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European guidelines on perioperative venous thromboembolism prophylaxis

Cardiovascular and thoracic surgery

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None of the predictive models for venous thromboembolism (VTE) prophylaxis have been designed for and validated in patients undergoing cardiothoracic and vascular surgery. The presence of one or more risk factors [age over 70 years old, transfusion of more than 4 U of red blood cells/fresh frozen plasma/cryoprecipitate, mechanical ventilation lasting more than 24 h, postoperative complication (e.g. acute kidney injury, infection/sepsis, neurological complication)] should place the cardiac population at high risk for VTE. In this context, we suggest the use of pharmacological prophylaxis as soon as satisfactory haemostasis has been achieved, in addition to intermittent pneumatic compression (IPC) (Grade 2C). In patients undergoing abdominal aortic aneurysm repair, particularly when an open surgical approach is used, the risk for VTE is high and the bleeding risk is high. In this context, we suggest the use of pharmacological prophylaxis as soon as satisfactory haemostasis is achieved (Grade 2C). Patients undergoing thoracic surgery in the absence of cancer could be considered at low risk for VTE. Patients undergoing thoracic surgery with a diagnosis of primary or metastatic cancer should be considered at high risk for VTE. In low-risk patients, we suggest the use of mechanical prophylaxis using IPC (Grade 2C). In high-risk patients, we suggest the use of pharmacological prophylaxis in addition to IPC (Grade 2B).

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

Afshari A *et al.* European Guidelines on venous thromboembolism prophylaxis. Executive summary. *Eur J Anaesthesiol* 2018; X:000-000

Introduction

Venous thromboembolism (VTE) comprising deep venous thrombosis (DVT) and pulmonary embolism contribute to a high incidence of perioperative mortality.[1] Identifying patients at higher risk for perioperative VTE is crucial before instituting preventive measures that seek to decrease the incidence of symptomatic events without increasing the risk for bleeding complications. Different predictive models have been developed in the surgical population,[2–4] but none has assessed predictive factors in patients undergoing cardiovascular surgery. The Caprini 'venous thromboembolism risk assessment model' was used in the 2012 *American College of Chest Physicians'* (ACCP) guidelines to define the individual risk for VTE in patients undergoing general, non-cardiovascular, surgery.[5] Although a recent investigation validated this

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model in critically ill surgical patients,[6] this risk stratification is still missing in the sections on cardiovascular and thoracic procedures. This is particularly true in the setting of cardiac surgery, where large differences in surgical techniques (e.g. internal thoracic arteries vs. one arterial graft and additional venous grafts), surgical complexity (e.g. conventional valve replacement with sternotomy vs. minimal invasive lateral approaches) and the use of cardiopulmonary bypass ('on pump' procedures vs. 'off pump' procedures) could significantly influence both the risk of VTE and haemorrhagic complications. As long as such models are not validated for these specific populations and procedures, the risk of VTE should be specifically assessed based on the existing literature and should not be generalised using non-specific predictive models. In addition, due to the increasing age of the cardiothoracic surgical population and the increased number of comorbidities, a specific approach should be used to balance the risk of VTE against the risk of bleeding.[7]

Risk stratification in cardiac surgery

In the 2012 ACCP guidelines, patients undergoing cardiac surgery were evaluated to have an intermediate risk of VTE, with a high risk of perioperative bleeding.[5]

In a recent retrospective analysis reviewing more than 90 000 patients from the Premier Perspective Comparative database in the United States, the incidence of symptomatic VTE varied between 0.70% in the absence of prophylaxis to 1.14% in patients who received fondaparinux.[8] The incidence of major haemorrhagic complications was 1.43%. Another retrospective study recently reviewed more than 2 million patients from the American College of Surgeons National Surgical Quality Improvement Program database, and compared the incidence of DVT between general surgery and cardiac surgery.[9] In this study, the incidence of DVT was 0.66% in general surgery and 2.07% in cardiac surgery.

