Bivalirudin in mechanical circulatory support

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Cardiac Critical Care Medicine

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Disclosures

- This whole talk is off label use

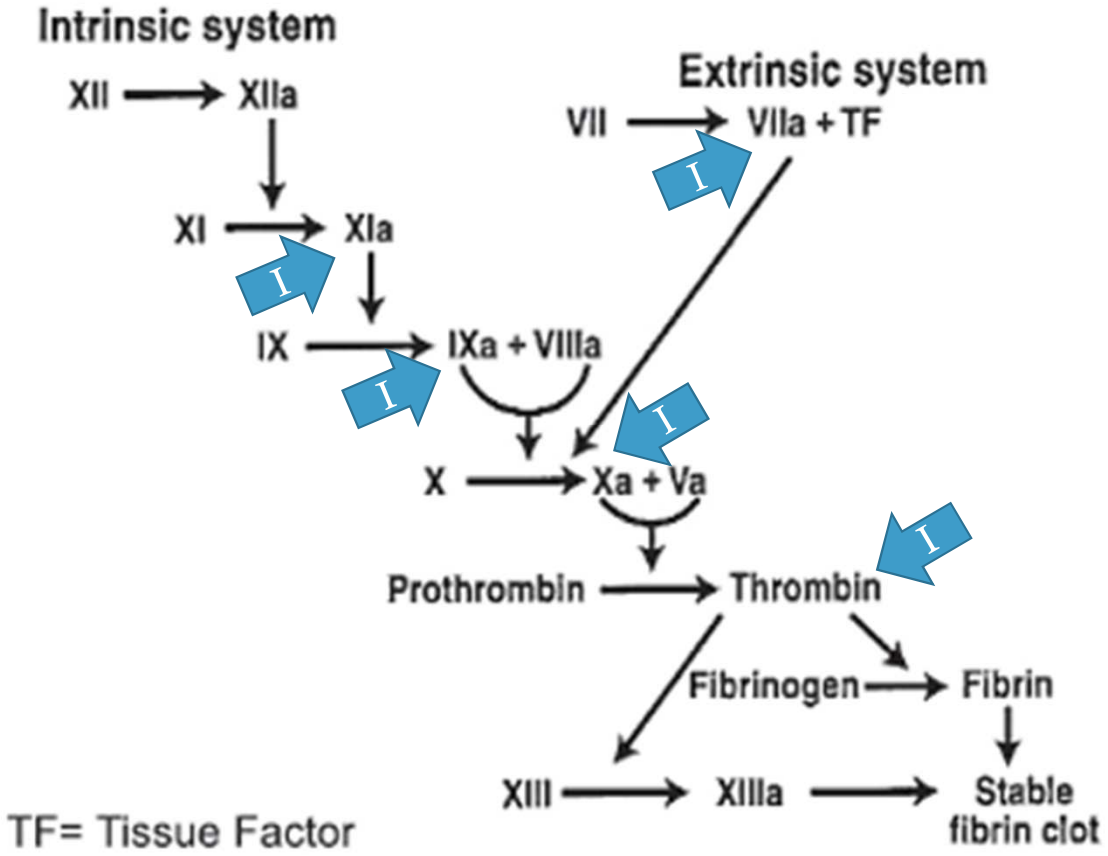
Outline

- The drug
- What is done at CHOP
- The “evidence” in mechanical circulatory support

