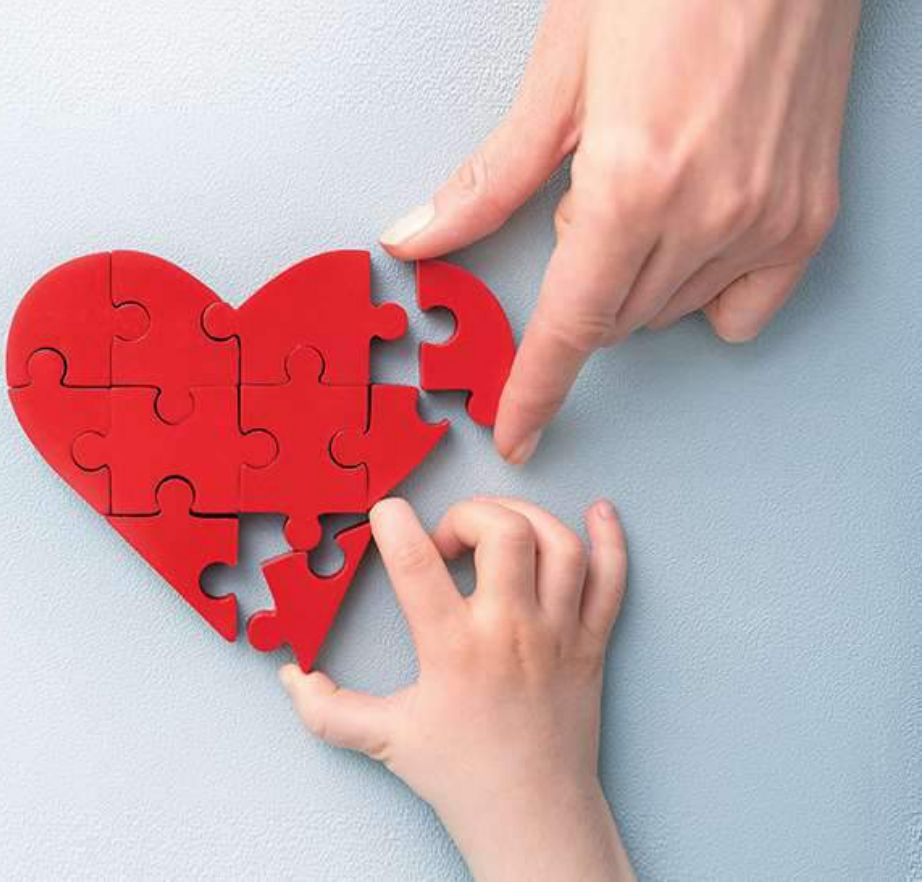
CARDIOLOGY 2024

# ANTICOAGULATION FOR ECMO
# THE DEBATE CONTINUES

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Cardiac Critical Care Medicine

