Intensive Care Med
https://doi.org/10.1007/s00134-022-06850-7

LASTING LEGACY IN INTENSIVE CARE MEDICINE

Thromboprophylaxis in critical care

Julie Helms[1,2*], Saskia Middeldorp[3,4] and Alex C. Spyropoulos[5,6,7]

Venous thromboembolism (VTE) in critically ill patients may be a life-threatening complication increasing duration of mechanical ventilation and stay in the intensive care unit (ICU). Both early diagnosis and effective and safe thromboprophylaxis are, therefore, daily challenges. Despite its major clinical impact, the risk of VTE in ICU has long been poorly characterized (Suppl. Figure 1), and high-quality evidence comparing pharmacologic and mechanical VTE prophylaxis strategies is still limited.

Although the anticoagulant effect of heparin was elucidated in 1939, it only became used from the 1950s to prevent VTE in post-surgical patients. In 1960, a landmark trial established heparin to be effective in reducing mortality from pulmonary embolism (PE), as only surgical options were considered previously [1]. Low-molecular-weight heparin (LMWH) was discovered in the 1980s and improved thromboprophylaxis through more consistent pharmacokinetics/pharmacodynamic, simplified dosing, reduced bleeding, and less frequent heparin-induced thrombocytopenia than with unfractionated heparin (UFH) [2].

Which pharmacological thromboprophylaxis for critically ill patients?

With regard to type of prophylaxis, LMWH might have superior efficacy compared to UFH in medical and surgical critically ill patients. PROTECT [3] is the largest RCT to date to compare LMWH (dalteparin, 5000 IU/day) and UFH (5000 IU/12 h) in 3764 critically ill patients, of whom 90% were mechanically ventilated. Patients at very high risk of bleeding were excluded. Dalteparin did not decrease the rate of proximal deep vein thrombosis (DVT) compared to UFH, but the rate of PE was significantly lower with dalteparin (1.3% vs. 2.3%) (HR 0.51; 95% CI 0.30–0.88; $p=0.01$), without difference in major bleeding or in-hospital death. Also, LMWH was more effective than low-dose heparin in preventing VTE after major trauma [4].

In a recent systematic review including 13 randomized controlled trials (RCTs) (9619 critically ill patients) and comparing the efficacy and safety of thromboprophylaxis in ICU, the authors showed with a moderate certainty that LMWH reduced the rate of DVT compared to UFH (OR 0.72 [95% CI 0.46–0.98]) and with a high certainty that it reduced the rate of DVT compared to control (OR 0.59 [95% CrI: 0.33–0.90]; high certainty), while UFH may reduce DVT compared to control (OR 0.82 [95% CrI: 0.47–1.37]) with a low certainty of evidence [5]. In this meta-analysis, the effect of LMWH compared to UFH on PE is uncertain, because of very low-quality of evidence.

Consistent with clinical studies which seem to provide a superior efficacy of LMWH compared to UFH, without an increase in bleeding complications, the European and American guidelines [2, 6] recommend pharmacological prophylaxis with LMWH over UFH in critically ill patients (Grade 1B) (Fig. 1). For patients with severe renal insufficiency, the guidelines suggest the use of UFH (Grade 2C), dalteparin (Grade 2B) or reduced doses of enoxaparin (Grade 2C) and monitoring of anti-Xa activity (Grade 2C). The guidelines also suggest no prophylaxis or the use of intermittent pneumatic compression in patients with a platelet count less than 50,000/mm^3 or a high risk of bleeding (Grade 2C) and the careful use of pharmacological prophylaxis in patients with severe liver failure.

*Correspondence: Julie.helms@chru-strasbourg.fr
[1] Université de Strasbourg (UNISTRA), Faculté de Médecine; Hôpitaux universitaires de Strasbourg, Service de Médecine Intensive-Réanimation, Nouvel Hôpital Civil, Strasbourg, France
Full author information is available at the end of the article

Mechanical thromboprophylaxis in critically ill patients

The place of mechanical thromboprophylaxis is still debated [5]. In the PREVENT trial [7], the use of adjunctive compression devices in addition to pharmacologic prophylaxis did not result in a reduction in DVT compared to pharmacologic prophylaxis alone. Consistently, the aforementioned meta-analysis [5] showed that compressive devices might reduce the risk of DVT compared to a control group made of a composite of no prophylaxis, placebo, or compression stockings only (OR 0.85 [95% CrI: 0.50–1.50]), although certainty evidence was low.

