

TITLE: Argatroban Protocol for Extracorporeal Membrane Oxygenation (ECMO)

I. INTRODUCTION

Direct Thrombin Inhibitors (DTI) bind thrombin directly, independent of Antithrombin, making them more reliable in patients with low or fluctuating Antithrombin activity. Additionally, DTIs do not bind to other plasma proteins or cells and as a result are not prone to day to day changes in serum chemistry or cell counts. Therefore, DTIs may provide a more predictable dosing regimen that allows for consistent anticoagulant effect with less bleeding compared to unfractionated heparin (UFH), making them useful in Extracorporeal Life Support (ECLS). DTIs also inhibit both clot-bound and circulating thrombin which can lead to improved efficacy. Finally, DTIs do not cause an immune mediated thrombocytopenia, such as heparin induced thrombocytopenia (HIT). For the reasons discussed above, emerging and expanding clinical experience with the use of DTIs in ECLS is expected in the coming years.

One potential problem, which potentially limits the use of DTIs, more so in cardiopulmonary bypass (CPB) than ECLS, is the lack of a pharmacologic antidote or reversal agent such as protamine in the case of UFH. However, unlike in CPB, the need to reverse anticoagulation during ECLS would rarely occur. If needed, in cases of severe bleeding, given their relatively short half-lives, DTIs can be decreased or discontinued. Three synthetic DTIs, argatroban, bivalirudin and lepirudin, have been used in CPB, ECLS and ventricular assist devices (VAD). Lepirudin is no longer manufactured. Argatroban has been most often cited in ECLS applications.

II. ARGATROBAN

Argatroban is a direct thrombin inhibitor that binds reversibly to both clot-bound and soluble thrombin. The use of Argatroban during ECMO is advised in patients identified with HIT, or where there is a high risk of HIT reoccurrence with sustained re-exposure to heparin. Literature supports the contraindication of heparin re-exposure in patients diagnosed with HIT if they had received heparin within the last 3-6 months.

Argatroban does not require the co-factor Antithrombin III for antithrombotic activity. Argatroban exerts its anticoagulant effects by inhibiting thrombin-catalyzed or -induced reactions, including fibrin formation; activation of coagulation factors V, VIII, and XIII; activation of protein C; and platelet aggregation.

A. Pharmacokinetics [7]

The main route of Argatroban metabolism is hydroxylation and aromatization of the 3-methyltetrahydroquinoline ring in the liver.

The half-life of Argatroban is 39 – 51 minutes

See Precautions for further information on alteration of pharmacokinetics due to hepatic or renal impairment.

1. Medication will be dispensed as:
 - Neonates and Pediatrics
 - i. ≤ 5 kg – 1 mg/mL dispensed in 3 mL syringes
 - ii. > 5 kg – 1 mg/mL dispensed in 50 mL syringes
 - Adults
 - i. 1 mg/mL dispensed in pre-mixed 50 mL vial

B. Dosing and Titration of Argatroban:

1. For Patients with Concerns of HIT:

- i. Priming ECMO Circuit with Argatroban (both initial and subsequent circuits)
 - a. NO HEPARIN to be used if Argatroban is used for priming.
 - b. All of other medications used for priming are unchanged and per ECMO priming protocol.
 - c. Loading dose of Argatroban for ECMO Circuitry is 50 mcg per 750 mL of prime
 - d. Ensure ACT >1000 before connection to patient
- ii. Patient Anticoagulation with Initial Cannulation (Argatroban therapy is to be started 30 minutes prior to initiation of ECMO):
 - a. Bolus Patient with 100 mcg/kg IV
 - b. Then begin Argatroban IV at 2 mcg/kg/min
- iii. Therapeutic Monitoring and Titration of Argatroban:
 - a. Monitor ACT every 12 hours after initiation of infusion. Notify physician if ACT >200
 - b. Monitor aPTT every 4 hours and titrate Argatroban infusion according to Titration Protocol. Maintain aPTT of 60 – 90 seconds
 - c. Follow platelet counts a minimum of every 8 hours

