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Prevention of perioperative venous thromboembolism : 2024 guidelines from the French Working Group on Perioperative Haemostasis (GIHP) developed in collaboration with the French Society of Anaesthesia and Intensive Care Medicine (SFAR), the French Society of Thrombosis and Haemostasis (SFTH) and the French Society of Vascular Medicine (SFMV) and endorsed by the French Society of Digestive Surgery (SFCD), the French Society of Pharmacology and Therapeutics (SFPT) and INNOVTE (Investigation Network On Venous ThromboEmbolic) network

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Godier, Anne; Lasne, Dominique; Pernod, Gilles; Blais, Normand; Bonhomme, Fanny; Bounes, Fanny; Bourguignon, Alex; Cohen, Ariel; de Maistre, Emmanuel; Fontana, Pierre; Galanaud, Jean-Philippe; Huet, Delphine Garrigue; Godon, Alexandre; Gouin-Thibault, & nbsplabelle [and 26 more]

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# Journal Pre-proof

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**Prevention of perioperative venous thromboembolism: 2024 guidelines from the French Working Group on Perioperative Haemostasis (GIHP) developed in collaboration with the French Society of Anaesthesia and Intensive Care Medicine (SFAR), the French Society of Thrombosis and Haemostasis (SFTH) and the French Society of Vascular Medicine (SFMV) and endorsed by the French Society of Digestive Surgery (SFCD), the French Society of Pharmacology and Therapeutics (SFPT) and INNOVTE (Investigation Network On Venous ThromboEmbolic) network**

Short title: Guidelines for perioperative venous thromboembolism

Anne Godier, Dominique Lasne, Gilles Pernod, Normand Blais, Fanny Bonhomme, Fanny Bounes, Alex Bourguignon, Ariel Cohen, Emmanuel de Maistre, Pierre Fontana, Jean-Philippe Galanaud, Delphine Garrigue Huet, Alexandre Godon, Isabelle Gouin-Thibault, Samia Jebara, Silvy Laporte, Thomas Lecompte, Dan Longrois, Jerrold H Levy, Grégoire Le Gal, Yves Gruel, Alexandre Mansour, Anne-Céline Martin, Mikael Mazighi, Pierre-Emmanuel Morange, Serge Motte, François Mullier, Philippe Nguyen, Nadia Rosencher, Stéphanie Rouillet, Pierre-Marie Roy, Jean-François Schved, Marie-Antoinette Sevestre, Pierre Sié, Sophie Susen, Charles Tacquard, André Vincentelli, Paul Zufferey, Patrick Mismetti, Pierre Albaladejo

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**Abstract**

**Background:** Any surgical procedure carries a risk for venous thromboembolism (VTE), albeit variable. Improvements in medical and surgical practices and the shortening of care pathways due to the development of day surgery and enhanced recovery after surgery, have reduced the perioperative risk for VTE.

**Objective:** A collaborative working group of experts in perioperative haemostasis updated in 2024 the recommendations for the Prevention of perioperative venous thromboembolism published in 2011.

**Methods:** The addressed questions were defined by 40 experts (GIHP, SFAR, SFTH and SFMV) and formulated in a PICO format. They performed the literature review and formulated recommendations according to the Grading of GRADE system. Recommendations were then validated by a vote determining the strength of each recommendation. Of note, these recommendations do not cover all surgical specialties. Especially, thromboprophylaxis in cardiac surgery, neurosurgery and obstetrics is not addressed.

**Results:** 78 recommendations were formalized into 17 sections, including patient-related VTE risk factors, types of surgery, extreme body weight, renal impairment, mechanical prophylaxis, distal deep vein thrombosis; 27 were found to have a high level of evidence (GRADE 1) and 41 a low level of evidence (GRADE 2) and 10 were expert opinion. All had strong agreement among the experts.

**Conclusions:** These guidelines help to weigh the perioperative risk for VTE (which includes the risk associated to surgery and the patient-related risk) against the adverse effects of thromboprophylaxis, either pharmacological or mechanical. This includes particularly the bleeding risk induced by antithrombotic drugs as well as costs.

**Key words:** Guidelines; thromboembolism; anticoagulant; bleeding; surgery

Any surgical procedure carries a risk for venous thromboembolism (VTE), albeit variable. The French Society of Anesthesia and Critical Care (SFAR) published Guidelines on the prevention of perioperative VTE in 2005, updated in 2011. Since then, improvements in medical and surgical practices and the shortening of care pathways due to the development of day surgery and enhanced recovery after surgery, have reduced the perioperative risk for VTE. These improvements led the French Working Group on Perioperative Haemostasis (GIHP) in collaboration with the SFAR, the French Society of Thrombosis and Haemostasis (SFTH), and the French Society of Vascular Medicine (SFMV) to update the recommendations, weighing the perioperative risk for VTE - which includes the risk associated to surgery, presumably lower than in the past, and the patient-related risk- against the adverse effects of thromboprophylaxis, either pharmacological or mechanical. This includes particularly the bleeding risk induced by antithrombotic drugs as well as costs. The term "thromboprophylaxis" by default refers to primary venous thromboprophylaxis; the term "secondary thromboprophylaxis" is used when it refers to the prevention of recurrent VTE. These recommendations do not apply to patients with inherited coagulation disorders.

Regarding methodology, the addressed questions were defined by experts and formulated in a PICO format (Population, Intervention, Comparison, Outcome). Whenever the outcomes were the same across the guidelines section, they were not reformulated in each recommendation. If the outcome criterion differed, it was then mentioned in the recommendation. Several working groups comprised of members from the GIHP, SFTH, and/or SFMV performed the literature review and formulated recommendations according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology. A level of evidence was defined for each of the quoted references based on the type of study and could be reassessed, considering the methodological quality of the study. A global level of evidence was determined for each endpoint based on the levels of evidence from each reference, the consistency of results among different studies, the direct or indirect nature of evidence, cost analysis, and the extent of the benefit. A "high" overall level of evidence justified formulation of a "strong" recommendation (we recommend doing/we do not recommend doing... GRADE 1+/1-). A "moderate or low" overall level of evidence led to the formulation of an "optional" recommendation (we suggest doing/we do not suggest doing... GRADE 2+/2-). When the level of evidence was very low or the literature almost non-existent, the recommendation could be formulated as an expert opinion (the experts suggest...). These recommendations were then validated through a voting process (n=37 participants), thereby determining the strength of each recommendation (rating scale ranging from 1 (complete disagreement) to 9 (complete agreement)). To make a recommendation with strong agreement, at least 70% of the members had to express their agreement, while fewer than 20% could express their opposition. In the absence of strong agreement, proposals were reformulated and submitted again to the vote to achieve consensus. In the end, all recommendations obtained a strong agreement.

This article includes the PICO questions, the corresponding recommendations, and 3 figures. Most PICO questions ask whether venous thromboprophylaxis is associated with a favorable benefit/risk ratio between thromboembolic and bleeding complications, i.e. whether venous thromboprophylaxis reduces the risk of thromboembolic complications more than it increases

the risk of bleeding. The rationale of each section and relevant references can be found in the supplementary data.

### Summary of recommendations

#### 1. Should protocols of perioperative venous thromboprophylaxis be implemented to reduce the risk of thromboembolic and bleeding complications?

R1.1 We recommend implementing local protocols of venous thromboprophylaxis to reduce the risk of perioperative complications. These protocols include early ambulation as well as pharmacological and mechanical prophylaxis, whose indication, methods, and duration depend on the risk for VTE of the patient and surgery, the bleeding risk, and the perioperative care pathway (Grade 1+).

#### 2. Do patient-related risk factors for VTE modify the management of venous thromboprophylaxis? (figure 1)

R2.1 After surgery with a low risk for VTE, if the patient has a major personal risk factor for VTE or several minor risk factors, we suggest using thromboprophylaxis with an anticoagulant for a minimum of 7 days (Grade 2+).

R2.2 If there is any notion of major thrombophilia without long-term anticoagulant treatment, experts suggest consulting a specialized center to document the type of thrombophilia and assess the risk for VTE (Expert opinion).

When surgery is associated with a high risk for VTE, venous thromboprophylaxis is required regardless of the patient-related risk factors for VTE. Conversely, when surgery is associated with a low risk for VTE, a personalized strategy is needed: routine thromboprophylaxis is not a priori required but the following patient-related risk factors for VTE should be considered when discussing the indication for postoperative thromboprophylaxis (table 1).

| <b>Table 1: Patient-related risk factors for VTE</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Major Risk Factors</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <ul style="list-style-type: none"> <li>• Personal history of VTE</li> <li>• Known major thrombophilia (see below)</li> <li>• Active cancer (treatment within the last six months)</li> <li>• Class III obesity or higher (Body Mass Index (BMI) <math>\geq 40 \text{ kg/m}^2</math>)<sup>#</sup></li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <i>Moderate or Minor Risk Factors</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <ul style="list-style-type: none"> <li>• Age <math>\geq 75</math> years<sup>#</sup></li> <li>• Heart failure or respiratory failure, chronic obstructive pulmonary disease</li> <li>• Chronic inflammatory disease (rheumatoid arthritis, inflammatory bowel disease, lupus, etc.)</li> <li>• Severe renal impairment (estimated Glomerular Filtration Rate (eGFR) <math>&lt; 30 \text{ mL/min/1.73 m}^2</math> according to Cockcroft and Gault formula)</li> <li>• Estrogen hormone treatment</li> <li>• Pregnancy or postpartum</li> <li>• Class I and II obesity (BMI 30 to <math>40 \text{ kg/m}^2</math>)</li> <li>• Recent prolonged bed rest</li> <li>• Neurological deficit <math>&lt; 1</math> month (stroke, spinal injury)</li> <li>• Use of orthopedic lower-limb immobilization or bed rest after surgery</li> </ul> |

# Age and body weight (and BMI) being continuous variables, the risk increases as they increase. Thresholds of 75 years for age and 40 kg/m<sup>2</sup> for BMI can be proposed (see dedicated section).

### **3. Which venous thromboprophylaxis should be used in orthopedic surgery to improve the benefit/risk ratio between thromboembolic and bleeding complications?**

#### *3.1 Patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA) (figure 2)*

R3.1.1 We recommend using pharmacological thromboprophylaxis after THA or TKA (Grade 1+).

R3.1.2 We recommend pharmacological thromboprophylaxis for 35 days after THA and 14 days after TKA (Grade 1+).

R3.1.3 We recommend one of the following:

- either an anticoagulant (Direct Oral Anticoagulant (DOAC), Low Molecular Weight Heparin (LMWH), or fondaparinux) for the entire duration of thromboprophylaxis (Grade 1+),
- or sequential thromboprophylaxis, starting with 5 days of anticoagulant followed by aspirin for 30 days after THA or 9 days after TKA, if the patient is successfully managed in an Enhanced Recovery After Surgery (ERAS) pathway and does not have any major risk factors for VTE\*\* or multiple minor risk factors (Grade 1+).

**\*\*Major Risk Factors:** Personal history of VTE, known major thrombophilia, active cancer, Class III obesity or greater (BMI  $\geq$  40 kg/m<sup>2</sup>)

#### *3.2 Hip fracture surgery*

R3.2.1 We recommend the use of LMWH or fondaparinux for 4 weeks after hip fracture surgery (Grade 1+).

R3.2.2 If surgery is delayed, we suggest starting thromboprophylaxis preoperatively, preferably with LMWH, with a minimal interval of 12 hours between the last LMWH injection and surgery (Grade 2+).

#### *3.3 Nonmajor orthopedic and trauma surgery of the lower limbs*

*Fracture of the femoral shaft, tibial plateau, patella, tibia or ankle, and Achilles tendon rupture*

R3.3.1 We recommend thromboprophylaxis with an anticoagulant (anti-Xa DOAC or LMWH) after surgery for femoral shaft fracture, tibial plateau, patella, tibia or ankle, or Achilles tendon rupture (Grade 1+).

R3.3.2 We suggest the use of anti-Xa DOAC over LMWH (Grade 2+).

R3.3.3 If surgery is delayed by more than 12 hours, we suggest starting thromboprophylaxis preoperatively, preferably with LMWH, with a minimal interval of 12 hours between the last LMWH injection and surgery (Grade 2+).

R3.3.4 We suggest continuing thromboprophylaxis until ambulation with full weight-bearing is achieved and for a minimum duration of 7 days (Grade 2+).

R3.3.5 We do not recommend aspirin for venous thromboprophylaxis (Grade 1-).

