Argatroban anticoagulation for adult Extracorporeal Membrane Oxygenation: A systematic review

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Abstract

Background: Extracorporeal Membrane Oxygenation (ECMO) is an established method of circulatory support in critically ill patients. Heparin is the widely used anti-coagulation treatment for patients on ECMO in view of its features. Nevertheless, heparin-induced thrombocytopenia (HIT) and acquired anti-thrombin III (AT-III) deficiency may lead to sub-therapeutic anticoagulation with potentially serious consequences. Direct thrombin inhibitors are being proposed as potential alternatives with argatroban and bivalirudin as main agents. We aimed to review the evidence supporting the effectiveness and safety of argatroban as a potential definitive alternative to heparin in the adult patient population undergoing ECMO support.

Methods: A web based systematic literature search was performed in Medline (PubMed) and Embase from inception until June 18th 2020.

Results: The search identified 13 publications relevant to the target (4 cohort studies and 9 case series). Case reports and case series with less than 3 cases were not included in the qualitative synthesis. The aggregate number of argatroban treated patients on Extra Corporeal Life Support (ECLS) was n = 317. In the majority of studies argatroban was used as a continuous infusion without loading dose. Starting doses on ECMO varied between 0.05 and 2 µg/kg/min and were titrated to achieve the chosen therapeutic target range. The activated partial thormboplastin time (aPTT) was the anticoagulation parameter used for monitoring purposes in most studies, whereas some utilized the activated clotting time (ACT). Optimal therapeutic targets varied between 43-70 to 60-100 seconds for aPTT and 150-210 to 180-230 seconds for ACT. Bleeding and thromboembolic complication rates were comparable to patients treated with unfractionated heparin (UFH).

Conclusions: Argatroban infusion rates and anticoagulation target ranges showed substantial variations. The rational for divergent dosing and monitoring approaches are discussed in this paper. Argatroban appears to be a safe and viable alternative to UFH in patients requiring ECLS. To establish an ideal dosing strategy, larger prospective studies on well-defined patient populations are warranted.

Background

Extracorporeal Membrane Oxygenation (ECMO) is an established method of circulatory support in critically ill patients. Veno-arterial (V-A) ECMO is appropriate in the context of cardiac failure. Veno-venous (V-V) ECMO is the intervention of choice for acute hypoxic and hypercapnic respiratory failure or so called Acute Respiratory Distress Syndrome (ARDS) [1, 2].

Unfractionated heparin (UFH) is the widely used anti-coagulation treatment for patients on ECMO in view of its features. It is easy to use; it has a short half-life; it can be monitored and it can, if necessary, be reversed with protamine.

Nevertheless, heparin-induced thrombocytopenia (HIT) and acquired anti-thrombin III deficiency may lead to sub-therapeutic anticoagulation with potentially devastating consequences.

HIT is secondary to either a non-immune mediated response (type 1) or an immune-mediated response (type 2) generating IgG antibodies against complexes between heparin and platelet factor 4 (PF4). The IgG-PF4 complex binds to platelets causing their activation with thrombus formation in the arterial and venous circulation. The development of significant thrombocytopenia should raise suspicion although the diagnosis is often challenged by other potential causes such as sepsis [3]. Recent reviews have focused on the pathophysiology of HIT and coagulation management of patients undergoing mechanical circulatory support (MCS) [4-8]. A recent paper has addressed current and future developments in surface modifications to improve haemocompatibility and replication of the anti-thrombotic and anti-inflammatory properties of the endothelium with a view to reduce or even avoid systemic anticoagulation during ECMO [9]. Thought provoking and controversial is the even more recent proposal for V-A ECMO support without routine anticoagulation [10]. Although appealing, this prospect remains not preferable at present. Therefore, the focus on alternative anticoagulant agents may well be justified.

Direct thrombin inhibitors are being proposed as potential alternatives [11, 12] with argatroban and bivalirudin as main agents [3, 13-16]. In this paper we aimed to review the evidence supporting the effectiveness and safety of argatroban as a potential definitive alternative to heparin in the adult patient population undergoing ECMO support.

Methods

Design

We have used the PICOS approach (Participants, Intervention, Comparison, Outcome and Study Design) for the selection of clinical studies following our systematic search (Table 1). To ensure clarity and transparency, the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) system has also been utilized through the screening process [17] (Figure 1).

Table 1 “PICOS” approach for the selection of studies in the systematic search process

PICOS	
1 Participants	Patients on Extracorporeal membrane oxygenation (both veno-venous and veno-aterial)
2 Intervention	Anticoagulation with Argatroban
3 Comparison	Comparison with Heparin anticoagulation if available
4 Outcomes	Optimal dosing of Argatroban,, anticoagulation related complications
5 Study design	Prospective and retrospective clinical studies, case series

Search

A web based systematic literature search was conducted in Medline (PubMed) and Embase from inception until June 18th 2020. The search strategy was developed and carried out with the help of an experienced librarian at the Karolinska Institutet University Library. It included free text terms and controlled vocabulary (MeSH and Emtree). The following free text terms were interrogated: Argatroban and ECMO or Extracorporeal Membrane Oxygenation or ECLS or Extra Corporeal Life Support or Extra Corporeal Oxygenation or Extra Corporeal Pump Oxygenation or Extra Pulmonary Oxygenation. For full documentation of search strategies, see Appendix [Supplementary Tables 1 and 2].

The search strategy was limited to clinical studies. Study selection to determine eligibility for inclusion in the systematic review and data extraction were performed independently by the three authors. Discordances were addressed by consensus. Language restriction was not applied. Book chapters, reviews, clinical guidelines, editorials and letters to the editor were excluded. Reports on paediatric patients and case reports with less than three cases were not included in the qualitative synthesis. However, for each case report relevant to the subject, the full text was reviewed and contextually integrated in the discussion part of the review. Studies integrated in the qualitative synthesis were also assessed for risk of bias by the three authors (Figure 2).

