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Evaluating the impact of continuous venovenous hemodiafiltration on the efficacy of prophylactic fondaparinux doses: a prospective single-center observational study

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Critically ill patients often need continuous renal replacement therapy (CRRT). This process can remove particles as large as 10 kDa, including medications such as fondaparinux. In this study, we investigated whether patients who received prophylactic doses of fondaparinux and are treated with continuous veno-venous hemodiafiltration (CVVHDF) would achieve prophylactic levels of anti-Xa factor activity. In this observational study, we compared two groups of patients: 20 individuals who underwent CVVHDF and 20 individuals who did not undergo CVVHDF. Each patient received a prophylactic subcutaneous dose of 2.5 mg daily of fondaparinux. Anti-Xa factor activity was measured on the third day of treatment with fondaparinux. Blood samples were collected at four time points: immediately before the administration of fondaparinux and then 3, 6, and 9 h later. Anti-Xa factor activity levels were below the recommended range in the control group and in most CVVHDF patients but significantly increased after fondaparinux administration. Interestingly, individuals who underwent CVVHDF had greater anti-Xa factor activity than control patients did at several time points. In critically ill patients treated with prophylactic fondaparinux, CVVHDF appears to have a statistically significant but small effect on Xa factor activity. However, the clinical significance of this finding is unknown.

Clinical Trial Registration: The study was prospectively registered at ClinialTrials.gov (NCT04671160).

Keywords Fondaparinux, Impact, Renal replacement therapy, Continuous veno-venous hemodiafiltration, Anti-Xa, Thromboembolic prophylaxis

Hemostatic abnormalities pose a daily challenge for many intensivists worldwide[1,2]. Maintaining a delicate balance between thrombosis and bleeding is crucial to prevent dangerous complications that can worsen patient outcomes[3,4]. In the intensive care unit (ICU) population, venous thromboembolism (VTE) is a significant threat due to various risk factors, and it impacts the length of hospital stay and duration of mechanical ventilation, and increases morbidity and all-cause mortality[5]. Low-molecular-weight heparins (LMWHs) or unfractionated heparin (UFH) are used for pharmacological VTE prophylaxis in critically ill patients[6]. One of the complications related to these agents is heparin-induced thrombocytopenia (HIT). HIT is an autoimmune-like reaction between antibodies and platelets that activates the latter. Clinically, HIT causes thrombocytopenia, hypercoagulability, and increased risk for thrombotic events[7]. The typical treatment for HIT involves discontinuing heparin, removing heparin-bonded catheters, and introducing either direct antithrombin inhibitors or fondaparinux.

In addition to coagulation disorders, acute kidney injury (AKI) is a common complication in critically ill patients, with an incidence of up to 40% in the ICU population[8,9]. AKI significantly contributes to increased morbidity and, more importantly, mortality[10–13]. Patients with severe AKI often require renal replacement therapy (RRT) to support impaired kidney function. In critically ill patients, continuous RRT modalities, such as continuous veno-venous hemodiafiltration (CVVHDF), are often preferred, as they offer improved

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hemodynamic stability and reduce the risk of rapid intravascular volume shifts[14,15]. CVVHDF can remove solutes with molecular weights up to approximately 10 kilodaltons (kDa), including metabolic waste products, electrolytes, acids, and certain medications. In addition to diffusion and solvent drag, adsorption to the dialysis membrane may also contribute to the clearance of some proteins and pharmaceuticals[16]. Fondaparinux, a synthetic anticoagulant with an average molecular weight of 1.7 kDa[17], is theoretically small enough to be filtered during CVVHDF. This raises concerns that its elimination during therapy could reduce anti-Xa factor activity and increase the risk of thromboembolic complications in critically ill patients. Its volume of distribution is relatively low (approximately 7–11 L), suggesting it remains largely within the intravascular compartment[27]. These pharmacokinetic properties, combined with its small molecular size, raise concerns about its potential removal during CRRT. However, the extent to which fondaparinux is cleared in this setting remains poorly understood. Importantly, patients with AKI requiring CRRT may be at risk of either excessive anticoagulation or subtherapeutic drug levels, depending on the balance between impaired renal clearance and extracorporeal removal. To date, data regarding the behaviour of fondaparinux during CRRT are extremely limited or absent. Most available studies have focused on intermittent haemodialysis (IHD), and few have explored fondaparinux pharmacokinetics during continuous modalities. Therefore, this study aimed to assess whether critically ill patients receiving prophylactic fondaparinux while undergoing CVVHDF achieve adequate anti-Xa factor activity. Clarifying this question is essential to guide dosing strategies and ensure safe and effective VTE prophylaxis in this high-risk population.

