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European guidelines on perioperative venous thromboembolism prophylaxis

Surgery in the elderly

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The risk for postoperative venous thromboembolism (VTE) is increased in patients aged more than 70 years and in elderly patients presenting with co-morbidities, for example cardiovascular disorders, malignancy or renal insufficiency. Therefore, risk stratification, correction of modifiable risks and sustained perioperative thromboprophylaxis are essential in this patient population. Timing and dosing of pharmacoprophylaxis may be adopted from the non-aged population. Direct oral anti-coagulants are effective and well tolerated in the elderly; statins may not replace pharmacological thromboprophylaxis. Early mobilisation and use of non-pharmacological means of thromboprophylaxis should be exploited. In elderly patients, we suggest identification of co-morbidities increasing the risk for VTE (e.g. congestive heart failure, pulmonary circulation disorder, renal failure, lymphoma, metastatic cancer, obesity, arthritis, post-menopausal oestrogen therapy) and correction if present (e.g. anaemia, coagulopathy) (Grade 2C). We suggest against bilateral knee replacement in elderly and frail patients (Grade 2C). We suggest timing and dosing of pharmacological VTE prophylaxis as in the non-aged population (Grade 2C). In elderly patients with renal failure, low-dose unfractionated heparin (UFH) may be used or weight-adjusted dosing of low molecular weight heparin (Grade 2C). In the elderly, we recommend careful prescription of postoperative VTE prophylaxis and early postoperative mobilisation (Grade 1C). We recommend multi-faceted interventions for VTE prophylaxis in elderly and frail patients, including pneumatic compression devices, low molecular weight heparin (and/or direct oral anti-coagulants after knee or hip replacement) (Grade 1C).

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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

Very few sets of guidelines have addressed the ageing issue. No recommendations are directly dedicated to the elderly, especially in the perioperative setting. However, if the venous thromboembolism (VTE) risk is known to increase with age, the bleeding risk is also increasing. Therefore, it was of utmost importance to address the elderly issue in these guidelines.

Risk factors for venous thromboembolism in the elderly

Large population-based epidemiological studies globally show that VTE is predominantly a disease of older age, and it rarely occurs prior to late adolescence.[1–8] Incidence rates increase markedly with age for men and women, as

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well as for deep vein thrombosis (DVT) and pulmonary embolism.[2,4,6]

Cushman *et al.*[2] conducted a longitudinal investigation of VTE cause in a cohort of middle-aged (>45 years) and older patients in the United States ($n = 21\,680$), and followed them for 7.6 years. The age-standardised incidence of first-time VTE was 1.92 per 1000 person-years. The incidence of first lifetime VTE increased with age, with rates among patients more than 65 years old more than three times those in patients aged 45 to 54 years. The researchers reported that incidence was similar in men and women. However, above the age of 75 years, the rate in men was twice that in women [5.5 (95% confidence interval (CI) 3.8 to 8.0) per 1000 person-years vs. 2.7 (95% CI 1.7 to 4.3) per 1000 person-years]. There was no antecedent trauma, surgery, immobilisation or diagnosis of cancer for 48% (175/366) of events.

Naess *et al.*[4] conducted a case–controlled population-based study in a county of 91 194 residents aged more than 20 years in Norway. The incidence rate for all first VTE events was 1.43 per 1000 person-years (95% CI 1.33 to 1.54); for DVT, it was 0.93 per 1000 person-years (95% CI 0.85 to 1.02) and for pulmonary embolism it was 0.50 per 1000 person-years (95% CI 0.44 to 0.56). The incidence rates increased exponentially with age and were slightly higher in women than in men.

Silverstein *et al.*[6] followed a population of a county in the United States (106 470 inhabitants) during a time period of 25 years and found that the incidence of VTE rose markedly with increasing age for both sexes, with pulmonary embolism accounting for most of the increase. Significantly, the researchers found that the rate of pulmonary embolism decreased markedly during the study; it was approximately 45% lower during the last 15 years of the study. This effect was seen for both men and women, and it was seen for all age strata. The incidence of DVT, however, remained constant for men across all age strata, decreased for women younger than 55 years and increased for women older than 60 years.

More evidence for the relevance of age as a risk factor for VTE was published by Oger[5] in a study of the incidence of VTE in a French community population. The researchers found that the rate of VTE increased with age. For patients older than 75 years, an incidence of more than 1% was found. This study also reported that the rate of pulmonary embolism as a proportion of total VTE increased with age.