Data analysis

Our search strategy identified a total of 207 publications as follows: 163 in EMBASE and 44 in Medline (PubMed). 37 duplicates were discarded through automated software and one was removed manually [18] leaving 169 publications for further screening (Figure 1).

During the initial screening process, 109 articles were excluded because they were deemed not relevant to the subject of our review (n=93) or for their design (n=16). Assessment of the remaining 60 full text publications identified further 47 items that were excluded for the following reasons: lack of valuable information (n=12), study design (n=3), case reports and case series with less than three cases (n=23) or studies on paediatric patients (n=9). Finally 13 studies qualified for inclusion in the qualitative synthesis. Type of the included studies is as follows: 9 retrospective case series, 4 retrospective cohort studies.

Results

Aggregate patient population from the analysed publications revealed a total of 1174 patients on ECLS. The type of ECLS support was as follows: V-A ECMO (n=655), V-V ECMO (n=479), combination of V-V and V-A ECMO (n=4), V-V ECMO + Extracorporeal Lung Assist (ECLA) (n=11), ECLA (n= 24), Tandem heart (n=1). A total of 317 ECLS patients received argatroban therapy. Of these 307 were supported by ECMO.

857 patients received anticoagulation with UFH. For the majority of patients the indication for argatroban anticoagulation was HIT or suspected HIT. Four patients were treated with argatroban for heparin resistance [18]. In one study the proportion of patients with HIT vs. heparin resistance was not specified for 26 of the 39 patients in the argatroban treatment group [19]. Thus, the actual number of patients undergoing argatroban anticoagulation for acquired heparin resistance may be higher than four. In addition, in one case series of four patients, argatroban was used in the setting of protamine-heparin complex induced thrombocytopenia [20]. Important outcomes, applied dosages and anticoagulation targets are listed in Table 2.

Table 2 Grading of manuscripts, patient population, argatroban dosing, anticoagulation targets and important outcomes

ACT Activated Clotting Time, aPTT accelerated Partial Thromboplastin Time, CRRT Continuous Renal Replacement Therapy, ECLS Extracorporeal Life Support, HIT Heparin-Induced Thrombocytopenia, VV ECMO Veno-Venous Extracorporeal Membrane Oxygenation, VA ECMO Veno-Arterial Extracorporeal Membrane Oxygenation, ECLA Extra Corporeal Lung Assist, POD Postoperative Day, PRBC Peripheral Red Blood Cells, UFH Unfractionated Heparin, VAD Ventricular Assist Device

Eight studies used aPTT [18-25] one study used ACT [26] and two studies used both parameters [27, 28]. No information was available on the utilized monitoring parameter in two studies [29, 30]. The aPTT target range fell between 43-70 and 60-100 s. For ACT, the utilized target was between 150-210 s and 180-230 s.

The risk of bias assessment of the studies included for qualitative synthesis is represented in Figure 2. Reports without control group [20-23, 26-30] were not evaluated. Four retrospective observational studies [18, 19, 24, 25] were assessed for risk of bias. Given the inherent lack of blinding in this type of studies, selection and performance bias were high throughout. Furthermore, little of no information was reported with regard to data handling precautions undertaken in order to minimize detection, attrition and reporting bias.

Discussion

Blood exposure to the foreign surface of the ECMO circuit generates an inflammatory response with concomitant activation of the coagulation pathway. Bleeding and thromboembolic complications remain critical issues affecting the outcome of patients undergoing MCS. There is significant variability in the need for anticoagulation according to the device used. The selection of drugs and their dosage is related to the type of device, patient-specific factors, length of treatment and the experience of the medical team [6]. Although heparin remains the most widely used anticoagulant, its pharmacokinetics can be unpredictable with a nonlinear and variable effect. Heparin binds to AT III to inactivate factors IIa and Xa, but the complex heparin-AT III will not inhibit thrombin already bound to fibrin making it ineffective against pre-existing clots [7, 8, 12]. AT III deficiency and the onset of HIT during treatment are serious

First Author	Study Design	Patient Population	Dosing and Anticoagulation Targets	Outcomes
Beiderlinden 2007	Case series	VV ECMO (n=9)	argatroban starting dose 2 µg/kg/min (n=1); 0.2 µg /kg/min (n=8) Average maintenance dose 0.15 µg/kg/min. aPTT target 50-60s	Starting dose of 2 µg /kg/min resulted in significant bleeding. Using 0.2 µg/kg/min anticoagulation target was reached within 4 hours (n=7) and after 8 hours (n=1) No significant bleeding / thromboembolism occurred
Cho 2019	Single center, retrospective case control study	Total population (n=35) Group I: argatroban anticoagulation (n=11) (VA ECMO n=4, VV ECMO n=5, combined VV + VA ECMO n=2) Group II: UFH anticoagulation (n=24) (VA ECMO n=6, VV ECMO n=16, combined VV + VA ECMO n=2)	aPTT target 43-85s Bolus 250 µg/kg followed by infusion starting at 0.5 µg/kg/min	Average cost of argatroban treatment per ECMO course is lower compared to UFH anticoagulation (15323 $ vs. 7092 $) The need for AT-III supplementation was the most significant factor accounting for differential costs of treatment argatroban was associated with quicker time to aPTT goal compared to UFH (5 hours vs. 7 hours) and higher percentage of therapeutic aPTTs (62 vs. 54%) no difference between group I and II in terms of bleeding or thrombotic events
Cornell 2007	Case series	VV ECMO (n=2), VA ECMO (n=2), Tandem Heart (n=1)	ACT target 210-230 s Starting dose 0.2-0.98 µg/kg/min. Maximum argatroban dose 0.2-3.5 µg/kg/min. 1 patient monitored aPTT with mean aPTT 44s.	No patient had adverse effects directly attributable to argatroban No ECLS circuit thrombosis detected Good correlation observed between aPTT and ACT values. Average RBC transfusion 77 ml/ kg Average Platelet transfusion 41 ml/kg,