The European guidelines recommend against the use of graduated compression stockings alone without pharmacological thromboprophylaxis for prevention of VTE in patients at intermediate and high risk (Grade 1B) [6, 8]. They recommend the use of mechanical prophylaxis for patients with contraindications for anticoagulation (Grade 1B) or in selected patients at very high risk of VTE prophylaxis in addition to pharmacological prophylaxis (Grade 2B), and suggest the use of intermittent pneumatic compression over graduated compression stockings (GCS, Grade 2B). The American guidelines do not support the use of combination therapy over either pharmacologic therapy or compression therapy alone [2].

Important considerations and pending questions

Even if these recommendations are clear, there are still several considerations that need to be taken into account for critically ill patients.

Although the availability of high-resolution reliable imaging allowed a more acute awareness for VTE over the past decades, compliance with VTE prophylaxis should still be improved. In a recent retrospective analysis of more than 1.4 million critically ill patients, 4% of patients did not receive any form of thromboprophylaxis within the first 24 h after ICU admission without obvious reason [9]. This, together with pharmacologic thromboprophylaxis being often withheld in ICU due to complications or surgical/invasive procedures, leading to less efficient thromboprophylaxis. Also, as risk factors for thromboprophylaxis failure include an elevated BMI, a personal/family history of VTE, or vasopressor use, it is likely that more aggressive and multimodal strategies should be used in some at-risk patients [10], maybe including mechanical thromboprophylaxis.

Then, anti-factor Xa thresholds protective of VTE are still a matter of debate in critically ill patients receiving

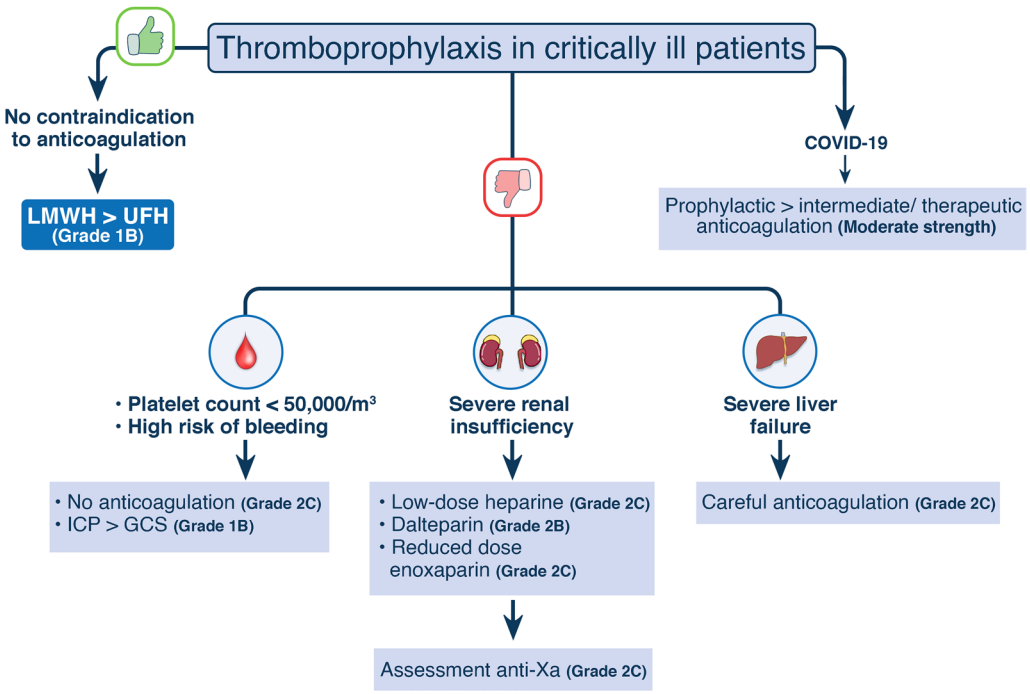

Fig. 1 Thromboprophylaxis in the critically ill. Grading of the recommendations are based on the European guidelines on perioperative venous thromboembolism prophylaxis in Intensive Care [6] and on mechanical thromboprophylaxis [8], and on the most recent guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19 from the International Society of Thrombosis and Haemostasis (ISTH) [15]. *COVID-19* coronavirus disease 2019, *GCS* graduated compression stockings, *HIT* heparin-induced thrombocytopenia, *IPC* Intermittent Pneumatic Compression, *LMWH* low-molecular weight heparin, *RCTs* randomized controlled trials, *UFH* unfractionated heparin