*Knee ligament repair, simple arthroscopy, meniscectomy, forefoot surgery, removal of osteosynthesis material*

R3.3.6 We suggest against routine pharmacological thromboprophylaxis after knee ligament repair, simple arthroscopy, meniscectomy, forefoot surgery, or removal of osteosynthesis material (Grade 2-).

R3.3.7 If the patient has a major personal VTE risk factor\*\* or several minor risk factors, we suggest thromboprophylaxis with an anticoagulant (anti-Xa DOAC or LMWH) (Grade 2+).

R3.3.8 If pharmacological thromboprophylaxis is prescribed, experts suggest a thromboprophylaxis duration of at least 7 days (Expert opinion).

*\*\*Major Risk Factors: Personal history of VTE, known major thrombophilia, active cancer, Class III obesity or greater (BMI  $\geq 40$  kg/m<sup>2</sup>) (see dedicated section)*

#### **4. Which venous thromboprophylaxis should be used in major abdominal and pelvic surgery (including gynecological and urological) to improve the benefit/risk ratio between thromboembolic and bleeding complications?**

R4.1 After abdominal and pelvic surgery with a high risk for VTE (whether cancer-related or not):

- We recommend thromboprophylaxis with LMWH for 4 weeks, including minimally invasive surgery or ERAS pathway (Grade 1+).
- We suggest that fondaparinux may be used as an alternative to LMWH (Grade 2+).

R4.2 We suggest that anti-Xa DOACs may be used as an alternative to LMWH after recovery of gastrointestinal function. (Grade 2+).

R4.3 After abdominal and pelvic surgery with an intermediate risk for VTE, we suggest thromboprophylaxis with LMWH for a minimum of 7 days. (Grade 2+).

R4.4 After abdominal and pelvic surgery with a low risk for VTE, we suggest against routine pharmacological prophylaxis. Pharmacological prophylaxis is suggested if the patient has a major personal VTE risk factor\*\* or several minor risk factors, or in the case of prolonged surgery or postoperative complications (Grade 2-).

*\*\*Major Risk Factors: Personal history of VTE, known major thrombophilia, active cancer, Class III obesity or greater (BMI  $\geq 40$  kg/m<sup>2</sup>)*

#### **5. Which venous thromboprophylaxis should be used in oncologic surgery to improve the benefit/risk ratio between thromboembolic and bleeding complications?**

R5.1 After cancer surgery with a high risk for VTE, we recommend thromboprophylaxis with LMWH for a minimum of 7 days (Grade 1+).

R5.2 We suggest beginning pharmacological prophylaxis postoperatively (refer to the dedicated section) (Grade 2+).

R5.3 We suggest using intermittent pneumatic compression (IPC) during and after oncologic surgery in case of very high risk for VTE<sup>#</sup> or when pharmacological prophylaxis is contraindicated (Grade 2+).

*# in particular the combination of a major patient-related risk factor for VTE and surgery with a high risk for VTE.*

This section discusses indications of thromboprophylaxis after surgery for breast cancer, head and neck cancer, or lung cancer.

#### **6. Which venous thromboprophylaxis should be used in vascular surgery to improve the benefit/risk ratio between thromboembolic and bleeding complications?**

R6.1 After carotid surgery, we suggest against routine venous thromboprophylaxis. (Grade 2-).

R6.2 After abdominal aortic surgery (open or endovascular) or open surgical arterial revascularization of the lower limbs, we suggest pharmacological venous prophylaxis until ambulation is resumed (Grade 2+).

R6.3 After arterial endovascular procedures (angioplasty and/or stenting) of the lower limbs, we suggest against routine venous thromboprophylaxis (Grade 2-).

R6.4 After lower-extremity revascularization (open or endovascular) for peripheral artery disease eligible for treatment with rivaroxaban 2.5 mg twice daily and aspirin 100 mg daily (with or without clopidogrel within the first month) to prevent major cardiovascular events, we suggest delaying the initiation of rivaroxaban until the end of venous thromboprophylaxis with LMWH, when indicated (Grade 2+).

R6.5 Experts suggest against IPC in the perioperative setting of lower-extremity arterial revascularization (expert opinion).

R6.6 After open surgery for varicose veins of the lower limbs (stripping), we suggest short-term pharmacological venous thromboprophylaxis ( $\leq 7$  days) (Grade 2+).

R6.7 After endovenous thermal ablation for varicose veins, we suggest against pharmacological venous thromboprophylaxis unless there are patient-related risk factors for VTE (Grade 2-).

## **7. When is the best time to introduce pharmacological venous thromboprophylaxis in order to improve the benefit/risk ratio between thromboembolic and bleeding complications?**

R7.1 In planned surgery, when pharmacological thromboprophylaxis is indicated, we suggest administering the first dose postoperatively to reduce the risk of bleeding (Grade 2+).

R7.2 When postoperative pharmacological thromboprophylaxis is indicated, we suggest starting it between the 12<sup>th</sup> and 24<sup>th</sup> postoperative hour\* (Grade 2+).

R7.3 In cases of high patient-related risk for VTE<sup>#</sup>, experts suggest starting thromboprophylaxis postoperatively between the 6th and 12th hour, beginning with LMWH regardless of the anticoagulant used the following day (expert opinion).

R7.4 In non-elective surgery, when surgery is delayed by more than 12 hours and pharmacological thromboprophylaxis is indicated, we suggest starting it preoperatively with LMWH, with a minimal interval of 12 hours between the last LMWH injection and surgery (Grade 2+).

R7.5 We recommend that safety time intervals be observed between pharmacological thromboprophylaxis and neuraxial anesthesia (Grade 1+).

\* : i.e. the following morning for planned surgery

# : Personal history of VTE or known major thrombophilia or active cancer or Class III obesity or greater ( $BMI \geq 40 \text{ kg/m}^2$ ) or combination of several non-major risk factors

### *Neuraxial anesthesia and pharmacological prophylaxis*

In regional anesthesia, neuraxial procedures (spinal, epidural, combined spinal-epidural anesthesia) carry a bleeding risk that is increased by prophylactic doses of anticoagulants. The removal of an epidural catheter is associated with the same bleeding risks as its placement. Therefore, these procedures must be planned and performed according to the recommended time interval from the last drug intake to the procedure, after 2 half-lives of the prophylactic anticoagulant. After the procedure, thromboprophylaxis is resumed following the same guidelines as after bleeding risk-associated surgery.

Table 2: Time from last intake of prophylactic anticoagulant to neuraxial procedure

| Anticoagulant at prophylactic doses | Half-life | Time from last anticoagulant intake to Neuraxial procedure |
|-------------------------------------|-----------|------------------------------------------------------------|
|-------------------------------------|-----------|------------------------------------------------------------|

|              |                                          |                                                       |
|--------------|------------------------------------------|-------------------------------------------------------|
| LMWH         | 5-7 hours                                | 12 hours (if eGFR > 30 mL/min/1.73m <sup>2</sup> )    |
| UFH SC       | 2 hours                                  | 4 hours                                               |
| Apixaban     | 12 hours*                                | 36 hours                                              |
| Rivaroxaban  | 5-9 hours (11-13 hours in the elderly) * | 24 hours (if eGFR > 30 mL/min/1.73m <sup>2</sup> )    |
| Dabigatran   | 11-15 hours if eGFR>50*                  | 24-36 hours (if eGFR > 50 mL/min/1.73m <sup>2</sup> ) |
| Fondaparinux | 17 hours (21 hours in the elderly)*      | 36 hours (if eGFR > 50 mL/min/1.73m <sup>2</sup> )    |

\* Data from the SmPC (Summary of Product Characteristics)

In cases of renal impairment (eGFR < 50 mL/min/1.73 m<sup>2</sup>), low body weight, and elderly patients, extending the delays or performing assays may be necessary.

When assays are performed, the hemostatic safety thresholds for neuraxial procedures are as follows: [DOAC] ≤ 30 ng/mL; Anti-Xa activity (LMWH) ≤ 0.1 IU/mL (or below the laboratory's limit of quantification); Anti-Xa activity (fondaparinux) ≤ 0.1 µg/mL (or below the laboratory's limit of quantification) (ESAIC/ESRA guidelines 2021)

## 8. Should intra- or postoperative intermittent pneumatic compression be used to reduce the risk of thromboembolic complications?

R8.1 We recommend using IPC if venous thromboprophylaxis is indicated but anticoagulants are contraindicated (Grade 1+).

R8.2 In cases of very high risk for VTE<sup>#</sup>, we suggest associating intra- or postoperative IPC with pharmacological prophylaxis (Grade 2+).

R8.3 Experts suggest that the use of IPC should not delay the resumption of ambulation (expert opinion).

## 9. Should graduated compression stockings be used during and/or after surgery to reduce the risk of thromboembolic complications?

R9.1 We recommend against the use of graduated compression stockings for perioperative thromboprophylaxis, regardless of the risk for VTE (Grade 1-).

## 10. Should inferior vena cava (IVC) filter be placed before surgery to reduce the risk of thromboembolic complications?

*Primary prophylaxis*

R10.1 We suggest that an IVC filter should not be used for primary VTE prevention (Grade 2-).

*Secondary prophylaxis*

R10.2 We suggest discussing the placement of a retrievable IVC filter preoperatively for high-bleeding-risk surgical procedures that must be performed less than one month after a pulmonary embolism and/or proximal deep vein thrombosis of the lower limbs (Grade 2+).

R10.3 We recommend scheduling the removal of the IVC filter as soon as therapeutic-dose anticoagulation is resumed without complication (Grade 1+).

## 11. Should venous thromboprophylaxis regimens be modified according to renal impairment to improve the benefit/risk ratio between thromboembolic and bleeding complications?

Severe renal impairment (estimated Glomerular Filtration Rate (eGFR) 15-30 mL/min/1.73 m<sup>2</sup>)

R11.1 We recommend adjusting pharmacological thromboprophylaxis to renal function (Grade 1+).

R11.2 In patients with severe renal impairment, we suggest LMWH over UFH or DOAC (Grade 2+).

R11.3 We recommend using the following LMWH according to the dosing regimens indicated by the marketing authorization (Grade 1+):

- enoxaparin 2000 IU x 1/day SC if eGFR is between 15 and 30 mL/min/1.73 m<sup>2</sup>
- tinzaparin 4500 IU x 1/day SC if eGFR is > 20 mL/min/1.73 m<sup>2</sup>

End-stage renal disease (eGFR <15 mL/min/1.73 m<sup>2</sup>)

R11.4 For patients with end-stage renal disease, we recommend using UFH at a dose of 5000 IU x 2/day SC, as other anticoagulants are not recommended (Grade 1+).

Table 3: Thromboprophylaxis and renal function

| Estimated GFR (mL/min/1.73m <sup>2</sup> ) | 15 | 20        | 30        | 50 |
|--------------------------------------------|----|-----------|-----------|----|
| UFH                                        |    |           |           |    |
| Tinzaparin                                 |    |           |           |    |
| Enoxaparin                                 |    | Half-dose | Half-dose |    |
| Fondaparinux 2.5 mg                        |    |           |           |    |
| Apixaban / rivaroxaban                     |    |           |           |    |
| Dabigatran                                 |    |           |           |    |

Red: not recommended according to the SmPC; orange: not recommended according to the GIHP; green: recommended

## 12. Should venous thromboprophylaxis regimens be modified according to obesity and extreme weight to improve the benefit/risk ratio between thromboembolic and bleeding complications?

12.1 Patients with obesity

R12.1.1 For patients with class I or II obesity (BMI between 30 and 39 kg/m<sup>2</sup>) requiring pharmacological thromboprophylaxis, we suggest using a standard dosing regimen (Grade 2+).

R12.1.2 For patients with class III obesity and above (BMI ≥ 40 kg/m<sup>2</sup>) requiring pharmacological prophylaxis, we suggest the following dosing regimens according to the specific indications for each anticoagulant (Grade 2+):

- enoxaparin 4000 IU x 2/day subcutaneously. An increased dose of 6000 IU x 1/day is also considered. The 6000 IU x 2/day dose may be reserved for patients > 150 kg.
- dalteparin 5000 IU x 2/day subcutaneously
- tinzaparin 75 IU/kg (actual weight) x 1/day subcutaneously

- fondaparinux 5 mg x 1/day subcutaneously
- apixaban: 2.5 mg x 2/day orally
- rivaroxaban: 10 mg x 1/day orally. There is little experience with direct anti-Xa DOACs for BMI > 50 kg/m<sup>2</sup> or weight > 150 kg.

R12.1.3 For patients with class III obesity undergoing surgery with a high risk for VTE, we suggest combining IPC with pharmacological prophylaxis (Grade 2+).