				Average Fresh Frozen Plasma transfusion 4 ml/ kg Argatroban infusion duration 6- 184 h 4 patients survived, one patient died secondary to irreversible cardiopulmonary failure.
Dingman 2019	Single centre retrospective cohort study	80 adult patients from medical, surgical and cardiac ICU. Primary target: assessment of initial argatroban dosing requirements in critically ill patients with and without ECLS Group I: (n=20) (VV ECMO n=10, VA ECMO n=10) Group II: CRRT (n= 20) Group III: no Extracorporeal support n=40	aPTT target 1.5-3 times of baseline value (up to a maximum of 100s). aPTT measured at 2, 6 and 10 hours after commencement of argatroban After 2 consecutive therapeutic values, monitoring interval was switched to q12 h Patients actual body weight was used for dosing (up to 140kg) Starting dose: 0.5 µg/kg/min Dose adjustments done by 25-50% increments	# First therapeutic dose 0.5 µg/kg/min in all 3 groups. No difference between groups in terms of first therapeutic dose, mean therapeutic dose, mean minimum and maximum doses during the treatment period # Numerically lower first therapeutic dose in VA ECMO compared to VV ECMO (0.309 vs. 0.452 µg/kg/min), although statistically not significant (p=0.07). # Significant difference between groups I, II and III in terms of time required for stable aPTT levels at 24, 31, 20 hours, respectively # ECLS group had more frequent supra-therapeutic aPTT values and required more frequent dose adjustments # Moderate inverse correlation between first therapeutic dose and modified SOFA score # Significant bleeding event in 8/20 patients on ECLS, 2/20

				patients on CRRT and 4/40 patients on no extracorporeal support. # ECLS group: circuit clotting (n=2); stroke (n=2). No thrombotic complications in groups II and III.
Felli 2013 (conference abstract)	Case series	3 adult cardiothoracic patients on VA ECMO receiving LVAD as a bridge to heart transplant. All three patients received argatroban due to HIT.	aPTT target 60-80s starting dose: 0.05 µg/kg/min and adjusted hourly at 0.04 µg/kg/min increments. For LVAD implantation dose was adjusted to achieve a target ACT of 280-300s	Lower than the generally recommended doses are sufficient for critically ill VA ECMO patients Targets were reached within 3-5 hours.
Hillebrand 2015	Single centre retrospective case series	VA ECMO (n=7) as bridge to LVAD secondary to cardiogenic shock Argatroban treatment secondary to HIT	Starting dose 2 mg/ h (with subsequent titration) aPTT target 70-80s Intraoperative aPTT target 70-80s. Post LVAD implantation Argatroban infusion dose 0-0.7µg/kg/min (One patient developed intracardiac thrombosis requiring LVAD removal and continuation of ECMO support. Argatroban dose in this patient was 0.2-2 µg/kg/min	Mean ECMO duration prior to LVAD implantation 10.4 days. Four patients survived, two patients died due to sepsis. One patient died secondary to uncontrollable intravascular thrombosis and MOF. 4 patients required re-exploration for bleeding. No neurologic deficits detected Anticoagulation (argatroban dosage and aPTT target) stabilized after POD#2. After POD#3, argatroban was switched to warfarin + acetyl salicylic acid
Kim 2018	Retrospective single centre case series	VA ECMO (n=5) VV ECMO (n=5) Argatroban treatment secondary to suspected HIT	Average initial dose 0.175 µg/kg/min Average maintenance dose 0.1 µg/kg/min Dose adjusted at 0.05-0.1 µg/kg/min	No significant bleeding or thrombotic complications Average duration of Argatroban treatment 8.5 days 60% ICU mortality

			increments to reach target ACT target 150-180s aPTT target 55-75s.	
Lubnow 2019	Retrospective single centre case series	507 ECMO cases (VV n=331, VA n=176) Group I (n=81) argatroban anticoagulation due to unexplained thrombocytopenia Group Ia: (n=16) confirmed HIT Group Ib: (n=10) argatroban continued due to suspicion of HIT Group Ic: (n=55) HIT excluded by laboratory testing and UFH resumed Group II (n=426) UFH anticoagulation	No information on argatroban dosing or anticoagulation target range	-No difference with regard to ICU length of stay and mortality between group I and II -No difference in functional outcome expressed by CPC scale between group I and II -Higher bleeding rate in patients who received argatroban despite similar aPTT values. (HIT 38%, HIT suspicion 30%, HIT excluded 30%) control group 22%. -No difference in thrombotic complications
Menk 2017	Retrospective single centre case control	Two matched groups, both on VV ECMO / ECLA secondary to ARDS Group I (n=39) anticoagulated with argatroban (due to HIT or Heparin resistance) (ECMO n=24, ECLA n=9, ECMO + ECLA n=6) Group II (n=39) anticoagulated with UFH (ECMO n=19, ECLA n=15 ECMO + ECLA n=5)	aPTT goal 50-75s argatroban starting dose 0.3 µg/kg/min Average maintenance dose 0.26 µg/kg/min.	No difference in bleeding and transfusion requirements between group I and II Although there was no statistical correlation between aPTT and bleeding risk, more than 2/3 of bleeding events were associated with a maximum aPTT >75s No difference between groups with regard to thromboembolic complications and frequency of circuit clotting Although no statistical correlation was found between aPTT and thromboembolic risk, almost all thromboembolic events were associated with aPTT values <50s. Argatroban dosage control:

