

GUIDELINES

European guidelines on perioperative venous thromboembolism prophylaxis

Intensive care

Jacques Duranteau, Fabio Silvio Taccone, Peter Verhamme and Walter Ageno, for the ESA VTE Guidelines Task Force

Venous thromboembolism is a common and potentially life-threatening complication that occurs in 4 to 15% of patients admitted to ICUs despite the routine use of pharmacological prophylaxis. We therefore recommend an institution-wide protocol for the prevention of venous thromboembolism (Grade 1B). The routine use of ultrasonographic screening for deep vein thrombosis is not recommended when thromboprophylactic measures are in place (Grade 1B), as the detection of asymptomatic deep vein thrombosis may prompt therapeutic anticoagulation that may increase bleeding risk but has no proven reduction of clinically significant thrombotic events. In critically ill patients, we recommend pharmacological prophylaxis with low molecular weight heparin over low-dose heparin (Grade 1B). For critically ill patients with severe renal insufficiency, we suggest the use of low-dose heparin (Grade 2C), dalteparin (Grade 2B) or reduced doses of enoxaparin (Grade 2C). Monitoring of anti-Xa activity may

be considered when low molecular weight heparin is used in these patients (Grade 2C). No study has prospectively evaluated the efficacy and safety of deep vein thrombosis prophylaxis in critically ill patients with severe liver dysfunction. Thus, the use of pharmacological prophylaxis in these patients should be carefully balanced against the risk of bleeding. For critically ill patients, we recommend against the routine use of inferior vena cava filters for the primary prevention of venous thromboembolism (Grade 1C). When the diagnosis of heparin-induced thrombocytopenia is suspected or confirmed, all forms of heparin must be discontinued (Grade 1B). In these patients, immediate anticoagulation with a nonheparin anticoagulant rather than discontinuation of heparin alone is recommended (Grade 1C).

Published online 6 November 2017

This article is part of the European guidelines on perioperative venous thromboembolism prophylaxis. For details concerning background, methods and members of the ESA VTE Guidelines Task Force, please, refer to:

Samama CM, Afshari A, for the ESA VTE Guidelines Task Force. European guidelines on perioperative venous thromboembolism prophylaxis. *Eur J Anaesthesiol* 2018; 35:73–76.

A synopsis of all recommendations can be found in the following accompanying article:

Afshari A, Ageno W, Ahmed A, *et al.*, for the ESA VTE Guidelines Task Force. European Guidelines on perioperative venous thromboembolism prophylaxis. Executive summary. *Eur J Anaesthesiol* 2018; 35:77–83.

Introduction

The risk of venous thromboembolism (VTE) in critically ill patients is substantial and is influenced by several factors, including underlying disorders, the duration of mechanical ventilation and the duration of ICU stay. Several studies have assessed the efficacy and safety of prophylactic strategies in this setting. We discuss the incidence, risk factors and prevention of VTE in critically ill patients admitted to ICU and we make recommendations for the prevention of VTE in this group. These recommendations are drawn from and expand other recent thromboprophylaxis guidelines such as those of the American College of Chest Physicians (ACCP).¹

From the Department of Anaesthesia and Intensive Care Medicine, Le Kremlin Bicêtre University Hospital, Assistance Publique – Hôpitaux de Paris, Paris, Université Paris-Sud, Hôpital de Bicêtre, Le Kremlin-Bicêtre, France (JD), Department of Intensive Care – Hopital Erasme, Université Libre de Bruxelles (ULB) – Brussels (FST), Vascular Medicine and Haemostasis Unit, University of Leuven, Leuven, Belgium (PV) and Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy (WA)

Correspondence to Jacques Duranteau, Department of Anaesthesia and Intensive Care Medicine, Le Kremlin Bicêtre University Hospital, 78 avenue du Général Leclerc, 94275 Le Kremlin Bicêtre, France
Tel: +33 1 45 21 34 41; e-mail: jacques.duranteau@aphp.fr