R12.1.4 After bariatric surgery, we suggest postoperative pharmacological thromboprophylaxis with LMWH or fondaparinux for a minimum of 10 days (Grade 2+).

## 12.2 Patients with low body weight

R12.2.1 For patients with low body weight, we suggest adjusting dosing regimens accordingly (Grade 2+).

## 13. Should pharmacological venous thromboprophylaxis be used after pediatric surgery to improve the benefit/risk ratio between thromboembolic and bleeding complications?

R13.1 We suggest that from puberty or the age of 14, pharmacological prophylaxis should follow the same recommendations as for adults (Grade 2+).

R13.2 Before puberty or the age of 14, experts suggest discussing the benefit-risk ratio of pharmacological prophylaxis if several risk factors for VTE are present (Expert opinion).

## 14. Which venous thromboprophylaxis should be used in intensive care patients to improve the benefit/risk ratio between thromboembolic and bleeding complications?

### Does venous thromboprophylaxis impact the occurrence of thromboembolic and bleeding complications in intensive care patients?

R14.1 We recommend using pharmacological prophylaxis in intensive care patients to reduce VTE complications (Grade 1+).

R14.2 In the absence of end-stage renal disease, we recommend LMWH at prophylactic doses over UFH (Grade 1+).

R14.3 When using LMWH for thromboprophylaxis, we suggest against monitoring anti-Xa levels for dosing adjustment (Grade 2-).

R14.4 We suggest adjusting LMWH dosing in patients with low body weight, in those with class III or greater obesity, and in patients with severe renal impairment (Grade 2+).

R14.5 For patients with stable severe renal impairment (estimated GFR between 15 and 30 mL/min/1.73 m<sup>2</sup>), we suggest using LMWH over UFH, according to the dosing regimens indicated by the marketing authorization (Grade 2+):

- enoxaparin 2000 IU x 1 subcutaneously per day if eGFR is from 15 to 30 mL/min/1.73 m<sup>2</sup>
- tinzaparin 4500 IU x 1 subcutaneously per day if eGFR is > 20 mL/min/1.73 m<sup>2</sup>

R14.6 In cases of end-stage renal disease (eGFR < 15 mL/min/1.73 m<sup>2</sup>), we recommend using UFH at a dose of 5000 IU x 2/day subcutaneously (Grade 1+).

R14.7 We recommended against the routine combination of IPC with pharmacological prophylaxis (Grade 1-).

R14.8 We recommend IPC when prophylactic anticoagulants are contraindicated, particularly in situations with a high risk of bleeding (Grade 1+).

R14.9 We recommend against Graduated Compression Stockings for venous thromboprophylaxis, regardless of the risk for VTE (Grade 1-).

**15. Does the administration of tranexamic acid modify the regimens of perioperative venous thromboprophylaxis?**

R15.1 We recommend that the administration of tranexamic acid should not modify the regimen of perioperative venous thromboprophylaxis (Grade 1-).

**16. Should venous pharmacological prophylaxis be modified according to laboratory testing to improve the benefit/risk ratio between thromboembolic and bleeding complications?**

**Does laboratory testing during venous pharmacological prophylaxis impact the occurrence and management of thromboembolic and bleeding complications?**

*Measuring the level of anticoagulation*

R16.1 We suggest not measuring anti-Xa levels during thromboprophylaxis with LMWH (Grade 2-).

R16.2 Experts suggest not measuring anticoagulation levels during prophylaxis with DOACs, fondaparinux, or UFH (Expert opinion)

R16.3 We suggest not measuring anticoagulation levels for patients with extreme body weights and those with renal impairment (refer to the dedicated sections) (Grade 2-)

R16.4 When facing bleeding during thromboprophylaxis with DOAC, LMWH, UFH, or fondaparinux, experts suggest measuring the level of anticoagulation to estimate the contribution of the anticoagulant to hemorrhage and to guide management (Expert opinion).

R16.5 Experts suggest implementing local procedures to define good practices for anticoagulation level measurement (sampling conditions, threshold values) and management (Expert opinion).

*Platelet count monitoring and risk of heparin-induced thrombocytopenia (HIT)*

R16.6 We suggest monitoring platelet count to detect heparin-induced thrombocytopenia (HIT) (Grade 2+):

- At initiation of prophylaxis with LMWH, then once to twice a week from day 4 to day 14 of treatment, followed by once a week for one month if prophylaxis the treatment is continued.
- At initiation of prophylaxis with UFH, then two to three times a week from day 4 to day 14 of treatment, followed by once a week for one month if prophylaxis is continued.
- If thrombosis occurs despite prophylaxis with UFH or LMWH.

**17. Does the diagnosis of a postoperative distal deep vein thrombosis modify the prescribed venous thromboprophylaxis regimen? (figure 3)**

*Postoperative compression ultrasound (CUS)*

R17.1 We recommend against routine screening for asymptomatic postoperative DVT (Grade 1-).

*Postoperative distal deep vein thrombosis (dDVT)*

R17.2 We recommend against routine treatment of postoperative isolated dDVT with therapeutic anticoagulation (Grade 1-).

R17.3 When facing postoperative isolated dDVT, we recommend assessing the risk of thrombotic extension (bilateral or multiple DVT (> 1 vein), personal history of VTE, active cancer) and the bleeding risk (related to the patient and procedure) to select the optimal management (Grade 1+).

R17.4 In the absence of risk factors for extension, we suggest starting or continuing anticoagulant thromboprophylaxis for 35 days without ultrasound monitoring (Grade 2+).

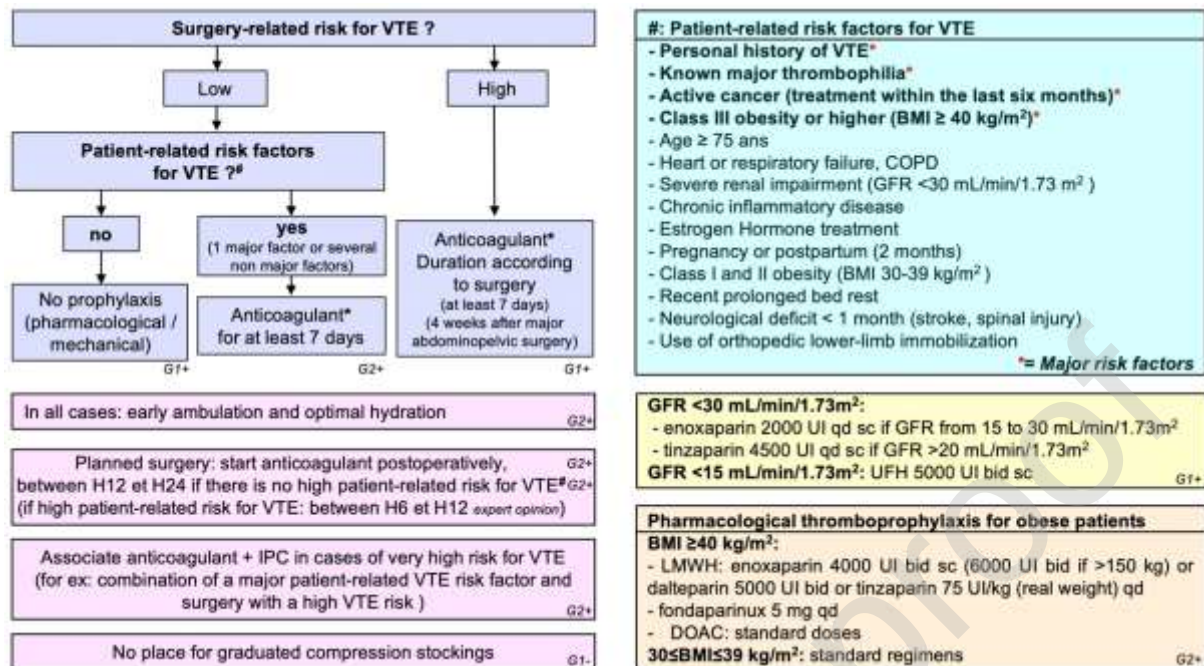
R17.5 In the presence of risk factors for extension, and if the bleeding risk is low, we suggest starting therapeutic anticoagulation for 6 to 12 weeks (Grade 2+).

R17.6 In the presence of risk factors for extension:

- If the bleeding risk is high, experts suggest initiating or continuing anticoagulant thromboprophylaxis for 6 to 12 weeks. A repeated leg vein CUS check may be suggested on day 7 (expert opinion).
- If the bleeding risk becomes low, thromboprophylaxis can be switched to therapeutic anticoagulation (expert opinion).

R17.7 If anticoagulant-based thromboprophylaxis is contraindicated, we suggest against therapeutic-dosing anticoagulation or placement of IVC filter. We suggest performing another CUS on day 7 to look for proximal extension (Grade 2-).

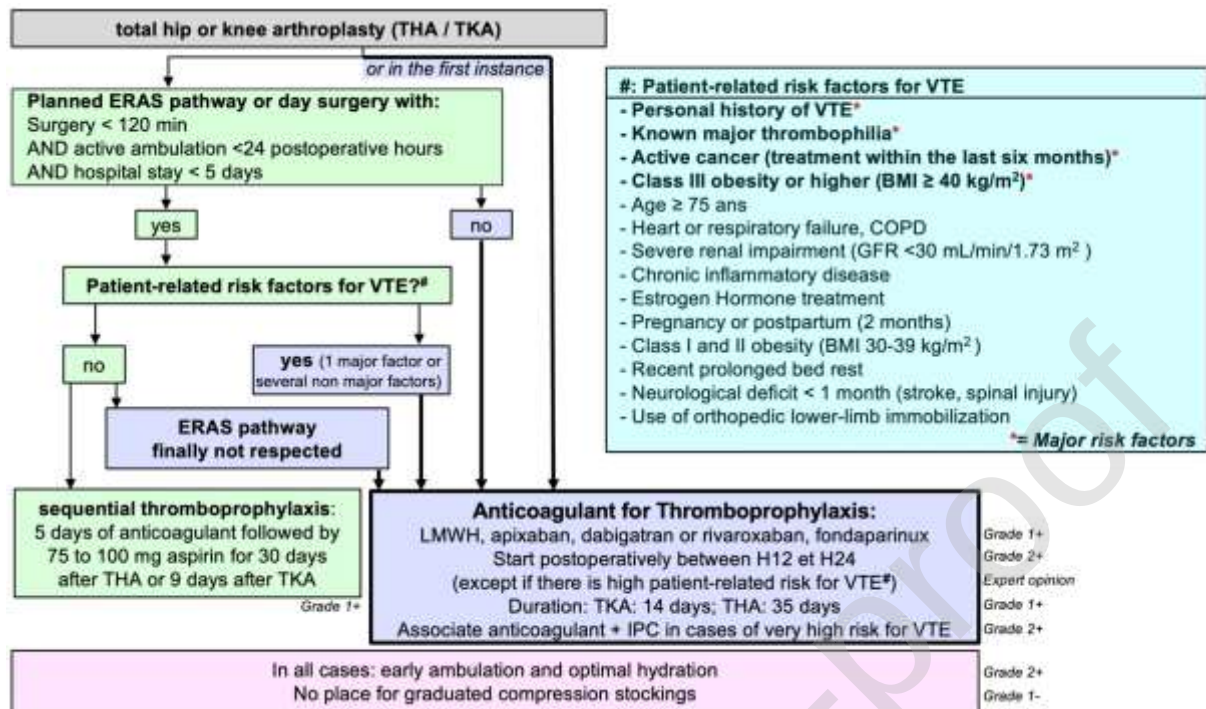
**Figure 1:**  
**Postoperative thromboprophylaxis: summary**



BMI: body mass index; DOAC: direct oral anticoagulant; DVT: deep vein thrombosis; GFR: glomerular filtration rate; IPC: intermittent pneumatic compression; LMWH: Low-molecular-weight heparin; VTE: venous thromboembolism.