In 2010, Schwann *et al.*[10] reviewed 1070 adult cardiac surgical patients who underwent duplex venous scan (DVS) screening in the perioperative period of cardiac surgery. In this study, the authors reported a 13% incidence of 'silent' DVT within 30 postoperative days. The incidence of DVT was 12.9% after coronary artery bypass graft (CABG), 20% after isolated valve surgery and 12.4% after combined CABG and valve surgery. Increased age (>70 years), blood product transfusion, prolonged mechanical ventilation (>24 h) and the need for postoperative reintubation of the trachea were strong predictors of postoperative DVT. There was no difference with regard to the re-exploration rate (1.7% DVT vs. 1.9% no-DVT). The 30-day mortality in the patients with DVT was 6.9% compared with 1.7% in patients without DVT ($P < 0.003$). Another recent study confirmed the relationship between blood product transfusion and the incidence of DVT in adults undergoing cardiac surgery.[11] In this study, the authors reported that red blood cell (RBC) transfusion is associated with a dose-dependent increase in the incidence of DVT (>1-U RBC), and this deleterious effect is exacerbated with the co-administration of fresh frozen plasma and/or cryoprecipitate.

Current evidence regarding the incidence of DVT and VTE in patients undergoing cardiac surgery is somewhat conflicting. Although the incidence of symptomatic VTE is relatively low (between 0.70 and 2.07% depending on the prevention strategy), studies that used a systematic screening strategy using DVS reported a high incidence of 'silent' DVT (≈13%). According to these data, risk factors for postoperative VTE are age more than 70 years, transfusion of blood products, postoperative mechanical ventilation more than 24 h and postoperative complications (e.g. reintubation, renal failure, neurological complications, infection and sepsis).

Most of these studies included both patients who underwent CABG surgery and valve replacement surgery. However, patients undergoing mechanical valve replacement surgery, implantation of a mitral or tricuspid valve, or valvuloplasty should be considered as a specific population, as they require 'bridging' anti-coagulation before intermediate or long-term oral anti-coagulation.[12] Patients after implantation of a bioprosthetic aortic valve may be considered as having the same risk category as CABG patients and will not require intermittent vitamin K antagonist therapy, but low-dose aspirin therapy.[12–15] Patients with pre and/or postoperative atrial fibrillation should equally be considered as a specific entity as they will require a specific approach.

Risk stratification in vascular surgery

Due to the limited data available for vascular patients, the 2012 ACCP guidelines included vascular patients with the group of patients undergoing general surgery. This approach may be supported by the recent study published by Aziz *et al.*,[9] in which the incidence of DVT was 0.69% in general surgery patients and only moderately increased to 0.99% in vascular surgery patients. Ramanan *et al.*[16] measured the incidence of VTE in a cohort of 45 548 patients undergoing vascular surgery. VTE was reported in 0.7% of patients, with an incidence of 0.2% of pulmonary embolism. Patients with thoraco-abdominal aortic aneurysm repair had the highest rate of VTE (4.2%), followed by thoracic endovascular repair (2.2%), open abdominal aortic surgery (1.7%) and endovascular aneurysm repair (EVAR) (0.7%). The incidence of VTE in patients undergoing peripheral bypass surgery was 1% and for carotid endarterectomy 0.2%. Significantly, the authors also reported that 41% of the VTE events were diagnosed after discharge, suggesting that high-risk patients could benefit from post-discharge prophylaxis.

In a large national survey comprising 12 469 patients, the incidence of DVT after repair of an unruptured abdominal aortic aneurysm (AAA) was 1.1%.[17] The 'in hospital'

incidence was higher (1.6%) in patients who underwent 'open surgery' compared with EVAR (0.4%). In another study published in 2012, Scarborough *et al.*[18] reviewed the incidence and predictors of VTE among 6035 patients undergoing open aortic surgery, and defined a scoring system for predicting postoperative VTE complications in this population. The following parameters were identified as being independent predictors of postoperative VTE and were used to develop a simple scoring system: preoperative dyspnoea, chronic steroid use, ruptured aneurysm, operative duration at least 5 h, BMI at least 30 kg m^{-2}, postoperative pneumonia, postoperative mechanical ventilation more than 48 h and re-operation.

In 2013, Davenport and Xenos[17] developed a similar risk index in patients undergoing repair for non-ruptured AAA. The factors associated with the highest risk were operative duration more than 4 h (4 points), followed by the administration of at least 5-U RBC and preoperative serum albumin 3 g dl^{-1} or less (3 points), and American Society of Anesthesiologists' (ASA) physical status 4 or 5, preoperative dyspnoea, open vs. endovascular repair, and/or the presence of wound infection (2 points). The incidence of VTE was 0.4% in patients with a score less than 4, 1.2% with a score of 4 to 7, 2.6% with a score of 8 to 10, and 4.6% with a score at least 11.