The risk of venous thromboembolism in critically ill patients

Autopsy studies have demonstrated the burden of fatal pulmonary embolism in hospitalised patients and highlighted that pulmonary embolism is a common preventable cause of in-hospital mortality. In these studies, pulmonary embolism contributed to death in approximately 5 to 10% of patients.^{2,3}

Because fatal or life-threatening pulmonary embolism is often the first clinical manifestation of VTE, prevention of the disease has become an established priority in ICUs. Critical care patients are prone to VTE, but the risk varied widely in reported historical studies, from 15% to well over 50%. Also, more contemporary data showed that the burden of VTE remains considerable despite the routine use of pharmacological prophylaxis, with VTE occurring in 4 to 15% of patients in ICUs.^{4–6}

The use of ultrasonographic screening for deep vein thrombosis

Because deep vein thrombosis (DVT) is often asymptomatic in critically ill patients and because fatal or life-threatening pulmonary embolism is often the first clinical manifestation of the disease, surveillance screening for DVT in selected patients has been advocated. Furthermore, the expertise of venous echography is readily available in ICUs because of its frequent use to assist in the placement of central venous catheters.⁷ Most studies with compression duplex ultrasound (DUS) surveillance have been performed in trauma patients. The ACCP guidelines recommend against routine DUS surveillance both in nonsurgical patients and following major surgery.¹ Compression DUS can be considered in selected high-risk patients with contraindications for pharmacological prophylaxis. No outcome studies have evaluated whether the routine surveillance for DVT in critically ill patients improves the outcome of such patients. The detection of asymptomatic or distal DVT may prompt therapeutic anticoagulation, which increases the bleeding risk but may not result in a reduction of the burden of clinically relevant VTE. Hence, routine DUS is not recommended when thromboprophylactic measures are in place, and when the diagnostic suspicion for the disease is low. Screening can be suggested in selected patients at a particularly high risk, such as patients with multiple trauma in whom there is an unavoidable delay before starting pharmacological prophylaxis due to the risk of haemorrhage, or patients with heparin-induced thrombocytopenia (HIT) or in at-risk patients unable to report pain.

The role of pharmacological prophylaxis for the prevention of venous thromboembolism in critically ill patients

Several randomised controlled trials have assessed the efficacy and safety of low-dose unfractionated heparin

(LDUH) and low molecular weight heparin (LMWH) for the prevention of VTE in critically ill patients. The results of five studies have been pooled by the authors of the 2012 ACCP clinical practice guidelines.¹ When combined, the results of these studies suggested that pharmacological prophylaxis nonsignificantly reduces the risk of symptomatic DVT and pulmonary embolism, and nonsignificantly increases the risk of major bleeding. A subsequent meta-analysis was published in 2013 and included seven trials with the addition of two studies reported as abstracts.⁸ Two of the included studies compared LDUH administered twice daily with placebo, one compared the LMWH nadroparin with placebo, and four studies compared LDUH administered twice daily with the LMWHs enoxaparin (40 mg once daily in two studies and 30 mg twice daily in one study) or dalteparin. Pharmacological thromboprophylaxis (including LDUH and LMWH) significantly reduced the rates of overall DVT (risk ratio 0.51, 95% confidence interval (CI) [0.41 to 0.63]) and pulmonary embolism (risk ratio 0.52, 95% CI [0.28 to 0.97]), but not the rates of symptomatic DVT (risk ratio 0.86, 95% CI [0.59 to 1.25]) when compared with placebo, while major bleeding (risk ratio 0.82, 95% CI [0.56 to 1.21]) and mortality rates (risk ratio 0.89, 95% CI [0.78 to 1.02]) were similar. LMWH significantly reduced the rates of symptomatic pulmonary embolism (risk ratio 0.58, 95% CI [0.34 to 0.97]) when compared with LDUH, with similar rates of symptomatic DVT (risk ratio 0.87, 95% CI [0.60 to 1.25]), major bleeding (risk ratio 0.97, 95% CI [0.75 to 1.26]) or mortality (risk ratio 0.93, 95% CI [0.82 to 1.04]). No studies are available with fondaparinux or the direct oral anticoagulants in this setting. Thus, until additional data become available, only LDUH and LMWH can be recommended for the prevention of VTE in critically ill patients, and on the basis of the results of direct comparisons, LMWHs seem to provide a more favourable efficacy profile than LDUH. Yet, failure rates of anticoagulant prophylaxis with LMWH or LDUH remain not negligible. In a recent study, 7.7% of critically ill patients receiving anticoagulant prophylaxis developed VTE.⁹ Previous VTE or a family history of VTE, and BMI, were independently associated with treatment failure.