This study aimed to determine whether patients receiving prophylactic doses of fondaparinux and treated with CVVHDF achieve adequate anti-Xa factor activity levels, considering that fondaparinux particles can pass through CVVHDF filter pores because their size is below the cutoff. Despite the long-standing clinical use of fondaparinux, evidence supporting this concern remains elusive. Therefore, assessing whether patients on fondaparinux for VTE prophylaxis and undergoing CVVHDF receive adequate doses to prevent severe thrombotic complications is crucial. Understanding this aspect will enable clinicians to adjust fondaparinux dosing for critically ill patients on CVVHDF, ensuring that anti-Xa factor activity reaches desired levels. This is the first study assessing the efficacy of fondaparinux during continuous renal replacement.

Patients and methods

We present the findings from an observational, prospective, open-label, single-center, nonrandomized clinical trial conducted in Poland. The study protocol received approval from the Independent Bioethics Committee for Scientific Research at the Medical University of Gdańsk (approval numbers NKBBN/382/2020 and NKBBN/382–496/2021). This study adhered to the ethical standards outlined in the 1964 Declaration of Helsinki and its subsequent amendments. Informed written consent was obtained from all participants before their enrollment. The trial was conducted in the Department of Anesthesiology and Intensive Care of the Medical University of Gdańsk, Poland, from June 2022 to April 2024 and was registered at clinicaltrials.gov (NCT04671160) before patient enrollment began.

Participants

Forty consecutive patients who fulfilled the inclusion criteria were enrolled in the study. Patients were treated in the ICU of the Department of Anesthesiology and Intensive Therapy. Eligibility for ICU treatment adhered to the guidelines set by the Polish Society of Anesthesiology and Intensive Therapy. The treatment followed the recommendations of various scientific societies and was supervised by a specialist in anesthesiology and intensive care around the clock. All participants received prophylactic doses of 2.5 mg fondaparinux (Arixtra, Aspen Pharma, Ireland) subcutaneously every 24 h. After enrollment, no patients were excluded from the study because of protocol violations. The participants were divided into two equally sized groups: a control group (patients not treated with CVVHDF) and a CVVHDF group (patients treated with CVVHDF). The inclusion criteria were as follows: (i) treatment in the ICU, (ii) age between 18 and 80 years, (iii) at least 72 h of CVVHDF treatment before enrollment (for the CVVHDF group), (iv) indications for anticoagulant prophylaxis with 2.5 mg fondaparinux once daily, and (v) provision of informed consent for participation in the study. Patients were excluded if they (i) had indications for fondaparinux use other than anticoagulant prophylaxis, (ii) had intracranial hemorrhage, (iii) had an incident of severe bleeding within a week before ICU admission that was not managed, (iv) had disseminated intravascular coagulation, (v) had heparin-induced thrombocytopenia, (vi) had hypersensitivity or allergic reactions to fondaparinux, (vii) had thrombocytopenia < 50 G L -1, (viii) had a prothrombin time of > 20 s or an INR of > 1.7, (ix) used antiplatelet drugs, or (x) had congenital coagulopathy. CVVHDF with regional citrate anticoagulation was administered via a Baxter Prismaflex device at a dose of 30 mL/kg/h, employing an ST-150 filter. Prism0CAL B22, Prism0CAL, PrismoCit 4 K, or Prismocitrate 18/0 (all from Baxter International, Deerfield, IL, USA) were used depending on the patient's clinical status.

