Anticoagulation for Ventricular Assist Device (VAD) Clinical Pathway
This pathway is intended as a guide for physicians, physician assistants, nurse practitioners and other healthcare providers. It should be adapted to the care of specific patient based on the patient's individualized circumstances and the practitioner's professional judgment.
Rationale
This clinical pathway was developed by a consensus group of JHACH physicians, advanced practice providers, nurses and pharmacists to standardize the anticoagulation therapy for pediatric mechanical circulatory support patients. Bivalirudin has been used as an alternative to unfractionated heparin and the use has been increasing in the setting of high-risk children supported with ventricular assist devices such as: heparin induced thrombocytopenia (HIT), hypoxemia, systemic inflammatory process, and/or failure of heparin therapy with resultant pump thrombosis, thromboembolic event or stroke.

Background
The advent of mechanical circulatory support has had a significant impact on the management of heart failure. While significant advancements have been made in VAD technology, understanding the hemostasis and antithrombotic management in neonates and children remains challenging. Consequently, VAD therapy has historically been associated with high rates of stroke and bleeding. Unfractionated heparin (UFH) has presented challenges as an anticoagulant for VAD therapy due to its heterogeneous biochemical composition and unpredictable pharmacokinetics. As a result, there has been increased interest in using the intravenous direct thrombin inhibitor (DTI), bivalirudin or argatroban. Initial outcomes report lower major bleeding and stroke event rates. Consequently, bivalirudin has become the anticoagulant of choice in pediatric VAD therapy.

Bivalirudin is specific and reversible DTI. Hirudin derivatives (e.g., lepirudin, desirudin) and hirudin analogues (e.g., bivalirudin) are bivalent direct thrombin inhibitors; that is, they bind to two distinct sites on thrombin-its active (catalytic) site and its fibrinogen-binding site (exosite 1). These bivalent binding properties contribute to their high affinity and high specificity for circulating and clot-bond thrombin. Catalytic binding site occupation functionally inhibits coagulant effects by preventing thrombin mediated cleavage of fibrinogen to fibrin monomers, and activation of factors V, VII, and XIII. Bivalirudin has little or no effect upon other serine proteases and unlike UFH does not require antithrombin III for antithrombotic activity. Elimination is primarily via proteolytic cleavage with approximately 20% being renal excretion. It is administered as a continuous intravenous (IV) infusion, has a rapid onset of action (approximately 2 minutes), and is reported to achieve steady state within 4 hours. Bivalirudin has a relatively short half-life of 26 min in the setting of normal renal function, although this may be prolonged up to 4 hours in the setting of renal dysfunction or renal replacement therapies. Bivalirudin exhibits linear dose and concentration dependent prolongation of activated clotting time, aPTT, PT, and thrombin time (TT). Most experience with dose titration in the literature is based on aPTT, although the dilute thrombin time (dTT) has gained interest as a more accurate laboratory monitoring parameter. Of note, bivalirudin will prolong INR.
There is currently no guideline recommended dosing for children. Current dosing has been based on clinical experience and extrapolation from adult data. Bleeding is the primary adverse event associated with its use. There is no specific antidote or reversal agent available at this time.

**Adverse Reactions/Effects:**
- Cardiovascular: Hypotension (≤12%)
- Central nervous system: Pain (≤15%), headache (≤12%)
- Gastrointestinal: Nausea (≤15%)
- Hematologic & oncologic: Minor hemorrhage (Protocol defined: 14%; heparin 26%; TIMI defined: 1%; heparin 3% [Lincoff, 2003])
- Neuromuscular & skeletal: Back pain (9% to 42%)

