

# Activated Partial Thromboplastin Time and Anti-IIa Monitoring in Argatroban Anticoagulation in COVID-19 Patients on Venovenous Extracorporeal Membrane Oxygenation

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## Abstract

Unfractionated heparin has long been considered the standard anticoagulation in ECMO, despite some pitfalls such as heparin resistance, heparin induced thrombocytopenia (HIT), etc. Recently, some centres started to increasingly use argatroban for this purpose, typically using activated partial thromboplastin time (aPTT) for its monitoring. Direct monitoring of the efficacy of argatroban using Anti-IIa is not yet an established method, although it might be more appropriate as it targets the same pathway. An observational study was performed in adult veno-venous ECMO patients hospitalized with SARS-CoV-2 infection anticoagulated with argatroban to an aPTT target of 40-60 s and Anti-IIa target of 0.4–0.6 µg/mL. Bleeding and thrombotic complications were monitored. Forty-four VV ECMO patients were included, with an overall hospital mortality of approx. 50%. No life-threatening thrombotic events were recorded. The risk of bleeding complications significantly increased with aPTT above 52.7 s and with Anti-IIa values over 0.78 µg/mL. Using the above cut-offs for both the aPTT and Anti-IIa and their combination, the negative predictive value for bleeding was approximately 90%. It seems that the generally recommended limits for Anti-IIa of 1.5 µg/mL may be high. However, further data are needed to confirm lower limits.

**Trial Registration:** retrospectively registered in ClinicalTrials.gov, NCT06038682.

## Keywords

argatroban, activated partial thromboplastin time (aPTT), extracorporeal oxygenation (ECMO), Anti-IIa, monitoring, anticoagulation

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## Background

Extracorporeal membrane oxygenation (ECMO) is a life-saving method for patients with lung and/or heart failure. Nevertheless, ECMO is associated with significant risks, and the mortality of patients needing this support remains relatively high.<sup>1</sup> Blood in the extracorporeal circuit is in contact with foreign surfaces, which necessitates anticoagulation during the ECMO run. Bleeding greatly complicates patient management and can be life-threatening; however, the same can be said of thrombotic events, of which oxygenator thrombosis is the most serious.<sup>2</sup> Nevertheless, bleeding events are more strongly associated with in-hospital mortality than thrombotic events.<sup>3</sup> Maintaining optimal effective anticoagulation without bleeding complications is a challenging task, and the ideal range of anticoagulation doses can be very narrow. Although unfractionated heparin (UFH) remains the most popular anticoagulant drug, many ECMO centres use novel drugs with potentially better anticoagulation management.<sup>4</sup> Among these drugs, low molecular weight heparin (LMWH) and argatroban (a representative of direct thrombin inhibitors, DTIs) appear to be among the most promising agents for ECMO anticoagulation.<sup>5</sup>

Monitoring of anticoagulant activity is crucial for adequate drug dosage. The activated partial thromboplastin time (aPTT) test is most widely used for the evaluation of anticoagulation (and, therefore, for adjusting the argatroban dose).<sup>6</sup> Although physicians are very familiar with its use, aPTT is not specific for DTIs, reflecting a combined coagulation activity at multiple levels. Besides, it suffers from laboratory interference<sup>7–9</sup> and the results can be distorted in proinflammatory states,<sup>10</sup> outliers of fVIII or fXII or lupus anticoagulant.<sup>5</sup> The Anti-IIa, on the other hand, directly reflects the strength of thrombin blockade, is not influenced by other coagulation disorders<sup>11</sup> and might be more suitable for monitoring DTIs action.<sup>12</sup>

The latest ELSO (extracorporeal life support organization) anticoagulation guidelines were published in 2021.<sup>13</sup> However, it does not specify exactly how to set up and monitor anticoagulation with DTIs. Therefore, DTI anticoagulation needs to be individualized and controlled by a local, center-specific protocol. According to the ISTH (International Society on Thrombosis and Haemostasis), argatroban has some advantages over UFH, but UFH is still considered the first-line anticoagulant in ECMO (in particular due to the lack of robust data for argatroban). The guidelines also suggest many problems with aPTT monitoring of argatroban anticoagulation. ISTH suggests that the Anti-IIa could resolve these issues.<sup>14</sup>

We hypothesise that the Anti-IIa may be a better indicator of argatroban anticoagulant activity than aPTT. However, to our knowledge, there is no study comparing aPTT and Anti-IIa in ECMO patients anticoagulated with argatroban in terms of bleeding/thrombotic risk.