Study protocol

Anti-Xa factor activity was assessed after 72 h of administration of a prophylactic dose of fondaparinux. The testing was conducted in the Central Clinical Laboratory of the University Clinical Center of Gdańsk, Gdańsk, Poland. Four arterial blood samples were collected to measure anti-Xa activity: the first sample was taken just before the administration of fondaparinux, and the subsequent samples were taken 3 h, 6 h, and 9 h after a prophylactic dose of fondaparinux was administered. Heparin solution was not used to flush the arterial catheters to prevent contamination. Blood was collected in tubes containing sodium citrate as an anticoagulant and then centrifuged at room temperature for 15 min (1500–2500× g) to separate the plasma. The activity assessment was performed via an STA–Liquid Anti-Xa test (Diagnostica Stago, Asnieres sur Seine, France) immediately after blood collection.

Statistical analyses

The study sample size ($n = 20$ in each group) was calculated ex ante on the basis of previous data in the literature, with an effect size of d = 1.2, α error probability = 0.05, power (1 − β) = 0.95, and an allocation ratio of 1:1. Interim analyses for futility or efficacy were not included in the study protocol. The primary endpoint was the change in anti-Xa factor activity after fondaparinux administration, compared between the control and CVVHDF groups. Owing to technical constraints preventing blinding and randomization, the person performing the statistical analyses was provided with blinded data.

Fisher's exact test was used for the comparison of categorical variables. Analyses of variance (ANOVA) with Tukey's post hoc test were used to compare variables with normal distributions. Pearson's or Spearman's correlation coefficients were used for correlation analyses. Results with a p-value of <0.05 were considered statistically significant. The data were analyzed via Prism 9 software (GraphPad, Boston, MA, USA).

Results

All patients were treated in the medical-surgical ICU for mixed admission causes. Septic shock was the leading cause of admission in the CVVHDF group, whereas respiratory failure was the leading cause of admission in the control group. Table 1 presents the detailed baseline characteristics of the population.

All patients in the control group and most in the CVVHDF group had anti-Xa factor activity below the recommended prophylactic range at all time points (Table 2). After fondaparinux administration, we observed a significant increase in anti-Xa factor activity at all the tested time points, regardless of the need for continuous renal replacement therapy (Fig. 1a,b). Interestingly, in several periods, the anti-Xa factor activity in the CVVHFD group was significantly greater than that in the control group (Fig. 1c).

We found no significant correlations between anti-Xa factor activity and the other examined factors, which were (i) BMI, (ii) antithrombin activity, (iii) dose of norepinephrine, (iv) SAPS score, (v) APACHE II score, and (vi) SOFA score (Table 3). The only exception was a moderate positive correlation between the SOFA score and anti-Xa activity before fondaparinux administration ($r = 0.339$, $p = 0.033$).

Discussion

This study aimed to determine whether CVVHDF affects the pharmacodynamics of prophylactic doses of fondaparinux, as assessed by anti-Xa factor activity levels. We established that patients treated with CVVHDF had significantly greater anti-Xa factor activity than did the control group. Despite this finding, most CVVHDF and control group patients had anti-Xa factor activity below the suggested range for preventing venous thromboembolism. However, it must be noted that there are no commonly accepted cutoff values for anti-Xa activity during fondaparinux administration.

Fondaparinux, a synthetic pentasaccharide, works by binding to antithrombin and enhancing its inhibitory effect on prothrombin conversion. It is used for DVT prophylaxis; however, LMWHs and UFH are the most common agents used for this purpose in critically ill patients[5]. Additionally, data comparing fondaparinux to other drugs are limited. A study by Eriksson et al. reported that fondaparinux was more effective than enoxaparin in preventing thromboembolic complications after hip fracture surgery[18]. The safety profiles of both agents were similar. Similar observations have also been reported in patients after major knee or hip surgery[19,20].