prophylactic LMWH, and personalizing thromboprophylaxis to decrease adverse events in this specific population not only at high risk of VTE, but also at high risk of bleeding complications, would need an alternative anticoagulation monitoring technique [11, 12]. In this line, when a targeted level of anticoagulation is not achieved in response to heparin dose increase, heparin resistance might be invoked. The hypercoagulability of critical illness, as described for example in SARS-CoV-2 or other acute infections, might be responsible for elevated factor VIII and fibrinogen levels leading to shortened aPTT, and binding of heparin to acute-phase inflammatory proteins that decreases its effects [13].

This leads us to consider the question of a possible specific thromboprophylaxis regimen in critically ill patients with coronavirus disease 2019 (COVID-19), who have early been identified at increased risk of thrombotic events [14]. Consistent with several negative RCTs, the most recent guidelines from the International Society of Thrombosis and Haemostasis (ISTH) recommend using prophylactic- over therapeutic- or intermediate-intensity anticoagulation to reduce risk of adverse events, including mortality and thromboembolism (moderate strength of recommendation, level of evidence B-Randomized RCTs) [15].

Take-home message

Considering the high risk of thrombosis in critically ill patients, general consensus currently establishes use of some form of heparin in pharmacological prophylaxis at the time of ICU admission, or mechanical thromboprophylaxis in those with contraindications to pharmacological thromboprophylaxis. LMWH is preferred over UFH for VTE prophylaxis in the ICU, unless in patients with severe renal insufficiency, where the use of low-dose heparin, dalteparin or reduced doses of enoxaparin might be preferred.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00134-022-06850-7.

Author details

[1] Université de Strasbourg (UNISTRA), Faculté de Médecine; Hôpitaux universitaires de Strasbourg, Service de Médecine Intensive-Réanimation, Nouvel Hôpital Civil, Strasbourg, France. [2] INSERM (French National Institute of Health and Medical Research), UMR 1260, Regenerative Nanomedicine (RNM), FMTS, Strasbourg, France. [3] Department of Internal Medicine and Radboud Institute of Health Sciences (RIHS), Nijmegen, The Netherlands. [4] Radboud University Medical Center, Nijmegen, The Netherlands. [5] The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, USA. [6] Institute of Health System Science, The Feinstein Institutes for Medical Research, Manhasset, USA. [7] Anticoagulation and Clinical Thrombosis Services, Northwell Health at Lenox Hill Hospital, 130 E 77th St, New York, NY 10075, USA.

Declarations

Conflicts of interest

JH has received honoraria for lectures from Diagnostica Stago, Pfizer PFE France and Sanofi Aventis France. SM has received personal fees from Daiichi Sankyo, Bayer, Pfizer, Boehringer Ingelheim, Portola/Alexion, AbbVie, BMS-Pfizer, Sanofi, and Viatris, all paid to her institution, and grants from Daiichi Sankyo, Bayer, Pfizer, and Boehringer Ingelheim. AS received consultant fees from Janssen, Bayer, Bristol Myer Squibb, Sanofi, Alexion, ATLAS Group and research Funds from Janssen.