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Saturday Feb 17th 2024

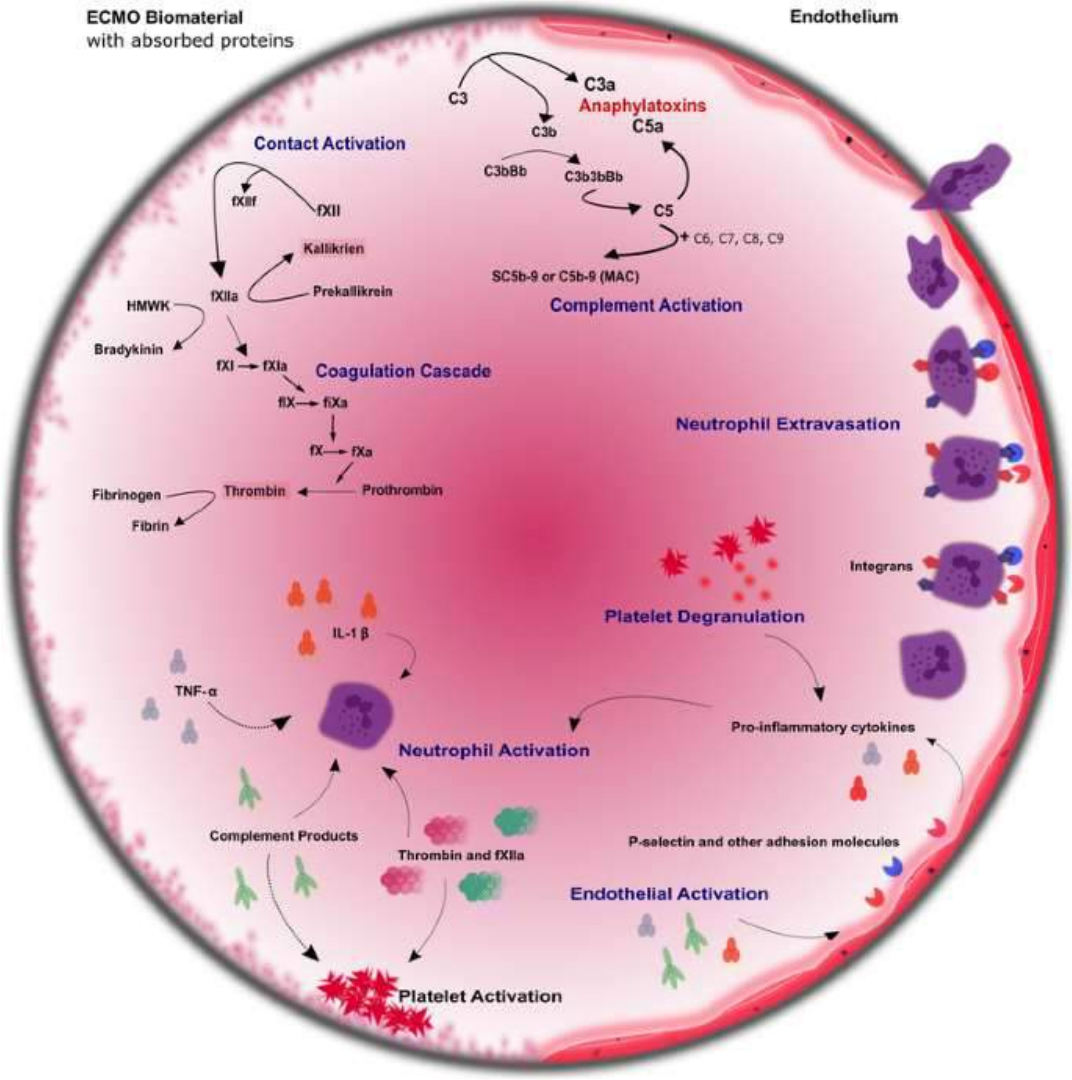
Children's Hospital of Philadelphia
Cardiac Center

# DISCLOSURES

- I will review off label use of medications

# GOALS

- Review challenges in effective ECMO Anticoagulation
- Review data behind anticoagulation strategies


ECMO Biomaterial
with absorbed proteins
Endothelium
C3
C3a
Anaphylatoxins
C5a
C3b
C3bBb
C3b3bBb
C5
+ C6, C7, C8, C9
SC5b-9 or C5b-9 (MAC)
Complement Activation
Contact Activation
fXIIf
fXII
Kallikrien
fXIIa
Prekallikrein
HMWK
Bradykinin
fXI → fXIa
Coagulation Cascade
fIX → fIXa
fX → fXa
Fibrinogen
Thrombin
Prothrombin
Fibrin
Neutrophil Extravasation
Integrans
Platelet Degranulation
IL-1 β
TNF-α
Neutrophil Activation
Pro-inflammatory cytokines
Complement Products
Thrombin and fXIIa
P-selectin and other adhesion molecules
Endothelial Activation
Platelet Activation