	CVVHDF group ($N = 20$)	Control group ($N = 20$)
Female	$N = 10$ (50%)	$N = 9$ (45%)
Age (yrs.)	58.2 (14.0)	60.5 (16.6)
BMI (kg m^{-2})	28.5 [24.0–37.0]	28.0 [24.5–32.5]
Cause of admission to the ICU	Septic shock $N = 9$ (45%) Acute pancreatitis $N = 4$ (20%) Respiratory failure $N = 3$ (15%) Polytrauma $N = 2$ (10%) Hypovolemic shock $N = 1$ (5%) Multiorgan failure $N = 1$ (5%)	Respiratory failure $N = 7$ (35%) Polytrauma $N = 5$ (25%) Subdural hematoma $N = 2$ (10%) Spinal cord injury $N = 2$ (10%) Acute pancreatitis $N = 1$ (5%) Suicide attempt $N = 1$ (5%) Septic shock $N = 1$ (5%) Altered consciousness $N = 1$ (5%)
Time since admission to the ICU (days)	6.0 [4.3-7.0]	9.5 [4.3–14.0]
Time since CVVHDF initiation (days)	5.5 [4.0–7.0]	N/A
Mechanical ventilation	$N = 9$ (45%)	$N = 11$ (55%)
Vasopressor administration	$N = 5$ (25%)	$N = 8$ (40%)
SAPS II score at admission	44.3 (13.1)	39.1 (13.7)
APACHE II score at admission	17.0 [14.3–20.0]	15.0 [9.3–20.8]
SOFA score on the study day	8.0 (3.1)	4.6 (2.4)
Creatinine (μmol L^{-})	N/A	71.5 (45.6)
ICU mortality n, (%)	4 (20%)	2 (10%)
Hospital mortality n, (%)	7 (35%)	3 (15%)

Table 1. Demographic and clinical characteristics of patients at study enrollment. The values are the number [%], median (IQR [range]), or mean (SD).

	Control group (*N* = 20)				CVVHDF group (*N* = 20)				*P* value (comparison between control and CVVHDF groups at the given time points)			
Anti-Xa factor activity (ug/mL)	0 h	+ 3 h	+ 6 h	+ 9 h	0 h	+ 3 h	+ 6 h	+ 9 h	0 h	+ 3 h	+ 6 h	+ 9 h
< 1.0	*N* = 20 [100%]	*N* = 20 [100%]	*N* = 20 [100%]	*N* = 20 [100%]	*N* = 20 [100%]	*N* = 18 [90%]	*N* = 17 [85%]	*N* = 19 [95%]	> 0.99	0.4872	0.2308	> 0.99
1.0-1.4	*N* = 0 [0%]	*N* = 0 [0%]	*N* = 0 [0%]	*N* = 0 [0%]	*N* = 0 [0%]	*N* = 2 [10%]	*N* = 3 [15%]	*N* = 1 [5%]				

Table 2. Number and percentage of patients in each group with anti-Xa factor activity within the prophylactic range at different times. Values are numbers [%].