A single-centre study of 192 patients undergoing elective AAA repair assessed the incidence of DVT using preoperative and postoperative DVS.[19] Despite mechanical prophylaxis, the incidence of DVT when early mobilisation and administration of low molecular weight heparin (LMWH) was instituted (not among those with bleeding or in need of transfusion) was 10.2% in patients undergoing open surgical repair of the AAA and 5.3% among EVAR patients. As previously discussed for cardiac surgical patients, the observed incidence represents the incidence of 'silent' DVT diagnosed by systematic screening with DVS.

Evidence regarding preventive strategies in cardiac and vascular surgery

Only a few older studies have assessed and compared the efficacy of different prophylactic strategies in patients undergoing cardiac and vascular surgery.[20,21] These studies were performed in the late 1980s and early 1990s in an entirely different surgical population. Although recent meta-analyses have suggested that VTE prophylaxis could significantly reduce the risk of VTE without increasing the risk of bleeding and cardiac tamponade, the quality of these meta-analyses is limited by the weak quality of the studies included.[22,23] In addition, these meta-analyses were unable to demonstrate superiority or any signs of improved safety of one form of prophylaxis over another.

Due to its relatively short half-life (2 to 4 h) and the availability of a specific reversal agent (protamine), unfractionated heparin (UFH) remains the 'gold standard' for perioperative anti-coagulation in patients undergoing cardiac and major vascular surgery. LMWHs are usually used to 'bridge' vitamin K antagonist therapy perioperatively and are the primary agents for perioperative VTE prophylaxis in other surgical settings. The elimination half-life of LMWHs is approximately 4 to 8 h, but pharmacokinetics vary among the agents due to their different compositions. Elimination is predominantly via the renal system and only the effect of larger chains can be neutralised by protamine. Dosing protocols vary from fixed dosages to weight-adjusted protocols, from once to twice-daily administration, while some agents require a lower dose in patients with severe renal impairment (creatinine clearance < 30 ml min^{-1}).[24] Monitoring of the effect of LMWH is usually performed using a chromogenic anti-Xa assay. The use of LMWH has been associated with an 80% reduction in the incidence of heparin-induced thrombocytopaenia (HIT), a potentially severe thrombotic complication.[25]

Due to the heterogeneity of different LMWHs used in clinical practice, the results obtained with one LMWH cannot be extrapolated to the entire group of agents.[26] To date, a limited number of studies have compared the safety and efficacy of UFH with LMWHs or fondaparinux in patients undergoing cardiac or aortic surgery. In a small retrospective investigation including approximately 200 patients following heart valve surgery, the administration of LMWH (dalteparin) was associated with a lower incidence of thrombotic events (4 vs. 11%) when compared with UFH, in addition to a lower risk of HIT (3 vs. 6%), HIT associated with thrombotic events (1 vs. 4%) and bleeding episodes (3 vs. 10%).[27] In two smaller studies performed in CABG patients, no difference in the incidence of bleeding events was reported when fondaparinux was compared with LMWH.[28,29]

In patients undergoing lower extremity arterial reconstruction, the efficacy and safety of UFH was compared with LMWH after stratification for the risk of VTE.[30] The anticoagulation of low-risk patients consisted of either two injections of 7500 IU UFH subcutaneously ($n = 158$) or one daily injection of 40 mg (4000 IU) LMWH up to discharge ($n = 169$). High-risk patients received either 25,000 IU UFH intravenous over 24 h and 4 days ($n = 48$), two-times ($n = 51$) or one-time weight-adjusted LMWH ($n = 49$) up to discharge (1 mg kg^{-1} or 100 U kg^{-1}). This study reported that the administration of LMWH significantly reduced the incidence of vascular re-occlusion in both high-risk and low-risk patients without increasing the incidence of bleeding complications. In a recent study performed in patients undergoing a large variety of vascular surgical procedures, Durinka *et al.*[31] reviewed the change in the incidence of VTE after the implementation of a strict VTE prophylaxis protocol with early (within 24 h postop.) medical DVT prophylaxis [UFH subcutaneous (s.c.) three times daily or enoxaparin]. The VTE prophylaxis protocol was based

on a multidisciplinary assessment of the risk, with inclusion of mechanical prophylaxis. The implementations of this standardised protocol reduced the overall incidence of VTE by 75%.