Bivalirudin

- Direct thrombin inhibitor
  - Heparin is indirect thrombin inhibitor

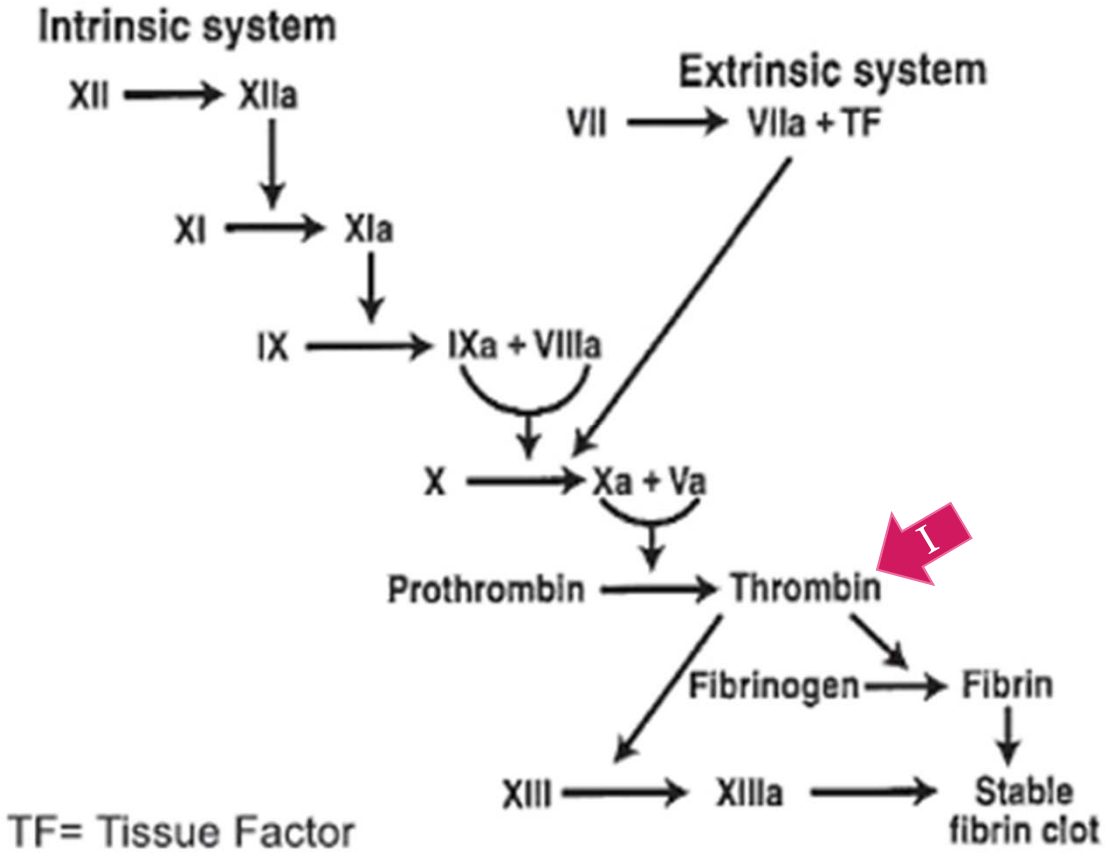
Clotting Cascade: Heparin + AT3



Heparin +ATIII

- Heparin needs ATIII
- ATIII can be low
  - Low level in neonates
  - Losses (e.g. chylothorax, Fontans with PLE)
- So why don't we just give ATIII
  - As FFP
  - As recombinant ATIII
  - Problem – leads to big swings
- Heparin induced thrombocytopenia (HIT)