**Pre VAD/MCS Implantation**
It is recommended that all patients have a coagulation work-up prior to VAD/MCS implantation that includes baseline laboratory work (<48 hrs. Pre-implant), as well as acquisition of complete past medical and family history for relevant thrombotic or bleeding events. Laboratory work highly recommended:
- CBC
- aPTT* (“Baseline aPTT. If the baseline aPTT is abnormal due to concomitant anticoagulation, ECMO, illness, etc. then suggest the latest aPTT that was within normal institutional range, 30-40 seconds)
- PT/INR
- Fibrinogen
- Basic metabolic panel (serum creatinine)

Optional laboratory work
- TEG with platelet mapping
- C-reactive protein (CRP)
- LDH
- Cystatin C
**Bivalirudin Administration**

Timing for initiation of bivalirudin may be variable and dependent on patient- and device-related factors. These factors include type of device and associated risk of thrombogenicity, surgical and coagulopathic bleeding, multi-organ dysfunction, inflammation and infection. Centers have described initiation between 6-72 hours post VAD implantation.

It is reasonable to **initiate** bivalirudin when:
- Surgical and coagulopathic bleeding has resolved (chest tube output <2 mL/kg/hr for at least 4 hours, and no other sources of active bleeding)
- aPTT within 15 seconds of baseline*
- INR <1.3
- Fibrinogen >100 mg/dL
- Platelet count >100,000 per microliter

It is reasonable to **delay** initiation of bivalirudin if:
- Ongoing bleeding (need for product replacement in last 12h)
- Abnormal coagulation profile (elevated INR, elevated aPTT after full protamine reversal, low platelet count)

**Initial Bivalirudin dosing**

<table>
<thead>
<tr>
<th>Renal function</th>
<th>Initial dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (&gt;60 mL/min/1.73 m²)</td>
<td>0.3 mg/kg/hr IV infusion</td>
</tr>
<tr>
<td>Mild-moderate (30-60 mL/min/1.73 m²)</td>
<td>0.2 mg/kg/hr IV infusion</td>
</tr>
<tr>
<td>Severe (&lt;30 mL/min/1.73 m²)</td>
<td>0.1 mg/kg/hr IV infusion</td>
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</tbody>
</table>

*Goal ranges based on patients with normal baseline aPTT. If patient’s baseline aPTT falls outside normal range prior to initiation of anticoagulation, evaluate and discuss goal aPTT range prior to initiating bivalirudin (1.5-2x for high bleeding risk, and 2-3x for standard bleeding risk)

**Given the risk of early bleeding, most of patients will begin in the “High risk” category for the first several days on support, then transition to “Standard risk”**

- Check aPTT 2 hours after first initiation (Caution about titrating with first level)
  - If aPTT has increased dramatically to >2-3x baseline PTT, then decrease bivalirudin by 50% and recheck in 4 hours
  - If PTT has increased to 1-1.5 x baseline, make no adjustment and repeat PTT in 4 hours as level may continue to rise
### Bivalirudin Titration and Maintenance

- Check aPTT 4 hours after any dose adjustment and for bleeding/clotting
- Centers have described maintenance lab schedule for Bivalirudin monitoring ranging from daily to once weekly: Frequency of monitoring will be dependent on patient and device stability
- Changes in renal function may affect bivalirudin clearance and may warrant closer monitoring
- Lab monitoring POD 0-7:
  - Daily CBC, SCr, BUN
  - Daily Coags: aPTT, PT, INR, Fibrinogen, Platelet
  - Daily evaluation for hemolysis: LDH, plasma free HGB (+/- haptoglobin)
  - TEG with platelet mapping if available either daily or QOD (and/or VerifyNow)
  - CRP every other day to assess for inflammation or possible infection
- Maintenance lab monitoring
  - Weekly CBC, Cr, BUN, full coagulation panel (PTT, PT, INR, fibrinogen)