Venous thromboembolism prophylaxis in critically ill patients with severe renal insufficiency

There are only limited data on the use of LMWH in patients with severe renal insufficiency [i.e. patients with creatinine clearance (CrCl) below 30 ml min⁻¹] where drug accumulation may occur.¹⁰ In contrast, UFH metabolism is less affected by renal function and a prolonged activated partial thromboplastin time (aPTT) in a patient with severe renal insufficiency suggests drug accumulation.¹⁰ Moreover, in critically ill patients with a high bleeding risk, UFH is rapidly eliminated after discontinuation and can be antagonised by protamine sulphate.¹¹

The use of LMWH has been shown to be effective and well tolerated in circuit thrombosis during haemodialysis in patients with end-stage renal failure.¹² However, no data on the optimal dosing of LMWH in unstable patients with continuous renal replacement therapies are available.

Among different LMWHs, the clearance of dalteparin and tinzaparin, which have the highest molecular weights, is less dependent on renal function than the clearance of LMWHs with a lower molecular weight, such as enoxaparin or nadroparin.¹⁰ In one study on dalteparin in ICU patients with severe renal failure, the anticoagulant activity remained within the expected ranges for VTE prophylaxis during the first 7 days of therapy.¹³ In another study,¹⁴ DVT prophylaxis with dalteparin (5000 IU once daily) was given to 156 critically ill patients with CrCL less than 30 ml min⁻¹. In 120 patients with anti-Xa level assessment, no patient showed drug bioaccumulation (defined as anti-Xa level >0.40 IU ml⁻¹). Major bleeding occurred in 7% of patients, all with anti-Xa levels of 0.18 IU ml⁻¹ or lower. For other LMWHs, a meta-analysis including studies performed in noncritically ill cohorts showed that anticoagulant activity and the risk of major bleeding were higher in patients with a CrCL less than 30 ml min⁻¹ when a standard therapeutic dose of enoxaparin was used in comparison with patients with higher CrCL.¹⁵ Data were insufficient for tinzaparin and, in general, for prophylactic doses of LMWH. In patients with prolonged administration of prophylactic LMWH, a reduced dose of enoxaparin may be considered to decrease the risk of bleeding. Alternatively, because dose reductions could expose patients to an increased risk of VTE, anti-Xa levels can be measured periodically, although this may not be available in all centres.

Few studies have investigated selective factor Xa or thrombin inhibitors in this setting. One study evaluating fondaparinux in a small number of high-risk postoperative patients with renal insufficiency suggested that the use of 1.5 mg of fondaparinux every 24 h for thromboprophylaxis in patients with renal insufficiency undergoing high-risk surgical procedures was well tolerated.¹⁶ No data are available on the direct oral anticoagulants in critically ill patients with renal insufficiency.

Deep vein thrombosis prophylaxis in patients with severe liver dysfunction

Coagulation abnormalities in acute liver failure or end-stage liver disease may significantly increase the risk of bleeding in patients receiving thromboprophylaxis. Nevertheless, the risk of DVT is similar in patients with or without liver cirrhosis.¹⁷ Moreover, in patients undergoing orthotopic liver transplantation, Alexander *et al.*¹⁸ showed that the overall incidence of VTE was 2%; remarkably, the incidence of VTE was higher in patients receiving thromboprophylaxis (3.6 vs. 1.4%; $P=0.06$).

No study has prospectively evaluated the efficacy and safety of DVT prophylaxis in this patient population. As LDUH is currently used to prevent thrombosis in cirrhotic patients treated with transjugular intrahepatic porto-systemic shunts (TIPSS),¹⁹ this may be considered as a first choice therapy in this setting.

