

Evaluation of Argatroban Dosing in Critically Ill Patients: Impact of Organ Dysfunction and Extracorporeal Support



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Background and Importance

- Argatroban is a direct thrombin inhibitor used to prevent and treat blood clots, especially in patients with heparin-induced thrombocytopenia (HIT).
- Argatroban should be initiated at ≤ 0.5 mcg/kg/min in critically ill patients (Disease severity / Hepatic dysfunction \rightarrow Argatroban dose \downarrow).¹⁻²⁾
- Critically ill patients may have additional pharmacokinetic alterations from organ dysfunction and extracorporeal support.

Aim and Objectives

- To evaluate the impact of: **1) Organ dysfunction (hepatic, renal)**
2) Extracorporeal support (ECMO, CRRT) on argatroban dosing requirements in critically ill patients
- To assess the appropriateness of the argatroban dosing protocol

Materials and Methods

Study Design

- Retrospective, single-center observational study
- Study period: Jan 2015–Dec 2024
- ICU patients receiving argatroban ≥ 24 hours

Study Definitions

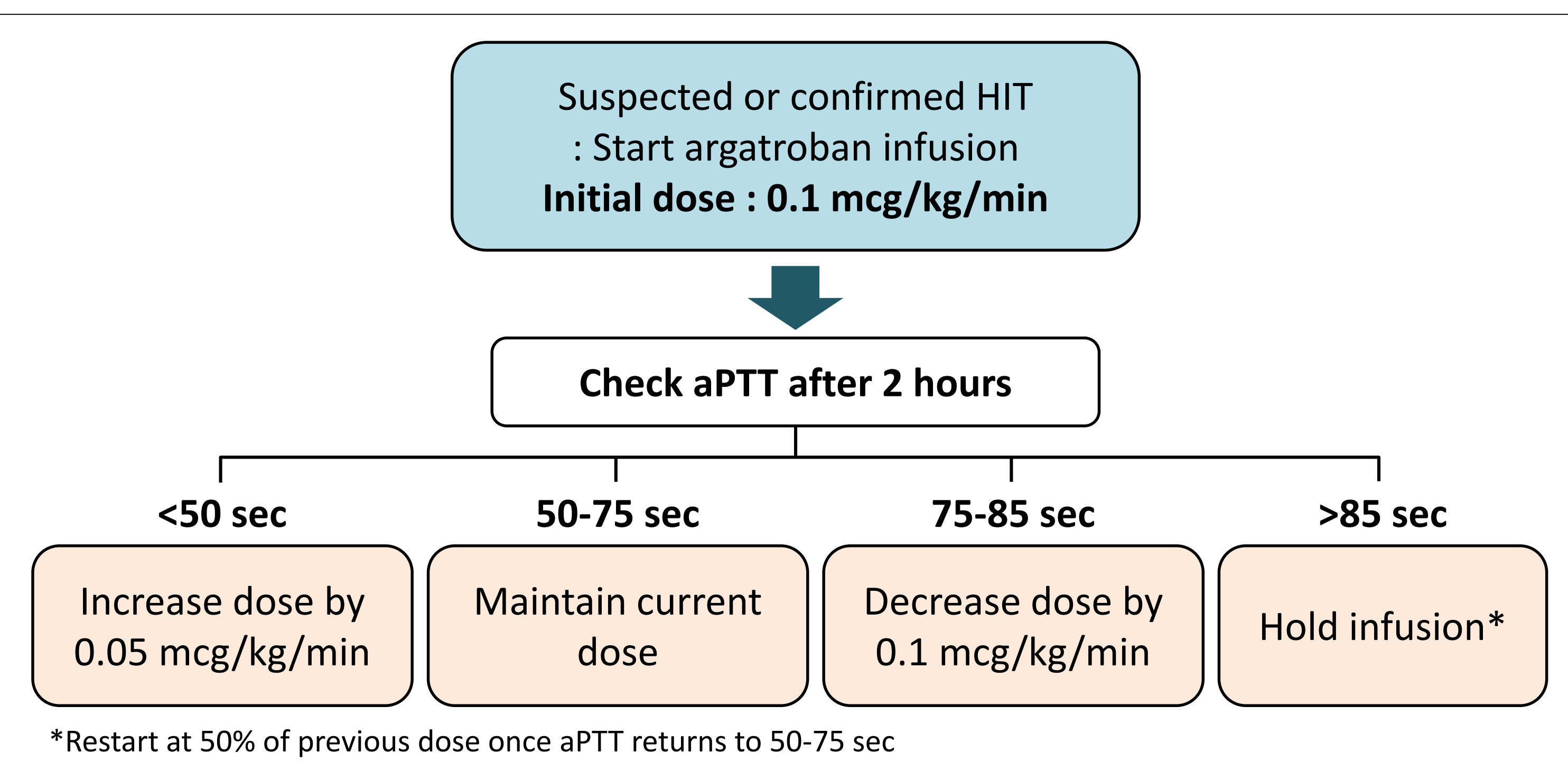
Hepatic dysfunction: AST/ALT ≥ 120 IU/L or total bilirubin ≥ 2 mg/dL or INR ≥ 1.7