The presented study aimed to: (a) determine the ranges of aPTT and Anti-IIa values indicating lower/higher risk of bleeding complications and, therefore, cut-off values for each of the tests, (b) evaluate the performance of these cut-off values in predicting the occurrence of bleeding events in VVECMO patients.

## Methods

### Study Site and Characteristics

A prospective observational monocentric study was performed at the Intensive Care Department of the University Hospital Ostrava, Czech Republic. The study was approved by the Ethics Committee of the University Hospital Ostrava (reference Number 416/2021), which also waived the need for informed consent. The trial was retrospectively registered in ClinicalTrials.gov, NCT06038682 on September 15, 2023, and complies with The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

### Inclusion and Exclusion Criteria, Protocol of Anticoagulation

Only adult patients hospitalized in the intensive care unit with SARS-CoV-2 infection on veno-venous extracorporeal membrane oxygenation (VV-ECMO) from April 2020 to July 2023 were included. The exclusionary criteria encompassed individuals under the age of 18 and patients not indicated to ECMO support. The patients were anticoagulated with argatroban according to the local ECMO protocol (see the Supplement). ECMO was initiated with a heparin bolus (50–70 U/kg intravenous, plus 5000 U in the priming volume) followed by argatroban (0.3 µg/kg/hour) anticoagulation with aPTT target of 40–60 s and Anti-IIa target of 0.4 to 0.6 µg/mL. The primary goal was to adjust the argatroban dose according to the Anti-IIa level if the patient did not experience bleeding events. If bleeding complications occurred, the anticoagulant dose could be adjusted by the treating physician, taking into account the clinical condition, state of the ECMO circuit, flow rate through the ECMO system and aPTT. If the aPTT was too high and the patient was not bleeding, efforts were made to titrate argatroban to Anti-IIa while diagnosing a plasma coagulopathy disorder, with possible administration of haemostatic agents according to the individual patient's risk to target aPTT values.

### Sample and Data Collection

aPTT was measured four times per day (6, 12, 18, and 24 o'clock), and Anti-IIa was measured twice per day (6 AM and 6 PM). In heavily bleeding patients, coagulation tests

were performed more frequently than every 12 h. Considering each such measurement separately would incorrectly inflate the number of measurements associated with bleeding events. For this reason, we used only the highest test value within each 12-h period.

To determine argatroban dose, Anti-IIa was used as primary guidance; however, aPTT values and the clinical situation (coagulopathy, thrombocytopenia, postoperative status, etc) were taken into account. Demographic data, Anti-IIa and aPTT results, and the presence of bleeding complications and life-threatening oxygenator thromboses were registered. Bleeding complications were evaluated according to the BARC score (Bleeding Academic Research Consortium).<sup>15</sup> The first 12 h of treatment were not included in the study because of the initial heparin exposure. ECMO parameters and circuit blood gases were monitored regularly according to best clinical practice and local ECMO protocol. If, during the oxygenation test, the post-oxygenator PO<sub>2</sub> dropped below approximately 25 kPa, or if low fibrinogen levels were repeatedly measured (below 2 g/L) despite initial fibrinogen supplementation, elective oxygenator exchange was performed. During the bleeding event, best clinical practice was followed by the treating physician and the patient continued to be monitored.

### Laboratory Assays

A chromogenic test INNOVANCE<sup>®</sup> DTI Assay (Siemens Healthcare Diagnostics; Sysmex CS-5100 analyser) was used for Anti-IIa determination. For aPTT measurement, Pathromtin<sup>®</sup> SL (Siemens Healthcare Diagnostics; Sysmex CS-5100 analyser) was used.

### Data Analysis

R software (version 4.2.3) was used for all statistical analyses. Data are presented as medians and interquartile ranges, and demographic variables are presented as absolute and relative frequencies (%). Multiple box plots combined with kernel density plots were used to analyse the associations between aPTT/Anti-IIa and bleeding complications. Further, to identify safety thresholds of both methods, aPTT/Anti-IIa decile categories were constructed and bleeding events assigned to each decile category. The absolute risk (%) and risk ratios of bleeding were calculated. The risk ratios were calculated relative to the category with the lowest absolute risk of bleeding complications. Finally, a combined criterion considering both aPTT and Anti-IIa was created and its diagnostic accuracy in predicting bleeding complications was evaluated.