### Maintenance Bivalirudin Titration*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
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<tbody>
<tr>
<td>aPTT 5 to 15 seconds out of range</td>
<td>Increase or decrease by 15% (round up to closest 2nd decimal)</td>
</tr>
<tr>
<td></td>
<td>Recheck 4 hours after dose change</td>
</tr>
<tr>
<td>aPTT in target range</td>
<td>No change, recheck 4 hours, then can decrease frequency when stable</td>
</tr>
<tr>
<td>aPTT &gt;15-30 seconds out of range</td>
<td>Increase or decrease by 25% (round up to closest 2nd decimal)</td>
</tr>
<tr>
<td></td>
<td>Recheck 4 hours after dose change</td>
</tr>
<tr>
<td>aPTT &gt; 3x baseline or &gt; 120 seconds</td>
<td>With normal renal function: hold 15 min and reduce by 30%</td>
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<tr>
<td></td>
<td>With mild to moderate renal dysfunction: hold 45 min; reduce by 40%</td>
</tr>
<tr>
<td></td>
<td>With severe renal dysfunction: hold 2 hours; recheck aPTT before restarting</td>
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*Goal ranges based on patients with normal baseline aPTT. If patient’s baseline aPTT falls outside normal range prior to initiation of anticoagulation, evaluate and discuss goal aPTT range prior to initiating bivalirudin (1.5-2x for high bleeding risk, and 2-3x for standard bleeding risk)

- Centers have reported using bolus of 0.25-0.5 mg/kg to achieve therapeutic aPTT
- Centers have reported using bivalirudin while on continuous hemofiltration and intermittent hemodialysis. With intermittent HD, bivalirudin was up titrated 20-30% during dialysis and then returned to baseline dosing afterwards
  - Centers have reported challenges with achieving therapeutic aPTT with continuous HD, requiring additional unfractionated heparin run through the MCS circuit and in the HD circuit while bivalirudin is running in the patient
Laboratory Information

- Diluted thrombin time (dTT)
  - dTT may be a more sensitive test for bivalirudin, with less interference from other sources
  - However, this test is not widely available at all centers, and there is limited information on its use in children
  - The plasma diluted thrombin time is slightly dependent on fibrinogen level
  - The dTT is prolonged with heparin contamination
  - Not affected by lupus inhibitors or elevated d-dimers

- Partial thromboplastin time (PTT)
  - Therapeutic PTT is dependent on individual patient's baseline PTT
  - A plateau effect with PTT is observed with bivalirudin concentrations >2 mcg/mL
  - Dose adjustment of bivalirudin should be based upon the goal of 1.5-2.5 x patient's baseline PTT
  - When baseline PTT is prolonged, accurate bivalirudin monitoring may not be possible

- International normalized ratio (INR)
  - DTI increases INR with potential for combined effects on INR with the co-administration of bivalirudin and warfarin.
  - See “Converting from Bivalirudin to Warfarin” section for more information

Other Patient Care Related Issues
Contamination and Compatibility

- AVOID line contamination when drawing aPTT- strongly consider a dedicated line for bivalirudin (peripheral IV or central line)
  - Compatible with other medications
  - Consider occasionally obtaining UFH levels or heparin absorbed PTT along with the aPTT to assure the samples are not contaminated.
  - If heparin absorbed PTT drawn, make sure that it is labelled appropriately, and that no clinical decision made based on hep absorbed PTT

Converting from Bivalirudin to Warfarin

- There is a potential for combined effects on INR with co-administration of bivalirudin/warfarin.
- A loading dose of warfarin should NOT be used
- Initiate therapy using the expected daily dose of warfarin
- Obtain daily INR with co-administration of bivalirudin and warfarin
- Bivalirudin and warfarin therapy should be overlapped for at least 5 days
- Bivalirudin can be discontinued when INR >3.5 on combined therapy. Repeat INR in 2 to 3 hours after discontinuation. Adjustment of warfarin may be needed if INR >3.5 during the 5 days overlap period.
- Bivalirudin should be resumed if the repeat INR is below desired therapeutic range. Repeat the procedure daily until the desired therapeutic range is reached.
Converting between Heparin and Bivalirudin
- Bivalirudin may be initiated immediately after discontinuation of heparin and vice versa.