# PEDIATRIC ECMO COMPLICATIONS

**Bleeding**
**70%**

**Thrombosis**
**37%**

**Patient Clot**
**13%**

**Circuit Clot**
**31%**

Dalton et al. Am J Resp and Crit Care Med. 2017

# ELSO COMPLICATION DATA

| | Neonatal Cardiac | | | Pediatric Cardiac | | |
|---|---|---|---|---|---|---|
| | Complications N (%) | After Complication Survival N (%) | Difference Between Average and After Complication Survival (%) | Complications N (%) | After Complication Survival N (%) | Difference Between Average and After Complication Survival (%) |
| Mechanical | | | | | | |
| Oxygenator failure | 123 (4) | 36 (29) | 16 | 205 (5) | 94 (46) | 11 |
| Pump malfunction | 37 (1) | 12 (32) | 13 | 49 (1) | 22 (45) | 12 |
| Cannula problem | 156 (5) | 52 (33) | 12 | 194 (5) | 92 (47) | 10 |
| Air in circuit | 101 (3) | 33 (33) | 12 | 105 (3) | 49 (47) | 10 |
| Patient | | | | | | |
| Seizure by EEG | 100 (4) | 41 (41) | 4 | 101 (3) | 42 (42) | 15 |
| Cerebral infarct | 93 (3) | 31 (33) | 12 | 231 (6) | 83 (36) | 21 |
| ICH | 326 (11) | 91 (28) | 17 | 251 (6) | 65 (26) | 31 |
| Brain death | 21 (1) | 0 | 45 | 107 (3) | 0 | 57 |
| Cardiac tamponade | 148 (5) | 62 (42) | 3 | 171 (4) | 66 (39) | 18 |
| Surgical site bleeding | 739 (26) | 257 (35) | 10 | 974 (25) | 496 (51) | 6 |
| GI hemorrhage | 35 (1) | 7 (20) | 25 | 79 (2) | 18 (23) | 34 |
| Amputation | 3 (0.1) | 2 (67) | -22 | 4 (0.1) | 3 (75) | -18 |

ECLS, extracorporeal life support; EEG, Electroencephalogram; ICH, intracranial hemorrhage.

Mechanical and Patient-Related Complications with Cardiac ECLS, 2009–2015

*Barbaro RP, Paden ML, Guner YS, et al. Pediatric Extracorporeal Life Support Organization Registry International Report 2016. ASAIO J 2017; 63:456–463*

# COMPLICATIONS WHILE ON ECMO FOR SURGICAL AND MEDICAL PEDIATRIC CICU HOSPITALIZATIONS

| Complication Type | Surgical N=329 | Medical N=120 | Time to onset (days) |
|---|---|---|---|
| Bleeding requiring reoperation | 83 (25.2%) | 4 (3.3%) | 1.4 (0.5–3.5) |
| Unplanned reoperation or re-intervention | 74 (22.5%) | 8 (6.7%) | 2.2 (1.0–4.0) |
| Hemothorax requiring intervention | 16 (4.9%) | 1 (0.8%) | 2.1 (0.5–3.4) |
| Stroke | 29 (8.8%) | 18 (15.0%) | 2.9 (0.8–5.6) |
| Seizure | 37 (11.3%) | 13 (10.8%) | 1.2 (0.5–2.3) |
| IVH > grade II | 8 (2.4%) | 2 (1.7%) | 0.7 (0.2–6.0) |
| Intracranial hemorrhage | 21 (6.4%) | 14 (11.7%) | 2.2 (1.1–7.1) |
| Brain death | 2 (0.6%) | 7 (5.8%) | 1.7 (1.0–6.0) |
| CRRT | 42 (12.8%) | 18 (15.0%) | 2.8 (0.9–5.5) |
| Infection *† | 21 (6.4%) | 12 (10.0%) | 4 (2–7) |
| Necrotizing enterocolitis† | 6 (1.8%) | 2 (1.7%) | 5.5 (3–6.5) |
| Hepatic failure | 18 (5.5%) | 14 (11.7%) | 2 (0–6.5) |

*Brunetti et al.. Pediatr Crit Care 2018;19:544-552*

# 2021 ELSO Adult and Pediatric Anticoagulation Guidelines

Ali B.V. McMichael,* Lindsay M. Ryerson,† Damian Ratano,‡§ Eddy Fan,‡ David Faraoni,¶ and Gail M. Annich‖

**Reviewers:** Graeme MacLaren,** Giles J. Peek,†† Marie E. Steiner,‡‡ Ravi R. Thiagarajan,§§

**Table 1. Summary of the Mechanism of Action, Advantages and Disadvantages of Anticoagulants During ECMO**

| Anticoagulant | Mechanism of Action | Half-Life (mins) | Advantages | Disadvantages |
|---|---|---|---|---|
| UFH | Main: binds to AT to inhibit thrombin and Xa | 60–90 (adults) and 35–75 (pediatrics) | Inexpensive; has antidote (protamine) | Binds to other plasma proteins; heparin induced thrombocytopenia |
| Bivalirudin | Reversibly binds to thrombin | 25 (adults) and 15–42 (pediatrics) | Does not require AT | No antidote, caution with blood stasis and renal dysfunction |
| Argatroban | Reversibly binds to thrombin | 39–51 | Does not require AT; not degraded by serine proteases | No antidote; variable dosing; caution with hepatic dysfunction |

AT, antithrombin; ECMO, extracorporeal membrane oxygenation; UFH, unfractionated heparin.