Clotting Cascade: Bivalirudin



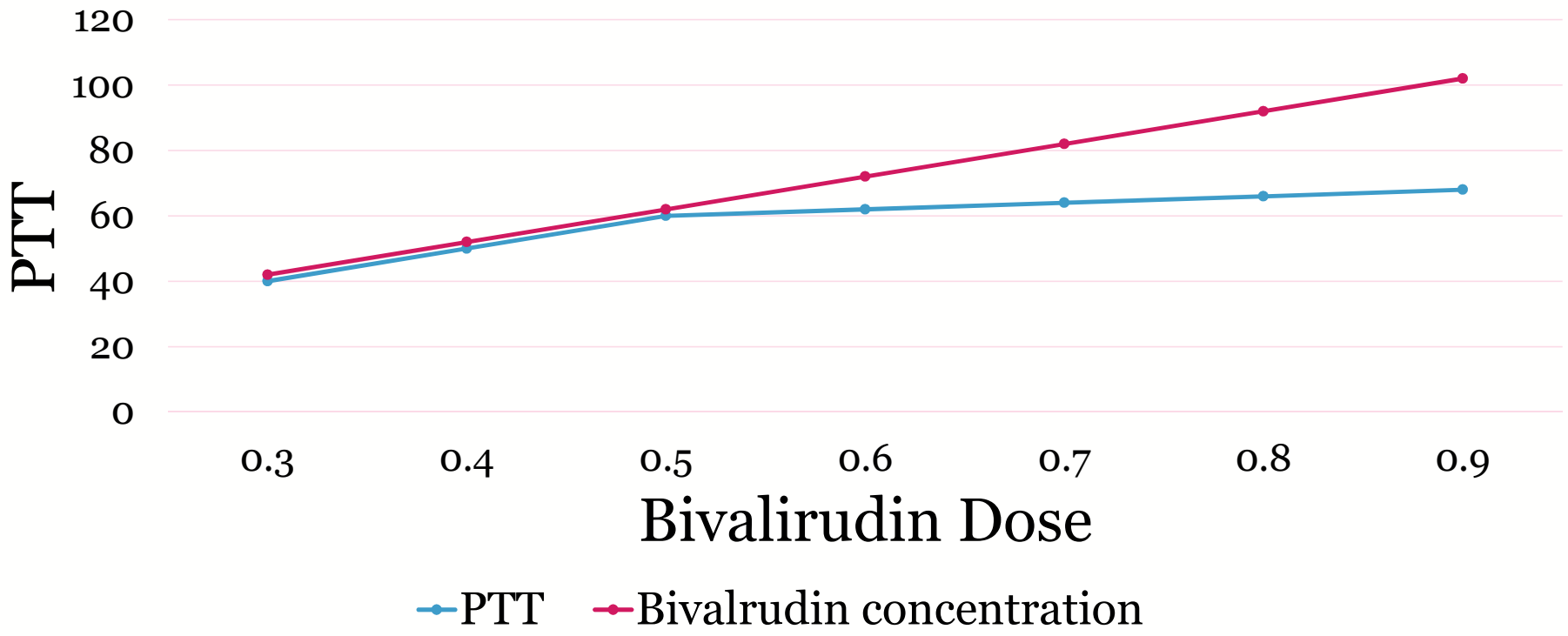
Bivalirudin

- Direct thrombin inhibitor
  - Heparin is indirect thrombin inhibitor
- Thins blood in 2 ways
  - Inhibits thrombin
  - Inhibits thrombin mediated platelet aggregation and activation
- Half-life is ~25 minutes
  - Longer in renal disease
- Does not cross react with HIT antibodies
- Safer than other DTIs (80% proteolytic cleavage, less bleeding)

Bivalirudin monitoring

- Typical
  - Activated partial thromboplastin time (aPTT)
    - Manufacturer recommended
    - Can be influenced by other factors (lupus Ab, coagulation factor deficiencies)
    - Dose response is non-linear
  - Activated clotting time (ACT)
    - Can be influenced by other factors (lupus Ab, coagulation factor deficiencies)
    - Dose response is non-linear

What do I mean by non-linear?



Bivalirudin monitoring

- Atypical
  - Ecarin clotting time (ECT)
  - Prothrominase-induced clotting time (PiCT)
  - Chromgenic anti-Iia
  - Diluted thrombin time (dTT)

What we do at CHOP - monitoring

- Diluted thrombin time (dTT)
  - Diluting patient plasma's
  - Adding back to normal plasma
  - The patient's bivalirudin (or any DTI) acts upon a predictable level of thrombin provided in the normal plasma
  - Less interference from other sources
    - Not affected by lupus inhibitors or elevated d-dimers
    - Slightly dependent on fibrinogen level
    - Can be prolonged with heparin contamination

What we do at CHOP – prior to initiation

- Baseline CBC, BMP (for Cr), PT/PTT, fibrinogen
- Dedicated line
- Consider no/lower bolus if:
  - Stroke
  - Potential for intracranial bleed
  - Bleeding/high risk for bleeding

What we do at CHOP – nuts and bolts

- Bolus: 0.15-0.3 mg/kg IVP (0.75 mg/kg IVP for cath)
- Maintenance: 0.3 mg/kg/hour (1.75 mg/kg/hour for cath)

- **Dosage adjustment in renal impairment:**
  - Children: Cl_{cr} < 60 mL/minute: Decrease infusion rate by 50%, follow DTT; no change in bolus dose
- **Dosage adjustment in hepatic impairment:** No dosage adjustment is needed

What we do at CHOP – nuts and bolts

- Bivalirudin Dosage Adjustment

DTT (sec)	Hold?	Dose Adjustment	Repeat DTT
<60	No	Increase by 20%	2-3 hours after change
60-90	No	No change	2-3 hours x1, then QD
91-100	No	Decrease by 20%	2-3 hours after change
>100	1 hour	Decrease by 50%	2-3 hours after change

- 2 DTTs are therapeutic → once daily
- Alternatively, PTT 1.5-2.5 times the patient's baseline value may be used to help guide therapy

What we do at CHOP – miscellaneous

- ***Conversion to oral anticoagulant:***
  - Combined effect on the INR w/ bivalirudin + warfarin
  - No loading dose of warfarin
  - Bivalirudin and warfarin therapy should be overlapped for at least 5 days
  - Bivalirudin therapy can be stopped when INR is >3.5
    - Repeat INR measurement in 2-3 hours
    - If INR is below therapeutic level, bivalirudin therapy may be restarted.
    - Repeat procedure daily until desired INR on warfarin alone is obtained.
- Converting from enoxaparin
  - Not before 8 hours from last dose of enoxaparin
  - If within 8-12 hours, no bolus
  - If after 12 hours, consider bolus
- Hold 4 hours (minimum) prior to surgery/LP

Mechanical Circulatory Support Literature

Extracorporeal Membrane Oxygenation

ECMO Systematic Review

Bivalirudin for Alternative Anticoagulation in Extracorporeal Membrane Oxygenation: A Systematic Review

Filippo Sanfilippo, MD, PhD[1,2], Sven Asmussen, MD[3,4], Dirk M. Maybauer, MD, PhD[4,5], Cristina Santonocito, MD[1], John F. Fraser, MD, PhD[4], Gabor Erdoes, MD[6], and Marc O. Maybauer, MD, PhD[4,5,7]