Aspirin is routinely administered after cardiac surgery and vascular surgery to preserve graft patency, and low-dose aspirin may also reduce the incidence of VTE.[32] In patients following orthopaedic surgery, a recent meta-analysis classified aspirin as being as efficacious as LMWH to prevent VTE.[33] The analysis of the INSPIRE study showed an approximately 30% reduction in the recurrence of venous thrombosis when aspirin was given,[34] while the ASPIRE trial did not report any benefit of aspirin administration.[35] Studies in cardiothoracic and vascular surgery are missing. Hence, in these scenarios, the role of low-dose aspirin monotherapy in the prevention of VTE is unclear. In a recent study, Mirhosseini *et al.*[36] randomised 120 patients undergoing elective OPCABG surgery to receive UFH (5000 IU s.c. every 8 h) or aspirin (80 mg daily) and heparin (5000 IU s.c. every 8 h). In this study, the incidence of postoperative DVT was significantly reduced (16.6 vs. 3.3%) when aspirin was administered in addition to s.c. heparin. These data suggest a potential role of low-dose aspirin in reducing the risk of DVT in this specific patient population.

Risk stratification in thoracic surgery

The incidence of VTE in patients undergoing thoracic surgery remains unclear, and varies with the underlying disease (e.g. cancer), the type of procedure (e.g. thoracotomy vs. minimally invasive), co-morbidities, the screening strategy and the prophylactic approach.[23] As reported in the study published by Gomez-Hernandez *et al.*[37], lung cancer, lung metastasis or pulmonary nodules represent the vast majority of the indications for thoracic surgery. Although the incidence of VTE was relatively low in the general thoracic population (0.18%), the incidence was significantly higher in patients presenting with two or more of the following risk factors: advanced age, obesity, cancer and history of DVT. Lung cancer patients undergoing thoracic surgery have at least a two-fold increased risk of DVT and a three-fold increased risk of pulmonary embolism compared with those without surgery.[38] In a study that explored the long-term incidence of VTE among 1001 surgical patients with lung cancer, the cumulative incidence of VTE was 2% at 1 month, 3% at 3 months and 5.3% at 30 months.[39] In a recent systematic review assessing 19 studies, Christensen *et al.*[40] reported a pooled risk of VTE of 2.0%, but with a large inter-study variation (0.2 to 19%). The authors were not able to draw any firm conclusions regarding a potential benefit of minimally invasive procedures vs. open thoracotomy due to the very limited number of patients who had minimally invasive procedures in the included studies. Although one might expect a lower incidence of VTE in patients undergoing minimally invasive thoracic surgery, a recent study reported an incidence of 1.9% (47/2445) in patients who underwent thoracotomy vs. 1.2% (33/2831) in patients with minimal access surgery. The incidence of VTE was 2% in a population of 3208 patients undergoing oesophagectomy.[41] After stratification for timing (pre-discharge vs. post-discharge), the authors reported that 17% of VTE occurred after discharge. High ASA classification, diabetes mellitus, preoperative dyspnoea, history of cardiovascular disease, arterial hypertension and preoperative anaemia were associated with pre-discharge VTE, while advanced age was the only item associated with post-discharge VTE.

In a recent study from Hachey *et al.*[42], the Caprini score was used for preoperative risk stratification in a cohort of 253 patients undergoing lung surgery for cancer. A Caprini score more than 9 was associated with a negative predictive value of 98.5% for VTE in this specific population. In a cohort of 97 patients undergoing oesophagectomy, a Caprini risk score more than 15 showed a negative predictive value of 100%.[43]

Evidence regarding preventive strategies in thoracic surgery

As discussed in the cardiovascular section, only a few studies have compared different prophylactic strategies in patients undergoing thoracic surgery. Among six studies published before 2000, none showed any statistically significant difference between different pharmacological strategies to reduce the incidence of VTE or increase the risk of bleeding.[23]

In a before-and-after study, Nagahiro *et al.*[44] reported the efficacy of intermittent pneumatic compression (IPC) in preventing pulmonary embolism in 706 patients undergoing thoracic surgery between 1995 and 2000. Among 344 patients not receiving any prophylactic treatment, seven (2%) had postoperative pulmonary embolism while IPC was found to prevent pulmonary embolism among 362 patients in the interventional group.

