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European guidelines on perioperative venous thromboembolism prophylaxis: Cardiovascular surgery

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RATIONALE

Venous thromboembolism (VTE), thus comprising deep venous thrombosis (DVT) and pulmonary artery embolism (PE), are associated with high morbidity and mortality [1–4]. However, particularly after major surgery, the risk of early institution of pharmacological thrombosis prophylaxis has to be balanced against the risk of postoperative bleeding events.

In a large analysis of the National Inpatient Sample (NIS) of patients after coronary artery bypass grafting surgery, the incidence of VTE was 1.3–1.75% and associated with an increased mortality of 6.8% vs 1.7% (adjusted odds ratio 1.92 [95% confidence interval 1.40–2.65] $p < 0.001$) [5].

According to a meta-analysis in cardiac surgery, risk factors for VTE are a history of VTE, obesity, heart failure, prolonged bed rest, and mechanical ventilation [3].

In vascular surgery, the reported incidence of VTE is 0.7%, with an incidence of PE of 0.2% [6]. The highest VTE rate was observed in patients with thoraco-abdominal aortic aneurysm [4.2%], followed by thoracic endovascular repair (TEVAR) [2.2%], open abdominal aortic surgery [1.7%], abdominal endovascular aneurysm repair (AEVAR) [0.7], infra-inguinal bypass graft surgery [1.0%], and carotid endarterectomy [0.2%].

Patient-related risk factors after open AAA repair are obesity, postoperative pneumonia, and prolonged postoperative mechanical ventilation (>48) [1].

Of note, according to current guidelines, early administration of aspirin, which is recommended in a large percentage of these patient populations, including the special condition of transcatheter aortic valve replacement (TAVI), as an antithrombotic drug to preserve graft/prosthesis patency and decrease thromboembolic complications, might be regarded as an effective medication to decrease VTE [7–9].

In cardiac surgery, the early administration of medical venous thrombosis prophylaxis reduces the risk of PE (RR, 0.45, 95% CI, 0.28–0.71; $p < 0.01$) and symptomatic VTE (RR, 0.44, 95% CI 0.28–0.71, $p < 0.01$) and is not associated with clinically relevant increased bleeding risk, including cardiac tamponade or the need for re-exploration of bleeding [3].

In vascular surgery, pharmacological prophylaxis has been associated with a trend towards a reduction of VTE and PE [2; 4].

Current literature on patients following cardiac or vascular surgery does not show a substantial difference in the efficacy of unfractionated heparin (UFH) or low molecular weight heparin (LMWH) when used for thrombosis prophylaxis [1]. LMWH can be administered once daily by subcutaneous injection, usually without routine coagulation monitoring. However, renal impairment might impact plasma levels and the need for dose adjustment and drug effect monitoring [10].

The pharmacological profile of UFH renders it more amenable to reversal, thus making it preferable in conditions of a higher bleeding risk as immediately postoperatively after major surgery. However, when using UFH, the increased risk of heparin-induced thrombocytopaenia complications and more challenging mobilization with i.v. use, particularly after major trauma/surgery, has to be considered [11].

The research questions used for the systematic literature review and summary of findings are provided in Tables 1 and 2.

This article is part of the Updated European guidelines on perioperative venous thromboembolism prophylaxis. For details concerning background, methods, classification of recommendations, and members of the ESA VTE Guidelines Task Force, please refer to:
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Table 1. PICOT Questions Utilized for Systematic Literature Review

A	Risk Cardiac Surgery
P	Adult cardiac surgery (>/= 18 yr. old)
I	Perioperative venous thrombosis prophylaxis, venous thromboprophylaxis
C	No prophylaxis, Caprini score, standard care
O	DVT, VTE, PE, mortality incidence, prevalence, predictors, thrombosis risk
T	In-hospital, 30-day
B	Risk Cardiac Intervention (TAVI)
P	Adult cardiac intervention (TAVI) (>/= 18 yr. old)
I	Perioperative venous thrombosis prophylaxis, venous thromboprophylaxis
C	No prophylaxis, Caprini score, standard care
O	DVT, VTE, PE, mortality incidence, prevalence, predictors, thrombosis risk
T	In-hospital, 30-day
C	Risk Vascular Surgery
P	Adult vascular surgery (>/= 18 yr. old)
I	Perioperative venous thrombosis prophylaxis, venous thromboprophylaxis
C	No prophylaxis: Caprini score, standard care
O	DVT, VTE, PE, mortality incidence, prevalence, predictors, thrombosis risk
T	In-hospital, 30-day
D	Risk Vascular Intervention (EVAR)
P	Adult vascular intervention (>/= 18 yr. old)
I	Perioperative venous thrombosis prophylaxis, venous thromboprophylaxis
C	No prophylaxis, Caprini score, standard care
O	DVT, VTE, PE, mortality incidence, prevalence, predictors, thrombosis risk
T	In-hospital, 30-day
E	Preventive Strategies Cardiac Surgery
P	Adult cardiac surgery (>/= 18 yr. old)
I	Perioperative venous thrombosis prophylaxis, venous thromboprophylaxis ASA/P2Y12, UFH, LMWH, Fondaparinux, DOAC, No mechanical prophylaxis
C	No prophylaxis, mechanical prophylaxis with ASA/P2Y12, UFH, LMWH, Fondaparinux, DOAC
O	VTE, DVT, PE, major bleeding, reoperation for bleeding, mortality
T	In-hospital, 30-day, 1-year
F	Preventive Strategies Cardiac Intervention (TAVI)
P	Adult cardiac intervention (TAVI), transcatheter mitral valve replacement, transcatheter pulmonary valve replacement (>/= 18 yr. old)
I	Perioperative venous thrombosis prophylaxis, venous thromboprophylaxis ASA/P2Y12, UFH, LMWH, Fondaparinux, DOAC, No mechanical prophylaxis
C	No prophylaxis, mechanical prophylaxis with ASA/P2Y12, UFH, LMWH, Fondaparinux, DOAC
O	VTE, DVT, PE, major bleeding, reoperation for bleeding, mortality
T	In-hospital, 30-day, 1-year
G	Preventive Strategies Vascular Surgery
P	Adult vascular surgery (>/= 18 yr. old)
I	Perioperative venous thrombosis prophylaxis, venous thromboprophylaxis ASA/P2Y12, UFH, LMWH, Fondaparinux, DOAC, No mechanical prophylaxis
C	No prophylaxis, mechanical prophylaxis with ASA/P2Y12, UFH, LMWH, Fondaparinux, DOAC
O	VTE, DVT, PE, major bleeding, reoperation for bleeding, mortality
T	In-hospital, 30-day, 1-year
H	Preventive Strategies Vascular Intervention (EVAR, TEVAR)
P	Adult vascular intervention (EVAR, TEVAR) (>/= 18 yr. old)
I	Perioperative venous thrombosis prophylaxis, venous thromboprophylaxis ASA/P2Y12, UFH, LMWH, Fondaparinux, DOAC, No mechanical prophylaxis
C	No prophylaxis, mechanical prophylaxis with ASA/P2Y12, UFH, LMWH, Fondaparinux, DOAC
O	VTE, DVT, PE, major bleeding, reoperation for bleeding, mortality
T	In-hospital, 30-day, 1-year