Deep vein thrombosis prophylaxis in patients with thrombocytopenia

Patients with a low platelet count present a significant increase in the risk of bleeding when receiving thromboprophylaxis. In a double-blind, randomised controlled study comparing enoxaparin with placebo for the prevention of VTE in noncritically ill patients, a platelet count of less than 100 000 mm⁻³ was an exclusion criterion.²⁰ In another study evaluating the risk of drug accumulation during dalteparin therapy in critically ill patients,¹⁴ patients with a platelet count lower than 75 000 mm⁻³ were not considered eligible.

Mechanical DVT prophylaxis is considered an alternative in these patients. In patients at a high risk of bleeding,²¹ including patients with a platelet count less than 50 000 mm⁻³, intermittent pneumatic compression (IPC) associated with graduated compression stockings (IPC+GCS) reduced the occurrence of VTE between days 1 and 6 from 9.2% (GCS alone) to 5.6% ($P=0.19$). In a study including patients with absolute contraindications to pharmacological prophylaxis, early bedside placement of an inferior vena cava (IVC) catheter was a well tolerated and effective alternative to short-term drug administration.²²

What to do in critically ill adult patients who develop heparin-induced thrombocytopenia while receiving heparin?

There is no clear evidence that UFH or LMWHs have any effect on the occurrence of all-cause thrombocytopenia in different patient populations.²³ However, heparin-induced thrombocytopenia (HIT) is a life-threatening complication that may develop after exposure to UFH or LMWHs, which is triggered by an autoimmune process with IgG auto-antibodies directed against platelet factor 4 (PF4).²⁴ These antibodies eventually activate platelets and increase the risk of both arterial and venous thrombosis.

In the event of suspected or confirmed HIT, all forms of heparin should be discontinued. In the absence of a high risk of bleeding, anticoagulation with a nonheparin anticoagulant should be initiated in all patients, but warfarin should not be started until thrombocytopenia resolves because of the risk of transient hypercoagulability and limb gangrene.²⁵ Currently available drugs are argatroban, fondaparinux, bivalirudin, lepirudin (limited availability) and danaparoid (risk of cross reaction with HIT antibodies in 5 to 10% patients).²⁶ Argatroban should be considered in patients with renal failure, as this drug is

metabolised by the liver and does not require dose adjustment in this setting. In 20 critically ill patients with HIT and renal failure, argatroban was associated with a rapid increase in platelet count; new thrombotic events were observed in 25% of patients and major bleeding in 15%.²⁷ In another retrospective study on critically ill patients with HIT ($n = 56$), no thromboembolic complications were observed during argatroban therapy.²⁸ Finally, argatroban can also provide effective anticoagulation in patients undergoing continuous renal replacement therapy.²⁹ However, the half-life of argatroban is markedly increased in some critically ill patients, such as after heart surgery, and further prolonged by hepatic dysfunction.³⁰ In 12 patients with multiple organ dysfunction/failure and treated with argatroban for suspected or diagnosed HIT, a decrease in the initial dosage was mandatory.³¹

In a small cohort of critically ill patients with suspected HIT, a prophylactic dose fondaparinux was effective to prevent new thrombotic events and avoided the enlargement of previously existing clots.³² Fondaparinux has also been used with an acceptable rate of thrombosis and without major bleeding events in patients with a left ventricular assist device who were diagnosed with HIT.³³ Fondaparinux had similar effectiveness and safety as argatroban in patients with suspected HIT.³⁴ Fondaparinux can also be used during continuous renal replacement therapy because of its low molecular weight and the lack of binding to proteins that facilitates drug elimination through renal replacement therapy techniques.³⁵ However, clinical experience with fondaparinux in HIT patients is still limited and deserves further studies, especially in critically ill patients. As an alternative, low doses of bivalirudin safely achieved adequate anticoagulant levels in critically ill patients with hepatic and/or renal dysfunction.³⁶ In particular, bivalirudin treatment was associated with a reduction of major bleeding ($P = 0.05$) compared with UFH in patients undergoing heart surgery and should be considered as one of the first therapeutic options in this patient population when HIT is diagnosed.³⁷