Publisher's Note

Received: 13 June 2022 Accepted: 29 July 2022
Published online: 29 August 2022

References

1. Barritt DW, Jordan SC (1960) Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. Lancet 1:1309–1312
2. Schunemann HJ, Cushman M, Burnett AE, Kahn SR, Beyer-Westendorf J, Spencer FA, Rezende SM, Zakai NA, Bauer KA, Dentali F, Lansing J, Balduzzi S, Darzi A, Morgano GP, Neumann I, Nieuwlaat R, Yepes-Nunez JJ, Zhang Y, Wiercioch W (2018) American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. Blood Adv 2:3198–3225
3. Group PIftCCCT, the A, New Zealand Intensive Care Society Clinical Trials G, Cook D, Meade M, Guyatt G, Walter S, Heels-Ansdell D, Warkentin TE, Zytaruk N, Crowther M, Geerts W, Cooper DJ, Vallance S, Qushmaq I, Rocha M, Berwanger O, Vlahakis NE (2011) Dalteparin versus unfractionated heparin in critically ill patients. N Engl J Med 364:1305–1314
4. Geerts WH, Jay RM, Code KI, Chen E, Szalai JP, Saibil EA, Hamilton PA (1996) A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. N Engl J Med 335:701–707
5. Fernando SM, Tran A, Cheng W, Sadeghirad B, Arabi YM, Cook DJ, Moller MH, Mehta S, Fowler RA, Burns KEA, Wells PS, Carrier M, Crowther MA, Scales DC, English SW, Kyeremanteng K, Kanji S, Kho ME, Rochwerg B (2022) VTE prophylaxis in critically ill adults: a systematic review and network meta-analysis. Chest 161:418–428
6. Duranteau J, Taccone FS, Verhamme P, Ageno W, Force EVGT (2018) European guidelines on perioperative venous thromboembolism prophylaxis: intensive care. Eur J Anaesthesiol 35:142–146
7. Arabi YM, Al-Hameed F, Burns KEA, Mehta S, Alsolamy SJ, Alshahrani MS, Mandourah Y, Almekhlafi GA, Almaani M, Al Bshabshe A, Finfer S, Arshad Z, Khalid I, Mehta Y, Gaur A, Hawa H, Buscher H, Lababidi H, Al Aithan A, Abdukahil SAI, Jose J, Afesh LY, Al-Dawood A, Saudi Critical Care Trials G (2019) Adjunctive intermittent pneumatic compression for venous thromboprophylaxis. N Engl J Med 380:1305–1315
8. Afshari A, Fenger-Eriksen C, Monreal M, Verhamme P, Force EVGT (2018) European guidelines on perioperative venous thromboembolism prophylaxis: mechanical prophylaxis. Eur J Anaesthesiol 35:112–115
9. Sahle BW, Pilcher D, Peter K, McFadyen JD, Bucknall T (2022) Trends and risk factors for omission of early thromboprophylaxis in Australian and New Zealand ICUs between 2009 and 2020. Intensive Care Med 48:590–598
10. Lim W, Meade M, Lauzier F, Zarychanski R, Mehta S, Lamontagne F, Dodek P, McIntyre L, Hall R, Heels-Ansdell D, Fowler R, Pai M, Guyatt G, Crowther MA, Warkentin TE, Devereaux PJ, Walter SD, Muscedere J, Herridge M, Turgeon AF, Geerts W, Finfer S, Jacka M, Berwanger O, Ostermann M, Qushmaq I, Friedrich JO, Cook DJ, Investigators PRfTiCCT, (2015) Failure of anticoagulant thromboprophylaxis: risk factors in medical-surgical critically ill patients*. Crit Care Med 43:401–410

11. Gratz J, Wiegele M, Dibiasi C, Schaden E (2022) The challenge of pharmacological thromboprophylaxis in ICU patients: anti-FXa activity does not constitute a simple solution. Intensive Care Med. https://doi.org/10.1007/s00134-022-06744-8
12. Hofmaenner DA, Singer M (2022) The challenge of pharmacological thromboprophylaxis in ICU patients: anti-FXa activity does not constitute the simple solution. Author's reply. Intensive Care Med. https://doi.org/10.1007/s00134-022-06744-8
13. Levy JH, Connors JM (2021) Heparin resistance—clinical perspectives and management strategies. N Engl J Med 385:826–832
14. Helms J, Severac F, Merdji H, Anglés-Cano E, Meziani F (2020) Prothrombotic phenotype in COVID-19 severe patients. Intensive Care Med 46:1502–1503
15. Schulman S, Sholzberg M, Spyropoulos AC, Zarychans R, Resnick HE, Bradbury C, Broxmeyer L, Connors JM, Falanga A, Iba T, Kaatz S, Levy J, Middeldorp S, Minichiello TA, Ramacciotti E, Samama M, Thachil J (2022) ISTH guidelines for antithrombotic treatment in COVID-19. J Thromb Haemost. https://doi.org/10.1111/jth.15808