A recent population-based study of residents of a large New England metropolitan area has revealed that the magnitude of VTE increases even more dramatically to 885/100 000 of the population in those who are 85 years and older.[9]

Anderson and Spencer[10] have identified and categorised risk factors for VTE into

(1) strong [odds ratio (OR) >10] – hip or leg fracture/replacement, major general surgery, major trauma, spinal cord injury
(2) moderate ($2 < OR < 9$) – arthroscopic knee surgery, central venous lines, chemotherapy, congestive heart or respiratory failure, HRT, malignancy, paralytic stroke, previous VTE, thrombophilia
(3) weak ($OR < 2$) – bed rest for more than 3 days, increasing age, laparoscopic surgery, obesity, varicose veins.

In a prospective cohort study in four US communities involving 4859 participants aged 65 years and older, 52% of the sample were classified as having intermediate or definite frailty.[11] After adjustment for age, race, sex, BMI and diabetes, the relative risk (RR) of total VTE for people who were frail compared with no frailty was 1.31 (95% CI 0.93 to 1.84). The comparably adjusted RR for idiopathic VTE was 1.79 (95% CI 1.02 to 3.13).

Similarly, Leibson *et al.*[12] found in a population-based nested case–control study that, contrary to previous assumptions, most VTE risk factors identified in non-nursing home populations do not apply to the nursing home residents who may be characterised as frail. Nursing home residents with infection, substantial mobility limitations or recent general surgery should be considered potential candidates for VTE prophylaxis.

Tsai *et al.*[13] have shown that among hospitalisations of adults, age, sex, race and other variables were important determinants of VTE. Each of the following pre-existing co-morbid conditions – AIDS, anaemia, arthritis, congestive heart failure, coagulopathy, hypertension, lymphoma, metastatic cancer, other neurological disorders, obesity, paralysis, pulmonary circulation disorders, renal failure, solid tumour without metastasis and weight loss – was associated independently with 1.04 (95% CI 1.02 to 1.06) to 2.91 (95% CI 2.81 to 3.00) times increased likelihood of VTE diagnosis. The presence of two or more such conditions was associated with a 180 to 450% increased likelihood of a VTE diagnosis.

Post-menopausal oestrogen replacement is associated with an increased risk of VTE, and this risk may be highest in the first year of use.[14] An estimated OR of 3.5 for VTE amongst users of HRT compared with controls suggests that this medical population as an at-risk population for VTE.[1] Similarly, another study has revealed in multi-variate analysis that the risk for VTE was even more increased among women who had lower extremity fractures [relative hazard, 18.1 (CI 5.4 to 60.4)] or cancer [relative hazard, 3.9 (CI 1.6 to 9.4)] and for 90 days after inpatient surgery [relative hazard, 4.9 (CI 2.4 to 9.8)] or non-surgical hospitalisation [relative hazard, 5.7 (CI 3.0 to

10.8)].[15] In addition, post-menopausal therapy with oestrogen and progestin increases risk for VTE in women with coronary artery disease. These risks should be considered when the risks and benefits of therapy are being weighed up.

Diabetes remains a debatable risk factor for VTE in the elderly as well as in the younger population. In a population-based case–control study from the United States, diabetes mellitus and diabetes complications were shown not to be independent risk factors of incident VTE.[16] On the contrary, the most recent Taiwan longitudinal nationwide cohort study indicated that type 2 diabetes mellitus patients carried greater risks of developing VTE than did the general population.[17] Further studies are needed to develop sufficiently sound conclusions.

Risk factors for venous thromboembolism and pulmonary embolism in the elderly undergoing surgery

Limited physiological reserves of older patients make them more vulnerable to postoperative stress and illness.[18] Frailty is broadly defined as a state of increased vulnerability resulting from age-associated declines in reserve and function across multiple physiological systems, such that the ability to cope with everyday or acute stressors is compromised.[19] Lee *et al.*[20] found that age at least 70 years (OR 5.61), at least two co-morbidities (OR 13.42) and white blood cell count of more than $10\,000\,\mu l^{-1}$ (OR 17.43) were independent risk factors for postoperative VTE in a cohort of Korean patients undergoing major abdominal surgery for colorectal cancer.