				-more dose adjustments (repeated aPTT measurements) were needed in the argatroban group during the first two days of treatment (usually dose reduction). -argatroban doses tended to stabilize after the first few days -UFH anticoagulation was more frequently sub-therapeutic compared to argatroban. -dosing stability was less pronounced over time compared to argatroban
Neissen 2019	Retrospective case series argatroban group n=59	Total population (n=200) (43 VV ECMO, 157 urgent or emergent VA ECMO) Group I (n=59): argatroban anticoagulation due to proven HIT (n=23) , suspected HIT (n=36) Group II: UFH anticoagulation (n=141)	No information on dosing Mean aPTT Group I: 58.4 ± 1.4 s Group II: 62.1 ± 1.6 s Mean ACT Group I: 162.9 ± 4.8 s Group II: 158 ± 5.9 s	No difference between group I and II with regard to length of hospital stay, 30 day and 1 year survival No patient thromboembolic complications Bleeding was higher in thrombocytopenia and less after argatroban administration Sub-therapeutic anticoagulation values were more frequent in HIT patients compared to UFH group No difference between UFH and argatroban with regard to mean aPTT and ACT
Patel 2015	Single centre retrospective case series	Total population (n=19) Group I (n=6): argatroban treatment due to suspected HIT (VV ECMO n=5, VA ECMO n=1). Group II (n=13): UFH anticoagulation (VV ECMO n=10, VA ECMO n=3)	No information on dosing or anticoagulation dose range	No difference between groups with regard to RBC and platelet transfusion requirements
Wadowski 2017	Single centre retrospective case series	(n=4) Indication for argatroban treatment:	#1 argatroban dose 0.033-0.753 µg/kg/min	#1 No bleeding events, patient survived

		protamine-heparin complex induced thrombocytopenia #1 33-year-old patient post MI, on VA ECMO as bridge to LVAD. #2 54-year-old patient after heart transplant secondary to ischemic cardiomyopathy #3 64-year-old patient after heart transplant requiring VA ECMO because of early graft rejection #4 54-year-old patient after heart transplant requiring VA ECMO due to early graft rejection (previous HIT history)	#2 0.026-0.061 µg/kg/min #3 0.005-0.05 µg/kg/min #4 0.001-0.778 µg/kg/min aPTT target 60s	# 2 No major events, patient survived # 3 developed thrombosis in femoral artery and in ECMO pump. The clinical course was complicated by several bleeding events and sepsis. Patient died # 4 developed bilateral Jugular and femoral vein thrombosis as well as rectal bleeding. Patient survived
Welp 2018	Retrospective cohort study n=68 ECMO runs with argatroban	Total population (n=277 patients, 298 ECMO runs) post cardiotomy VA ECMO. Group I (n=230 ECMO runs): only UFH anticoagulation Group II (n=16 ECMO runs) only argatroban anticoagulation (due to HIT) Group3 (n=52) UFH switched to argatroban (due to HIT)	aPTT target: 60-80s	Length of UFH exposure is an independent risk factor for thromboembolic complications Lowest incidence of thromboembolic complications in group II Lower incidence of bleeding in group II Length of ECLS is a risk factor for bleeding

events, which affect outcome. Although it is argued that the incidence of HIT in ECMO patients is low [31], its consequences are significant. Patients on V-A ECMO are more likely to experience severe thrombocytopenia and arterial thromboembolism; those on V-V ECMO are more likely to require device or circuit exchange due to oxygenator thromboembolism [32]. Direct thrombin inhibitors (DTIs) have received significant attention in recent years with preference towards argatroban and bivalirudin [11, 12, 33]. Bivalirudin has a half life of approximately 25 minutes, which may be a limitation in areas of blood stagnation, especially during V-A ECMO with non-pulsatile flow [34]. Instead argatroban has a half-life of approximately 45 minutes, which makes it a better candidate as an alternative anticoagulant agent. Furthermore, its pharmacokinetic profile does not appear to be significantly affected by age or gender [35].

Argatroban and liver function

Argatroban undergoes liver dependent metabolism with four different metabolites, one of which possesses approximately 30% of the parent compound's activity [36]. Results from *in vitro* observations support the involvement of the hepatic microsomal cytochrome P-450 enzyme: CYP 3A4 and 3A5 in this pathway [37]. Nevertheless, the inhibition of CYP 3A4 and 3A5 did not result in altered argatroban pharmacokinetics in human studies suggesting the involvement of other significant biochemical processes in its hepatic clearance [38]. Critically ill patients often have some degree of liver function impairment, which may have multiple aetiologies, such as decreased cardiac output, redistribution of splanchnic circulation, poor oxygenation, disseminated intravascular coagulation and congestion due to right heart failure. Liver dysfunction is associated with pharmacokinetic changes resulting in a two to three fold half time prolongation for argatroban [35], which necessitates significant dose reductions in such patients. Multiple studies indicate altered pharmacokinetic profile of argatroban in critically ill patients [21, 39-42]. Saugel *et al.* found significantly lower average dose requirements in ICU patients with liver dysfunction compared to those without (0.1 vs. 0.31 μg/kg/min) [41] .