### Results

Forty-four patients were enrolled in the study. Table 1 describes the basic demographic and outcome parameters of

**Table 1.** Basic and Outcome Parameters of the Study Group.

|                                                 | Median (IQR) or n (%) |
|-------------------------------------------------|-----------------------|
| Total number of patients                        | 44                    |
| APACHE II Score                                 | 33 (14, 44)           |
| Total time on ECMO (h)                          | 24,528                |
| Total number of aPTT measurements               | 5104                  |
| Total number of Anti-IIa Assay measurements     | 2012                  |
| Total number of bleeding events                 | 731                   |
| Total number of non-bleeding periods            | 4415                  |
| Age (years)                                     | 48 (43, 54)           |
| Sex (male)                                      | 29 (65.9)             |
| BMI (kg/m <sup>2</sup> )                        | 31.1 (26.8, 35.9)     |
| Time on ECMO (days)                             | 19 (14, 28)           |
| Hospital mortality (yes)                        | 21 (47.7)             |
| Bleeding-associated mortality (BARC 5b)         | 1 (2.3)               |
| Any occurrence of bleeding complications        | 39 (88.6)             |
| Life-threatening bleeding (BARC 3a)             | 4 (9.1)               |
| Total elective circuit exchanges                | 35                    |
| Hours of ECMO run per elective circuit exchange | 700.8                 |
| Life-threatening oxygenator thromboses (total)  | 0                     |

The values represent the median and the interquartile range (lower and upper quartile) or absolute and relative frequencies (%).

the study group. Despite the relatively low age of these patients (median 48 years) and ECMO support, 47.7% of them died. The majority of the patients were overweight or obese.

In all, 39 (88.6%) patients developed at least one bleeding event. Life-threatening bleeding occurred in 4 (9.1%) patients (BARC 3b), of which one patient (2.3% of all patients) died in direct relation to bleeding complications (BARC 5b). The remaining bleedings were classified as BARC 2 and BARC 3a (external bleeding around the inlets, into the lungs, into the soft tissues around the inlets, etc). In total, there were 4415 bleeding-free periods (ie, 12-h intervals) and 731 bleeding events (Table 2, bleeding event totals), ie, approximately 19 events per patient who experienced bleeding. The first and simplest view on the differences between the occurrence of bleeding complications and Anti-IIa/aPTT results is provided in Figure 1.

The next analysis showed the percentage (absolute risk) of bleeding complications in each aPTT/Anti-IIa category (Figure 2), which gives a clearer picture and allows the calculation of risk ratios to be calculated. Here, we can observe a slow but steady increase in the occurrence of bleeding complications in the higher aPTT deciles, while a U-shaped distribution is observed in the case of the Anti-IIa.

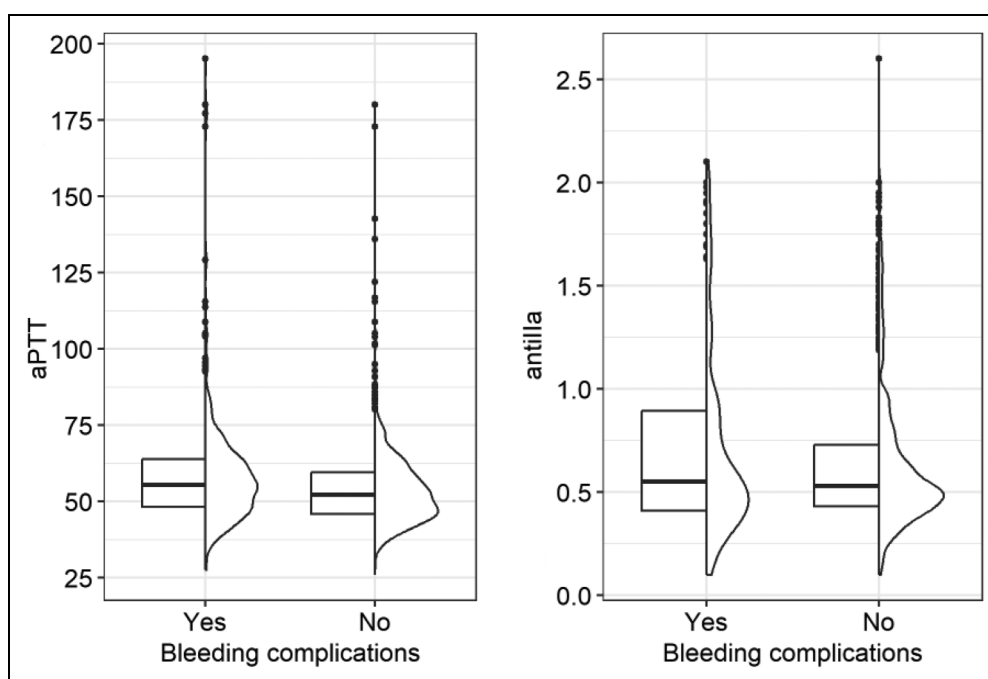
These values were used for the calculation of risk ratios depicted in the forest plot (Figure 3). The risk ratios are calculated relative to the category with the lowest absolute risk of bleeding complications in the given target for