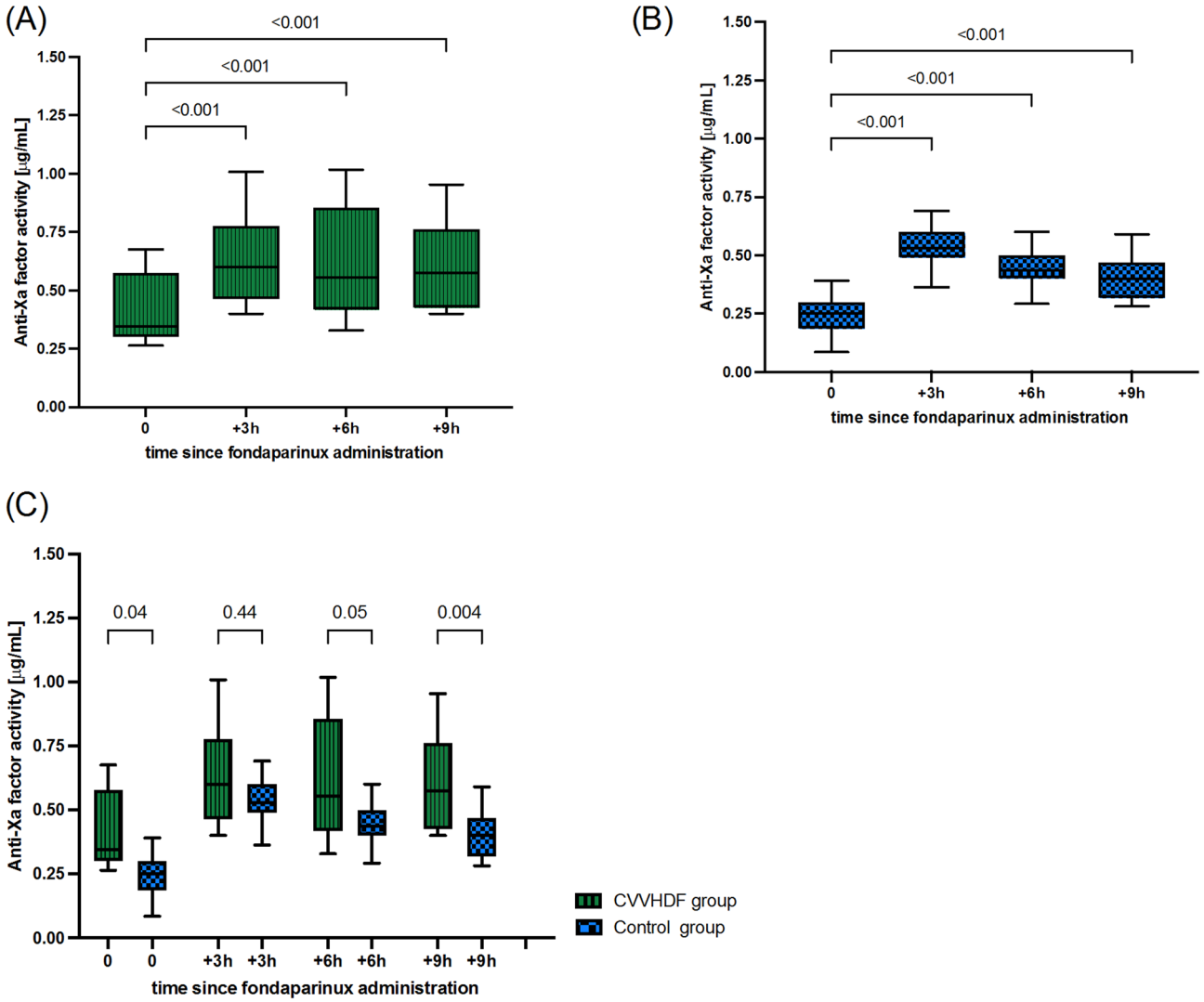

Fig. 1. Anti-Xa factor activity changes over time. (**A**) Comparison of anti-Xa factor activity changes at different time points within the CVVHDF group. (**B**) Comparison of anti-Xa factor activity changes at different time points within the control group. (**C**) Comparison of anti-Xa factor activity changes between the CVVHDF and control groups at the corresponding time points. P values are given above each comparison.

	BMI	Antithrombin activity	Dose of norepinephrine	SAPS score	APACHE II score	SOFA score
Anti Xa activity before fondaparinux administration	$P=0.097$	$P=0.243$	$P=0.891$	$P=0.331$	$P=0.535$	**P= 0.033**
Anti Xa activity 3 h after fondaparinux administration	$P=0.829$	$P=0.831$	$P=0.309$	$P=0.171$	$P=0.883$	$P=0.550$
Anti Xa activity 6 h after fondaparinux administration	$P=0.614$	$P=0.284$	$P=0.607$	$P=0227$	$P=0.992$	$P=0.081$
Anti Xa activity 9 h after fondaparinux administration	$P=0.082$	$P=0.446$	$P=0.515$	$P=0.111$	$P=0.766$	$P=0.119$

Table 3. P values for correlations between anti-Xa factor activity and other examined factors. Values in bold indicate statistically significant results, defined as $P < 0.05$.