A number of reports assessed the impact of hepatic dysfunction on argatroban dosing requirements in patients on ECLS [21, 43-45]. Dolch *et al.* reported a nearly 100-fold dose reduction (from 1.6 to 0.02 μg/kg/min) in a young lung transplant patient on V-V ECMO and acute liver dysfunction. The dose reduction resulted in target range aPTT levels (aPTT 45-60s) without any increased rate of bleeding or thromboembolic events [43]. Felli *et al.* also used substantially reduced initial infusion rates (starting at 0.05 μg/kg/min) in critically ill ECLS patients [22]. Rouge and colleagues applied a dose reduction, albeit of a lesser degree (from 1 to 0.5 μg/kg/min), necessitated by liver impairment in a patient on V-V ECMO [44].

On the other hand Dingman *et al.* found an inverse correlation between argatroban dose and disease severity, as reflected by the modified SOFA score, in a cohort of 20 ECLS patients [18]. Although most patients had impaired liver function classified as Child Pugh class B, further analysis of serum bilirubin, which is the hepatic component of the modified SOFA score, did not show correlation with argatroban dosing requirements. Beiderlinden and colleagues also assessed the relationship between argatroban dosing and liver dysfunction in a cohort of 9 V-V ECMO patients with hepatic impairment [21]. They measured Indocyanine Green clearance, which is a validated marker of hepatic perfusion and function [46] as well as an independent predictor of mortality in ICU patients [47] . The authors observed no correlation between argatroban dosing and Indocyanine Green clearance [21]. These findings further underline the challenge in obtaining accurate characterization of liver function in the critically ill, by means of trending a single laboratory parameter. Importantly, in the setting of critical illness, hepatic elimination of argatroban may be substantially diminished, even in the face of only moderately altered conventional liver function parameters.

Argatroban and renal function

Renal impairment and the use of continuous renal replacement therapy (CRRT) are very common in patients on ECLS. Renal dysfunction does not significantly alter argatroban clearance [35, 48]. Neither is

its elimination influenced by the use of haemodialysis or CRRT [42, 49]. A recent study reported no differential dosing requirements between ICU patient cohorts on ECLS vs. CRRT [18]. Neither was there any differential dosage requirement revealed between patients receiving various CRRT modalities such as sustained low efficiency dialysis vs. continuous veno-venous hemofiltration) [18].

Anticoagulation targets and monitoring

Most studies utilized aPTT for therapeutic monitoring of argatroban anticoagulation [18-23, 25, 43, 50-53]. On the other hand, some reports used ACT or a combination of ACT and aPTT for the titration of the argatroban effect [26-28, 54-59].

ACT ranges showed substantial variation across the studies included in the qualitative synthesis. Low limits fall between 150-210 s [26, 27] and high limits between 180-230 s [26, 27] (Table 2). In the reviewed literature, a case report by Johnston *et al.* applied the highest upper limit for target ACT of 400 s and noted no bleeding complications [56].

The recommended target aPTT for anticoagulation with DTIs in HIT is 1.5 to 3 times the baseline aPTT value [60, 61]. In the reviewed literature, aPTT target ranges for argatroban in ECMO patients show variations within a relatively wide interval. For studies included in the qualitative synthesis, the lower limit fell between 43-70s [19, 21, 23, 25] and the upper limit between 60 and 100s [18, 20, 21, 25]. In published case reports not included in the qualitative synthesis, the lower limit falls between 45 [43, 55] and 80 s [56] and the higher limit between 60 [20, 21, 43, 52, 54, 57, 58] and 90 s [51, 55, 56, 59]. In summary, most studies appear to target an aPTT corridor in the vicinity of 50-70 s. The optimal target interval may be influenced by various factors such as recent operations, severe thrombocytopenia, the presence of significant bleeding, and recurrent major thromboembolic complications despite target range aPTT. Indeed, a case report by Sin *et al.* demonstrates that a number of distinct target intervals may be applied throughout the treatment course of a single patient, depending on the prevailing clinical circumstances. The authors of this paper used four different aPTT target intervals through the ICU management course of their patient [53].

Menk *et al.* evaluated a cohort of ARDS patients on V-V ECMO or pumpless Extracorporeal Lung Assist (pECLA) receiving argatroban. The authors found no correlation between bleeding and the maximum aPTT value or the number of aPTT values above 75s. Neither was there any difference with regard to mean aPTT between patients with or without bleeding complications. However, two thirds of bleeding events were associated with maximum aPTT values above 75 s. In the same study, the incidence of thromboembolic events was low, though practically all thromboembolic events occurred when minimal aPTT value were below 50 [19]. These observations further support the legitimacy of choosing an aPTT target corridor falling in the range of 50-70 s. With regard to controllability of target range anticoagulation in ECMO patients, Menk and colleagues noted more frequent dose adjustment requirements during the first two days following argatroban therapy initiation compared to UFH. The number of dose adjustments substantially decreased over time for argatroban but less so for UFH. Furthermore, significantly more sub-therapeutic levels were noted in the UFH group [19]. Cho *et al*

observed shorter time to reach aPTT goal in argatroban treated ECMO patients compared to a control group anticoagulated with UFH (5 vs. 7 hours respectively) [25]. They also found a higher percentage of target-range aPTT values in the argatroban treated cohort compared to the control group [25]. These findings suggest that adequate titration of argatroban anticoagulation is not more challenging than anticoagulation using UFH.

Besides argatroban, a number of additional confounders, typically encountered in a critical care setting, may cause aPTT prolongation: haemodilution, alterations in the level of clotting factors, disseminated intravascular coagulation, antiphospholipid antibodies to name only a few. Thus, aPTT values during argatroban therapeutic monitoring should be interpreted with caution and thorough consideration given to the complete clinical picture.

