

Direct Thrombin Inhibitor (DTI) Harmonization Protocol for VADs

BACKGROUND

Bivalirudin is a direct thrombin inhibitor (DTI). It does not require AT3 for activity. Onset occurs in 2 minutes when given by continuous infusion, with half-life of 26 minutes with normal renal function, and up to 4 hours in severe renal failure. Titration can be done using multiple assays, but has most commonly been performed with aPTT. Steady state requires 4 hours.

ACTION REVISED DATE: 04/24/2020

BIVALIRUDIN

1. Pre-VAD implantation work-up (<48 hours pre VAD/MCS):

- Baseline labs: CBC with diff, aPTT*, PT/INR, fibrinogen, basic metabolic panel (BMP)
- Optional labs: TEG with PM, CRP, LDH, cystatin C, HIT screen, ROTEM

2. Intra-op management

- Standard heparin anticoagulation for cardiopulmonary bypass with full protamine reversal in OR
- Standard blood product replacement to normalize coagulation parameters and establish hemostasis in OR

3. Early post-op management

- Labs (aPTT, PT/INR, fibrinogen, BMP, CBC) within 2 hours of arrival to ICU
- Optional: dilute thrombin time (dTT), TEG ± PM, ROTEM
- It appears reasonable to start bivalirudin once:
 - Surgical and coagulopathic bleeding resolved (< 2 ml/kg of chest tube output for 4 hours and no other sources of active bleeding)
 - aPTT within 15 sec of baseline* (or institutional normative range)
 - INR <1.3
 - Fibrinogen > 200
 - Platelet count >100,000
- Correct with blood product replacement as needed, being mindful of risk of dilutional coagulopathy with multiple PRBC transfusions, and correct any surgical bleeding as needed

Standard Goals: In order to learn more about what the ideal level of bivalirudin anticoagulation is, suggested standard goals based on national data have been set as a suggestion. This also helps with clarity for teams at the bedside. Not only are their goal

ranges but target PTTs that are central to the range so that patients with a ptt of 61 when the goal is 60-80 will be managed so time within a goal range could possibly be higher.

- **Early Post-op (24-72 hours, high risk for bleeding) target aPTT 55 (goal range 50-60)**
- **Maintenance (standard risk for bleeding) target aPTT 70 (goal range 60-80)**
- **Maintenance (High risk for thrombosis) target aPTT 80(goal range 70-90)**

TABLE 1: Initial Bivalirudin Dosing	
Goal: aPTT	Goal: dilute thrombin time (dTT)
<ul style="list-style-type: none"> • <i>High risk (of bleeding): aPTT 50-60 sec</i> 	<ul style="list-style-type: none"> • <i>High risk (of bleeding): dTT 50-60 sec</i>
Renal function (GFR)	Initial dosing
Normal (>60ml/min/1.73 m2)	0.3 mg/kg/hr IV infusion
Mild-moderate (30-60ml/min/1.73 m2)	0.2 mg/kg/hr IV infusion
Severe (<30ml/min/1.73 m2)	0.1 mg/kg/hr IV infusion

- Check aPTT 2 hours after first initiation. Cautious about titrating with first level.
 - If aPTT has jumped dramatically to >2-3 x baseline PTT, then decrease Bival by 50% and recheck in 2-3 hours
 - If PTT has increased to 1-1.5 x baseline, make no adjustment and repeat PTT in 2-3 hours as level may continue to rise

TABLE 2: Maintenance Bivalirudin titration	
Goal: aPTT	Goal: dTT
<ul style="list-style-type: none"> • <i>Standard risk: aPTT 60-80 sec</i> • <i>High risk (of thrombosis): aPTT 70-90 sec</i> 	<ul style="list-style-type: none"> • <i>Standard risk: dTT 60-80 sec</i> • <i>High risk (of thrombosis): dTT 70-90 sec</i>
If aPTT 5 to 15 sec out of range:	If dTT 5 to 15 sec out of range:
<ul style="list-style-type: none"> • Increase or decrease by 15% (round up to closest 2nd decimal) • Recheck 2-3 hours after dose change 	<ul style="list-style-type: none"> • Increase or decrease by 15% (round up to closest 2nd decimal) • Recheck 2-3 hours after dose change
If aPTT in target range, no change.	If dTT is in target range, no change:
<ul style="list-style-type: none"> • Recheck 2-3 hrs, then can decrease frequency when stable 	<ul style="list-style-type: none"> • Recheck 2-3 hrs, then can decrease frequency when stable
If aPTT ≥15-30 sec out of range	If dTT ≥15-30 sec out of range:
<ul style="list-style-type: none"> • Increase or decrease by 25% (round up to closest 2nd decimal) • Recheck 2-3 hours after dose change 	<ul style="list-style-type: none"> • Increase or decrease by 25% (round up to closest 2nd decimal) • Recheck 2-3 hours after dose change
If aPTT >3x baseline or ~120 sec:	If dTT >100sec:
<ul style="list-style-type: none"> • With <u>normal</u> renal function: hold 15 min and reduce by 30% • With <u>mild to moderate</u> renal dysfunction: hold for 45 min and reduce by 40% • With <u>severe</u> renal dysfunction: hold 2 hours and recheck PTT before restarting 	<ul style="list-style-type: none"> • With <u>normal</u> renal function: hold 15 min and reduce by 30% • With <u>mild to moderate</u> renal dysfunction: hold for 45 min and reduce by 40% • With <u>severe</u> renal dysfunction: hold 2 hours and recheck PTT before restarting