In another retrospective study, a group of 169 patients with IPC was compared with a group of 154 patients who received IPC and UFH (2500 to 5000 IU s.c. twice daily).[45] Pulmonary embolism was reported in only one of the 169 patients included in the IPC group, while no pulmonary embolism was reported in the group of patients who received both IPC and UFH. The small number of patients included, the retrospective nature of the study and the single-centre design limited the extrapolation of the results to a larger cohort of patients. In a retrospective study, enoxaparin 40 mg daily was compared with fondaparinux 2.5 mg daily in medical and thoracic surgical patients.[46] Although the authors reported no significant difference in the incidence of VTE, a lower incidence of bleeding was observed in

the enoxaparin group. In another study including 117 patients undergoing oesophagectomy, nadroparin (4100 IU) once daily was associated with a higher incidence of VTE (9.1%) when compared with twice-daily administration (0%).[47] The results of this small 'pseudo-randomised' study should be interpreted with caution and need to be confirmed in a further large and well designed prospective study.

Recommendations

Cardiac and vascular surgery

- In the absence of risk factors, we suggest considering the risk of VTE as moderate in patients undergoing coronary artery by-pass graft (CABG) and bioprosthetic aortic valve implantation surgery (Grade 2C). If the risk of bleeding is to be considered high, we suggest the use of mechanical prophylaxis using IPC (Grade 2C).
- The presence of one or more risk factors [age above 70 years, transfusion of more than four units of RBC concentrate/fresh frozen plasma/cryoprecipitate/fibrinogen concentrate, mechanical ventilation more than 24 h, postoperative complication (e.g. acute kidney injury, infection/sepsis, neurological complication)] should place the cardiac population at high risk for VTE. In this context, we suggest the use of pharmacological prophylaxis as soon as satisfactory haemostasis has been achieved, in addition to IPC (Grade 2C).
- Patients undergoing other valve surgery and those with atrial fibrillation should be considered a specific entity at high risk of VTE, as they will mostly require postoperative therapeutic medical 'bridging' prior to long-term anti-coagulation.
- Patients undergoing peripheral vascular surgery are considered to have a low risk of VTE and low risk of bleeding. Stringent medical prophylaxis appears to reduce the event rate significantly. In this population, we suggest medical therapy (Grade 2C).
- In patients undergoing AAA repair, particularly when an open surgical approach is used, the risk of VTE is higher with a high bleeding risk. These patients should be considered as having a moderate risk. Patients with additional risk factors including BMI at least 30 kg m^{-2}, preoperative dyspnoea, chronic steroid usage, ruptured aneurysm, open surgery, operative duration at least 5 h, transfusion of at least 5 U, postoperative mechanical ventilation more than 48 h, postoperative complication (acute kidney injury, infection/sepsis) and re-operation, should be considered as moderate-to-high risk. In this context, we suggest the use of pharmacological prophylaxis as soon as satisfactory haemostasis is achieved (Grade 2C).
- We suggest that low-dose aspirin could be used to decrease the incidence of VTE in cardiac and vascular patients but should not be considered as the sole agent in high-risk patients. (Grade 2C).
- UFH is associated with the highest risk of developing the pro-thrombotic condition of HIT. Therefore, in an attempt to minimise the risk of HIT, we suggest that UFH should be used as briefly as possible and replaced by LMWH as soon as the bleeding risk decreases (Grade 2C).
- In patients with severely impaired renal function (creatinine clearance <30 ml min^{-1}) and a high risk of haemorrhagic complications, we suggest close monitoring of the administration of therapeutic UFH and LMWH and adaptation of the dosage (Grade 2C).

Thoracic surgery

- Based on the current literature, patients undergoing thoracic surgery in the absence of cancer could be considered at low risk of VTE. However, as the vast majority of patients undergoing thoracic surgery have a diagnosis of primary or metastatic cancer, they should be considered at high risk for VTE with an equally high bleeding risk.
- In the absence of evidence regarding patients undergoing minimally invasive procedure, the same risk stratification should be applied as described above.
- In low-risk patients, we suggest the use of mechanical prophylaxis using IPC (Grade 2C). In high-risk patients, we suggest the use of pharmacological prophylaxis in addition to IPC (Grade 2B).

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