**Table 2.** Diagnostic Performance of aPTT > 52.7 s and Anti-IIa Assay > 0.78 µg/mL.

|                                            | aPTT > 52.7 s     |          | Anti-IIa Assay > 0.78 µg/mL |          | Combined Criterion |          |
|--------------------------------------------|-------------------|----------|-----------------------------|----------|--------------------|----------|
|                                            | Positive          | Negative | Positive                    | Negative | Positive           | Negative |
| <i>Bleeding complications</i>              |                   |          |                             |          |                    |          |
| Yes                                        | 447               | 284      | 228                         | 503      | 487                | 244      |
| No                                         | 1961              | 2454     | 971                         | 3444     | 2258               | 2157     |
| <i>Measures of diagnostic accuracy (%)</i> |                   |          |                             |          |                    |          |
| Accuracy                                   | 56.4 (55.0, 57.7) |          | 71.4 (70.1, 72.6)           |          | 51.4 (50.0, 52.8)  |          |
| Sensitivity                                | 61.1 (57.5, 64.7) |          | 31.2 (27.8, 34.7)           |          | 66.6 (63.1, 70.0)  |          |
| Specificity                                | 55.6 (54.1, 57.1) |          | 78.0 (76.8, 79.2)           |          | 48.9 (47.4, 50.3)  |          |
| Positive predictive value                  | 18.6 (17.0, 20.2) |          | 19.0 (16.8, 21.4)           |          | 17.7 (16.3, 19.2)  |          |
| Negative predictive value                  | 89.6 (88.4, 90.7) |          | 87.3 (86.2, 88.3)           |          | 89.8 (88.6, 91.0)  |          |

Measures are reported with 95% confidence intervals.

Predicting the occurrence of bleeding complications within the next 12 h.

**Figure 1.** aPTT and Anti-IIa Distribution According to Bleeding Complications. The Distribution of aPTT (Seconds, Left) and Anti-IIa (µg/mL, Right) Values According to Bleeding events.

anticoagulation, ie, the third decile for aPTT (42.8–45.3 s) and Anti-IIa (0.40–0.44 µg/ml).

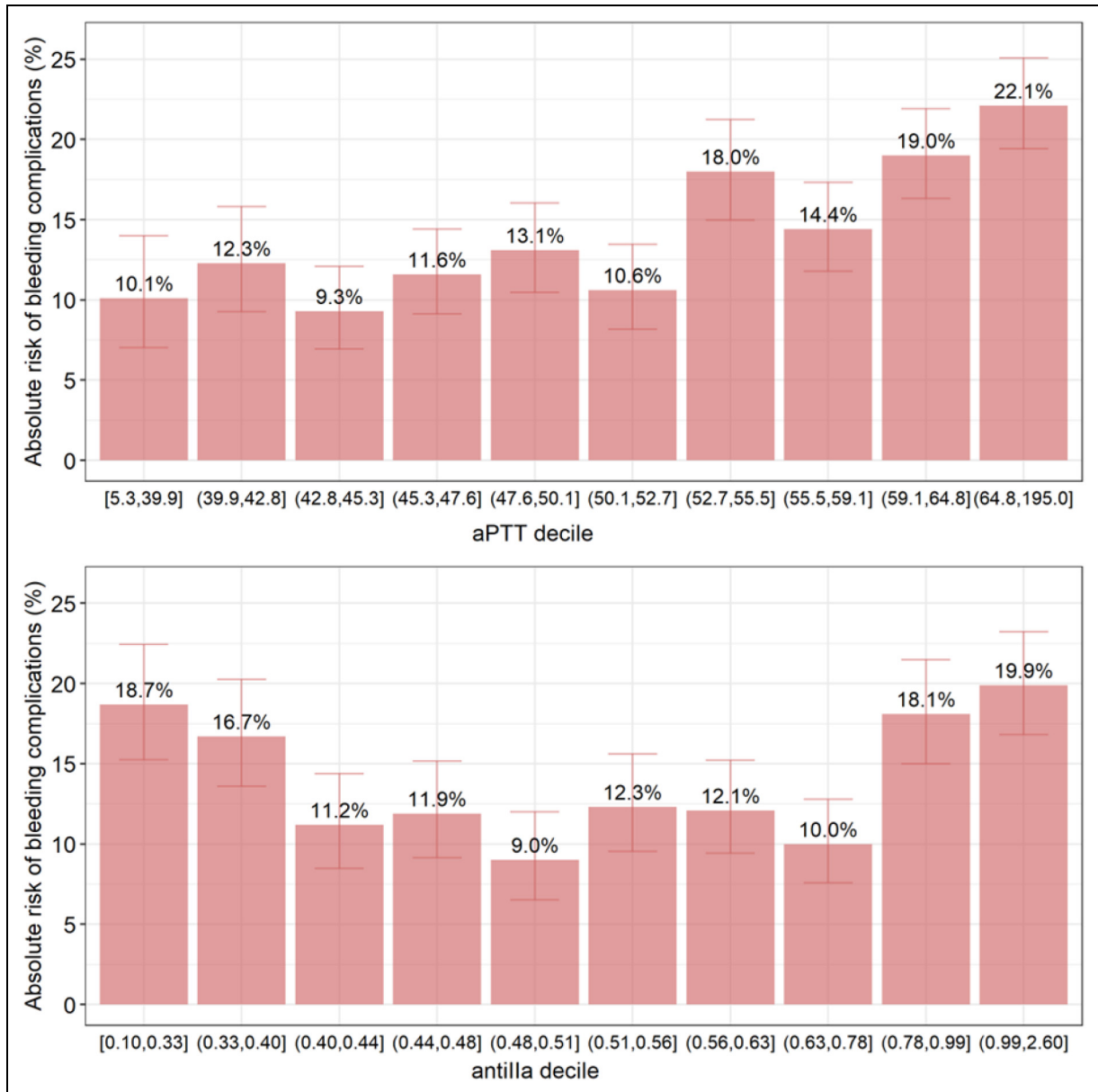
In the case of aPTT, the upper four deciles (ie, values above 52.7 s) were associated with a significantly increased risk of bleeding complications. In the case of Anti-IIa, the situation is somewhat more complicated, as a U-shaped trend can be observed (bleeding in the first two deciles is very likely due to other causes of bleeding, not argatroban; see comments in the Discussion).