2. For Patients Transitioning From Heparin to Argatroban During ECMO Due to Antithrombin III Deficiency (ATIII Activity $<60\%$ and/or heparin usage >50 units/kg/hr x 12 hours):

- i. Start Argatroban at 2 mcg/kg/min (consider dose adjustment in hepatic impairment, see section D below)
- ii. Discontinue Heparin drip as soon as Argatroban infusion begins
- iii. Monitor patient ACT every 1 hour for 2 hours after Argatroban infusion started and every 12 hours thereafter. Notify physician if ACT >200 .
- iv. Monitor aPTT q 4 hours after Argatroban infusion started and titrate Argatroban infusion according to Titration Protocol. Maintain aPTT of 60 – 90 seconds
- v. Follow platelet counts a minimum of q 8 hours

C. Recommended Titration Protocol:

aPTT (seconds)	STANDARD INFUSION RATE CHANGE	HEPATIC DYSFUNCTION INFUSION RATE
Less than 60	Increase by 0.5 mcg/kg/min	Increase by 0.25 mcg/kg/min
60 to 90	None	None
90 to 110	Hold infusion for 30 minutes Decrease by 0.5 mcg/kg/min	Hold infusion for 30 minutes Decrease by 0.25 mcg/kg/min
110 to 120	Hold infusion for 45 minutes Decrease by 1 mcg/kg/min	Hold infusion for 45 minutes Decrease by 0.5 mcg/kg/min
Greater than 120	Stop infusion Call MD STAT	Stop infusion Call MD STAT

***Target aPTT range may be adjusted per physician discretion based on clinical status**

D. Precautions:

1. Hepatic Impairment: Consider starting at a lower rate of 1 mcg/kg/min in patients with hepatic impairment.[7] Patients with hepatic impairment were not studied in percutaneous coronary intervention (PCI) trials. At a dose of 2.5 mcg/kg/min, hepatic impairment is associated with decreased clearance and increased elimination half-life of argatroban (to 1.9 mL/kg/min and 181 minutes, respectively, for patients with a Child-Pugh score >6).
2. Renal Impairment: No dosage adjustment is necessary in patients with renal dysfunction. The effect of renal disease on the pharmacokinetics of argatroban was studied in 6 subjects with normal renal function (mean Clcr = 95 ± 16 mL/min) and in 18 subjects with mild (mean Clcr = 64±10 mL/min), moderate (mean Clcr = 41 ± 5.8 mL/min), and severe (mean Clcr = 5 ± 7 mL/min) renal impairment. The pharmacokinetics and pharmacodynamics of argatroban at dosages up to 5 mcg/kg/min were not significantly affected by renal function. [7]
3. Argatroban is classified as Pregnancy Category B. [7]

REFERENCES:

1. [Angiomax \(bivalirudin\) Prescribing Information](#) (PDF). The Medicines Company. Archived from [the original](#) (PDF) on April 26, 2012. Retrieved 2 December 2011.
2. *ELSO Anticoagulation Guidelines 2014*. Retrieved 21 September 2016.
3. Ranucci M, Ballotta A, Kandil H, et al. Bivalirudin-based versus conventional heparin anticoagulation for post cardiectomy extracorporeal membrane oxygenation. *Critical Care*. 2011;15(6):R275. doi:10.1186/cc10556.
4. Nemours Alfred I. DuPont Hospital for Children Protocol for Bivalirudin.
5. Ranucci M. Bivalirudin and post-cardiectomy ECMO: A word of caution. *Crit Care*. 2012;16:427–.
6. Jyoti A, Maheshwari A, Daniel E, Motihar A, Bhathiwal RS, Sharma D. Bivalirudin in Venovenous Extracorporeal Membrane Oxygenation. *The Journal of Extra-corporeal Technology*. 2014;46(1):94-97.
7. GlaxoSmithKline product insert. Retrieved 21 September 2016.
8. Oregon Health Sciences University Hospital Cardiopulmonary Bypass Program and Kosair Children's Hospital Argatroban Protocol.
9. Children's Healthcare of Atlanta direct thrombin inhibitor Protocol