Zhang *et al.* undertook a systematic review to assess the risk factors for VTE after total hip arthroplasty (THA) and total knee arthroplasty (TKA). They included level I and level II studies published between 2003 and 2013 on risk factors for VTE of total joint arthroplasty.[21,22] In total, 45 articles were included in their review. Risk factors found to be associated with VTE after both THA and TKA included older age, female sex, higher BMI, bilateral surgery and surgery time more than 2 h. The researchers did not provide a (pooled) risk estimate. Sun *et al.*[23] retrospectively assessed a cohort of 537 Chinese patients who underwent knee arthroscopy and found age a strongly significant risk factor for DVT.

Saleh *et al.*[24] conducted a systematic review to assess the incidence of VTE after shoulder arthroplasty. They included 14 studies and reported a cumulative incidence of 0.2 to 16%. The most prominent risk factors for development of VTE were previous VTE, thrombophilia, major surgery, advanced age (>60 years), current malignant disease, immobility and bed confinement.

Akpinar *et al.*[25] retrospectively assessed a cohort of 1206 patients who had undergone THA, TKA or trauma surgery and found advanced age (≥65 years) [OR 4.9 (95% CI 1.1 to 22.0)] and immobility a high risk for developing postoperative VTE.

In a population-based historical cohort study in the United States, all ($n = 4833$) residents undergoing a first arthroscopic knee operation during the 18-year period of 1988 to 2005 were followed for the incidence of deep venous thrombosis or pulmonary embolism. In total, 18 developed postoperative VTE, all within the first 6 weeks after surgery. Risks for postoperative VTE were significantly increased for advanced patient age [hazard ratio 1.34 for each 10-year increase in patient age ($P = 0.03$)] and hospitalisation either before or after knee arthroscopy (hazard ratio 14.1; $P < 0.001$).[26]

Because pulmonary embolism risk rises faster than that of DVT, the relative incidence of pulmonary embolism and, therefore, the fatal impact of VTE, also increases with age.[27–29] It has been argued, however, that the association between age and VTE and pulmonary embolism might be mediated by underlying co-morbidities that could be the actual risk factors.[1,30]

It has to be noted that age may be a proxy of immobility and coagulation activation.[31–33] Dagrosa *et al.*[34] assessed 12123 patients who underwent robotic-assisted laparoscopic radical prostatectomy (RALRP) in the timeframe 2009 to 2012. Univariate analysis demonstrated that nine co-morbidities were associated with age: history of congestive heart failure, myocardial infarction (MI), cerebrovascular attack (CVA), transient ischaemic attack, bleeding disorder, chronic obstructive pulmonary disease, percutaneous coronary intervention, cardiac surgery and American Society of Anesthesiologists' physical status ($P < 0.05$). Postoperatively, five medical complications were associated with age-related co-morbidities: MI, CVA, pneumonia (PNA), DVT, pulmonary embolism and urinary tract infection (UTI). On multi-variate analysis, age was found to be an independent risk factor for postoperative PNA ($P < 0.05$), but not for MI ($P = 0.09$), UTI ($P = 0.3$), CVA ($P = 0.2$) or DVT/pulmonary embolism ($P = 0.7$). The researchers concluded that although patient age may generate concern for medical complications following surgery, the results suggested that age is not an independent risk factor for these medical complications after RALRP.

Are risk factors still important if the elderly are going through a perioperative early mobilisation programme?

Pearse *et al.*[35] carried out a level III study on the result of achieving early walking following total knee replacement after implementation of a rapid rehabilitation protocol. They assessed the influence of the protocol on the development of DVT as determined by Doppler ultrasound scanning on the fifth postoperative day. Early mobilisation was defined as beginning to walk less than 24 h after knee replacement. Sample size was 97 patients

who received 122 knee replacements. A historical cohort was used for comparison (98 patients, 125 TKAs). All the patients received low molecular weight heparin (LMWH) thromboprophylaxis and wore compression stockings postoperatively. In the early mobilisation group, 90 patients (92.8%) began walking successfully within 24 h of their operation. The incidence of DVT decreased from 27.6% in the control group to 1.0% in the early mobilisation group ($P < 0.001$).