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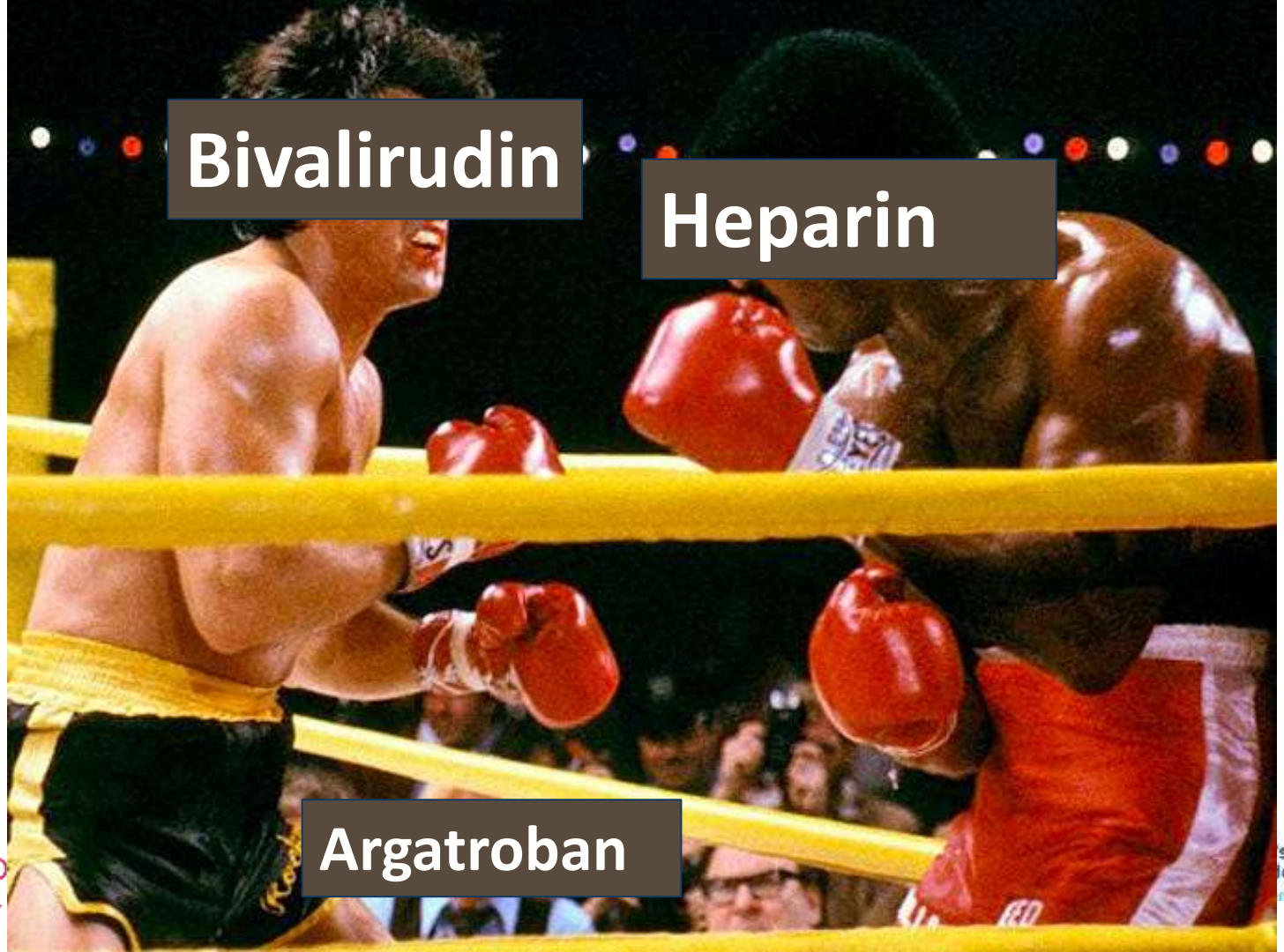
For VA-ECMO, given the concerns of systemic emboli, the routine use of anticoagulation is currently recommended. A recent retrospective study on VA-ECMO patients suggested that the absence of anticoagulation is safe in adult VA-ECMO patients and is associated with decreased transfusion and hemorrhagic complication without an increase in thrombotic events.[53]