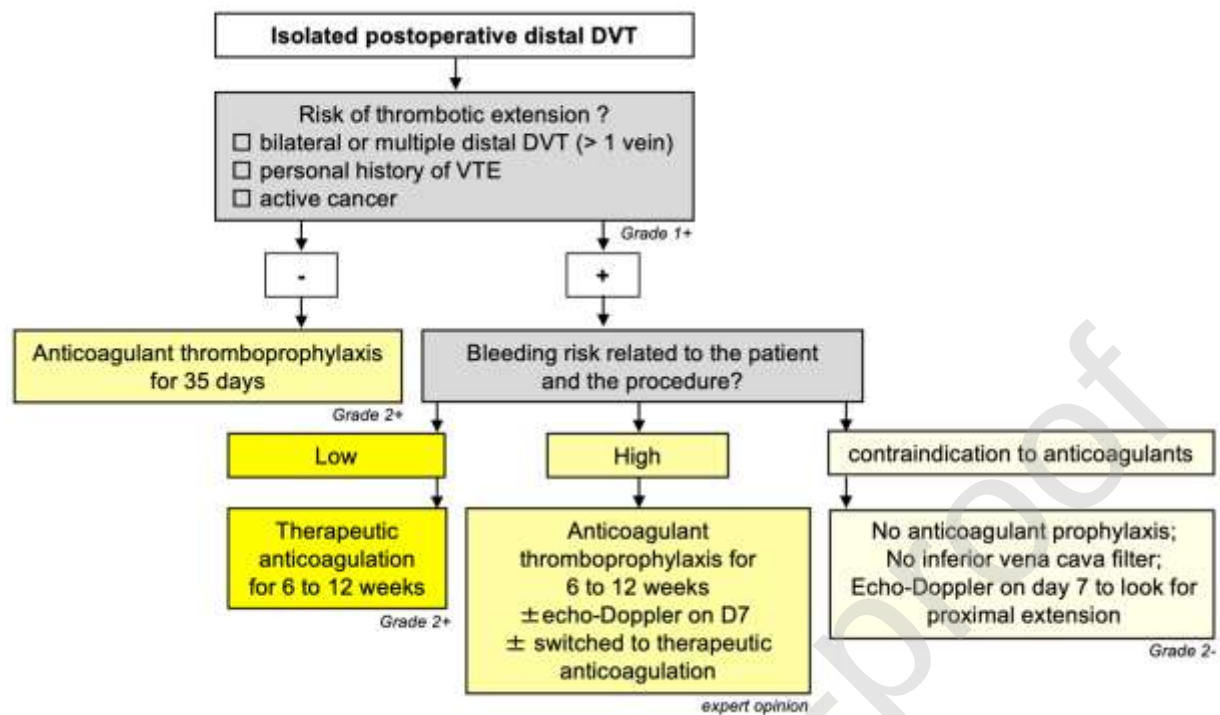
For thromboprophylaxis after total hip or knee arthroplasty, see figure 2

**Figure 2:**  
**Thromboprophylaxis after total hip arthroplasty (THA) or total knee arthroplasty (TKA)**



BMI: body mass index; COPD: Chronic obstructive pulmonary disease; DOAC: direct oral anticoagulant; ERAS: enhanced recovery after surgery; GFR: glomerular filtration rate; IPC: intermittent pneumatic compression; LMWH: Low-molecular-weight heparin; THA / TKA: total hip or knee arthroplasty; VTE: venous thromboembolism.

**Figure 3:**  
**Management if isolated postoperative distal deep vein thrombosis**



*DVT: deep vein thrombosis, VTE: venous thromboembolism*

**Supplementary data**

Journal Pre-proof

**Prevention of perioperative venous thromboembolism: guidelines from the French Working Group on Perioperative Haemostasis (GIHP) developed in collaboration with the French Society of Anaesthesia and Intensive Care Medicine (SFAR), the French Society of Thrombosis and Haemostasis (SFTH) and the French Society of Vascular Medicine (SFMV) and endorsed by the French Society of Digestive Surgery (SFCD), the French Society of Pharmacology and Therapeutics (SFPT) and INNOVTE (Investigation Network On Venous ThromboEmbolic) network**

### **Rationale of the recommendations**

Index:

1. Implementation of perioperative venous thromboprophylaxis protocols
2. Patient-related risk factors for VTE
3. Orthopedic surgery
4. Abdominal and pelvic surgery (cancer-related or not)
5. Oncologic Surgery (excluding abdominal and pelvic surgery)
6. Vascular surgery
7. Timing of pharmacological venous thromboprophylaxis initiation
8. Intermittent pneumatic compression
9. Graduated compression stockings
10. Inferior vena cava filter
11. Renal impairment
12. Obesity and extreme weights
13. Pediatric surgery
14. Patients in intensive care unit
15. Tranexamic acid and regimens of perioperative venous thromboprophylaxis
16. Laboratory testing during venous pharmacological prophylaxis
17. Postoperative distal deep vein thrombosis

## 1. Implementation of perioperative venous thromboprophylaxis protocols

In the SFAR-2011 guidelines, the indication for venous thromboprophylaxis was primarily based on the risk for VTE, combining risks related to the surgery and the patient [1]. The bleeding risk was less considered, and the perioperative care pathway was not a determining factor. Surgeries traditionally considered to be at high risk for VTE, such as total hip or knee replacements, were performed during conventional hospitalization, and anticoagulant thromboprophylaxis was routinely prescribed. However, improvements in surgical and anesthetic techniques and reduced hospital stay durations have decreased the risk for VTE [2–5]. This led to the consideration of lighter or shorter thromboprophylaxis protocols or those based on other classes of antithrombotics to reduce postoperative bleeding risk. However, few rigorously methodological studies have been conducted to compare traditional thromboprophylaxis schemes to lighter ones [6,7]. Optimization of the perioperative care pathway, including enhanced recovery after surgery (ERAS) and day-surgery, contributes to reducing risk, but is not sufficient alone to eliminate the need for pharmacological thromboprophylaxis, especially for patients with additional risk factors [4–7]. Moreover, this pathway optimization involves various surgeries, each associated with its own VTE risk, for patients with individual VTE risk factors, making it impossible to propose a universal thromboprophylaxis regimen.

In practice, the assessment of the risk for perioperative VTE includes:

- the VTE risk of surgery;
- the patient-related risk factors for VTE (see dedicated section);
- the type of perioperative care pathway. While ERAS and outpatient surgery help reduce VTE risk, a disrupted pathway increases it: for a given surgical procedure, patients who have a longer than average operative time, do not ambulate within the first 24 hours, present a complication, or have a longer-than-average hospitalization face an increased risk for VTE [3,4] and require conventional thromboprophylaxis.

Implementing perioperative venous thromboprophylaxis protocols has improved patient management: it has increased adherence to prophylaxis prescriptions in both planned and urgent ERAS [8–13]. Large cohort studies across various surgeries have reported that this practice has decreased thromboembolic events [14–17] and postoperative complications [8,9].

## 2. Patient-related risk factors for VTE

VTE is multifactorial, combining acquired and genetic risk factors [3,18,19]. The presence of patient-related risk factors for VTE increases the VTE risk of surgery, as reported in case-control or cohort studies. For example, a case-control study showed that the VTE risk after knee arthroscopy was significantly higher in the presence of other acquired or genetic risk factors [20].

Risk assessment models have been developed to stratify the VTE risk based on scores combining surgical risk and patient-related factors. These models have a moderate predictive value, and their use has not demonstrated any benefit compared to the empirical risk estimation by the clinician [21]. Their main interest seems to be to remind clinicians of the risk factors to

consider, similar to the list proposed here. In outpatient surgery, Pannucci *et al.* showed that the accumulation of risk factors could multiply the risk for VTE by 20, but their retrospective study did not assess all risk factors [22]. The Caprini score, published in 2005 and extensively studied, considers risk factors related to the patient and surgery, with relatively low weight given to surgery [23]. However, in the meta-analysis by Pannucci *et al.*, the benefit-risk balance assessed by this score was in favor of pharmacological prophylaxis only for very high-risk patients [24]. These studies emphasize that different risk factors do not have the same weight and that this weight also varies according to publications, thus, it is not possible to propose a number of minor risk factors beyond which thromboprophylaxis is necessary; this is a case-by-case discussion.

For all proposed scores, a personal history of VTE is considered a major risk factor justifying thromboprophylaxis. The same applies to active cancer. However, this criterion encompasses situations associated with very different VTE risks depending on the initial site and histological type of cancer (major thrombogenicity associated with brain, pancreatic, gastric, ovarian, uterine, lung, and kidney tumors, as well as myeloma, much less marked in breast cancers for example), the metastatic stage, and the cancer therapies used (chemotherapy, tamoxifen, immunotherapy...). Class III obesity or higher also leads to the prescription of pharmacological thromboprophylaxis even in cases of low-risk surgery.

Among thrombophilias, only major thrombophilias are included in major VTE risk factors [18,25–27]; an isolated minor thrombophilia (for example, heterozygous Factor V Leiden mutation) is not an indication in itself for pharmacological prophylaxis. Thrombophilia should be understood as a predisposition to thrombosis, the mechanism of which lies in the plasma compartment of coagulation and can be detected by laboratory tests (phenotypic and/or genetic [26,27]). Major thrombophilias include antiphospholipid syndrome, antithrombin deficiency, protein C or S deficiency, homozygous Factor V Leiden mutation or homozygous Prothrombin 20210A Gene Mutation, combination of heterozygous Factor V Leiden mutation and heterozygous Prothrombin 20210A Gene Mutation. However, isolated heterozygous Factor V Leiden or Prothrombin 20210A Gene mutation are not major thrombophilias. Major thrombophilias form a heterogeneous set with high albeit variable VTE risks. Antiphospholipid antibodies are also heterogeneous (according to the type and degree of positivity of laboratory tests), with variable VTE risks [28]. The antibodies are considered only when their persistence has been established.

In practice, a known constitutional thrombophilia should always be searched for in the history to stratify the risk for postoperative VTE and discuss the possible indication for venous pharmacological prophylaxis after surgery associated with a low VTE risk:

- Major thrombophilia associated with long-term anticoagulant treatment: pharmacological prophylaxis is prescribed postoperatively until the previous anticoagulant treatment is resumed (or until bridging with therapeutic dose LMWH if indicated).
- Major thrombophilia without long-term anticoagulant treatment (for example, patients without a history of thrombosis): pharmacological prophylaxis is prescribed postoperatively.
- Minor thrombophilia: no systematic venous pharmacological prophylaxis.
- No known thrombophilia, no personal history of VTE: there is no indication to perform thrombophilia testing to stratify the risk for postoperative VTE (except in cases of a documented family history of major constitutional thrombophilia) [26]. Advice from a hemostasis specialist or a specialized center should be considered for complex patients or situations.

A study from the RIETE registry showed that 7.4% of women under 50 using hormonal contraceptives developed postoperative VTE, mainly after non-major orthopedic surgery of the lower limbs [29]. A case-control study showed that oral contraceptives in women under 50 were associated with a higher risk for VTE after knee arthroscopy compared to those not taking them [20].

An analysis of an American medical-administrative database suggests that the effect of age on the postoperative VTE risk depends on the presence of comorbidities, the functional status of the patient, and the type of surgery. Advancing age was a predictive factor for VTE after low-risk surgery in patients without any other underlying comorbidity [30]. A prospective cohort study showed that age  $\geq 60$  years was an independent risk factor for VTE after outpatient surgery [22]. Several age thresholds associated with an increased VTE risk can be proposed, but it is a continuum, and the risk especially increases exponentially after 70-75 years [31].

A case-control study showed an association between renal impairment and the risk for VTE. The risk was multiplied by 7 in patients with severe renal impairment (estimated GFR  $< 30$  mL/min) compared to patients with normal renal function [OR 7.0 (95% CI: 2.2–21.8)] [32]. This study also found an interaction between surgery and renal impairment. While surgery increased the risk by 7 times in patients without renal impairment compared to the non-operated group, the risk was 14 times higher in operated patients with renal impairment (estimated GFR  $< 60$  mL/min). However, age and chronic kidney disease are also bleeding risk factors. The decision to prescribe thromboprophylaxis based on these factors alone must be balanced against the bleeding risk.

In two case-control studies involving patients who had arthroscopy or a cast, both age ( $> 55$  years), and the presence of comorbidity (heart failure, chronic kidney disease, COPD...) were independent factors for VTE [33,34]. The association between these comorbidities and VTE is regularly found in cohort studies [35–37]. Chronic inflammatory diseases including inflammatory bowel diseases (Crohn's disease and ulcerative colitis) are also risk factors for VTE [38], leading to the suggestion of thromboprophylaxis during any hospitalization for surgery in these patients. Acute conditions also increase the VTE risk. Thus, sepsis, major inflammatory syndrome, acute renal failure, or transfusion lead to discuss thromboprophylaxis (acute conditions are found in the list of risk factors under the term "prolonged bed rest" associated with them).

Preoperative administration of erythropoietin is no longer considered a risk factor for VTE because three recent systematic reviews have concluded that it was not associated with an increased risk for VTE. Specifically, a meta-analysis of randomized trials comparing the administration of iron alone or in combination with erythropoietin did not demonstrate an increase in the risk for venous or arterial thrombosis [39].