Contingency tables and measures of diagnostic performance of both tests separately and in combination with the given detected cut-off values are presented in Table 2. The sensitivity of both aPTT and Anti-IIa using

these cut-offs is low, and the same is true for their combination. The only value that can be considered clinically relevant is the negative predictive value of approx. 90% for all these tests. This result indicates that (at a bleeding prevalence of 14.2%), we can predict that if Anti-IIa, aPTT or both are outside these high-risk deciles, the likelihood that the patient will be free of bleeding complications in the next 12 h is almost 90%.

## Discussion

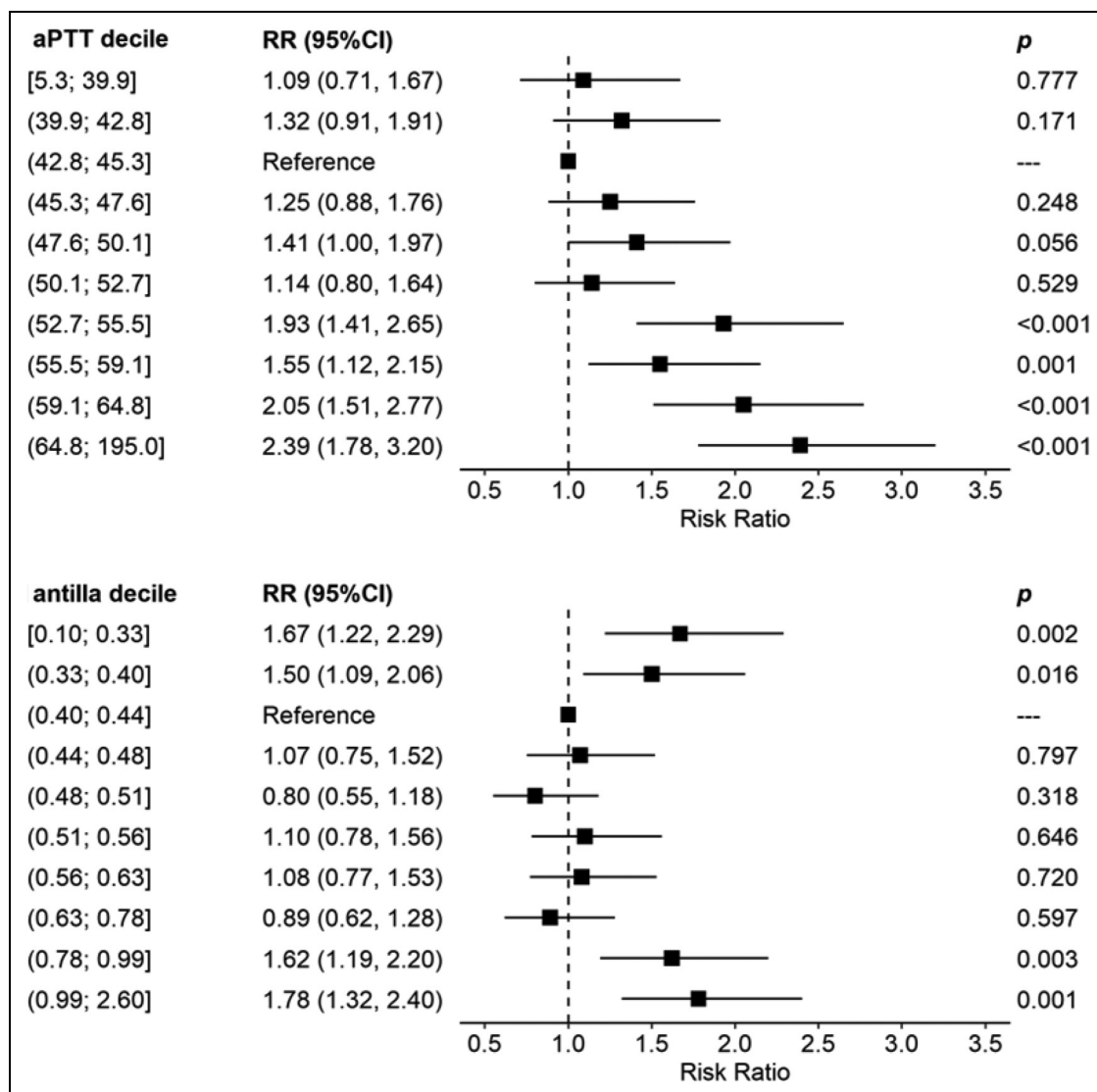
This study aimed to find the safest range (and, therefore, cut-off values) of aPTT and Anti-IIa in argatroban