Bivalirudin
Heparin
Argatroban

# ANTICOAGULANTS – HEPARIN

- Dependent on Antithrombin
- Inhibits unbound thrombin and factor Xa
  - No effect on clot-bound thrombin
- Reversed with protamine
- Hepatic and Renal clearance
- 1-2 hour half life
- Age-dependent activity
- Antithrombin deficiency leads to resistance

# AGE DEPENDENT ANTITHROMBIN III LEVELS

| Day of Life | Serum ATIII Range (% of Adult Values) |
|---|---|
| 1 | 63 (39–87) |
| 5 | 67 (41–93) |
| 30 | 78 (48–108) |
| 90 | 97 (73–121) |
| 180 | 104 (84–124) |

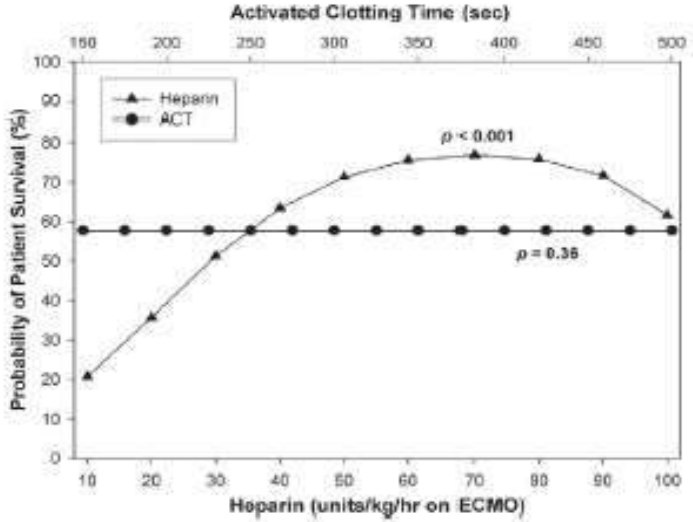
*ATIII, antithrombin III*



Logston et al. *Journal of Ped Pharm and Therapeutics. 2018*

# ANTICOAGULATION AND PEDIATRIC ECMO

- Retrospective review of 604 pediatric ECMO patients
- Survival is improved by increased heparin dose up to 70 units/kg/hr independent of ACT levels
- ACT levels did not necessarily correlate with increased heparin doses




| | Survivors | Non survivors | p Value |
|---|---|---|---|
| All patients (n) | 349 | 255 | |
| ECMO time (hours) | 171 ± 103 | 197 ± 166 | 0.017 |
| ACT (seconds) | 225 ± 40 | 229 ± 62 | 0.36 |
| Heparin (units/kg/hr) | 49 ± 20 | 39 ± 22 | <0.001 |

Baird CW, Zurakowshi D, Robinson B, et al. Ann Thorac Surg 2007;83:912-20.

# Variability in anticoagulation management of patients on extracorporeal membrane oxygenation: an international survey

**Melania M. Bembea, MD, MPH[1,2], Gail Annich, MD[3], Peter Rycus, MPH[4], Gary Oldenburg[1], Ivor Berkowitz, MD[1,2], and Peter Pronovost, MD, PhD[1]**

- 72% had written protocol for anticoagulation and blood product management
- 69% anticoagulation managed by ICU team
- 100% use of heparin (various doses)
  - 8% DTI use in prior 6 months
  - Various adjunct meds



*Pediatr Crit Care Med 2013;14:e77*

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| | | |
|---|---|---|
| ACT goal (sec) (n=116 respondents) | Minimum ACT goal, mean (SD) | 183 (13), range 140–220 |
| | Maximum ACT goal, mean (SD) | 210 (15), range 170–240 |
| | We do not follow ACT (n=3 respondents) | |



*Pediatr Crit Care Med 2013;14:e77*

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| | | |
|---|---|---|
| Anti-factor Xa measurements (n=115 respondents) | Routinely | 46 (40%) |
| | Occasionally | 29 (25%) |
| | Never | 40 (35%) |