Furthermore, a disrupted perioperative care pathway can be a risk factor for VTE: postoperative medical or surgical complications or a failure of the ERAS pathway increases the risk and leads to suggest pharmacological prophylaxis [40,41].

Regarding the duration of pharmacological prophylaxis justified by patient-related risk factors, no trial has compared different durations. In a cohort study of patients undergoing various outpatient surgeries, VTE occurred 8 days (interquartile range 5-13 days) after surgery [6]. Thus, we propose a minimum duration of one week to cover the most at-risk period, which aligns with European recommendations [2].

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### 3. Orthopedic surgery

#### 3.1 Patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA)

The progress in anesthesia and prosthetic surgery, alongside the development of ERAS pathways and day surgery, likely explains the observed lower incidence of VTE following total hip (THA) and knee arthroplasty (TKA) today [4]. However, despite anticoagulant thromboprophylaxis, the incidence of symptomatic VTE at 90 days is estimated between 1.1% and 1.8%, and that of pulmonary embolism (PE) between 0.35% and 0.8% [6,7,42], which justifies the prescription of thromboprophylaxis started postoperatively.

Anticoagulants (DOACs, fondaparinux, or LMWH) are the recommended antithrombotics for thromboprophylaxis. Enoxaparin is the most studied LMWH; it has been used as a reference control in pivotal trials demonstrating the benefits of DOACs after THA and TKA [43–48]: compared to enoxaparin 4000 IU x 1/day, apixaban 2.5 mg x 2/day [44,44] and rivaroxaban 10 mg x 1/day [45,46] were more effective in reducing major VTE (proximal DVT + PE) without increased major or clinically relevant bleeding events, while dabigatran [47,48] was non-inferior in efficacy and had a comparable bleeding risk. Network meta-analyses of these trials suggest that among anticoagulants, the anti-Xa DOACs seem to have a better clinical benefit-risk profile [49,50], and apixaban appears to be associated with fewer clinically relevant bleeding events than rivaroxaban [49,51,52]. They also suggest that compared to enoxaparin 4000 IU x 1/day, enoxaparin 3000 IU x 2/day [50,53] and fondaparinux [49,50,54] are more effective for VTE prevention but increase major bleeding, while VKAs [50,54] are significantly less effective and therefore not recommended. Anti-XI(a) anticoagulants are under development and do not have marketing authorization in 2024.

The lower risk for VTE observed today has led to consider aspirin for thromboprophylaxis to reduce costs, on the assumption that this antiplatelet agent would be effective and could reduce bleeding complications. Numerous observational studies report the use of aspirin alone after THA or TKA, with very variable rates of symptomatic VTE at 90 days, ranging from 0.1 to 3.5% [7,55–58]. Only two randomized trials, CRISTAL and EPCAT2, have compared aspirin to anticoagulants [6,7]. CRISTAL [7] demonstrated that aspirin 100 mg x 1/day compared with enoxaparin 4000 IU x 1/day SC after THA and TKA resulted in a significantly higher rate of symptomatic VTE within 90 days, (3.45% vs. 1.82% (difference 1.97%; 95% CI: 0.54%-3.41% p=0.007)) with no reduction in major bleeding complications. Aspirin has also been evaluated in sequential thromboprophylaxis, combining an anticoagulant followed by aspirin. In the randomized EPCAT2 trial [6], after 5 days of prophylaxis with rivaroxaban 10 mg in patients undergoing THA or TKA, extended prophylaxis with aspirin was not significantly different from rivaroxaban in the prevention of symptomatic VTE, with no difference in major bleeding complications. This sequential thromboprophylaxis was given to patients without additional VTE risk factors, with a short stay in the operating room (<90 minutes) and in hospitalization (average 3.5 days) [6]. Therefore, we propose that sequential thromboprophylaxis combining 5 days of anticoagulant followed by aspirin (75 to 100 mg/day) be an option for patients with no VTE risk factors managed in a successful optimized care pathway. An optimized pathway (ERAS or outpatient) includes at least three conditions: surgery < 120 min, ambulation with active foot flexion within the first 24 postoperative hours, and a hospital stay of less than 5 days. Concurrent use of non-aspirin NSAIDs should be considered with caution (not specified in the trial) as they can interfere with the antithrombotic effect of aspirin and also increase the

bleeding risk, particularly gastrointestinal. If the patient has additional VTE risk factors or if the optimized care pathway could not be completed (surgery > 120 min, or ambulation with foot flexion not achieved within the first 24 hours postoperatively, or hospitalization exceeding 5 days for any reason), pharmacological prophylaxis is performed with an anticoagulant alone for its entire duration (DOAC, fondaparinux, or LMWH).

Regarding the duration of thromboprophylaxis, it should be noted that while VTE predominates in the first week, it also occurs in the following weeks, even in an ERAS pathway [4]. After THA, a randomized trial showed that extended thromboprophylaxis for one month is more effective for VTE prevention than thromboprophylaxis during hospitalization only [59]. The Cochrane group meta-analysis [60] suggested that extended thromboprophylaxis up to day 35 is also more effective than a 14-day duration for VTE prevention without an increase in major bleeding, whether with LMWH or DOACs. After TKA, the data are more fragile and do not allow concluding on a potential benefit from extended thromboprophylaxis beyond the recommended 14 days [60,61]. Therefore, after TKA, an extension between the 14th and 35th day is left to the discretion of clinicians. Randomized trials on sequential thromboprophylaxis have incorporated the same duration of 35 days total after THA and 14 days after TKA. There is no recent randomized trial evaluating shorter durations in the context of ERAS or day-surgery.

### 3.2 Hip fracture surgery (HFS)

The incidence of symptomatic VTE at 3 months following hip fracture surgery (HFS) remains high despite anticoagulant thromboprophylaxis, ranging between 2.5% and 4.5% in recent cohort studies [62,63]. LMWH were the first recommended anticoagulants as they reduce VTE compared to placebo [64]. A Cochrane group meta-analysis concludes that heparins (unfractionated heparin and LMWH) reduce both distal and proximal DVTs compared to control [65].

Data on fondaparinux are the most robust. Short-term prophylaxis with fondaparinux 2.5 mg/day is more effective than enoxaparin in reducing the risk for major VTE (asymptomatic proximal DVT and symptomatic VTE) [66]. Extended prophylaxis with fondaparinux for 3 additional weeks reduces symptomatic VTE compared to placebo [67]. These two trials showed no significant difference in the incidence of major bleeding between fondaparinux and its comparators. Nevertheless, a meta-analysis of four trials in major orthopedic surgery (THA, TKA, and hip fracture) concluded in an increase in major bleeding risk with fondaparinux compared to enoxaparin [68]. Furthermore, the bleeding risk observed with fondaparinux in clinical practice appears higher than in randomized trials (5.2 vs. 2.7%) [69]. The following bleeding risk factors have been identified for fondaparinux: first administration earlier than 6 hours post-surgery, body weight under 50 kg, moderate renal impairment (eGFR < 50 mL/min), and male gender [68–70]. Since fondaparinux, administered between 3 to 9 hours post-surgery, has comparable efficacy and a bleeding risk that decreases over time, it is proposed to start thromboprophylaxis not earlier than 8 hours after surgery [68]. Finally, fondaparinux has only been evaluated in the postoperative setting, leading to the start of prophylaxis preoperatively with LMWH if surgery is delayed more than 12 hours after the patient's arrival.

After hip fracture, the risk for VTE increases if surgery is delayed [71,72]. The initiation of LMWH thromboprophylaxis postoperatively is associated with an increased mortality compared to thromboprophylaxis started preoperatively [73].

LMWHs are prescribed at doses equal to or greater than 4000 IU anti-Xa (*e.g.*, dalteparin 5000 IU, enoxaparin 4000 IU, tinzaparin 4500 IU...). Thromboprophylaxis is started upon admission if surgery is delayed by more than 12 hours. Fondaparinux is prescribed at a dosage of 2.5 mg x 1/day SC, for patients over 50 kg without moderate renal insufficiency (eGFR >50 mL/min/1.73m<sup>2</sup>). It is started at least 8 hours post-surgery, and preoperative administration of LMWH is suggested if surgery is delayed by more than 12 hours.

The use of DOACs for thromboprophylaxis following HFS has been reported in cohorts and two randomized trials [74]. However, the poor methodological quality of these studies does not support the recommendation of DOACs for this indication.

Aspirin is not recommended: the PEP trial [75] showed that aspirin is more effective than placebo, but aspirin has not been compared to LMWH, and its relative efficacy is unknown in this high thrombotic risk situation. In 2010, the British guidelines modified their thromboprophylaxis regimen after HFS, switching from aspirin to LMWH. The before/after evaluation of this practice change showed a halving of symptomatic DVTs [76].

### 3.3 Nonmajor orthopedic and trauma surgery of the lower limbs

In non-major orthopedic and trauma surgery, a meta-analysis showed that LMWH reduced symptomatic VTE compared with no pharmacological prophylaxis [77]. The incidence of major bleeding during LMWH prophylaxis (0.5%) is lower than in major orthopedic surgery. Regarding DOACs, the PRONOMOS trial, which included over 3000 patients undergoing non-major lower limb orthopedic surgery, showed that rivaroxaban 10 mg is more effective than enoxaparin in reducing symptomatic VTE without increasing major bleeding events [78]. Thus, the net clinical benefit favors rivaroxaban, leading to recommend it over LMWH after non-major orthopedic surgery. On the basis of the class effect, as with LMWH, we suggest using any anti-Xa DOAC, basing the choice on their own safety profile [49,79]. However, to date, published data in non-major orthopedic surgery only concern rivaroxaban.

Non-major orthopedic and trauma surgery of the lower limbs encompasses various types of surgery associated with variable risks for VTE (Fracture of the femoral shaft, tibial plateau, patella, tibia or ankle, and Achilles tendon rupture, Knee ligament repair, simple arthroscopy, meniscectomy, forefoot surgery, removal of osteosynthesis material...). Although this risk remains low to moderate, it increases in the case of immobilization, trauma, and even more if the trauma requires surgery [80]. Anticoagulant prophylaxis is systematically recommended when the VTE risk is deemed sufficient (= major VTE >1% (symptomatic and asymptomatic proximal)) and if the net clinical benefit remains favorable (= risk for major VTE greater than the risk for major bleeding). This analysis is primarily based on surgery subgroups from the PRONOMOS study [78].

After knee ligament repair, the incidence of symptomatic VTE has been estimated at 0.5% [81]. In the PRONOMOS trial, the incidence of major VTE with LMWH prophylaxis was 0.7%, but with a higher incidence of major bleeding at 1.1%, leading to a net clinical benefit rather unfavorable to systematic thromboprophylaxis [78]. For other surgeries, such as upper limb [82] or forefoot surgery [83], the risk for VTE is judged too low to warrant thromboprophylaxis. For diagnostic knee arthroscopy or meniscectomy, the POT-KAST trial did not demonstrate the effectiveness of prophylaxis with LMWH. The incidence of symptomatic VTE without thromboprophylaxis was 0.4% [84]. In these situations where the risk of VTE is low, the indication for pharmacological prophylaxis depends on the patient-related VTE risk factors (see dedicated section). There is no argument for preferring an anti-Xa DOAC over a LMWH.

Aspirin was compared to enoxaparin in a randomized trial involving 12,000 patients operated for extremity fractures [85]. It was non-inferior to enoxaparin for 3-month mortality (average age 44 years). Regarding secondary outcomes, the incidence of PE was similar but the incidences of DVT and bleeding in critical organs were higher with aspirin.

There is limited data on the duration of pharmacological prophylaxis. In the case of cast immobilization, the duration of prophylaxis in clinical trials is usually extended until the cast is removed. After ankle fracture surgery, a trial suggests that a 6-week prophylaxis rather than one week is associated with a reduction in VTE if the containment is plastered throughout the immobilization but not if switched to an orthosis [86]. For knee ligament surgery, a 14-day prophylaxis is not superior to a 7-day prophylaxis in reducing the VTE risk [87].

Patients with major VTE risk factors (personal history of VTE, active cancer, known major thrombophilia, BMI  $\geq 40$  kg/m<sup>2</sup>) are usually excluded from randomized trials. There is no data suggesting whether duration of thromboprophylaxis should be modified for these patients. For surgery with low VTE risk, when anticoagulant prophylaxis is justified by patient-related VTE

risk factors (see dedicated section), a minimum duration of one week is proposed to cover the most at-risk period.