The Ecarin Chromogenic Assay (ECA) is viewed as a highly specific assay for monitoring Direct Thrombin Inhibitors. It has a linear dose response curve rendering it suitable for usage as a proxy measurement of Direct Thrombin Inhibitor drug levels in blood. Seidel *et al.* reported no correlation between aPTT and argatroban levels measured by ECA. In this study, approximately two thirds of patients were found to be in the therapeutic aPTT range (45-85 s) while only 9 % showed target argatroban blood levels by ECA (0.5-1.5 μg/ml), with most patients falling below the therapeutic ECA range [62]. No information was available, whether ECMO was used in this particular cohort. The findings are in agreement with the observation by Smythe *et al.* who reported normal coagulation profile by thromboelastography (TEG) despite aPTT and ACT showing therapeutic range anticoagulation (59 and 240 s, respectively) [59]. These observations may suggest a potential risk for under treatment when using conventional coagulation assays (aPTT, ACT) to guide argatroban therapy. Whether monitoring argatroban effect by ECA would translate to reduced incidence of thromboembolic or bleeding complications remains to be explored.

Dosing

Several reports suggest that the overall level of critical illness, as reflected by various ICU disease severity scores, is an important determinant of argatroban dosing requirements in ICU patients, both with [18] and without [41] ECMO support . This is also consistent with the observations of Begelman *et al.*, who demonstrated a requirement for progressive argatroban dose reduction as the number of failed organ systems increased [39]. Similarly, inverse correlation was shown between argatroban dosing requirements and disease severity scores in patients on ECLS [18].

The reviewed literature suggests that significant dose reductions are needed compared to the manufacturer recommended initial argatroban dose at 2 μg/kg/min. In a series by Beiderlinden *et al.*, the only patient who received an initial dose of 2 μg/kg/min suffered serious haemorrhagic complications resulting in a dose reduction by a factor of 10 in subsequent patients [21]. The majority of case reports and series utilize a starting dose range between 0.1-0.3 μg/kg/min. Loading dose is usually not utilized except for occasional reports [25, 56]. When comparing patients on argatroban with or without ECMO support, Dingman and colleagues found no significant difference in argatroban dosing requirements

[18]. Furthermore, V-A ECMO patients had a numerically lower first therapeutic argatroban dose compared to V-V ECMO patients (0.309 vs. 0.452 µg/kg/min). However, this did not reach the level of statistical significance (p=0.075). The time required reaching anticoagulation target in ECLS patients with argatroban infusion showed significant inter-patient variations ranging from 4 to 20 hours [18, 21, 25]. Variations in patient characteristics, clinical status, and aPTT targets may account for such differences.

Mortality, length of hospital stay, ICU length of stay, and functional outcome

Argatroban is well tolerated over extended periods, with two studies reporting treatment duration exceeding 80 days [43, 45]. To date, argatroban administration has not been directly linked to increased mortality in ECMO patients [19, 25, 28, 29]. In fact, to our knowledge no case report has suggested argatroban treatment as a major culprit for mortality. Length of hospital stay and ICU length of stay appear to be independent of the type of anticoagulation [25, 28, 29]. One report assessed functional outcomes of patients treated with argatroban compared to those managed with UFH and found no difference [29].

Bleeding

Several studies demonstrated no difference in terms of major bleeding episodes [25] or transfusion requirements between ECMO patients with or without argatroban anticoagulation [19, 30]. Kawada *et al.* observed decreased perioperative bleeding in patients undergoing aortic surgery using left heart bypass with argatroban anticoagulation compared to a control group managed on UFH. The authors provided some evidence that suppressed thrombin-dependent thrombocyte activation in the argatroban group could contribute to such differential effect [63]. On the other hand, Lubnow *et al.* reported higher bleeding rate in patients treated at least temporarily with argatroban compared to the ECMO control group managed with UFH [29]. In this context, it is important to point out that argatroban treatment was started on clinical suspicion of HIT. One of the hallmarks of HIT is thrombocytopenia, which in itself may result in increased bleeding risk. Indeed, Neissen and colleagues reported a higher rate of bleeding in patients with thrombocytopenia and lower rates were found after argatroban treatment implementation [28]. Dingman *et al.* noted higher rates of bleeding events and transfusions requirements in argatroban treated patients on ECLS compared to argatroban treated patients without ECLS, which is an expected finding, given the increased rate of haemorrhagic complications associated with the use of ECLS [18] . Some reports note major bleeding episodes in conjunction with argatroban treatment, which occurred in a perioperative context [23, 64] or at dosages substantially higher than the usually applied range in ICU practice [21]. Available data in the literature on reversal of argatroban effect is scarce. Successful reversal of residual argatroban effect-related bleeding using recombinant factor VII concentrate has been described [64]. Taken together, when applied in adequate doses argatroban is not associated with an elevated haemorrhagic risk compared to UFH. Before initiating argatroban anticoagulation, thorough consideration should be given to concomitant factors associated with increased risk of bleeding such as thrombocytopenia, septic coagulopathy and the use of platelet inhibitors.

Patient and circuit thrombosis

Patient thromboembolic complications are an important source of ECMO related morbidity and mortality. Several studies found no difference in the rate of patient related thromboembolic complications in cohorts treated with argatroban versus UFH [19, 25, 28, 29]. Other studies where no statistical comparison could be made to a control group found an overall low incidence of thromboembolic complications [18, 23, 27].

In general, ECMO system clotting with argatroban anticoagulation was uncommon [18, 21, 26]. Menk *et al.* reported no difference with regard to circuit clotting between patients on argatroban vs. UFH anticoagulation, except for a subgroup on pump-less ECLA, where the number of clotting events was higher in the argatroban group. This observation may possibly be explained by low flow states prevalent in pump-less systems [19].