- 9 studies, 58 patients, 24 pediatrics
- 2 studies compared it to heparin, no difference in complications (though in 1 heparin required more transfusion)
- Some used loading dose (0.1 to 0.5 mg/kg), some did not
- Largest pediatric series:
  - Doses ranged from 0.045 mg/kg/hr to 0.48 mg/kg/hr
- Recombinant factor VII may reverse it
  - Has been associated with thrombotic complications

ECMO

Bivalirudin in Pediatric Patients Maintained on Extracorporeal Life Support

Erin L. Nagle, PharmD; William E. Dager, PharmD, FCCM; Jeremiah J. Duby, PharmD; A. Josh Roberts, PharmD; Laura E. Kenny, RN; Manasa S. Murthy, PharmD; Robert K. Pretzlaff, MD

- That large pediatric case series was from UC Davis (12 pts.)
- Bolus dose didn't change PTT 1-2 hours later

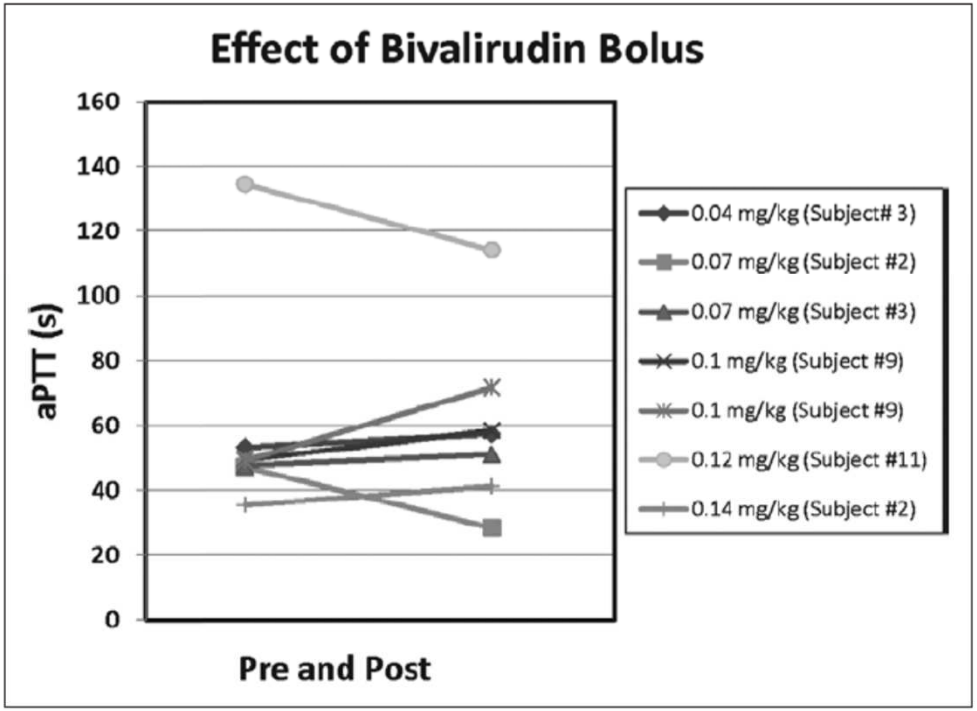


Figure 1. Activated partial thromboplastin time (aPTT) response to bolus dose.

ECMO

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- That large pediatric case series was from UC Davis (12 pts.)
- Positive correlation of bivalirudin infusion adjustment to PTT change was poor but significant, $r^2 = 0.264$, p=0.04

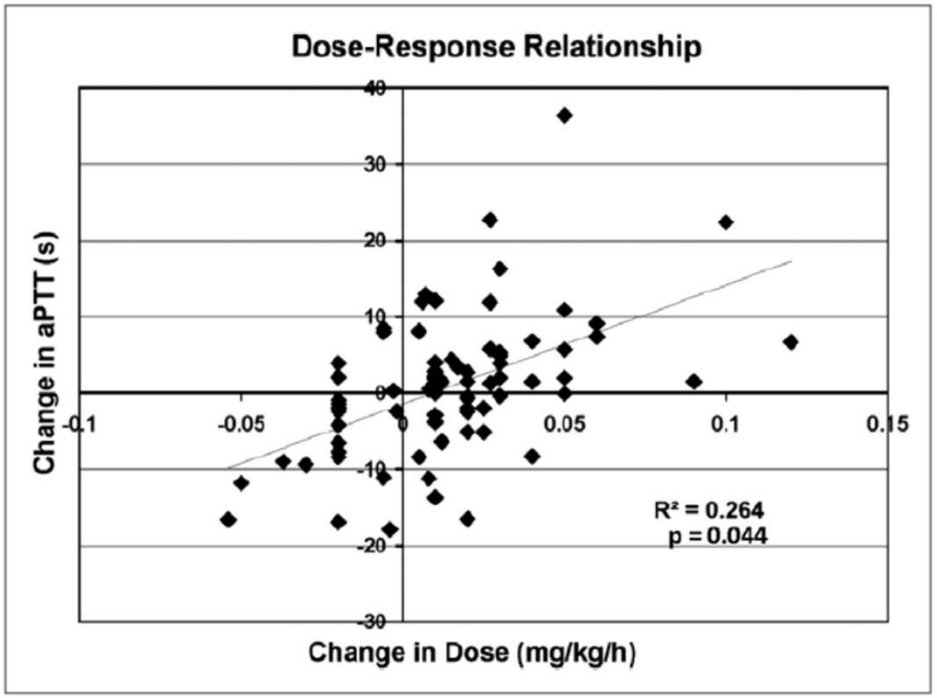


Figure 2. Activated partial thromboplastin time (aPTT) response to bivalirudin dose change.