*Pediatr Crit Care Med 2013;14:e77*

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| | | |
|---|---|---|
| ATIII measurements (n=117 respondents) | Routinely | 60 (51%) |
| | Occasionally | 36 (31%) |
| | Never | 21 (18%) |



*Pediatr Crit Care Med 2013;14:e77*

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| | | |
|---|---|---|
| TEG measurements (n=116 respondents) | Routinely | 21 (18%) |
| | Occasionally | 29 (25%) |
| | Never | 66 (57%) |



*Pediatr Crit Care Med 2013;14:e77*

# ANTICOAGULANTS – BIVALIRUDIN

- Direct thrombin inhibitor
- Inhibits unbound and clot-bound thrombin
- No Reversal agent
- PTT and Direct Thrombin Time
- Proteolytic degradation
- 25 minute half life
- Less variability in pharmacokinetics

# Bivalirudin-based versus conventional heparin anticoagulation for postcardiotomy extracorporeal membrane oxygenation

Marco Ranucci[1*], Andrea Ballotta[1], Hassan Kandil[1], Giuseppe Isgrò[1], Concetta Carlucci[1], Ekaterina Baryshnikova[1] and Valeria Pistuddi[1], for the Surgical and Clinical Outcome Research Group

- Retrospective single center comparative analysis of heparin vs. bivalirudin for adult and pediatric postcardiotomy ECMO.
- 8 heparin patients & 13 bivalirudin patients
- ACT, PTT, TEG *r* time monitoring
- Bivalirudin group: less bleeding & thrombotic events, less overall blood loss, less transfusions, less AT, lower cost in pediatric patients



*Critical Care 2011;15:R275*

# Prospective Exploratory Experience With Bivalirudin Anticoagulation in Pediatric Extracorporeal Membrane Oxygenation

Lindsay M. Ryerson, MD[1,2]; Kelsey R. Balutis, MD[1,2]; Donald A. Granoski, RRT[2,3]; Lee-Ann R. Nelson, MSc[4]; M. Patricia Massicotte, MD[1]; Laurance L. Lequier, MD[1,3]; Mary E. Bauman, RN, MN[1]

- Single center pilot study of PICU and Pediatrc CICU patients
- Determine if bivalirudin led to less circuit interventions in patients previously treated with heparin
- *KID-CLOT team guided management
- 20 ECMO runs: 80% heparin failure, 20% primary bivalirudin
- Bivalirudin group: Lower circuit interventions, no difference in patient thrombotic events, more bleeding events



*Pediatr Crit Care Med 2020; 21:975–985*

# Evaluation of Bivalirudin As an Alternative to Heparin for Systemic Anticoagulation in Pediatric Extracorporeal Membrane Oxygenation

Mohammed Hamzah, MD[1]; Angela M. Jarden, MSN[2]; Chidiebere Ezetendu, MD[1]; Robert Stewart, MD[3]

- Retrospective single center comparative analysis pre- and post-bivalirudin implementation
- 32 PICU patients: 16 heparin and 16 bivalirudin
- Bivalirudin: faster time to therapeutic
- Heparin: more bleeding, more thrombotic events (p=0.1), more PRBCs and FFP, higher cost per day
- Similar recovery, decannulation, mortality rates



*Pediatr Crit Care Med 2020;21:827-834*

# BIVALIRUDIN VS HEPARIN

| Parameters | Heparin ($n=27$) | Primary bivalirudin ($n=8$) | p Value (comparing heparin and primary bivalirudin groups) |
|---|---|---|---|
| Time to achieve target aPTT (h) | 12 (5.75,26) | 14.5 (6.7,16) | 0.373 |
| Percent aPTT in target range T-7 days (median) | 44.0 (21.0, 53.0) | 65.0 (47.5, 72.0) | 0.014 |
| Percentage of aPTT with >30% variability from goal, median (IQR) | 30.0 (18.0, 58.0) | 9.0 (3.0, 17.5) | 0.003 |

aPTT: activated partial thromboplastin time.