Pharmacological prophylaxis is started postoperatively. However, in the case of delayed surgery (more than 12 hours) in a traumatized and immobilized patient, preoperative administration of LMWH is usually carried out in trials.

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#### 4. Abdominal and pelvic surgery (cancer-related or not)

There is a continuum of postoperative VTE risk in abdominal and pelvic surgery from low to high risk.

##### 1. Abdominal and pelvic Surgery with high risk for VTE

This category includes surgical procedures considered major, though there is no consensus definition. This concept implies prolonged surgery duration (a classic threshold is 2 hours), extensive resection, or underlying oncologic or inflammatory disease [88]. Notable procedures include:

- Major hepatectomy, pancreatic surgery, colectomy, gastrectomy;
- Prostatectomy, nephrectomy, cystectomy;
- Abdominal or pelvic lymph node dissection;
- High-route hysterectomy;
- Surgery for uterine and ovarian cancer.

In a North American retrospective study, hospital readmission due to VTE occurrence after major abdominal surgery was 1.1% at 90 days [89]. The mortality rate was then 9.2%. Surgery at highest risk includes pancreatectomy and cystectomy. In urological cancer surgery, the risk for VTE is high after cystectomy (2.6 to 11.6%). After prostatectomy, it ranges from 0.2-0.9% to 3.9-15.7% depending on the surgical technique and the performance of a lymph node dissection. After nephrectomy, the risk varies from 0.7 to 11.6% [90]. In urological non-cancer surgery, living-donor nephrectomy and renal transplantation are the procedures with the highest risk (0.4 to 1.4% and 1.3 to 5.3%, respectively) [91].

After gynecologic oncology surgery (uterine, cervical, ovarian cancer), postoperative VTE risk has decreased but remains high [92] and depends on the type of cancer: 1.2% for vulvar cancers, 1.1% to 1.5% for cervical cancers, 1.4 to 2.4% for uterine cancers and 2.4 to 7.5% at 30 days for ovarian cancers [92–94]. When surgery involves the pelvic vessels, pelvic venous thromboses are frequent, even without DVT of the lower limbs, and are associated with a high risk of PE [95]. The VTE risk is increased in the presence of ascite [92], disseminated disease [92,93], history of VTE [94], and also depending on surgical characteristics: laparotomy is associated with a higher risk than laparoscopy, as is complex or prolonged surgery [92,93].

The randomized ENOXACAN-II trial demonstrated that 4-week thromboprophylaxis with LMWH was more effective than one-week prophylaxis for VTE prevention after surgery for abdominal or pelvic cancer, without increasing bleeding complications [96]. Similar results were recorded after laparoscopic surgery for colorectal cancer [97]. The randomized trial by Rasmussen et al., which also included major non-carcinological surgery, found similar results [98]. In 2019, a Cochrane Collaboration meta-analysis of randomized trials concluded that 4-week thromboprophylaxis after major abdominal and pelvic surgery reduced VTE compared to prophylaxis limited to hospitalization, without increasing bleeding [99]. These results were confirmed in the Knoll meta-analysis, which also included observational studies [100]. ERAS pathways are not associated with a significant reduction in the incidence of VTE [1]. Therefore, the same 4-week duration is proposed after major surgery in an ERAS or outpatient setting.

LMWH and fondaparinux 2.5 mg x 1/day are the reference drugs for postoperative VTE prevention [88,101–103]. DOACs do not have the marketing authorization for VTE prevention after abdominal and pelvic surgery as of early 2024. However, two recent randomized trials suggest that DOACs are an interesting option: in laparoscopic colorectal surgery, after a 7-day period of LMWH, continuing prophylaxis with rivaroxaban reduced VTE compared to placebo

[103]. After gynecologic oncology surgery, 4-week thromboprophylaxis with apixaban 2.5 mg x 2/day did not induce more bleeding complications than 4000 IU of enoxaparin, without difference in VTE incidence [104]. In this latter trial, DOAC prophylaxis was associated with high level of satisfaction compared to LMWH, and adherence to treatment was excellent (> 80%). In contrast, adherence to LMWH outside of randomized trials has been reported lower, around 60% [105]. Therefore, we suggest using anti-Xa DOACs as an alternative to LMWH after major abdominal and pelvic surgery requiring 4 weeks of pharmacological prophylaxis, after recovery of gastrointestinal function, and in the absence of surgical complications. No data are available either for dabigatran or in the field of urological surgery (the ARTS study is ongoing [105]).

## 2. Abdominal and pelvic Surgery with intermediate risk for VTE

For major abdominal and pelvic surgery, the absence of cancer and inflammation can modulate the estimation of VTE risk: for example, sigmoidectomy for diverticular disease away from an inflammatory flare-up, living-donor nephrectomy, and vaginal hysterectomy for fibroids [91,106–108]. Nevertheless, the level of evidence is low. On a case-by-case basis, a shorter duration of thromboprophylaxis (*e.g.*, 7 to 10 days compared to the previous 4 weeks) is acceptable. LMWHs are usually preferred in this indication [102,109].

Furthermore, a meta-analysis suggested that low prophylactic doses of LMWH ( $\leq 3400$  IU once daily: dalteparin 2500 IU/day, enoxaparin 2000 IU/day, nadroparin 2850 IU/day) might be as effective as SC UFH (5000 IU 2 or 3 times/day) and safer, with a reduced risk of major bleeding (RR = 0.76 [95% CI 0.63-0.92],  $p=0.005$ ) [109]. These low doses of LMWH could be useful after surgery with intermediate VTE risk if the patient has a high bleeding risk. In other situations, standard doses of LMWH (> 3400 IU/day) remain the reference.

## 3. Abdominal and pelvic Surgery with low risk for VTE

They are mostly considered non-major surgeries. These include:

General Surgery: scheduled cholecystectomy, non-complex wall surgery, proctologic surgery, appendectomy.

Urology: open surgery for benign prostatic hyperplasia, transurethral resection of the prostate or bladder, ureteroscopy, testicular, penile, or urethral surgeries.

Gynecology: conization, surgery for Bartholin gland cyst, myomectomy, operative hysteroscopy.

In the absence of pharmacological prophylaxis, the incidence of VTE after non-major abdominal and pelvic surgery in an outpatient setting is low, estimated at 0.1-0.2% [22]. In urology, the risk for symptomatic VTE is estimated at 0.3-1.0% for artificial sphincter surgery, 0.3-1.1% after urethroplasty, and 0.2% after transurethral resection of the prostate [91]. In general surgery, the 30-day VTE risk after inguinal hernia repair in day surgery is less than 0.1% [110]. After laparoscopic cholecystectomy, the incidence of symptomatic VTE is estimated at 0.6%; laparotomy is associated with a higher incidence of VTE compared to laparoscopy [111]. In gynecologic surgery, procedures such as conization, Bartholin gland cyst surgery, ovarian cystectomy, operative hysteroscopy, and myomectomy are associated with a low postoperative VTE risk of 0.1 to 0.2% at 90 days [112]. The VTE risk increases by 35% for each additional hour of surgery after hysterectomy for benign conditions [113]. The risk is higher after laparotomy than after laparoscopy or vaginal approaches [112,113].

In these various contexts, including emergency surgeries (*e.g.*, cholecystectomy, appendectomy, adnexal torsion, testicular torsion), pharmacological prophylaxis is not

systematically required. We suggest that the prescription of thromboprophylaxis integrates patient-related risk factors, the duration of surgery, and the occurrence of postoperative complications. The duration of thromboprophylaxis should then be a minimum of 7 days, LMWH being preferred [102,109].

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## 5. Oncologic Surgery (excluding abdominal and pelvic surgery)

Cancer is a major risk factor for VTE [114]. VTE affects approximately 2% of patients undergoing cancer surgery and accounts for up to 50% of postoperative deaths [115–117]. However, there is significant heterogeneity in thromboprophylaxis practices after cancer surgery [118], reflecting the limited number of interventional studies on the subject, the variability in risks for VTE and for bleeding complications associated with cancer, and in medical-economic considerations [119,120]. The perioperative VTE risk depends on cancer-related factors, such as the type and stage of cancer and the treatment. It is particularly high for patients undergoing surgery for primary cancer of the pancreas, stomach, ovary, kidney, or brain [89]. The risk increases further in case of locally advanced or metastatic cancer, systemic treatment (chemotherapy, immunotherapy, targeted therapies), personal history of VTE [121], or postoperative complications (surgical site infection, reoperation) [89,122,123]. Other oncological surgeries carry a lower risk (*e.g.*, ear, nose and throat (ENT), breast, lung). Minimally invasive surgical techniques and ERAS pathways may reduce VTE risk, but their potential benefit is poorly documented. The Caprini score could be useful for selecting high-risk patients, but the threshold values differ depending on the surgery and the study thus is difficult to use [124–126]. A thromboprophylaxis strategy considering homogeneous patient groups rather than using risk scores facilitates prophylaxis prescription in care units.

### Breast cancer:

Breast cancer, the most frequent cancer in women, illustrates the thromboprophylaxis discussion. The VTE risk after breast cancer surgery is low, likely due to the superficial nature of the surgery, and is reported at less than 0.5%, mainly in the first postoperative month [127,128]. Therefore, routine postoperative pharmacological prophylaxis is not justified [129]. However, this risk varies with the invasiveness of the cancer [130], the type of surgery [131,132], cancer treatments [128], and patient-related risk factors, particularly age and obesity [129,130,132]. Mastectomy is associated with more VTE than conservative surgery [131,132], especially with immediate reconstruction [129,132]. Surgery lasting more than 3 hours increases the risk [129], as does neoadjuvant chemotherapy in the three months preceding surgery [128,130,131]. Tamoxifen therapy increases the risk fivefold (95% CI 2.3–12.7) [128]. In the absence of robust trials, it is suggested that simple outpatient lumpectomy, with or without axillary lymph node dissection, does not require pharmacological prophylaxis in the absence of high personal risk factors [129]. However, more complex surgery (mastectomy with immediate reconstruction), surgery associated with perioperative chemotherapy (neoadjuvant or adjuvant), or tamoxifen treatment might justify thromboprophylaxis. In the absence of specific data on thromboprophylaxis duration, a minimum duration of 7 days is proposed. These suggestions align with those of the American Society of Breast Surgeons [129].

### Head and Neck Cancer Surgery:

Thromboprophylaxis after head and neck cancer surgery has been scarcely studied and depends on the type of surgery [133–135]. Some authors suggest a low postoperative VTE incidence (0.5%), while others highlight the risk of both VTE and bleeding, increased during major reconstruction and flap placement [134,135]. The Caprini score, heavily dependent on the type of surgery performed, has been proposed to distinguish low-risk (0.5%; score <7) from high-risk (2.2%; score ≥7) patients [135], and to propose pharmacological prophylaxis for high-risk patients and those undergoing major surgery if the bleeding risk is not prohibitive. Thromboprophylaxis does not seem to reduce the risk of graft thrombosis or necrosis. In summary, it is proposed that most outpatient surgeries for head and neck cancer be performed

without pharmacological prophylaxis and that prophylaxis be prescribed for the duration of hospitalization if applicable. Conversely, if the bleeding risk is acceptable, pharmacological prophylaxis is indicated after major surgery with reconstruction or flap placement. In the absence of specific data on thromboprophylaxis duration, a minimum duration of 7 days is proposed.

#### Thoracic Surgery:

The benefits of thromboprophylaxis in thoracic surgery have been poorly evaluated. After surgical resection with a lobectomy or pneumonectomy for lung cancer, the incidence of VTE at one month is high, between 2 and 5%, despite prophylaxis; one-third occurs after hospitalization; the risk persists after hospital discharge and in the three months following surgery, and VTE increases mortality by a factor of 8 [136]. While pharmacological prophylaxis is recommended, its optimal duration has not been evaluated. Some international guidelines [136,137] suggest continuing it for up to a month by analogy with major abdominal and pelvic surgery, but no study has compared short versus prolonged prophylaxis. A randomized trial compared LMWH prophylaxis to placebo in the 30 days following pulmonary resection for cancer, with systematic CT angiography and lower limb venous ultrasound at 30 days. The small number of patients included (n=103) did not allow for conclusive results, but no increased bleeding risk was associated with LMWH [138]. Regarding mechanical means, a small non-randomized study did not find any reduction in VTE in the group wearing pneumatic compression compared to the group without compression, suggesting it should not be used routinely [139]. DOACs have not been evaluated in this surgery.