Fondaparinux should be subcutaneously administered at a daily dose of 2.5 mg for VTE prophylaxis and superficial vein thrombosis treatment[21,22]. Subcutaneous fondaparinux 2.5 mg daily has complete bioavailability, instant onset of action, a 15–20 h half-life, and direct renal excretion without any metabolism in healthy subjects. Thus, treatment monitoring is not required in the general population[17]. A lower dose of 1.5 mg administered once daily is recommended in exceptional circumstances that might cause drug accumulation, such as age greater than 75, weight less than 50 kg, or decreased creatinine clearance (CrCl)[23,24]. The FONDAIR study suggested that lower doses of fondaparinux may be safe and effective in critically ill patients with renal impairment[24]. Another observational study indicated that doses of 2.5 mg and 1.5 mg of fondaparinux appeared to be safe and effective for thromboprophylaxis in elderly acutely ill patients with renal dysfunction[25].

In the ICU population, many factors may impair the bioavailability of fondaparinux, and these include the following: edema of subcutaneous tissue, as well as vasopressor administration, may affect absorption[26]; excretion may be impaired in patients with renal insufficiency[27]; and finally, in patients with liver insufficiency, antithrombin deficiency might be observed, causing overexcretion of fondaparinux, which will not have a site at which to bind[28]. In contrast, one study reported increased levels of anti-Xa factor activity in patients treated with vasopressors[29]. Anti-Xa factor activity was reported to be strongly correlated with the fondaparinux plasma concentration. Therefore, the plasma level of fondaparinux may be used to monitor treatment efficiency[30]. Unfortunately, there are insufficient data to prove the necessity of monitoring anti-Xa activity in critically ill patients. Additionally, there are no guidelines regarding dose adjustments for these patients. Moreover, the optimal anti-Xa activity is mainly speculative.

Unexpectedly, we observed increased anti-Xa activity in patients receiving renal replacement therapy. A possible explanation for this phenomenon may be impaired renal function in those patients. Renal clearance of fondaparinux may explain this observation, as in patients with CrCl < 30 ml min-1, the clearance of fondaparinux is decreased by more than half[31]. On the other hand, the theoretical assumption that fondaparinux should be removed by high-flux membranes and not by low-flux membranes was supported in hemodialysis patients[30]. Notably, real fondaparinux removal by high-flux membranes was lower than the calculated value. The high affinity of fondaparinux for plasma proteins and its ability to bind to antithrombin may partly prevent drug removal during dialysis[32]. To date, there are no data regarding fondaparinux removal during CVVHDF or other renal replacement modalities.

This investigation has several limitations that should be acknowledged. First, it was a single-center open-label study, which may limit the generalizability of the findings. The results might not be applicable to other institutions that utilize different CRRT devices, solutions, equipment, or follow alternative prescribing practices. Second, the study involved a relatively small and heterogeneous patient population, with varying underlying pathologies, comorbidities, and vasopressor requirements, all of which could have influenced the observed results. Third, residual kidney function was not formally assessed, and it may have contributed to the clearance of fondaparinux in patients undergoing CVVHDF. Finally, although anti-Xa activity was used as a surrogate marker for fondaparinux effect, direct measurements of fondaparinux concentrations in the blood, the post-filter limb of the CRRT circuit, or the effluent were not performed. Such measurements would provide a more definitive understanding of the drug's pharmacokinetics in the setting of continuous renal replacement therapy.

Conclusions

We observed a statistically significant difference in anti-Xa factor activity following prophylactic fondaparinux administration between critically ill patients undergoing continuous veno-venous hemodiafiltration and those without continuous renal replacement therapy. Interestingly, CVVHDF appeared to be associated with higher anti-Xa levels, contrary to our initial hypothesis that fondaparinux might be cleared through the filtration process. In critically ill patients treated with prophylactic fondaparinux, CVVHDF appears to have a statistically significant but small effect on Xa factor activity. However, the clinical significance of this finding is unknown. Further studies are needed to determine the optimal dosing strategy and monitoring protocol for fondaparinux in this patients population.