**Figure 2.** The Absolute risks of the Occurrence of Bleeding Complications in Individual Categories. Deciles are Shown for aPTT (Seconds, Top) and Anti-IIa (µg/mL, bottom). The Whiskers Indicate the 95% Confidence Intervals of the Absolute Risks Determined Using the Clopper-Pearson Method.

anticoagulation during ECMO and the predictive performance of thus identified cut-off values for the risk of bleeding complications. To achieve a homogeneous study population, only patients with SARS-CoV-2 were included in the study, as this disease affects (among other processes) coagulation. The risk of bleeding increases with aPTT above 52.7 s, indicating that the target for aPTT should be closer to 50 s than 60 s as recommended in the guidelines. Similarly, the guideline-recommended Anti-IIa target of up to 1.5 µg/mL also appears very high as we observed an increase in bleeding risk above 0.78 µg/mL.

Clinically, the goal of anticoagulant treatment and monitoring is not to achieve an extra strong blockade of a particular coagulation factor but to achieve an uncomplicated ECMO run. If a patient has a thrombophilic condition or has been diagnosed with venous thrombosis, it is essential to take an individualized approach to anticoagulation treatment and, for example, target a higher anticoagulation level than typically used in standard ECMO procedures. At present, although there are recommendations for ECMO anticoagulation,<sup>13</sup> no strict formal guidelines on monitoring anticoagulation in ECMO patients are in place and the practice is usually guided by centre-specific protocols.



**Figure 3.** Forest Plots Indicating the Risk Ratios of Bleeding Complications. Deciles were Used for aPTT (Seconds, Top) and Anti-IIa ( $\mu\text{g/mL}$ , Bottom) Containing the Low Cut-off of the Target Range as a Reference.

aPTT was originally developed to monitor UFH but, due to its wide availability, it has also become a standard monitoring method for DTIs.<sup>16</sup> Values of approximately 60 to 80 s were previously recommended for ECMO; however, lower values of approximately 40 to 60 s were suggested to be safer.<sup>17</sup> aPTT is affected by multiple factors, particularly in proinflammatory conditions; they can be also inaccurate when levels of fibrinogen or fVIII drop.<sup>10</sup> False aPTT prolongation could be caused by hemolysis, hepatic failure, high plasma triacylglycerides, hemodilution, high levels of fibrin degradation products, antiphospholipid syndrome, etc.<sup>8</sup> On the other hand, false aPTT shortening can be caused by complicated venepuncture and *in vivo* activation of the external pathway with hypercoagulation.<sup>9</sup> In DTI monitoring, aPTT reaches a plateau at a certain level, not responding to a further

dose increase.<sup>7</sup> aPTT was also reported to be inferior to DTI-specific Anti-IIa when evaluating anticoagulation with argatroban.<sup>16,18</sup> In addition, aPTT monitoring is based on the assumption that the patient's baseline aPTT is comparable to normal controls. In critically ill patients, however, the baseline aPTT often differs from normal controls, making target values questionable.<sup>13</sup> Conversely, it is important to note that aPTT is a widely affordable test that does not increase the cost of anticoagulation monitoring, even if performed multiple times a day. It is widely accessible in medical facilities and is straightforward to perform. However, in light of the aforementioned pitfalls, it is imperative to exercise caution when interpreting its results.