The role of mechanical prophylaxis

This is discussed elsewhere in [EJA-D-17-00379 – Afshari A *et al.*]

The use of inferior vena cava filters

There are no randomised controlled trials that have assessed the role of IVC filters in critically ill patients with contraindications to anticoagulant prophylaxis. In two prospective cohort studies, the Angel Catheter device was placed in a total of 68 patients at a high risk of pulmonary embolism admitted to ICUs.^{22,38} In the first study, the filter was implanted in 51 of 68 patients for the primary prevention of VTE; the majority of patients (55%) were admitted because of trauma, and

all but three patients had contraindications to anticoagulant therapy.²² In the second study, in seven of eight enrolled patients, the filter was implanted for the primary prevention of VTE; three had contraindications to anticoagulant therapy and the majority ($n = 6$) were admitted because of trauma.³⁸ All devices were retrieved without complications. Until additional evidence becomes available, the use of IVC filters should be considered only for patients with absolute contraindications to anticoagulant prophylaxis in whom IPC cannot be used.

Recommendations

- In critically ill patients, we recommend against the routine use of compression DUS screening of DVT (Grade 1B).
- We recommend an institution-wide protocol for the prevention of VTE that includes the use of mechanical thromboprophylaxis, that is IPC (Grade 1B).
- For critically ill patients, we recommend using thromboprophylaxis with LMWH or LDUH (Grade 1B) and we recommend LMWH over LDUH (Grade 1B).
- For VTE prophylaxis in critically ill patients with severe renal insufficiency, we suggest the use of LDUH (Grade 2C), dalteparin (Grade 2B) or reduced doses of enoxaparin (Grade 2C). Monitoring of anti-Xa activity may be considered when LMWH is used in these patients (Grade 2C).
- The use of pharmacological prophylaxis in patients with severe liver dysfunction should be carefully balanced against the risk of bleeding. If a treatment is administered, the use of LDUH or LMWH is suggested (Grade 2C).
- We suggest no prophylaxis or the use of IPC in patients with a platelet count less than $50\,000\text{ mm}^{-3}$ and a high risk of bleeding (Grade 2C).
- For critically ill patients, we recommend against the routine use of IVC filters (IVCFs) for the primary prevention of VTE (Grade 1C). We suggest the use of IVCF in patients who can neither receive pharmacological prophylaxis nor IPC (Grade 2C).
- In critically ill patients with a suspected or confirmed diagnosis of heparin-induced thrombocytopenia (HIT), all forms of heparin must be discontinued (Grade 1B). In these patients, immediate anticoagulation with a nonheparin anticoagulant rather than discontinuation of heparin alone is recommended, unless there is a strong contraindication to anticoagulation (Grade 1C). The selection of nonheparin anticoagulants should be based on patient characteristics: argatroban is the first choice in patients with renal insufficiency, and bivalirudin in patients undergoing or after cardiac surgery (Grade 2C). The use of fondaparinux can also be considered in these patients (Grade 2C).

Acknowledgements relating to this article

Assistance with the guideline chapter: none.

Financial support and sponsorship: expenses of two meetings of the VTE Task Force (Brussels and Berlin) were covered by the ESA for the ESA members.

Conflicts of interest: PV has received honoraria for lectures and advisory boards from Bayer-Healthcare, Boehringer-Ingelheim, Pfizer, Daiichi-Sankyo, Medtronic, Portola and Bristol-Myers-Squibb and received research support from Bayer-Healthcare, Boehringer-Ingelheim, Leo-Pharma, Sanofi and Daiichi-Sankyo. WA has received research grants from Bayer and participated in advisory boards for Bayer, Boehringer-Ingelheim, Daiichi Sankyo and BMS Pfizer.