Cost-effectiveness

Cost effectiveness plays a major role when opting for a certain therapeutic modality. A recent retrospective study by Cho and colleagues compared the average cost of ECMO course in a cohort of patients anticoagulated with argatroban vs. UFH [25]. The authors found that despite higher drug cost the ECMO course was more cost-effective in the argatroban group compared to the UFH group (7092 vs. 15323 $). Factors included in the cost analysis were drug cost, blood product costs, and costs associated with laboratory tests. The most significant factor accounting for higher cost in the UFH group was the frequent need for AT-III substitution.

Conclusions

Although heparin remains the most widely used anticoagulant drug, HIT is a known complication of heparin treatment limiting its use in certain clinical situations. Alternatives are available. Argatroban does not require the presence of AT III. It has a favourable pharmacokinetic, pharmacodynamic and safety profile, which has established it as a major drug of choice for alternative anticoagulation in patients with HIT requiring ECLS. Besides it represents a cost effective option. This systematic review presents an analytic synopsis of available clinical studies on argatroban anticoagulation on ECLS dependent patients. Anticoagulation with argatroban in ECLS patients appears a safe and effective method. However, the available studies have relatively limited sample size with an inherent risk of being underpowered to detect differences in various outcomes such as complication rates. Lack of randomized controlled trials and the retrospective nature of the available observational studies is a further limiting factor with regard to susceptibility to bias. Furthermore, when comparing various reports the reader should be mindful of variations in disease severity scores, and applied anticoagulation target ranges, which warrants circumspection when extrapolating data to various patient populations. Given these limitations, adequately powered prospective randomized studies are needed to further corroborate argatroban as the major alternative to heparin in the adult ECLS patient population.

Key messages

- HIT and acquired AT-III deficiency may lead to sub-therapeutic anticoagulation with heparin and potentially devastating consequences.
- Direct thrombin inhibitors such as bivalirudin or argatroban are potential alternatives with increasing popularity.
- Renal dysfunction does not significantly alter argatroban clearance.
- Liver dysfunction is associated with pharmacokinetic changes resulting in a two to three-fold half time prolongation for argatroban.
- The majority of case reports and series utilize a starting dose of argatroban in the range between 0.1-0.3 μg/kg/min without loading dose.
- Argatroban is well tolerated over extended periods and to date has not been directly linked to increased mortality in ECMO patients.
- Argatroban is a cost effective anticoagulation strategy compared to UFH in ECMO patients.

Abbreviations

ALI: Acute lung injury; ARDS: Acute respiratory distress syndrome; ACT: activated clotting time; aPTT: activated partial thromboplastin time; AT-III: anti-thrombin III, CRRT: continuous renal replacement therapy; ECLA: Extracorporeal Lung Assist; ECLS: Extracorporeal life support; ECMO: Extracorporeal membrane oxygenation; ELSO: Extracorporeal Life Support Organization; HIT: heparin-induced thrombocytopenia, IgG: Immunoglobulin G; MCS: mechanical circulatory support; PICOS approach: Participants, Intervention, Comparison, Outcome and Study Design approach; PF4: platelet factor 4; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SOFA score: Sequential Organ Failure Assessment score; UFH: unfractionated heparin, V-V: veno-venous, V-A: veno-arterial.

Declarations

Authors' contributions

JG, MC and MOM participated in conception and design of the study, analysis and interpretation of data, and drafting of the article. DMM performed a critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript. JG* and MC* contributed equally as first authors.

Competing interests

The authors declare that they have no competing interests.