Renal dysfunction: SCr ≥ 1.5 mg/dL or eGFR < 60 ml/min or CRRT support

Statistical Analysis

- Mann–Whitney test: Group comparisons of argatroban doses and aPTTs
- Multiple linear regression: Predictors of mean argatroban dose
- The institutional argatroban dosing protocol is shown in Figure 1.

Figure 1. Institutional argatroban dosing protocol used in the ICU.



Results

1. Patient Characteristics (Table 1)

A total of **46 critically ill patients** receiving argatroban were included.

Table 1. Baseline patient characteristics

Characteristic (Total n=46)	mean \pm SD	median (IQR)
APACHE II score	22.7 \pm 8.21	22 (16-28)
SOFA score	9.43 \pm 4.23	10 (5.75-12.25)
Child-Pugh score, n(%)		
Class A		4 (8)
Class B		39 (84)
Class C		3 (6)
ECMO, n(%)		33 (71)
CRRT, n(%)		18 (39)

2. Argatroban Therapy (Table 2)

Table 2. Argatroban dosing and monitoring

Characteristics	Total (n=46)
Argatroban doses (mcg/kg/min)	
Initial dose	0.19 \pm 0.28
First therapeutic dose ^a	0.32 \pm 0.32
Second therapeutic dose ^b	0.38 \pm 0.42
Mean dose	0.35 \pm 0.38
First aPTT (s)	45.8 \pm 15.3
First therapeutic aPTT (s)	52.5 \pm 7.78
Second therapeutic aPTT (s)	56.8 \pm 9.53
Mean aPTT (s)	53.9 \pm 10.9

a. First therapeutic dose : the argatroban dose at the first target aPTT

b. Second therapeutic dose : the argatroban dose at two consecutive target aPTT

3. Impact of Organ Dysfunction and Extracorporeal Support

- Hepatic dysfunction: Significantly lower therapeutic dose (0.27 vs 0.55 mcg/kg/min, $p < 0.05$)
- Renal dysfunction, ECMO, CRRT: No significant difference in dosing
- Child-Pugh score independently predicted mean dose ($p < 0.01$) (Table 3).

Table 3. Multiple linear regression analysis of mean argatroban dose

	β	SE	p-value
Age (yr)	-0.001	0.004	0.834
APACHE II score	0.010	0.011	0.350
SOFA score	-0.028	0.02	0.161
Total bilirubin (mg/dL)	0.001	0.014	0.971
Child-Pugh score	-0.147	0.06	0.018
Serum creatinine (mg/dL)	0.143	0.099	0.157

4. Safety Outcomes (Table 4)

- ECMO support was associated with higher bleeding incidence ($p < 0.05$).

Table 4. Safety outcomes in patients without ECMO or with ECMO support

Outcome	Total (n=46)	Non-ECMO (n=13)	ECMO (n=33)	p-value
Bleeding events, n(%)	22 (48)	3 (23)	19 (58)	0.037
Thrombotic events, n(%)	13 (28)	3 (23)	10 (30)	0.628

Conclusion and Relevance

Study Outcomes

- Hepatic dysfunction appears to influence dosing requirements more than extracorporeal support (ECMO, CRRT).
- ECMO patients may require closer monitoring to minimize bleeding.
- Individualized target aPTT, based on baseline coagulation status and clinical conditions, is essential for optimal anticoagulation.

Further research is needed to validate dosing strategies and standardize protocols in patients receiving extracorporeal support.

References

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- Dingman JS, Smith ZR, Coba VE, Peters MA, To L. Argatroban dosing requirements in extracorporeal life support and other critically ill populations. Thromb Res. 2020;189:69-76.

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