Direct monitoring of the thrombin blockade with the Anti-IIa (which specifically measures the degree of

thrombin inhibition) is a drug-calibrated method for DTI anticoagulation.<sup>19</sup> Higher doses of argatroban, however, result in the flattening of the concentration-response relationship, making detection of overdose by aPTT difficult.<sup>20</sup> On the other hand, Anti-IIa measurement is not widely utilized in most clinical laboratories and in many laboratories it would have to be introduced first. Its cost is approximately four times higher than that of aPTT (at our institution). However, based on our observations, the interpretation of values is significantly more straightforward due to the test's independence from non-specific errors commonly encountered in aPTT tests. This independence enables a more direct assessment of thrombin inhibition. Consequently, it may be clinically more straightforward to ascertain whether a bleeding complication is attributable to direct anticoagulation or if it is indicative of a coagulation disorder elsewhere.

Vu et al compared aPTT with Anti-IIa for monitoring argatroban anticoagulation in 93 adult (non-ECMO) patients.<sup>21</sup> The argatroban dose was significantly lower in the Anti-IIa group (median 0.78 µg/kg/min, IQR 0.49–1.45) than in the aPTT group (median 1.96 µg/kg/min, IQR 0.73–2.79,  $p < 0.001$ ). There were fewer severe bleeding complications in the Anti-IIa group (3 vs 7), but the results did not reach statistical significance. Guy et al compared the aPTT with different Anti-IIa in 25 samples from 8 patients and concluded that the Anti-IIa was more suitable for controlling DTI dosage than aPTT.<sup>11</sup> Still, however, there is a lack of robust data comparing Anti-IIa therapy with aPTT, especially in critically ill ECMO patients.

Patients with COVID-19 show a number of differences in coagulation and are particularly at risk for thrombotic complications. A number of papers have addressed this topic in detail<sup>22–25</sup>; the analysis of this coagulopathy is beyond the scope of this text.

Our local ECMO aPTT protocol target was 40–60 s. ELSO guidelines discuss targeting aPTT to 1.5 to 2.5 times the patient's pretreatment baseline aPTT; in clinical practice, however, this is difficult to apply as pretreatment aPTT is almost never known.<sup>13</sup> It appears that it may be safer to use low-dose anticoagulation instead of the standard dose from the perspective of bleeding complications, as it could be sufficient to ensure a safe ECMO run without an increase in thrombotic complications.<sup>26–28</sup> The target range for Anti-IIa is more difficult to determine in view of the lack of robust data on ECMO anticoagulation. Alberio et al recommended argatroban as one of the possible substitutes for heparin anticoagulation in patients with heparin-induced thrombocytopenia (HIT),<sup>29</sup> with an Anti-IIa target of 0.4–1.5 µg/mL. The same target range was recommended by Kleinschmidt<sup>30</sup> as well. Our local guidelines based on pharmacology recommendations took these results into account, while aiming for the lowest risk target range of 0.4–0.6 µg/mL. Despite this, almost 90% of our patients developed at least one bleeding event.

No life-threatening oxygenator thrombosis (ie, circuit thrombosis that would lead to a sudden pump failure necessitating immediate circuit exchange) occurred in our patient group despite this low range. Nevertheless, it is necessary to say that if transmembrane circuit pressure started to increase, preventive circuit exchange was performed where needed; in all, only 35 such preventive circuit exchanges were performed in our study group of 44 patients over 24,528 h of ECMO support. Anticoagulation in our group was, therefore, sufficient to prevent serious thrombotic complications.

The mortality in our study group comprising 44 VV ECMO patients with COVID-19-associated ARDS (CARDS) anticoagulated with argatroban was approximately 50%, which is similar to other ECMO centres.<sup>31–33</sup> The absolute risk of bleeding significantly increased once the aPTT value of 52.7 s was reached – a 93% increase in the relative risk of a bleeding event was observed in the 52.7 s–55.5 s decile (relative risk of 1.93, 95% confidence interval 1.41–2.65, see Figure 3). It is important to note that this decile was still within the target range in our study as well as in most recommendations.<sup>13,17</sup> This indicates that in COVID-19 patients on ECMO support, the target range reaching up to 60 s could be revised towards lower values.