SIMPLE TITRATION RULE: Adjust your bivalirudin infusion the same % as the difference between the current aPTT and goal aPTT you are trying to achieve

Example: Goal aPTT 75, and current aPTT 55 (difference of 20), then go up 20%

NOTE:

- **aPTT may be impacted with the following:**
 - heparin contamination (from line) (↑aPTT)** (can use concomitant anti-XA (HAL) and/or INR/PT to identify contamination, since INR/PT will NOT increase with heparin contamination alone, BUT will increase with bival concentration)
 - traumatic phlebotomy, high pressure exerted on syringe during sampling (↑aPTT)
 - Stasis draw - either from a sluggish IV for a lab that sat in the lab for too long can be falsely low
 - low fibrinogen, low FXII, VIII (>30-40% depletion) (Example: chylous effusion, excessive PD drainage, liver dysfunction, consumption within clot) (↑aPTT)
 - plateau aPTT: may be seen at high concentrations of bivalirudin (>1mg/L), consider using PT/INR and/or dTT, or DTI specific assay ecarin TT(Hemoclot, HemosIL DTI) [Stago, or STA-R Evolution]
- **dTT may be impacted by the following:**
 - heparin contamination (from line) (↑dTT)** (can use concomitant INR/PT to identify contamination, since INR/PT will NOT increase with heparin contamination alone, BUT will increase with bival concentration)
 - fibrinogen levels
 - NOT impacted by lupus inhibitors or elevated d-dimer
 - Stasis draw - either from a sluggish IV for a lab that sat in the lab for too long can be falsely low

ARGATROBAN

- Partial hepatic metabolism: no need to dose based on renal dysfunction
- If your hepatic function changes, then you should re-check your levels and titrate more cautiously
- Half life: 39-51 min, may be prolonged further with hepatic dysfunction

The recommended starting dose of Argatroban is 0.5 mcg/kg/min.

- Titration increments are typically 0.2-0.5 mcg/kg/min with final therapeutic doses typically between 1-5 mcg/kg/min.
- Doses as high as 5-8 mcg/kg/min have been used with the recommended maximum in the adult literature of 10 mcg/kg/min.

TABLE 3: Initial Argatroban Dosing:	
Goal: aPTT <ul style="list-style-type: none"> • <i>High risk (of bleeding): aPTT 50-60 sec</i> 	Goal: dilute thrombin time (dTT) <ul style="list-style-type: none"> • <i>High risk (of bleeding): dTT 50-60 sec</i>
Initial dosing: 0.5 mg/kg/min IV infusion - consider lower dosing if know hepatic dysfunction with baseline elevated INR	

TABLE 4: Maintenance Argatroban titration	
Goal: aPTT <ul style="list-style-type: none"> • <i>Standard risk: aPTT 60-80 sec</i> • <i>High risk (of thrombosis): aPTT 70-90 sec</i> 	Goal: dTT <ul style="list-style-type: none"> • <i>Standard risk: dTT 60-80 sec</i> • <i>High risk (of thrombosis): dTT 70-90 sec</i>
If aPTT 5 to 15 sec out of range: <ul style="list-style-type: none"> • Increase or decrease by 15% (round up to closest 2nd decimal) • Recheck 2-3 hours after dose change 	If dTT 5 to 10 sec out of range: <ul style="list-style-type: none"> • Increase or decrease by 15% (round up to closest 2nd decimal) • Recheck 2-3 hours after dose change
If aPTT in target range, no change. <ul style="list-style-type: none"> • Recheck 2-3 hrs, then daily after 2 consecutive in range values 	If dTT is in target range, no change: <ul style="list-style-type: none"> • Recheck 2-3 hrs, then daily after 2 consecutive in range values
If aPTT ≥15-30 sec out of range <ul style="list-style-type: none"> • Increase or decrease by 25% (round up to closest 2nd decimal) • Recheck 2-3 hours after dose change 	If dTT ≥10-20 sec out of range: <ul style="list-style-type: none"> • Increase or decrease by 25% (round up to closest 2nd decimal) • Recheck 2-3 hours after dose change
If aPTT >3x baseline or ~120 sec: <ul style="list-style-type: none"> • With <u>normal</u> hepatic function: hold 15 min and reduce by 30% • With <u>significant</u> hepatic dysfunction: hold 2 hours and recheck PTT before restarting 	If dTT >100sec: <ul style="list-style-type: none"> • With <u>normal</u> hepatic function: hold 15 min and reduce by 30% • With <u>significant</u> hepatic dysfunction: hold 2 hours and recheck PTT before restarting

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Disclaimer: The ACTION network is focused on quality improvement efforts such as harmonizing best practice protocols, disseminating them among institutions, and helping centers to improve care practices at the local level. This protocol was developed as a consensus tool for pediatric VAD programs. The information in the protocols are based on center practices, individual opinions, experiences, and, where available, published literature. Centers may choose to adapt this protocol to include in their center-specific protocols with reference to ACTION with the understanding that these are meant as guidelines and not standard of care. (Revised: 04/24/2020)