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Figures

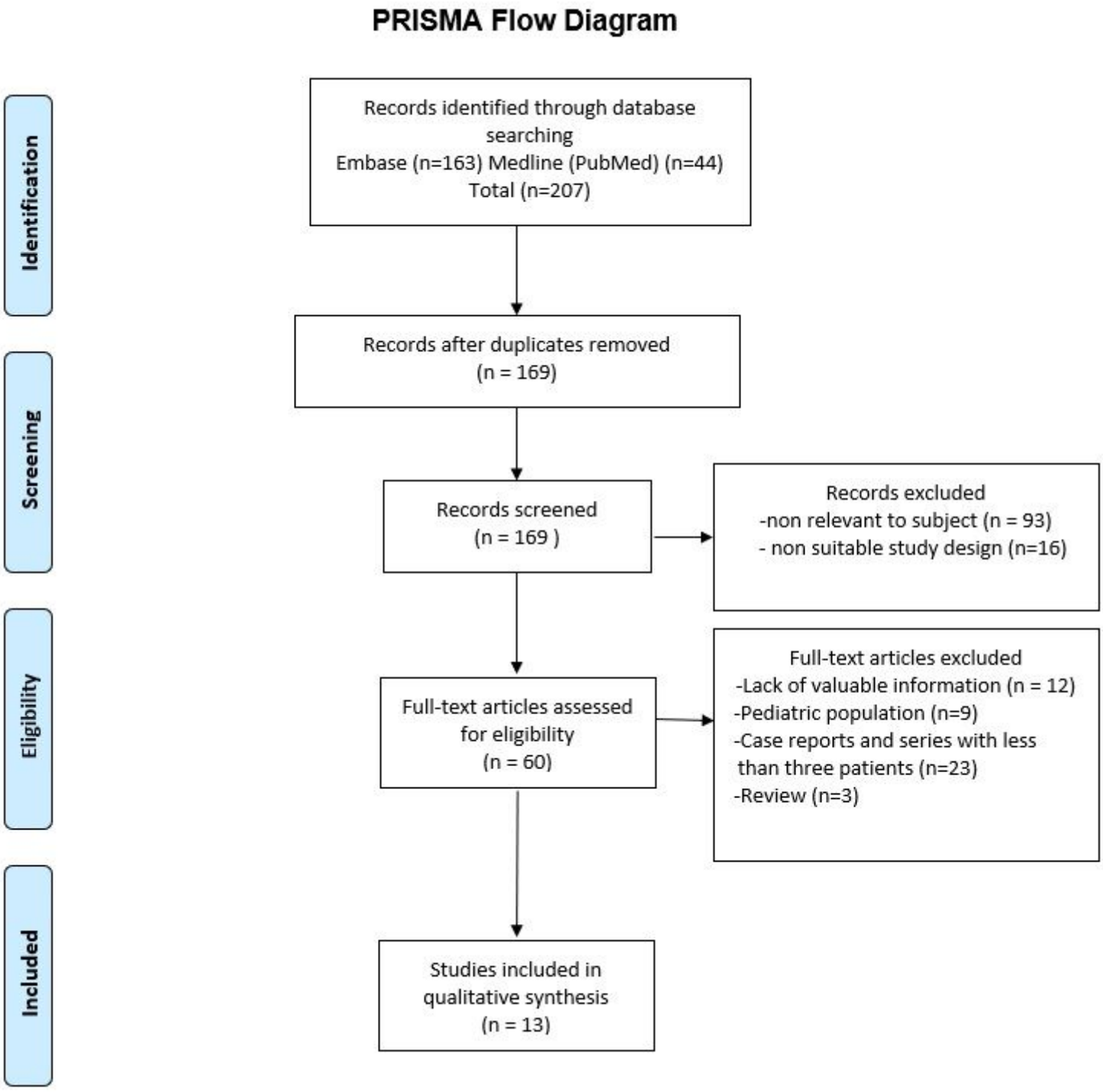

Figure 1

Flow diagram of the systematic search

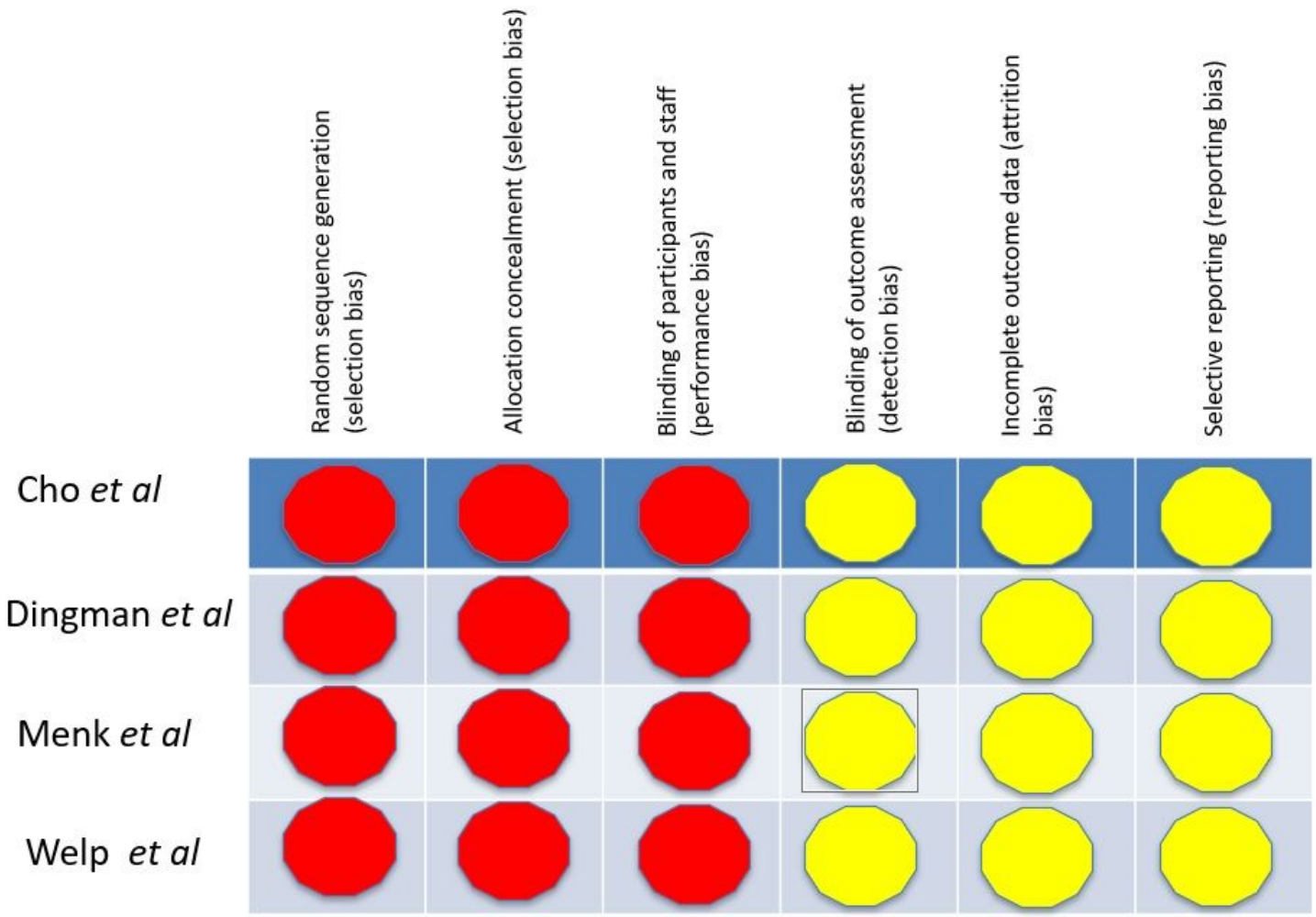

Figure 2

Risk of bias assessment for the studies selected for qualitative synthesis. Studies without control group were not assessed for risk of bias. Red circle: high risk for bias, Yellow circle: insufficient amount of data available for risk of bias assessment

Supplementary Files

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- SupplTable1.docx
- SupplTable2.docx