Data availability

The data used to support the findings of this study are included within the article or are available from the corresponding author upon request.

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References

1. Minet, C. et al. Venous thromboembolism in the ICU: main characteristics, diagnosis and thromboprophylaxis. *Crit. Care.* **19** (1), 287 (2015).
2. McLeod, A. G. & Geerts, W. Venous thromboembolism prophylaxis in critically ill patients. *Crit. Care Clin.* **27** (4), 765–780 (2011).
3. Neuenfeldt, F. S., Weigand, M. A. & Fischer, D. Coagulopathies in intensive care medicine: balancing act between thrombosis and bleeding. *J. Clin. Med.* **10** (22). (2021).
4. Levi, M. & Opal, S. M. Coagulation abnormalities in critically Ill patients. *Surg. Intensive Care Med.* (2016).
5. Malato, A. et al. The impact of deep vein thrombosis in critically ill patients: a meta-analysis of major clinical outcomes. *Blood Transfus.* **13** (4), 559–568 (2015).
6. Helms, J., Middeldorp, S. & Spyropoulos, A. C. Thromboprophylaxis in critical care. *Intensive Care Med.* **49** (1), 75–78 (2023).
7. Ghaziri, D. et al. Novel Fondaparinux protocol for anticoagulation therapy in adults with renal failure and suspected heparin-induced thrombocytopenia: a retrospective review of institutional protocol. *BMC Pharmacol. Toxicol.* **24** (1), 2 (2023).
8. Koeze, J. et al. Incidence, timing and outcome of AKI in critically ill patients varies with the definition used and the addition of urine output criteria. *BMC Nephrol.* **18** (1), 70 (2017).
9. Paudel, M. S. et al. A study of incidence of AKI in critically ill patients. *Ren. Fail.* **34** (10), 1217–1222 (2012).
10. Hoste, E. A. et al. Acute renal failure in patients with sepsis in a surgical ICU: predictive factors, incidence, comorbidity, and outcome. *J. Am. Soc. Nephrol.* **14** (4), 1022–1030 (2003).
11. Cartin-Ceba, R. et al. Risk factors for development of acute kidney injury in critically ill patients: a systematic review and meta-analysis of observational studies. *Crit. Care Res. Pract.* **2012** (1), 691013 (2012).
12. Vivino, G. et al. Risk factors for acute renal failure in trauma patients. *Intensive Care Med.* **24** (8), 808–814 (1998).
13. Ricci, Z., Cruz, D. & Ronco, C. The RIFLE criteria and mortality in acute kidney injury: A systematic review. *Kidney Int.* **73** (5), 538–546 (2008).
14. Honore, P. M. et al. Septic AKI in ICU patients. Diagnosis, pathophysiology, and treatment type, dosing, and timing: a comprehensive review of recent and future developments. *Ann. Intensive Care.* **1** (1), 32 (2011).