Husted *et al.*[36] conducted a level IV study and assessed 1977 consecutive, un-selected patients who were operated on for primary THA, TKA or bilateral simultaneous TKA (BSTKA) in a fast-track setting between 2004 and 2008. All patients received DVT prophylaxis with LMWH starting 6 to 8 h after surgery until discharge. An overall risk of death potentially related to the operation of 0.15% was found, which was deemed to compare favourably with the literature. During the last 2 years (854 patients), when patients were mobilised within 4 h postoperatively, and the duration of DVT prophylaxis was shortest (1 to 4 days), the mortality was 0% (95% CI 0 to 0.5). The incidence of DVT in TKA was 0.60% (0.2 to 2.2), in THA it was 0.51% (0.1 to 1.8) and in BSTKA it was 0% (0 to 2.9). The incidence of pulmonary embolism in TKA was 0.30% (0.1 to 1.7), in THA it was 0% (0 to 1.0) and in BSTKA it was 0% (0 to 2.9).

In 2013, a group of researchers published results from a study including 4659 arthroplasty procedures.[37] They found 90-day postoperative rates of symptomatic pulmonary embolism events and VTE of 0.84 and 0.41%, respectively, in patients with length of stay (LOS) 5 days or less and in-hospital thromboprophylaxis only. They compared their rates with literature: two Danish nationwide studies found symptomatic VTE in more than 1% of THA and TKA procedures despite prolonged prophylaxis, and the incidence was increasing across the study period (1995 to 2007). The researchers attributed the difference between their data and the literature to the fast-track set-up including early mobilisation in their study, and as LOS in Denmark was about 11 days in year 2000.

Chandrasekaran *et al.*[38] published a rather small level III study in which 50 patients who underwent mobilisation on the first postoperative day were compared with 50 patients who had strict bed rest on the first postoperative day. There was a significant reduction in the incidence of VTE complications in the mobilisation group (seven in total) compared with the control group (16 in total) ($P = 0.03$). Furthermore, in the mobilisation group, the odds of developing a thromboembolic complication was significantly reduced the greater the distance the patient mobilised ($P = 0.005$).

Pertaining to the field of cardiac surgery, Freeman and Maley[39] previously observed that, if ICU patients on mechanical circulatory support were kept in bed, their probability of VTE increased, alongside poorer/reduced pulmonary function that increased risk of PNA, longer LOS, further deconditioning and a greater need for postoperative rehabilitation. To counteract these risks, the researchers introduced a protocol including early extubation and early mobilisation. This protocol included a range of motion exercises on the day of surgery, dangling at the bedside and being out of bed to a chair. The postoperative protocol included being out of bed to a chair two to three times per day, and walking in the room/hall. Both protocols of early extubation/mobilisation successfully reduced the number of complications and LOS for this patient population.

When do we start venous thromboembolism prophylaxis and at what dose in the elderly?

Recommendations for VTE prophylaxis in elderly patients are typically extrapolated from non-age-specific VTE prophylaxis trials. There are relatively few high-quality studies to guide decisions concerning the timing of VTE prophylaxis in the elderly population.

Ramanathan *et al.*[40] investigated the impact of delayed initiation/interruption of chemical prophylaxis on VTE rates in 9961 surgical patients. Interrupted prophylaxis (interruption for >24 h) was associated with more VTE compared with complete prophylaxis (started within 24 h of admission, no interruptions) (10.2 vs. 2.0 per 1000, $P < 0.01$) and 5.2 greater odds. Admission to a surgical service and prolonged hospital stay were independently associated with increased likelihood of VTE.

Nunez *et al.*[41] observed in a single-institution prospective non-randomised study that weight-adjusted dosing of enoxaparin had resulted in an increase of goal anti-Xa levels from 19 to 59% ($P < 0.0001$).

There are limited high-quality data comparing different LMWH with each other or with UFH in elderly patients. In a single-centre retrospective study, 210 patients (median age 81 years) were treated with fondaparinux 1.5 or 2.5 mg daily. The authors concluded that, in elderly acutely ill-hospitalised medical patients, thromboprophylaxis with fondaparinux 2.5 or 1.5 mg daily was well tolerated and effective in preventing VTE without significantly increasing bleeding risk.[42]

Another group has observed that preoperative subcutaneous heparin has significantly reduced postoperative VTE events (17.6 vs. 2.6%, $P = 0.035$) when compared with intermittent compression boots and postoperative pharmacoprophylaxis.[43]

The DIRECT (Dalteparin's Influence on the Renally Compromised: Anti-Ten-A) trial included critically ill patients ($n = 138$) with a creatinine clearance less than 30 ml min^{-1} given dalteparin (5000 IU daily) in the prophylactic setting. No bioaccumulation of dalteparin was observed.[44] Another randomised clinical trial that

enrolled patients with a median creatinine clearance of $34.7 \pm 11.4\,ml\,min^{-1}$ randomised to receive enoxaparin (40 mg) or tinzaparin once daily in the prophylactic setting found that factor Xa did not accumulate significantly in patients who were given tinzaparin but did accumulate in the enoxaparin group ($P < 0.0001$).[45] Tinzaparin might, therefore, be preferable in patients with renal insufficiency.