ECMO – postcardiotomy, central cannulation

- Ranuchi et al.
- Made change to bivalirudin in June 2009
- Looked at 8 patients with heparin & 13 with bilvalirudin
- RA, LA AAo
- Started H @ 5 to 10 IU/kg/hour
- Started B @ 0.03 to 0.05 mg/kg/hour
- Followed ACT, aPTT, and thromboelastography

ECMO

Table 2 Demographics and extracorporeal membrane oxygenation details of the patient population

Parameter	H-group (*n* = 8)	B-group (*n* = 13)	*P* value
Age (years)	13.9 ± 19	36.5 ± 29	0.045
Pediatric patients	5 (62%)	4 (31%)	0.154
Weight (kg)	37 ± 45	51 ± 34	0.446
Time on cardiopulmonary bypass (minutes)	230 ± 146	269 ± 142	0.562
ECMO positioning in the operating room	6 (75%)	9 (69%)	0.772
Time on ECMO (hours)	80 ± 52	143 ± 73	0.036
Use of intra-aortic balloon pump	1 (12%)	5 (38%)	0.336
Total bleeding (ml/kg/day)°	51 ± 46	16 ± 13	0.015
Total packed red cells (ml/kg/day)	25 (51)	15 (20)	0.067
Total fresh frozen plasma (ml/kg/day)	12 (76)	5.9 (9)	0.020
Total platelets (ml/kg/day)	33 (53)	3 (7)	0.008
Total purified antithrombin (IU/kg/day)	13 (31)	7 (13)	0.048
Cost in adults (€/day)	3,313 ± 2,818	1,807 ± 886	0.165
Cost in children (€/day)	760 ± 237	312 ± 56	0.008

Data presented as mean ± standard deviation, number (%) or median (interquartile range). ECMO, extracorporeal membrane oxygenation. ° during the first 48 hours

But…

- 2 of 9 heparin pts survived
- 3 of 13 bivalirudin pts survived
- 1 infant had thromboembolic event (bivalirudin group)
- And they cautioned in blood stagnation
  - Bivalirudin gets rapidly cleaved
  - On CPB
  - In the heart (dilated atria, smoke)

ECMO – adults, H vs B

- Retrospective
- 72 patient (44 bivalirudin)
- Bivalirudin group with more cardiogenic & less septic shock
- No difference in:
  - Thrombotic events
  - In hospital morality
  - 30-day mortality
  - % time in therapeutic range
  - Neurologic events
  - Vascular complications
  - Major bleeding
  - Minor bleeding

Ventricular Assist Devices

VAD – adult, bridge after VAD placement

- Retrospective, case matched, HIT excluded
- Thrombotic complications
  - Heparin 5%, Bivalirudin 20%, Nothing 27%
- Cost
  - Bivalirudin = $6200 per patient
  - Heparin = $150 per patient
- But…
  - mean dose of bivalirudin was 0.082 mg/kg/hour (we start 0.3)

Comparison of Anticoagulation Strategies After Left Ventricular Assist Device Implantation

Alexander Kantorovich,*† Jodie M. Fink,‡ Michael A. Militello,§ Seth R. Bauer,§ Edward G. Soltesz,¶ and Nader Moazami¶

VAD

Bivalirudin for Treatment of LVAD Thrombosis: A Case Series

Lynne M. Sylvia,*† Linda Ordway,‡ Duc T. Pham,§¶ David DeNofrio,‡¶ and Michael Kiernan‡¶