15. Badawy, S. S. & Fahmy, A. Efficacy and cardiovascular tolerability of continuous veno-venous hemodiafiltration in acute decompensated heart failure: a randomized comparative study. *J. Crit. Care*. **27** (1), 106e7–10613 (2012).
16. Voigt, M. et al. Retention of beneficial molecules and coagulation factors during haemodialysis and haemodiafiltration. *Sci. Rep.* **9** (1), 6370 (2019).
17. Zhang, Y., Zhang, M., Tan, L., Pan, N. & Zhang, L. The clinical use of Fondaparinux: A synthetic heparin pentasaccharide - PubMed. *Progr. Mol. Biol. Transl. Sci.* **163** (2019).
18. Eriksson, B. I., Bauer, K. A., Lassen, M. R. & Turpie, A. G. Steering committee of the pentasaccharide in Hip-Fracture surgery S. Fondaparinux compared with Enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. *N Engl. J. Med.* **345** (18), 1298–1304 (2001).
19. Bauer, K. A., Eriksson, B. I., Lassen, M. R. & Turpie, A. G. Steering committee of the pentasaccharide in major knee surgery S. Fondaparinux compared with Enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. *N Engl. J. Med.* **345** (18), 1305–1310 (2001).
20. Lassen, M. R., Bauer, K. A., Eriksson, B. I., Turpie, A. G. & European Pentasaccharide Elective Surgery Study Steering C. Postoperative Fondaparinux versus preoperative Enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. *Lancet* **359** (9319), 1715–1720 (2002).
21. Stevens, S. M. et al. Executive summary: antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. *Chest* **160** (6), 2247–2259 (2021).
22. Kakkos, S. K. et al. (eds) 's Choice – European society for vascular surgery (ESVS) 2021 clinical practice guidelines on the management of venous thrombosis. *Eur. J. Vasc. Endovasc. Surg.* **61** (1), 9–82. (2021).
23. Di Nisio, M. & Porreca, E. Prevention of venous thromboembolism in hospitalized acutely ill medical patients: focus on the clinical utility of (low-dose) Fondaparinux. *Drug Des. Devel Ther.* **7**, 973–980 (2013).
24. Ageno, W. et al. Safety and efficacy of low-dose Fondaparinux (1.5 mg) for the prevention of venous thromboembolism in acutely ill medical patients with renal impairment: the FONDAIR study. *J. Thromb. Haemost.* **10** (11), 2291–2297 (2012).
25. Silvestri, F. et al. Safety and efficacy of thromboprophylaxis with fondaparinux in elderly acutely ill medical patients with renal impairment: a retrospective single center study. *Italian J. Med.* **7** (4). (2013).
26. Dörffler-Melly, J. et al. Bioavailability of subcutaneous low-molecular-weight heparin to patients on vasopressors. *Lancet* **359** (9309), 849–850 (2002).
27. Donat, F. et al. The pharmacokinetics of Fondaparinux sodium in healthy volunteers. *Clin. Pharmacokinet.* **41** (Suppl 2(Supplement 2), 1–9 (2002).
28. Perez, R. et al. Critical care hepatology: definitions, incidence, prognosis and role of liver failure in critically ill patients. *Crit. Care* **26** (1). (2022).
29. Cumbo-Nacheli, G., Samavati, L. & Guzman, J. A. Bioavailability of Fondaparinux to critically ill patients. *J. Crit. Care*. **26** (4), 342–346 (2011).
30. Michaličková, D. et al. Population pharmacokinetics-pharmacodynamics of Fondaparinux in dialysis-dependent chronic kidney disease patients undergoing chronic renal replacement therapy. *Eur. J. Clin. Pharmacol.* **78** (1), 89–98 (2021).
31. Al-Shaer, M. H. & Ibrahim, T. Safety and efficacy of Fondaparinux in renal impairment. *J. Pharm. Technol.* **31** (4), 161–166 (2015).
32. Paolucci, F., Clavies, M. C., Donat, F. & Necciari, J. Fondaparinux sodium mechanism of action: identification of specific binding to purified and human plasma-derived proteins. *Clin. Pharmacokinet.* **41** (Suppl 2(Supplement 2), 11–18 (2002).

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Author contributions

AA - Aleksander AszkiełowiczRO - Radosław OwczukKPS - Karol P. SteckiewiczConceptualization: AA, RO; data curation: AA, KPS; formal analysis: KPS; data interpretation: AA, KPS, RO; funding acquisition: AA, RO; investigation: AA, KPS; methodology: AA, RO; project administration: AA; resources: AA; software: KPS; supervision: RO; validation: AA; visualization: KPS; writing – original draft: AA, KPS; writing review & editing: AA, KPS, RO. All authors have read and agreed to the published version of the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Informed consent

Informed consent was obtained from all subjects involved in the study.

Institutional review board

The study protocol was approved on 3 July 2020 and 21 May 2021 by the Independent Bioethics Committee for Scientific Research at the Medical University of Gdańsk (approval no. NKBBN/382/2020 and NKBBN/382–496/2021). The study was performed in accordance with the ethical standards provided in the 1964 Declaration of Helsinki and its later amendments. All participants gave informed written consent before enrollment in the study.

Additional information

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