Converting between Bivalirudin and Enoxaparin
- The dose of enoxaparin should be given immediately after discontinuation of the bivalirudin infusion
- Begin the bivalirudin infusion no earlier than 8 hours after the last dose of enoxaparin. If starting within 8-12 hours, do NOT use a bolus dose of bivalirudin. If starting after 12 hours, consider a bolus dose of bivalirudin followed by maintenance dose per protocol.

Additional Ideas for Drawing Labs to Avoid Contamination - Bivalirudin ONLY
Peripheral sticks are the gold standard method. If concerns arise regarding the accuracy of a lab result, a peripheral stick should be done to confirm or deny the result.

Arterial Line - Bivalirudin does not need to be held
- Heparin Naïve (Normal Saline flush +/- Papaverine):
  - Draw 3-5 mL of waste
  - Draw lab
  - Return waste (hospital-specific policies)
- Heparin Flush:
  - Draw 3-5 mL of waste
  - Draw lab
  - Return waste (hospital-specific policies)
  - If concern for contamination add Hepzyme to neutralize

PICC Line for Blood Draws (Bivalirudin infusing via alternate line)
- Heparin Naïve - Normal Saline continuous flush KVO
  - Draw 3-5 mL of waste
  - Draw lab
  - Return waste (hospital-specific policies)
- Heparin Flush:
  - Clamp both ports of line for 1-3 minutes
  - Flush with 5mL NS
  - Draw 3-5 mL of waste
  - Draw lab
  - Return waste (hospital-specific policies)
  - If concern for contamination add Hepzyme to neutralize
Single Lumen or Double Lumen PICC or Central Line with Bivalirudin

Lumen 1: Bivalirudin Infusing
Lumen 2: Blood Draw Lumen

Normal Saline running through Lumen 2 (heparin naïve lumen)
- Stop bivalirudin or clamp both ports for 1-3 minutes
- If ports are clamped, unclamp Lumen 2
- Flush with 5mL NS
- Draw 3-5 mL of waste from Lumen 2
- Draw lab
- Return waste (hospital-specific policies)
- Restart bivalirudin

Heparin flush going though Lumen 2 (lab will likely be contaminated)
- Stop bivalirudin or clamp both ports for 1-3 minutes
- If ports are clamped, unclamp
- Flush with NS
- Draw 3-5 mL of waste from
- Draw lab
- Return waste (hospital-specific policies)
- RESTART BIVALIRUDIN
- If concern for contamination add Hepzyme to neutralize
References

Outcomes
- Utilization of pathway
- Rate of thrombosis
- CVA
- Bleeding requiring reoperation

Education Plan
- Heart Institute Section Specific Division Meetings
Anticoagulation for Ventricular Assist Device (VAD): Initial Bivalirudin Dosing

**Inclusion**
Patients receiving MCS/VAD implantation

**Exclusion**
Patients not requiring MCS/VAD management

**Obtain Baseline Coagulation Labs**
CBC, aPTT, PT/INR, Fibrinogen,

Bleeding resolved (chest tube output < 2 mL/kg/hr for > 4 hours)
- aPTT within 15 seconds of baseline
- INR < 1.3
- Fibrinogen > 100 mg/dL
- Platelet count > 100,000 per microliter

**Above criteria met**

**Initial Bivalirudin dosing**
- Early Post-op (24-72 hours, high risk for bleeding) aPTT goal range 50-60 seconds*
- Standard bleeding risk: 60-80 seconds
- High risk for thrombosis: aPTT 50-60 seconds

*If patient’s baseline aPTT falls outside normal range prior to initiation, evaluate and