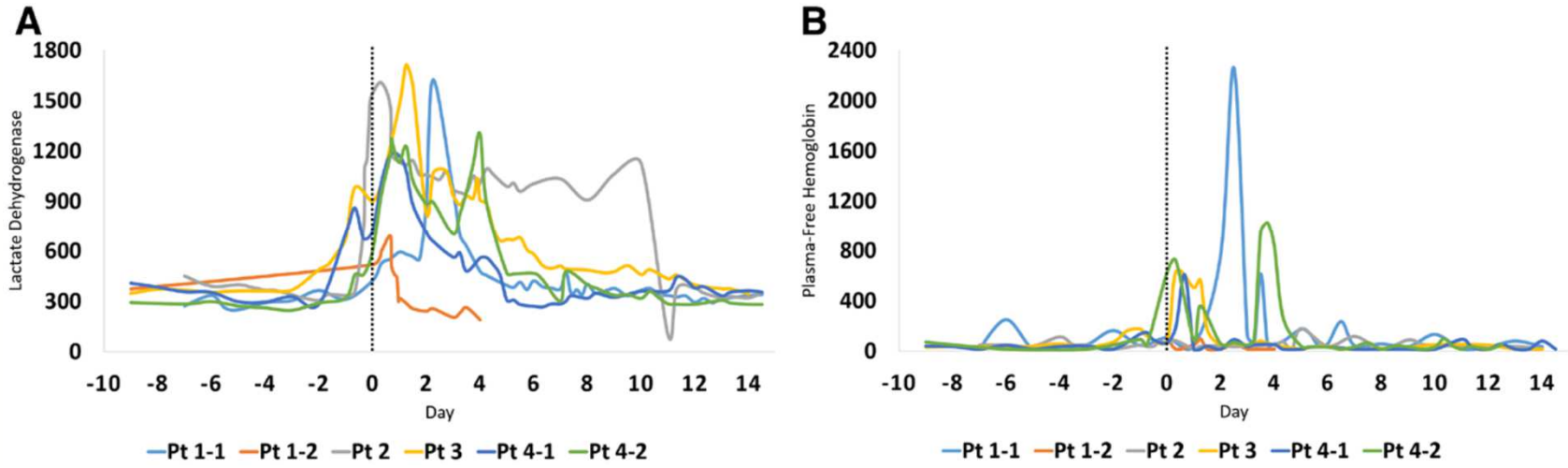
- 10 suspected cases of VAD thrombosis
- Initiated per protocol
  - 0.03 to 0.15 mg/kg/hour
  - based on renal function and baseline INR
- 9 responded
  - 7 discharged
  - 2 had to remain in house until transplant for recurrence
- median duration of bivalirudin therapy was 22 days (range: 11–237)
- median cost of bivalirudin therapy was $79,800 (range: $31,359–
- $1,281,737)