## 6. Vascular surgery

For aortic surgery the laparoscopic approach does not appear to change the incidence of DVT. After endovascular repair of an aortic aneurysm, the reported incidence of DVT is 6%, indicating a high risk for VTE. The incidence of VTE after thoracic aortic surgery or carotid surgery is unknown [140]. Most series of carotid surgery do not report the prescription of postoperative anticoagulant prophylaxis. After peripheral vascular surgery, VTE incidence ranges from 1.8% (ultrasound) to 28% (venography). In the meta-analysis by Haykal *et al.*, pharmacological prophylaxis was associated with a non-significant reduction in the risk for DVT and PE [141].

Following the results of the Voyager PAD trial [142], rivaroxaban at a dose of 2.5 mg twice daily, combined with 100 mg of aspirin daily, received approval for postoperative use after lower limb arterial vascular surgery (open or endovascular below the inguinal ligament) to prevent major cardiac events (death, myocardial infarction, stroke) and major limb vascular events (amputation, acute ischemia, surgical re-intervention). This regimen is initiated within 10 days postoperatively (with or without clopidogrel for the first month). However, if postoperative venous thromboprophylaxis with LMWH is prescribed, the protocol calls for delaying the introduction of rivaroxaban until the LMWH is discontinued (day 5-10) [143].

Data on CPI are scarce. It is generally advised against using CPI in the perioperative setting of lower limb arterial revascularization surgery as it might impair arterial perfusion. However, it has been suggested that CPI could be beneficial in critical limb ischemia, but this has not been evaluated perioperatively [144].

After varicose vein surgery, data on venous thromboembolic complications are primarily observational, heterogeneous, and have significant bias risks. Without pharmacological thromboprophylaxis, the incidence of DVT diagnosed by CUS after open surgery is approximately 5% [145], while the incidence of clinical DVT after endovascular treatment is about 2% [146]. No randomized trial has evaluated the effect of pharmacological prophylaxis after endovascular treatment, but observational data suggest a reduced risk for DVT, associated with prophylaxis duration from 1 to 14 days [146]. A randomized trial in open surgery, excluding high thrombotic risk patients, reported a significant reduction in DVTs after a short three-day pharmacological prophylaxis without a significant increase in bleeding risk [147].

For thermal endovascular procedures, such as laser treatment of varicose veins, a Swiss prospective registry reports a very low rate of venous thromboembolism (VTE) (<1%), regardless of whether patients received thromboprophylaxis [148]. A systematic review of 221 studies (randomized, prospective, or retrospective cohorts) reports a reduction in DVTs with pharmacological prophylaxis (0.52%) compared to mechanical prevention alone (2.26%), without reduction in PE (0.45% vs. 0.23%). However, the individual VTE risk assessment was very heterogeneous across studies. Better risk stratification is needed to evaluate benefit-risk ratio of thromboprophylaxis and select patients at high venous thromboembolic risk requiring postoperative thromboprophylaxis [143,146].

## 7. Timing of pharmacological venous thromboprophylaxis initiation

The optimal timing for initiating pharmacological prophylaxis reduces the risk for VTE without unacceptably increasing the bleeding risk. It must integrate the asynchronous nature of these two risks and their therapeutic and prognostic consequences:

- Bleeding events have a more significant impact on vital and functional prognosis compared to VTE [140].
- The risk of bleeding appears to be earlier than the thromboembolic risk: reported bleeding events occur within the first 24 to 48 hours postoperatively, whereas VTE occurs beyond 48 hours in orthopedic and abdominal and pelvic surgery and up to several weeks after surgery [4,149–151]. However, registries also suggest that the thromboembolic risk could be earlier, particularly in the presence of VTE risk factors [4].
- The management of postoperative VTE has greatly simplified in recent years with a facilitated diagnostic strategy (clinical score / angio-CT / ultrasound) that avoids detrimental diagnostic delays; very early mobilization recommended in the case of DVT and/or PE; and the possibility of outpatient management or after a short hospitalization, which allows the ERAS pathway to remain uncompromised; a simplified treatment with direct oral anticoagulants (DOACs); and a short recommended duration of anticoagulant treatment after surgery-provoked DVT/PE, from 3 to 6 months maximum [152].

Therefore, delaying the initiation of thromboprophylaxis may reduce the bleeding risk while maintaining relative antithrombotic efficacy. Additionally, a first administration the day after surgery (between 12 to 24 hours postoperatively) would help standardize care schedules for all patients in the same surgical unit, optimize care organization, and avoid potential misuse.

### 7.1. Pre- or postoperative initiation of pharmacological prophylaxis?

In abdominal and pelvic surgery, several studies conclude that preoperative administration increases the risk of bleeding but not efficacy [153,154]. A meta-analysis of 22 randomized trials, including 11 in abdominal and cardiothoracic surgery, showed that initiating thromboprophylaxis beyond the 8<sup>th</sup> and up to the 24<sup>th</sup> postoperative hour is as effective and safe as preoperative administration [155]. Preoperative administration of the first dose is associated with a significant increase in non-major bleeding events compared to postoperative administration, without a significant increase in major bleeding events. It is also associated with a non-significant reduction in VTE, mainly asymptomatic VTE (but only 10 out of 114 VTEs were symptomatic). The scope of this meta-analysis was limited by the heterogeneity of the studies, which evaluated different antithrombotics, different preoperative timings, different surgical procedures and techniques, and different anesthesia techniques.

In orthopedic surgery, a systematic review showed that LMWH injected preoperatively or in the early postoperative period (before the 4<sup>th</sup> hour) increase the risk of bleeding but not efficacy [156]. A randomized trial involving 210 patients showed that delaying administration until the day after surgery significantly reduced the bleeding risk without increasing the risk for VTE [157]. Similar data were observed for bleeding risk from subgroups of two randomized trials where LMWH were administered either preoperatively or at the 18<sup>th</sup> postoperative hour [46]. However, in this analysis, there was an increase in the risk for major VTE (symptomatic DVT/PE and proximal phlebographic DVT) with administration delayed to the 18<sup>th</sup> hour. Overall, in elective surgery, the clinical benefit of preoperative administration is not demonstrated, and the bleeding risk leads to the first dose of thromboprophylaxis being administered postoperatively.

However, certain preoperative medical conditions expose patients to a higher risk for VTE (*e.g.*, acute illness such as sepsis or recent respiratory or cardiac decompensation). Similarly, delaying

urgent surgical indications can increase the risk for VTE (due to mobility restrictions related to bed rest, dehydration, *etc.*). Hip fracture is an example where patient-related risk factors and delayed surgical management significantly increase the incidence of VTE (see dedicated section). In such situations, pharmacological prophylaxis should be initiated preoperatively, preferably with LMWH, for their ease of use. The last prophylactic dose of LMWH should be administered at least 12 hours before surgery.

## **7.2. Time interval from surgery to postoperative pharmacological prophylaxis**

The timing between the end of surgery and the first thromboprophylaxis dose has been primarily evaluated in major orthopedic surgery. There is an inverse relationship between the delay in the first dose and major bleeding after THA, TKA, and hip fracture surgery [68]. A randomized trial including 210 TKA patients showed that delaying LMWH administration to 24 hours post-surgery reduced blood loss, transfusions, and major bleeding without increasing DVT [157]. For fondaparinux, a meta-regression of orthopedic trials showed that delaying the first dose to 3 to 9 hours post-surgery reduced bleeding risk but not efficacy [68]. A randomized trial found that administering fondaparinux 12 to 24 hours post-surgery was as effective and safer than 8 to 10 hours post-surgery [158].

The development of rivaroxaban was initially based on a first dose between 6 and 8 hours after surgery, showing reduced VTE risk compared to LMWHs but increased bleeding risk [51]. In later trials rivaroxaban was initiated 6 to 24 hours after surgery [6,78]. Although no direct randomized comparison exists between these regimens, a non-exhaustive registry suggests that efficacy is maintained with delayed administration but does not reduce bleeding risk [159].

For apixaban, the development program was based on a first dose between 12 and 24 hours after surgery, typically around 19 hours, resulting in same efficacy and safety as LMWH after major orthopedic surgery [160].

In conclusion, administering the first dose on the day of surgery (6 to 12 hours postoperatively) or the day after surgery (12 to 24 hours postoperatively) is feasible with LMWH. The choice between these timings may depend on the patient-related VTE risk, with earlier timing for high-risk patients and later timing for those without significant risk factors.

For other anti-Xa anticoagulants, administering on the day of surgery appears to increase bleeding risk (fondaparinux and rivaroxaban) or has not been evaluated (apixaban), leading to a preference for administration the day after surgery. The administration of tranexamic acid does not alter this schedule.

## 8. Intermittent pneumatic compression

The efficacy of IPC is well established: the randomized CLOT3 trial demonstrated that IPC was effective in preventing proximal DVT after an ischemic stroke [161]. Postoperatively, a meta-analysis of 5 randomized trials concluded that IPC was effective for VTE prevention after major abdominal and pelvic surgery, without increasing the risk of bleeding [162]. Two randomized trials also showed the benefit of intraoperative IPC: when used intraoperatively during neurosurgery for intracranial tumors, IPC reduced postoperative VTE [163]. Similarly, during intraoperative minimally invasive surgery for lung cancer, IPC alone (without postoperative anticoagulant) reduced the incidence of asymptomatic distal DVT compared to the group without IPC [164].

However, IPC is not more effective for VTE prevention than other preventive methods used alone, notably heparins [162].

The combination of IPC with pharmacological prophylaxis is more effective than IPC alone: a randomized trial showed that after gastrectomy, IPC alone was associated with a higher incidence of VTE compared to the combination of IPC and LMWH [165]. The combination of IPC with pharmacological prophylaxis also appears to be superior to pharmacological prophylaxis alone for VTE prevention, as suggested by two meta-analyses of randomized trials [166,167], with one also finding a benefit for PE prevention [167]. However, the level of evidence is low, with a high risk of bias and significant heterogeneity among the studies, particularly regarding types of surgery and levels of VTE risk. In patients at high risk for VTE, defined by a Caprini score of 11 or higher, IPC combined with 4000 IU enoxaparin was more effective than enoxaparin alone in preventing VTE after major surgery, primarily abdominal and pelvic surgery [168]. Similarly, in orthopedic surgery, an open randomized trial including 1800 patients showed that the combination of IPC and LMWH was superior to LMWH alone in preventing DVT during hospitalization [169]. The benefit of the combination is also reported with DOAC, as the addition of IPC to 10 mg rivaroxaban reduced DVT after TKA compared to DOAC alone [170]. The low level of evidence leads to the recommendation of combining IPC with pharmacological prophylaxis only for patients at very high risk for VTE (notably, the combination of a major patient-related VTE risk factor and surgery with a high VTE risk).

In Intensive Care, a meta-analysis of 4 randomized trials concluded that IPC reduced VTE compared to no prophylaxis, but there was no difference in efficacy between IPC and LMWH, even though LMWH was associated with more bleeding complications [171]. Additionally, combining IPC with LMWH did not provide a benefit compared to LMWH alone, confirming the results of a randomized trial that included 2000 ICU patients and showed that the addition of IPC to heparin prophylaxis (LMWH or UFH) did not reduce proximal DVT [172].

Regarding the equipment, no well-conducted study allows for one type of IPC device preference over another. One of the meta-analyses suggests that foot-level IPC is less effective than calf and/or thigh-level IPC [166]. IPC is contraindicated in the presence of skin lesions, as it can exacerbate them [161]. Most importantly, the use of IPC should not delay the resumption of ambulation.

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## 9. Graduated compression stockings (GCS)

A meta-analysis of 20 studies involving 2853 patients comparing GCS (socks, stockings, tights) to a control group suggested a possible effect of GCS on the perioperative risk for PE (OR 0.38, 95% CI 0.15-0.96). However, 11 of the 20 studies in this meta-analysis also used pharmacological prophylaxis, and 12 were of insufficient methodological quality [173]. Conversely, the British NICE guidelines reported a network meta-analysis that showed that GCS did not reduce the risk for perioperative VTE compared to a control group and was less effective than all other prophylactic methods (pharmacological and IPC) [174].

Furthermore, the randomized GAPS trial evaluated the addition of GCS in 1858 surgical patients receiving pharmacological prophylaxis with LMWH. The addition of GCS provided no benefit [175]. These findings were confirmed by the analysis of a medico-economic registry including 24,273 patients from 2006 to 2016. After propensity score matching, the comparison of LMWH + GCS versus LMWH alone showed a relative risk of 0.999 (95% CI 0.998-1.000), confirming the lack of efficacy of GCS in the perioperative setting when pharmacological prophylaxis is prescribed [176]. A meta-analysis confirmed that the addition of GCS to pharmacological prophylaxis did not reduce the risk for postoperative VTE but increased skin lesions and costs [177].