A U-shaped distribution of the risk of bleeding complications was observed in the Anti-IIa, with the lowest two ( $\leq 0.40$  µg/mL) and highest two ( $> 0.78$  µg/mL) deciles being associated with a much higher risk of bleeding complications than the “mid-range” deciles from 0.40 to 0.78 µg/mL. The increased rate of bleeding complications in the two lowest deciles is likely not associated with thrombin blockade (patients in this range often have no anticoagulation at the time) but rather, it might be caused by a possible general anticoagulation cascade disruption in their serious condition. The target range of 0.4–1.5 µg/mL recommended for patients with HIT by Alberio et al<sup>29</sup> or by Kleinschmidt et al<sup>30</sup> is, in our opinion, too wide, as the ninth decile of 0.78–0.99 µg/mL was already associated with a significant increase in the occurrence of bleeding complications by 62%, (relative risk of 1.62, 95% confidence interval 1.19–2.20, see Figure 3).

The performance of aPTT and Anti-IIa in predicting bleeding complications within the next 12 h (Table 2) indicated poor predictive performance of both of these tests. We also made an attempt to account for the fact that the lowest two deciles of Anti-IIa were associated with a significantly increased rate of bleeding complications by creating a combined endpoint, assuming that the occurrences of bleeding at low Anti-IIa values would be due to reasons not associated with thrombin blockade and that such events would be to a large degree covered by aPTT. For this reason, we also created a combined endpoint of  $\text{aPTT} > 52.7$  s and  $\text{Anti-IIa} > 0.78$  µg/mL. Unfortunately, no notable improvement was recorded, with a negative

predictive value of aPTT alone being approximately the same as that of Anti-IIa or the combined endpoint – slightly under 90%. From a practical clinical perspective, therefore, supplementing aPTT with Anti-IIa for the general prediction of bleeding occurrence is, despite our expectations, not beneficial. In general, aPTT alone showed a higher sensitivity for bleeding complications in our group than Anti-IIa alone. However, if the intention is solely to adjust argatroban dose, Anti-IIa could still be a better choice, as it directly evaluates the intensity of argatroban-induced thrombin blockade.

No oxygenator thrombosis occurred in our study – only elective/preventive oxygenator exchanges were performed based on routine checks of the ECMO circuit (35 exchanges in total per 24,528 h of ECMO support). For this reason, we consider argatroban anticoagulation in our study group to have been sufficient despite aiming for lower Anti-IIa/aPTT targets.

## Limitations

This is a single-centre trial with only 44 participants. In our study, we performed no intervention based solely on one or the other test – the dose of argatroban was adjusted based on a combination of results of both tests and the clinical situation (bleeding or risk of thrombosis), with Anti-IIa being prioritised. Therefore, it is difficult to draw any firm conclusions to establish specific thresholds. Also, the absolute dose of argatroban was not measured, so we could not describe the correlation between aPTT/Anti-IIa levels and argatroban dose.

## Conclusion

Increased risk of bleeding complications was observed from aPTT value of 52.7 s and Anti-IIa value of 0.78 µg/mL, indicating that the target range for the Anti-IIa up to 1.5 µg/mL may be too high. Neither aPTT nor Anti-IIa testing were able to reliably predict the development of bleeding complications within the next 12 h in ECMO patients with SARS-CoV2. On the other hand, aPTT values of <52.7 s and Anti-IIa values of 0.4–0.78 µg/mL were capable of relatively good prediction (90%) of the absence of bleeding complications.

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Not applicable

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## Ethical Considerations

The study was approved by the Ethics Committee of the University Hospital Ostrava.

## Consent to Participate

**FB:** Conceptualization, Original draft preparation, Approval of the final text; **MF:** Conducting the research and investigation process, Approval of the final text; **PS:** Supervision, Critical revision of the manuscript, Approval of the final text; **SN:** Digitalization of the dataset, Approval of the final text; **ZK:** Digitalization of the dataset, Approval of the final text; **OJ:** Conducting the research and investigation process, Approval of the final text; **TR:** Digitalization of the dataset, Approval of the final text; **AK:** Statistical analysis, Approval of the final text; **JJ:** Statistical analysis, text editing and translation, Approval of the final text; **JS:** Conducting the research and investigation process, Approval of the final text and **JM:** Review & Editing, Approval of the final text

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## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Data Availability Statement

Data is available on reasonable request.

## Supplemental Material

Supplemental material for this article is available online.

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