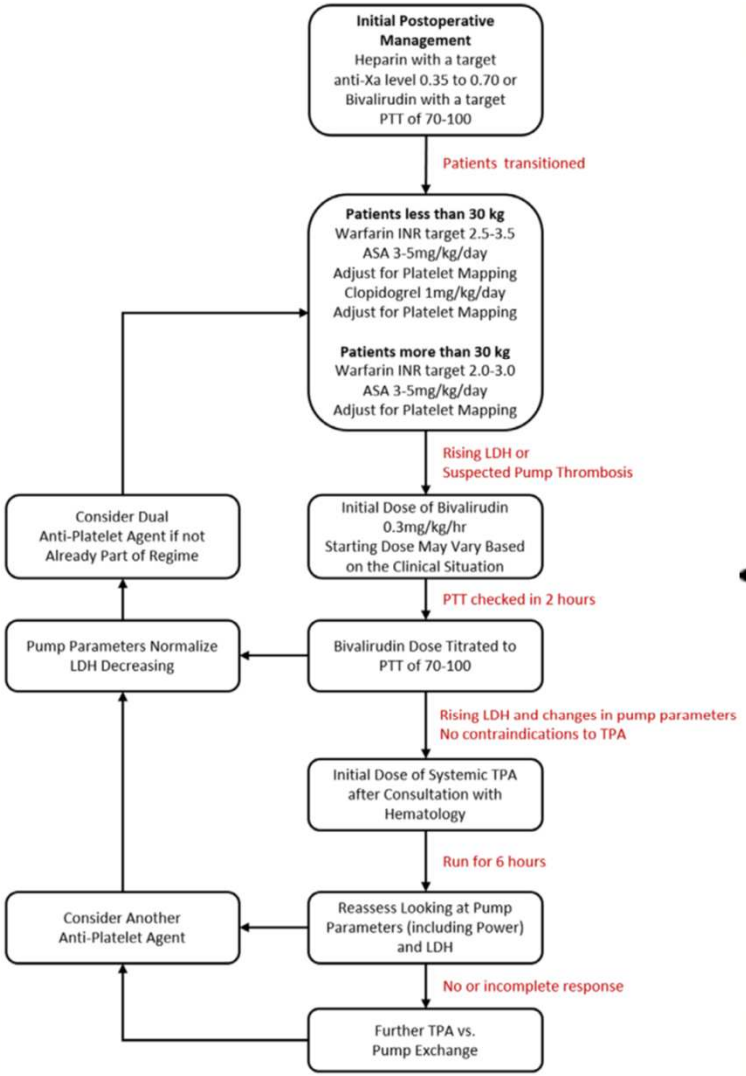
VAD

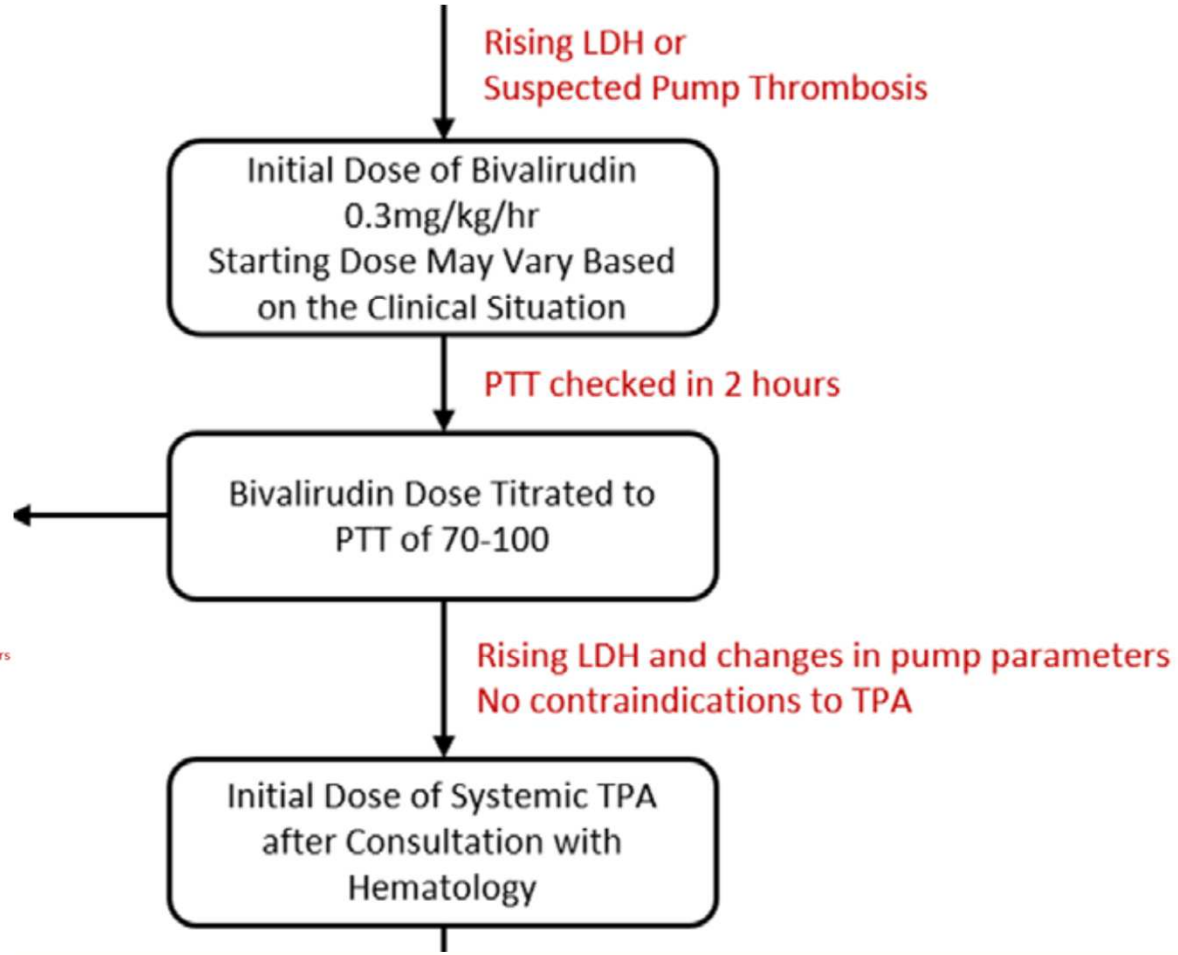
Successful Treatment of Pediatric Ventricular Assist Device Thrombosis

Devin Chetan,*† Holger Buchholz,*† Mary Bauman,†‡ Vijay Anand,†§ Paula Holinski,†§ and Jennifer Conway*†

- Another case series (10 HeartWare patients)
  - 4 had pump thrombosis (pump parameter change, rise in LDH & pHgb)