A recent Canadian consensus stated there is no high-level evidence to recommend one LMWH or UFH over another in elderly patients with active malignancy[46]. In contrast, Tincani *et al.*[47] recommend UFH to be the anti-coagulant of choice in the treatment of patients with renal failure, at high risk of bleeding, and in whom rapid reversal of anti-coagulation may be required.

Limongelli *et al.*[48] have conducted analysis on 1018 consecutive patients who had undergone total thyroidectomy for benign and malignant diseases with/without preoperative prophylaxis and found the risk of developing VTE was eight times less than developing a postoperative bleed.

The most recent Cochrane Database Systematic Review, although not specifically addressing the elderly, concludes that multi-faceted interventions (graduated compression stockings, sequential compression devices and anti-coagulant medications such as LMWH) are well tolerated and can prevent blood clotting in patients at risk of these complications.[11]

A recent meta-analysis included nine phase 3 randomised controlled trials comparing direct oral anticoagulants (DOACs) against LMWH in the prevention of VTE in 29 403 elective post-arthroplasty patients.[49] The elderly population was defined as adults aged at least 75 years. The risk of VTE or VTE-related deaths in elderly patients after elective arthroplasty was similar with DOACs compared with LMWH (OR 0.62, 95% CI 0.30 to 1.26; $P = 0.18$; $I = 44\%$) but bleeding risk was significantly lower (OR 0.71, 95% CI 0.53 to 0.94; $P = 0.02$; $I = 0\%$). Analysis of individual DOACs showed superior efficacy but similar safety for apixaban when compared with LMWH. Efficacy and safety profiles of rivaroxaban and dabigatran were similar to LMWH. In elderly patients, after elective arthroplasty, DOACs have demonstrated similar efficacy but superior safety when compared with enoxaparin for VTE prophylaxis.

Statins are currently under investigation as anti-thrombotic therapies.[50] They have been shown to demonstrate an anti-inflammatory effect via reduction of pro-inflammatory cytokines, chemokines and inflammation-sensitive plasma markers, importantly C-reactive protein.[51] A positive effect of statins significantly reducing symptomatic VTE was shown in a randomised trial[52] and a Cochrane Systematic Review.[53] In contrast to other lipid-lowering drugs, statins are therapeutic and also preventive against VTE among at-risk medical inpatients and also the general population in a dose-dependent manner, although this effect has not been observed in the elderly population, as was shown in the PROSPER study.[54] Further, interpreting the JUPITER trial results, Perez and Bartholomew[55] caution against substitution of proven prophylaxis and anti-coagulation with statins, especially for patients at high risk of VTE. The most recent meta-analysis by Sardar *et al.*[56] concluded that, in participants of clinical trials aged 75 and older, DOACs did not cause excess bleeding and were associated with equal or greater efficacy than conventional therapy.

Recommendations

- Age over 70 years is a risk factor for postoperative VTE (Grade B).
- In elderly patients, we suggest identification of co-morbidities increasing the risk for VTE (e.g. congestive heart failure, pulmonary circulation disorder, renal failure, lymphoma, metastatic cancer, obesity, arthritis, post-menopausal oestrogen therapy) and correction if present (e.g. anaemia, coagulopathy) (Grade 2C).
- We suggest against bilateral knee replacement in elderly and frail patients (Grade 2C).
- We suggest timing and dosing of pharmacological VTE prophylaxis as in the non-aged population (Grade 2C).
- In elderly patients with renal failure, low-dose unfractionated heparin may be used or weight-adjusted dosing of LMWH (Grade 2C).
- In the elderly, we recommend careful prescription of postoperative VTE prophylaxis and early postoperative mobilisation (Grade 1C).
- We recommend multi-faceted interventions for VTE prophylaxis in elderly and frail patients, including pneumatic compression devices, LMWH (and/or direct oral anti-coagulants after knee or hip replacement) (Grade 1C).

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