Kaushik et al *Perfusion* 2023

# BIVALIRUDIN VS HEPARIN

- Retrospective Review
- 89 Pediatric ECMO Runs, 8 VV ECMO

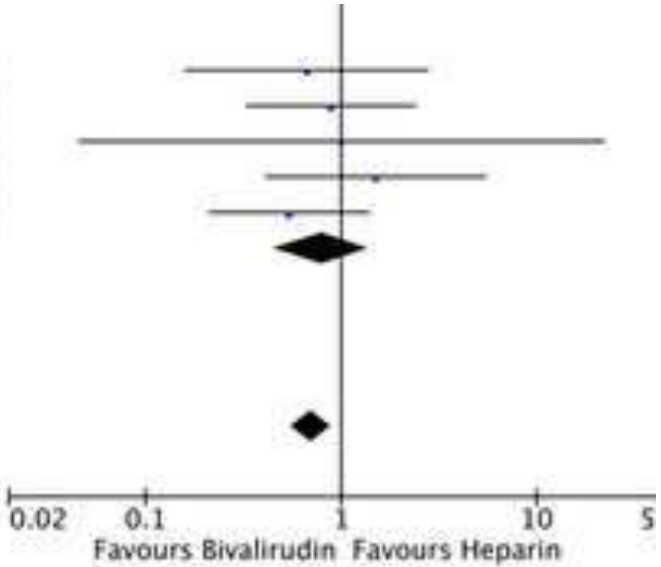
| Variable | Pediatric | |
|---|---|---|
| | Bivalirudin Estimate (95% CI) | *p* |
| Hospital mortality | 0.56 (0.21–1.49) | 0.24 |
| ECMO-free days (14 d)[d] | 1.9 (–0.2 to 3.9) | 0.07 |
| Hospital-free days (35 d)[d] | 4.2 (0.4–8.1) | 0.03 |
| Anticoagulant dose changes per day[b] | 0.75 (0.47–1.19) | 0.23 |
| Activated partial thromboplastin time, laboratories per day | 0.36 (–0.40 to 1.11) | 0.35 |
| Any transfusion during first 24 hr on ECMO | 0.28 (0.10–0.81) | 0.02 |
| Any transfusion day 2 through first week on ECMO[c] | 0.46 (0.09–2.38) | 0.36 |
| Other circuit interventions | 0.95 (0.34–2.69) | 0.93 |
| Any ischemic complication | 0.62 (0.16–2.44) | 0.49 |
| Required additional run on ECMO | 1.89 (0.54–6.64) | 0.32 |

ECMO = extracorporeal membrane oxygenation.

Seelhammer et al. *Critical Care Medicine*. 2021

# BIVALIRUDIN VS HEPARIN

| | | | | | | |
|---|---|---|---|---|---|---|
| **3.2.2 Pediatrics** | | | | | | |
| Machado 2021 | 6 | 18 | 6 | 14 | 2.7% | 0.67 [0.16, 2.82] |
| Rabinowitz 2021 | 11 | 32 | 13 | 35 | 5.7% | 0.89 [0.33, 2.41] |
| Ranucci 2011 | 4 | 5 | 4 | 5 | 0.6% | 1.00 [0.05, 22.18] |
| Schill 2020 | 6 | 13 | 12 | 33 | 3.4% | 1.50 [0.41, 5.51] |
| Seelhammer 2021 | 10 | 24 | 37 | 65 | 6.3% | 0.54 [0.21, 1.40] |
| **Subtotal (95% CI)** | | **92** | | **152** | **18.7%** | **0.79 [0.46, 1.38]** |
| Total events | 37 | | 72 | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.67$, df = 4 (P = 0.80); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 0.82 (P = 0.41) | | | | | | |
| **Total (95% CI)** | | **605** | | **677** | **100.0%** | **0.70 [0.55, 0.89]** |
| Total events | 256 | | 333 | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 9.71$, df = 11 (P = 0.56); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 2.89 (P = 0.004) | | | | | | |
| Test for subgroup differences: $Chi^2 = 0.14$, df = 1 (P = 0.71), $I^2 = 0\%$ | | | | | | |