References

- Kahn SR, Lim W, Dunn AS, *et al.* Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th edn: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141** (2 Suppl):e195S–e226S.
- Alikhan R, Peters F, Wilmott R, Cohen AT. Fatal pulmonary embolism in hospitalised patients: a necropsy review. *J Clin Pathol* 2004; **57**:1254–1257.
- Anderson FA Jr, Wheeler HB, Goldberg RJ, *et al.* A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch Intern Med* 1991; **151**:933–938.
- Attia J, Ray JG, Cook DJ, *et al.* Deep vein thrombosis and its prevention in critically ill adults. *Arch Intern Med* 2001; **161**:1268–1279.
- PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Cook D, Meade M, Guyatt G, *et al.* Dalteparin versus unfractionated heparin in critically ill patients. *N Engl J Med* 2011; **364**:1305–1314.
- Patel R, Cook DJ, Meade MO, *et al.* Burden of illness in venous thromboembolism in critical care: a multicenter observational study. *J Crit Care* 2005; **20**:341–347.
- Frankel HL, Kirkpatrick AW, Elbarbary M, *et al.* Guidelines for the appropriate use of bedside general and cardiac ultrasonography in the evaluation of critically ill patients – part i: general ultrasonography. *Crit Care Med* 2015; **43**:2479–2502.
- Alhazzani W, Lim W, Jaeschke RZ, *et al.* Heparin thromboprophylaxis in medical-surgical critically ill patients: a systematic review and meta-analysis of randomized trials. *Crit Care Med* 2013; **41**:2088–2098.
- Lim W, Meade M, Lauzier F, *et al.* Failure of anticoagulant thromboprophylaxis: risk factors in medical-surgical critically ill patients. *Crit Care Med* 2015; **43**:401–410.
- Frydman A. Low-molecular-weight heparins: an overview of their pharmacodynamics, pharmacokinetics and metabolism in humans. *Haemostasis* 1996; **26** (Suppl 2):24–38.
- Crowther MA, Berry LR, Monagle PT, Chan AK. Mechanisms responsible for the failure of protamine to inactivate low-molecular-weight heparin. *Br J Haematol* 2002; **116**:178–186.
- Lim W, Cook DJ, Crowther MA. Safety and efficacy of low molecular weight heparins for hemodialysis in patients with end-stage renal failure: a meta-analysis of randomized trials. *J Am Soc Nephrol* 2004; **15**:3192–3206.
- Cook D, Douketis J, Meade M, *et al.* Venous thromboembolism and bleeding in critically ill patients with severe renal insufficiency receiving dalteparin thromboprophylaxis: prevalence, incidence and risk factors. *Crit Care* 2008; **12**:R32.
- Douketis J, Cook D, Meade M, *et al.* Prophylaxis against deep vein thrombosis in critically ill patients with severe renal insufficiency with the low-molecular-weight heparin dalteparin: an assessment of safety and pharmacodynamics: the DIRECT study. *Arch Intern Med* 2008; **168**:1805–1812.
- Lim W, Dentali F, Eikelboom JW, Crowther MA. Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. *Ann Intern Med* 2006; **144**:673–684.
- Hester W, Fry C, Gonzalez D, *et al.* Thromboprophylaxis with fondaparinux in high-risk postoperative patients with renal insufficiency. *Thromb Res* 2014; **133**:629–633.
- Al-Dorzi HM, Tamim HM, Aldawood AS, Arabi YM. Venous thromboembolism in critically ill cirrhotic patients: practices of prophylaxis and incidence. *Thrombosis* 2013; **2013**:807526.
- Alexander BR, Antigua AD, Rosenberg AF, *et al.* Chemoprophylaxis use and risk of venous thromboembolism and death in adult patients following orthotopic liver transplantation. *J Pharm Pract* 2016; **29**:218–223.
- Sanyal AJ, Freedman AM, Luketic VA, *et al.* Transjugular intrahepatic portosystemic shunts compared with endoscopic sclerotherapy for the prevention of recurrent variceal hemorrhage. A randomized, controlled trial. *Ann Intern Med* 1997; **126**:849–857.
