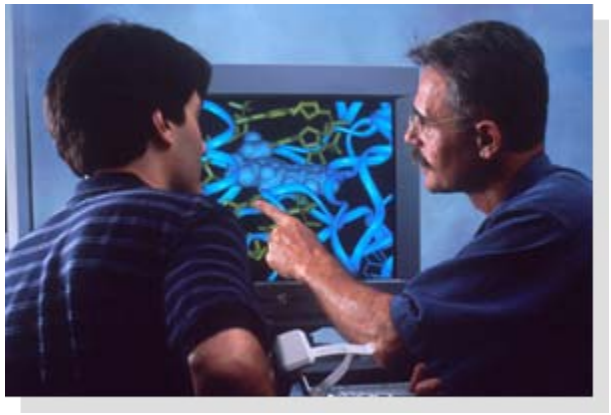
- NIH funding mitigates substantial investment risk, thus the program provides a strong incentive for third-party investors to finance projects earlier in the commercialization development process
- Third party investors will conduct due diligence prior to investing incentivizing Phase II applicants to formulate credible business plans
- Third party involvement can provide post award project management and oversight

Define eligible applicant as current NIH Phase II awards (grants and contracts) and awards that ended within the previous 2 years whose research areas align with the NHLBI mission.

Support research activities needed to meet and comply with federal regulatory requirements

Peer review considerations will balance technical and commercial merits and the regulatory strategy.

NHLBI Resources:
Training of New Clinical Investigators



National Heart Lung and Blood Institute