Initial Postoperative Management
Heparin with a target anti-Xa level 0.35 to 0.70 or Bivalirudin with a target PTT of 70-100
Patients transitioned
Patients less than 30 kg
Warfarin INR target 2.5-3.5
ASA 3-5mg/kg/day
Adjust for Platelet Mapping
Clopidogrel 1mg/kg/day
Adjust for Platelet Mapping
Patients more than 30 kg
Warfarin INR target 2.0-3.0
ASA 3-5mg/kg/day
Adjust for Platelet Mapping
Rising LDH or Suspected Pump Thrombosis
Initial Dose of Bivalirudin 0.3mg/kg/hr Starting Dose May Vary Based on the Clinical Situation
PTT checked in 2 hours
Bivalirudin Dose Titrated to PTT of 70-100
Rising LDH and changes in pump parameters No contraindications to TPA
Initial Dose of Systemic TPA after Consultation with Hematology
Run for 6 hours
Reassess Looking at Pump Parameters (including Power) and LDH
No or incomplete response
Further TPA vs. Pump Exchange
Consider Another Anti-Platelet Agent
Pump Parameters Normalize LDH Decreasing
Consider Dual Anti-Platelet Agent if not Already Part of Regime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- Patient 1
  - 1st time – heparin only w/out plt inhibitor (neuro) → exchanged pump
  - 2nd time – changed to bivalirudin, transplanted 4d later
- Patient 2
  - Thrombosis of VAD – exchanged. Bridged with bivalirudin 2nd time
- Patient 3
  - Got local then systemic tPA. Bivalirudin after that
  - Readmitted several times thrombosis → bivalirudin used each time
- Patient 4: Several episodes of thrombosis → bivalirudin not used

VAD – Berlin

Bivalirudin Versus Heparin as an Anticoagulant During Extracorporeal Membrane Oxygenation: A Case-Control Study

Marina Pieri, MD,* Natalia Agracheva, MD,* Enrico Bonaveglio, MD,* Teresa Greco, MSc,*
Michele De Bonis, MD,† Remo Daniel Covello, MD,* Alberto Zangrillo, MD,* and Federico Pappalardo, MD*

- 10 tx with Bivalirudin
- 10 matched historical controls tx with Heparin
- Fewer PTT swings >20%
- No difference in
  - Bleeding
  - Thromboemoblic complications
  - High PTT
  - # of anticoagulation dose adjustment

"Failed" conventional therapy; Berlin EXCOR

- Bivalirudin 0.685 mg/kg/hour (range, 0.1–0.8 mg/kg/hour
- Epoprostenol 2 ng/kg/min (range 2–20 ng/kg/min)

Table 4 Anticoagulation

No.	Failed conventional treatment	Reason for alternate anti-coagulation	Conversion to BV/EP (VAD POD)	Therapeutic BV dose (mg/kg/hour)	EP dose (ng/kg/min)	ASA	Dipyridamole	Clopidogrel	BV/EP duration (days)
1	Yes	New diagnosis HIT	7	0.26	2	No	Yes	No	15
2	No	HIT	0	0.1	20	Yes	Yes	Yes	45
3	Yes	VAD thromboses, stroke	7	0.8	10	Yes	Yes	Yes	50
4	No	Prosthetic MV	0	0.65	2	Yes	Yes	Yes	97
5	Yes	VAD thromboses, peripheral thromboembolism	13	0.72	4	Yes	Yes	Yes	142
6	Yes	VAD thromboses, stroke	32	0.8	2	Yes	No	Yes	48

ASA, acetylsalicylic acid; BV, bivalirudin; EP, epoprostenol; HIT, heparin-induced thrombocytopenia; MV mitral valve; POD, post-operative day; VAD, ventricular assist device.

1 stroke

VAD placement

- Typically de-aired anterograde
  - Attach to LV, fill with blood, then have to connect to aorta
- They do retrograde
  - Sewing ring, attach to aorta, fill backwards, then attach to fibrillating LV
  - 60-90 seconds
- Less time with stasis of blood in the VAD

(Remember bivalirudin gets degraded by proteolysis!)

A modified technique for implantation of the HeartWare™ left ventricular assist device when using bivalirudin anticoagulation in patients with acute heparin-induced thrombocytopenia

Michiel Morshuis[a], Jochen Boergermann[a], Jan Gummert[a] and Andreas Koster[b,*]

Berlin at CHOP

- Bivalirudin is our first line bridge

Cardiopulmonary Bypass

Bypass (few case reports in peds)

- 2 infants w/ HIT:
  - Bolus 1mg/kg
  - Infusion 2.5mg/kg/hr
  - 50mg to CPB circuit
  - Kept ACT >400
- 11yo w/ HIT needed VAD
  - Bolus 1mg/kg 15 minute before bypass anticipation
  - ACT 385 (goal 400 or >2.5x baseline). 2nd bolus of 0.85mg/kg
  - Infusion increased from 2.5 to 3 (up to 5 when giving pRBCs and MUF)
  - Also bolused pump
  - Lower venous reservoir level to avoid stagnation; venous sampling line flushed with air after use
  - Tranexamic acid bolus and infusion given as well
  - Argatroban used post-operatively

Summary

- Bivalirudin has clear advantage when there is HIT
- There are theoretical advantages in other patients requiring mechanical support
- Evidence is shaky but there is probably a role for bivalirudin in
  - Tx of VAD thrombosis
  - Prevention of VAD thrombosis after heparin failure
  - Maybe ECMO if dosed properly (especially if central cannulation)
- PTT monitoring is likely not sufficient
- Whatever you do…make a protocol
- Typical procedures need alteration to avoid blood stasis

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