**Renal function**
- Normal > 60mL/min/1.73 m2
- Mild-moderate (30-60 mL/min/1.73 m2)
- Severe (< 30mL/min/1.73 m2)

**Initial dosing**
- 0.3 mg/kg/hr IV infusion
- 0.2 mg/kg/hr IV infusion
- 0.1 mg/kg/hr IV infusion

**Check aPTT 2 hours after initiation**

If aPTT > 2 to 3 times baseline aPTT
- decrease bivalirudin 50%
- recheck in 4 hours

If aPTT > to 1.5 times baseline aPTT
- make no dose adjustment
- repeat aPTT in 4 hours and proceed to maintenance pathway

**Above criteria not met/ongoing bleeding (need for product in last 12 hours) or abnormal coagulation profile, discuss with provider(s) and re-evaluate**

Source: ACTION Network
**Anticoagulation for Ventricular Assist Device (VAD):**

**Maintenance Bivalirudin Dosing**

**POD 0-7**
- Lab Monitoring
- Daily CBC, ScR, BUN
- Daily aPTT, PT, INR*, Fibrinogen, Platelet
- Daily assessment for hemolysis: LDH, plasma free HGB, haptoglobin
- TEG with PM

*Note: Bivalirudin falsely elevates INR; discuss with ECMO team if warranted

**Maintenance Lab Monitoring**
- Weekly CBC, ScR, BUN
- Weekly anticoagulation panel (aPTT, PT, INR, fibrinogen)

**Maintenance Bivalirudin titration**
- Standard risk for bleeding: aPTT goal range 60-80
- High risk for thrombosis: aPTT goal range 70-90
- High risk of bleeding: aPTT goal range 50-60

- **aPTT 5 to 15 sec out of range:**
  - ↑ or ↓ by 15% (round to closest 2nd decimal)
  - Recheck aPTT in 4 hours
- **aPTT in target range:**
  - No change, recheck 4 hours, and ↓ frequency of aPTT when stable
- **aPTT >15-30 sec out of range:**
  - ↑ by 25% (round to closest 2nd decimal)
  - Recheck aPTT in 4 hours
- **aPTT > 3x baseline or > 120 sec:**
  - Normal renal function: hold 15 min and ↓30%
  - Mild/moderate renal dysfunction: hold 45 min, ↓40%
  - Severe renal dysfunction: hold 2 hrs, recheck aPTT before restarting, ↓40%

**Additional Consideration**
- May consider a bolus of 0.25-0.5 mg/kg to achieve therapeutic aPTT
- Intermittent hemodialysis
  - Intermittent HD: bivalirudin often requires up titrated 20-30% during dialysis and then returned to baseline dosing afterwards.
  - Achieving therapeutic aPTT with continuous HD may be difficult, and require additional unfractionated heparin run through the MCS circuit and in HD circuit in addition to bivalirudin
- CRRT
  - Drug clearance is dependent on effluent flow rate, filter type, and method of renal replacement.
  - Close monitoring and adverse reactions due to drug accumulation is important.
  - Consult with clinical pharmacist may be beneficial.

**Pharmacotherapy Conversions**
- **Bivalirudin to Warfarin**
  - Initiate therapy of warfarin + daily INR
  - Anticipate overlap of bivalirudin and warfarin for 5 days
  - Discontinue bivalirudin when INR >3.5 AND re-check INR 3 hours following bivalirudin discontinuation
- **Heparin to Bivalirudin**
  - Initiate bivalirudin immediately following UFH discontinuation
- **Bivalirudin to Enoxaparin**
  - Administer enoxaparin following bivalirudin discontinuation
- **Enoxaparin to bivalirudin**
  - Initiate bivalirudin > 8 hours following last dose of enoxaparin, depending on enoxaparin dosing frequency

Source: ACTION Network
Disclaimer

Clinical Pathways are intended to assist physicians, physician assistants, nurse practitioners and other health care providers in clinical decision-making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. The ultimate judgment regarding care of a particular patient must be made by the physician in light of the individual circumstances presented by the patient.

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