ASA: acetylsalicylic acid; DOAC: direct oral anticoagulant; DVT: deep vein thrombosis; EVAR: endovascular treatment of abdominal aortic aneurysms; LMWH: low molecular weight heparin; PE: pulmonary embolism; TAVI: transcatheter aortic valve implantation; TEVAR: thoracic endovascular aortic repair; UFH: unfractionated heparin; VTE: venous thromboembolism.

Table 2. The Summary of Findings and Risk of Bias Assessment

First Author	Year	Type	Patients	Size	Intervention	Findings	Risk of Bias
Kwok M	2015	Metanalysis	Cardiac Surgery	16 Randomized controlled trials 49 Observational studies 3 Meta-analysis	Thromboprophylaxis and incidence and risk factors for deep vein thrombosis and pulmonary embolism	Early initiation of venous thrombosis prophylaxis in non-bleeding patients was associated with a reduced risk of pulmonary embolism (relative risk 0.45, 95% confidence interval 0.28–0.72, p = 0.0008) or symptomatic venous thromboembolism (relative risk 0.44, 95% confidence interval 0.28–0.71, p = 0.0006) compared to control without significant heterogeneity	High
Haykal T	2021	Metanalysis	Vascular Surgery	8 Randomized controlled trials 3.130 patients	Thromboprophylaxis with unfractionated or low molecular heparin	Trend towards the lesser incidence of deep venous thrombosis (risk ratio 0.34, 95%confidence interval 0.11-1.05, p = 0,06, $I^2 = 68\%$) and pulmonary embolism (relative risk 0.17, 95% confidence interval 0.002-1.22, p = 0.08, $I^2 = 41\%$) when comparing patients with thrombosis prophylaxis to those to those with placebo	High
Panhawar MS	2019	Observational	Coronary artery bypass Surgery	331.950 Patients of National Inpatient Sample	None	Venous thrombosis after coronary artery bypass graft surgery is rare (1.3%) but associated with an increased morbidity and mortality compared to patients without (6.8% vs1.7%, adjusted odds ratio 1.92, 95% confidence interval 1.40-2.65, p = 0.001)	High
Toth S	2020	Metanalysis	Vascular Surgery	2 prospective cohort studies 1 retrospective cohort study 2 randomized controlled studies 5.248 Patients included in meta-analysis	None	Lower incidence of venous thrombosis after prophylaxis when compared to patients without (relative risk 0.70, 95% confidence interval 0.26-1.87)	High
Wilsey HA	2019	Retrospective cohort study	Coronary artery bypass surgery	850 Patients	Unfractionated heparin versus low molecular weight heparin	Venous thromboembolism (2.12% vs1.41 %, p = 0.43) group and bleeding events (1.18% vs 0.94%, p = 1.00) in the unfractionated heparin group vs the low molecular weight heparin were not significantly different	High
Ramanan B	2013	Observational	Vascular Surgery	45.548 Patients of National Surgical Quality Improvement Program (2007-2009)	None	Venous thrombosis and pulmonary embolism frequent after chest and abdominal vascular surgery and are associated with 4- fold mortality (deep vein thrombosis 1.5% vs 6.2%, p = 0.05 and pulmonary embolism 1.5% vs 5.7%, p = 0.05)	High

RECOMMENDATIONS

In cardiac surgery:

- We recommend early initiation (between 6h-24h) post-surgery of pharmacological VTE prophylaxis in the absence of significant bleeding risk. (Grade 1C)

In vascular surgery:

- We suggest early initiation (<24h) of pharmacological VTE prophylaxis should be considered in patients with an increased procedural risk, such as open Thoracoabdominal aortic aneurysm, Abdominal aortic aneurysm repair and Thoracic Endovascular Aortic Repair, and in patients with increased VTE risk factors. (Grade 2C)

Therapeutic approach:

- We suggest Low Molecular Weight Heparin should be considered a first-line therapy over Unfractionated Heparin in view of the increased risk of Heparin-induced thrombocytopenia in cardiac and vascular surgery. (Grade 2B)

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CONFLICT OF INTERESTS

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