CARDIOLOGY 2024

Children's Hospital of Philadelphia Cardiac Center

Hasegawa, D. et al , 2023. *ASAIO Journal*

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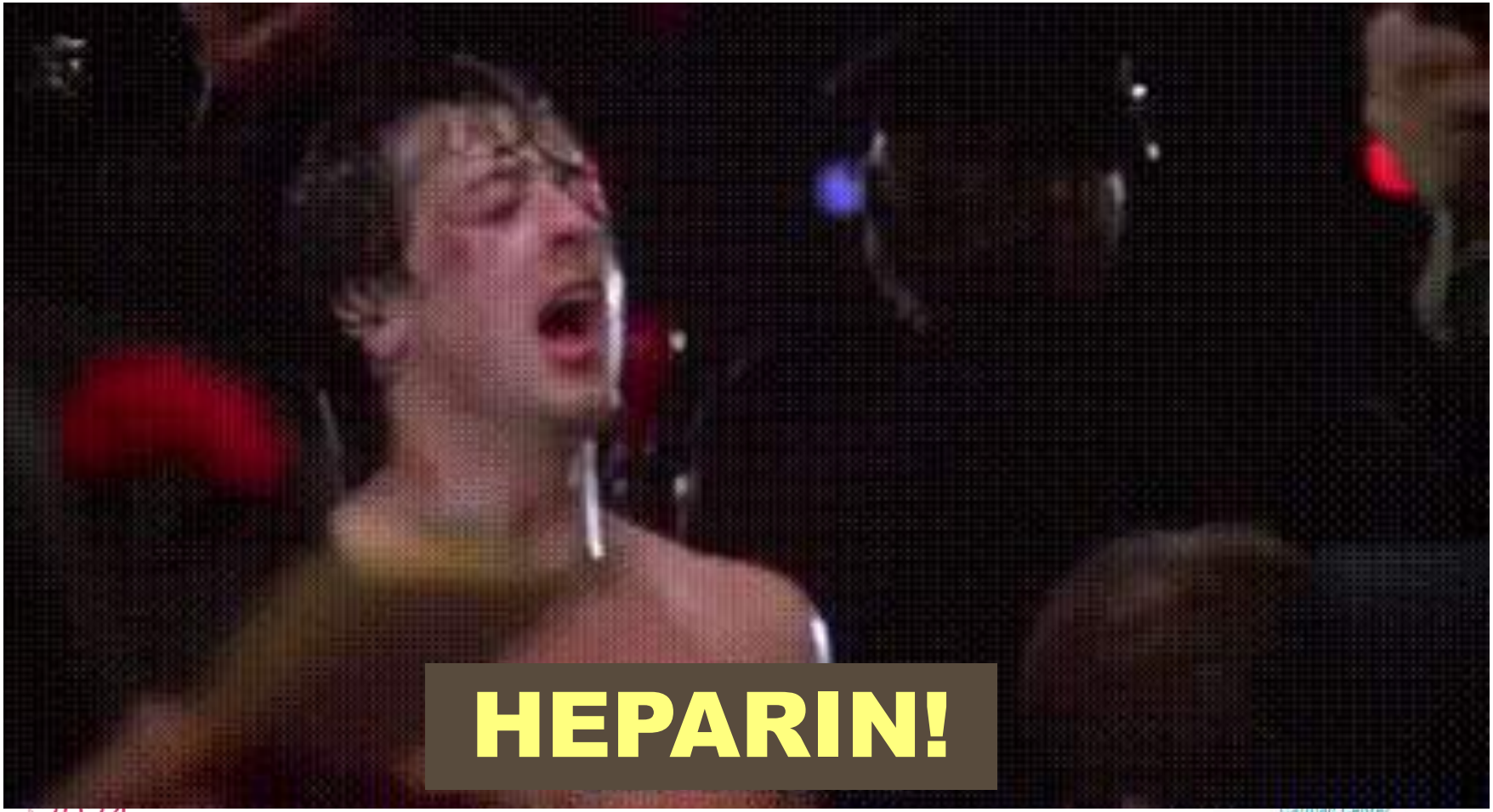
Several retrospective case series have examined the use of DTIs compared with UFH for pediatric and adult ECMO patients.[13–29] Large, prospective randomized trials are needed to confirm the efficacy and superiority of DTIs before their use as the primary anticoagulant for ECMO patients.


HEPARIN!

# SUMMARY

- Data is not there yet
- At least Equivalent
- Probably better in adult-sized patients
- Probably better in difficult-to-anticoagulated patients
- Based on VAD Data, potentially better in long-runs

# THANK YOU

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