- Samama MM, Cohen AT, Darmon JY, *et al.* A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. *N Engl J Med* 1999; **341**:793–800.
- Vignon P, Dequin PF, Renault A, *et al.* Intermittent pneumatic compression to prevent venous thromboembolism in patients with high risk of bleeding hospitalized in intensive care units: the CIREA1 randomized trial. *Intensive Care Med* 2013; **39**:872–880.
- Taccone FS, Bunker N, Waldmann C, *et al.* A new device for the prevention of pulmonary embolism in critically ill patients: results of the European Angel Catheter Registry. *J Trauma Acute Care Surg* 2015; **79**:456–462.
- Alikhan R, Bedenis R, Cohen AT. Heparin for the prevention of venous thromboembolism in acutely ill medical patients (excluding stroke and myocardial infarction). *Cochrane Database Syst Rev* 2014; **5**:CD003747.
- Warkentin TE. Heparin-induced thrombocytopenia. *Curr Opin Crit Care* 2015; **21**:576–585.
- Srinivasan AF, Rice L, Bartholomew JR, *et al.* Warfarin-induced skin necrosis and venous limb gangrene in the setting of heparin-induced thrombocytopenia. *Arch Intern Med* 2004; **164**:66–70.
- Tardy-Poncet B, Wolf M, Lasne D, *et al.* Danaparoid cross-reactivity with heparin-induced thrombocytopenia antibodies: report of 12 cases. *Intensive Care Med* 2009; **35**:1449–1453.
- Tardy-Poncet B, Nguyen P, Thiranos JC, *et al.* Argatroban in the management of heparin-induced thrombocytopenia: a multicenter clinical trial. *Crit Care* 2015; **19**:396.
- Kim S-C, Tran N, Schewe J-C, *et al.* Safety and economic considerations of argatroban use in critically ill patients: a retrospective analysis. *J Cardiothorac Surg* 2015; **10**:19.
- Klingele MBH, Lerner-Gräber A, Fliser D, *et al.* Use of argatroban: experiences in continuous renal replacement therapy in critically ill patients after cardiac surgery. *J Thorac Cardiovasc Surg* 2014; **147**:1918–1924.
- Keyl C, Zimmer E, Bek MJ, *et al.* Argatroban pharmacokinetics and pharmacodynamics in critically ill cardiac surgical patients with suspected heparin-induced thrombocytopenia. *Thromb Haemost* 2016; **115**:1081–1089.
- Saugel B, Phillip V, Moessmer G, *et al.* Argatroban therapy for heparin-induced thrombocytopenia in ICU patients with multiple organ dysfunction syndrome: a retrospective study. *Crit Care* 2010; **14**:R90.
- Wester JP, Leyte A, Oudemans-van Straaten HM, *et al.* Low-dose fondaparinux in suspected heparin-induced thrombocytopenia in the critically ill. *Neth J Med* 2007; **65**:101–108.
- Benken ST, Tillman N, Dajani S, *et al.* A retrospective evaluation of fondaparinux for confirmed or suspected heparin-induced thrombocytopenia in left-ventricular-assist device patients. *J Cardiothorac Surg* 2014; **9**:55.
- Kang M, Alahmadi M, Sawh S, *et al.* Fondaparinux for the treatment of suspected heparin-induced thrombocytopenia: a propensity score-matched study. *Blood* 2015; **125**:924–929.
- Sharathkumar AA, Crandall C, Lin JJ, Pipe S. Treatment of thrombosis with fondaparinux (Arixtra) in a patient with end-stage renal disease receiving hemodialysis therapy. *J Pediatr Hematol Oncol* 2007; **29**:581–584.
- Kiser TH, Fish DN. Evaluation of bivalirudin treatment for heparin-induced thrombocytopenia in critically ill patients with hepatic and/or renal dysfunction. *Pharmacotherapy* 2006; **26**:452–460.
- Pappalardo FAN, Covello RD, Pieri M, *et al.* Anticoagulation for critically ill cardiac surgery patients: is primary bivalirudin the next step? *J Cardiothorac Vasc Anesth* 2014; **28**:1013–1017.
- Cadavid CA, Gil B, Restrepo A, *et al.* Pilot study evaluating the safety of a combined central venous catheter and inferior vena cava filter in critically ill patients at high risk of pulmonary embolism. *J Vasc Interv Radiol* 2013; **24**:581–585.