A literature review summarized the data concerning the usefulness of GCS in the management of symptomatic venous insufficiency and post-thrombotic syndrome. It suggested that the only indication for GCS would be in patients with significant venous insufficiency, *i.e.*, patients wearing GCS long-term [178]. However, there are no specific perioperative data concerning this patient population.

## 10. Inferior vena cava (IVC) filter

### Primary thromboprophylaxis

The data regarding the use of IVC filters for primary prevention of VTE are limited and mainly concern two populations: patients undergoing bariatric surgery and trauma patients [179,180]. The evidence does not support the preventive use of IVC filters. In bariatric surgery, a systematic review of non-randomized studies on the preventive use of IVC filters showed no significant difference in the incidence of VTE between the filter group and the placebo group [180]. In trauma patients, while several observational studies suggest a potential benefit of filters, a meta-analysis of randomized trials including trauma patients concluded that preventive IVC filter did not reduce the incidence of PE [179]. There is no well-designed study to draw conclusions for patients with complex pelvic trauma, which induces frequent pelvic thrombosis. In summary, for primary thromboprophylaxis, the lack of established benefit and the risks and costs associated with IVC filter placement discourage their perioperative use. However, if an IVC filter is placed, its removal should be anticipated and planned after the period of high VTE risk.

### Secondary thromboprophylaxis

The role of IVC filters in patients with recent proximal DVT of the lower limbs or PE was addressed in French recommendations in 2019 [181]. IVC filter is proposed before high bleeding risk surgery that must be performed less than one month after proximal DVT or PE. IVC filter is also discussed before high bleeding risk surgery that must be performed from one to three months after proximal DVT or PE if therapeutic anticoagulation cannot be resumed before the 72nd postoperative hour because of an unacceptable post-operative bleeding risk. However, the benefit of preoperative placement of an IVC filter for secondary prevention of VTE has been minimally evaluated. A study using administrative data of 33 740 patients who underwent IVC filter for DVT associated with cancer found that a filter was placed in 38% of patients due to associated bleeding risk [182]. In 80% of cases, the IVC filter placement procedures occurred within 30 days of initial DVT diagnosis. Despite higher overall mortality in patients with a filter, filter placement was associated with increased survival without PE compared to those without a filter. The authors concluded that filters might offer benefits in the first month following diagnosis when anticoagulants are contraindicated. In a series of 247 patients with cancer-associated VTE and a contraindication to anticoagulation (mainly bleeding but also recent surgery for 24% of patients), the placement of an IVC filter within 14 days of VTE diagnosis was associated with a lower risk of death from PE but a higher risk of VTE recurrence compared to a matched cohort without a filter [183].

Filter placement is associated with procedural complications (vascular perforation, hemorrhage) and risks related to filter retrieval. Long-term maintenance of a filter also increases VTE risk, as demonstrated by the PREPIC 1 trial [184]: 400 patients with DVT were randomized to receive either standard anticoagulation alone or anticoagulation associated with a permanent IVC filter. Filter placement reduced the incidence of PE but increased the long-term incidence of DVT recurrence, particularly thromboses of the inferior vena cava above the filter. In another trial, PREPIC 2, where filters were systematically removed at 3 months, this increase in VTE recurrence was not observed [185], supporting the systematic removal of retrievable filters. Additionally, a retrospective analysis of 111 patients with a prophylactic preoperative IVC filter inserted before abdominal surgery suggested that non-removal of the filter increased the thrombosis risk [186]. It is thus recommended to remove the filter after the high-risk thrombotic period, ideally at least one month post-bariatric surgery or severe trauma.

In summary, for secondary prevention, the risk for VTE associated with prolonged filter maintenance leads to prefer retrievable IVC filters, with planned removal within the first few weeks once the bleeding risk is controlled. Maximum implantation durations vary by manufacturer, but retrieval becomes more challenging the longer the filter remains in place. The use of predefined algorithms can improve the retrieval rate [187].

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## 11. Renal impairment

Renal function must be considered to prescribe thromboprophylaxis, as chronic kidney disease is a risk factor for thrombotic and bleeding events, both generally and in the perioperative context [188–191]. Additionally, most anticoagulants are eliminated by the kidneys. Anticoagulants have been developed using the Cockcroft-Gault formula to assess renal function. Therefore, dosage and regimen adjustments for severe and end-stage renal impairment are based on the glomerular filtration rate (GFR) estimated on the Cockcroft-Gault equation, even though the recommendations from the French National Authority for Health and the francophone Society of Nephrology, Dialysis and Transplantation advocate using the CKD-EPI Equation.

### Severe Renal impairment

Until 2017, LMWHs were contraindicated in cases of severe renal impairment (estimated GFR  $<30$  mL/min/1.73 m<sup>2</sup>), and UFH was the standard drug. Following the European labelling harmonization of LMWH by the European Medicines Agency, it is now possible to prescribe LMWH in cases of severe renal impairment according to the dosage regimens indicated in the marketing authorization. However, the data supporting these modifications are limited. In the absence of severe renal impairment, the reduced dose of 2000 IU enoxaparin is less effective for VTE prevention than the standard dose [192,193]. However, pharmacokinetic data suggest that in cases of eGFR  $<30$  mL/min, this reduced dose leads to anticoagulation levels comparable to those obtained with standard prophylaxis regimens in the absence of severe renal impairment [194,195]. A meta-analysis of randomized trials comparing LMWH and UFH in general surgery concluded that bleeding complications were more frequent with UFH than with low-dose LMWH ( $<3400$  IU anti-Xa) outside of CKD [109]. Moreover, the bleeding risk associated with prophylaxis increases in severe renal impairment, whether with LMWH or UFH, with some studies reporting a higher risk with UFH [196]. A subgroup analysis of the PROTECT trial conducted in critical care did not show an increase in bleeding complications with 5000 IU of dalteparin once daily compared to 5000 IU of UFH twice daily in patients with severe renal impairment, or even in dialysis patients [197]. The absence of UFH accumulation in cases of severe renal impairment remains to be demonstrated. Finally, heparin-induced thrombocytopenia (HIT) risk is higher with UFH than with LMWH [198]. These data and the number of daily injections lead to prefer LMWH.

Non-heparin anticoagulants are partially or totally eliminated by the kidney. In cases of severe renal impairment, their use for postoperative prophylaxis must be considered carefully and according to their marketing authorization:

- Dabigatran is used at a reduced dose of 150 mg once daily instead of 220 mg once daily when the eGFR is between 30 and 50 mL/min/1.73 m<sup>2</sup> and is contraindicated when the eGFR is  $<30$  mL/min/1.73 m<sup>2</sup>.
- Apixaban and rivaroxaban do not require dosage adjustment when the eGFR is between 15 and 30 mL/min/1.73 m<sup>2</sup>. However, published data are very limited in the perioperative period. They are contraindicated when the eGFR is  $<15$  mL/min/1.73 m<sup>2</sup>.
- Fondaparinux 2.5 mg/day is contraindicated when the eGFR is  $<50$  mL/min/1.73 m<sup>2</sup> (fondaparinux 1.5 mg is not available in France).

The elimination half-life of DOAC is longer than that of LMWH, and the absence of a specific antidote for apixaban and rivaroxaban makes their perioperative management complex in this situation.

### End-Stage kidney Disease

In cases of end-stage kidney disease (eGFR <15 ml/min/1.73 m<sup>2</sup>), UFH should be used at a dosage of 5000 IU twice daily subcutaneously since LMWH and DOAC are contraindicated, in accordance with the Summary of Product Characteristics (SmPC) [194,195]. The dose of 5000 IU three times daily has not shown superiority over the dose of 5000 IU twice daily [199,200].

Aspirin has not been evaluated compared to heparin in patients with severe renal impairment. Moreover, renal impairment is a thrombotic risk factor, leading to a preference for anticoagulant prophylaxis.

Journal Pre-proof

## 12. Obesity and extreme weights

These recommendations are mainly based on data regarding bariatric surgery and a low level of evidence.

Two distinct issues come together: obesity and weight. Obesity is a patient-related VTE risk factor, leading to discuss perioperative pharmacological prophylaxis. High weight, in a tall individual without obesity, does not correlate with an increased VTE risk but raises concerns about anticoagulant dosing when indicated. While the fixed dose of LMWH covers a wide weight range (45-100 kg), for extreme weights, doses are adjusted to achieve comparable anticoagulation levels to standard weights with standard doses. Thus, BMI rather than weight is used to discuss prophylaxis regimens for obese patients.

Obesity increases the risk for perioperative DVT and PE [22,201–203]. This increased VTE risk is observed across various surgical procedures, irrespective of specialty [202,203], whether in elective or emergency surgery, conventional hospitalization or outpatient settings [22,203]. The risk increases continuously with the BMI [201][1]. However, a BMI value of 40 kg/m<sup>2</sup> is often cited as the threshold associated with a significant increase in risk [22,202].

In bariatric surgery, the perioperative VTE risk has decreased with surgical technique improvement, reduced operative times and hospital stays, and the development of ERAS pathway. However, PE remains one of the leading causes of death following bariatric surgery [204], and the incidence of symptomatic VTE in recent studies is 0.5-1.5% despite pharmacological prophylaxis [205–207]. While VTE are less frequent after bariatric surgery than bleeding complications, they appear to be more fatal [208]. The presence of other risk factors increases the VTE risk, particularly a personal history of VTE, age, and male sex [209,210]. Surgical risk factors include revision surgery and, most notably, surgical complications [210]. Compared to laparoscopic bariatric procedures, open laparotomy procedures are associated with an increased VTE risk [210], whereas robot-assisted techniques do not appear to reduce this risk [211].

Pharmacological prophylaxis after bariatric surgery is associated with a reduced VTE risk [210,212,213]. LMWH is favored over UFH in studies, though this preference is based on a low level of evidence. In a non-randomized prospective study, anti-Xa levels in patients on enoxaparin after bariatric surgery were more often within the target range than those in patients on UFH [214]. However, there was no observed difference in VTE or major bleeding. A registry study concluded that patients receiving LMWH prophylaxis had a lower incidence of VTE than those receiving UFH prophylaxis, without an increase in bleeding [215]. Additionally, UFH is associated with a higher incidence of HIT than LMWH [198].

The proposal to adjust LMWH dosages based on BMI or weight also relies on studies with a low level of evidence [215–220]:

- LMWH anti-Xa level measurement allows for the evaluation of plasma concentration and the comparison with expected values. It decreases as BMI and weight increase and increases with higher LMWH doses. However, the target prophylactic level is unknown, and the correlation with VTE occurrence is not established, suggesting that anti-Xa levels should not be monitored nor dosage-adjusted based on this level.
- Increasing LMWH doses appears to reduce VTE risk but raises concerns about the associated bleeding risk. A retrospective study (mean BMI of 50 kg/m<sup>2</sup>) suggested that the incidence of VTE was reduced with the 4000 IU twice daily regimen compared to the 3000 IU twice daily regimen, without an increased bleeding risk [221]. Another retrospective study including

hospitalized patients over 100 kg reported that changing the dose from 4000 IU once daily to 4000 IU twice daily was associated with a reduction in VTE in patients with a BMI  $\geq 40$  kg/m<sup>2</sup>, also without an increased bleeding risk [222]. However, no well-conducted randomized trial has determined the optimal dosages [223,224].

- The enoxaparin 4000 IU twice daily regimen appears suitable for weights up to 150 kg [225]. Beyond 150 kg, a regimen of 6000 IU twice daily may be necessary.
- A higher LMWH dose (*e.g.*, enoxaparin 6000 IU once daily SC) has also been proposed for weights over 100 kg [226,227], but the bleeding risk is not well evaluated.
- The choice of prophylaxis regimen should consider the available anticoagulant formulations that may not be appropriate (risk of dosing errors).

Enoxaparin 4000 IU twice daily is the most described LMWH regimen. However, prescribing dalteparin 5000 IU twice daily and tinzaparin 75 IU/kg are possible options [223]. Only tinzaparin has in its labeling the option to adjust the dose according to actual weight as an alternative to the fixed-dose for patients with extreme weights [228,229]. The anticoagulant level reached with the recommended dose in the labeling of 50 IU/kg was evaluated in a recent study in obese medical patients (median weight 125 kg, median BMI 41.9 kg/m<sup>2</sup>). The median anti-Xa level was 0.25 IU/mL, and the target anti-Xa level of 0.2 to 0.4 IU/mL was achieved in 80/121 plasma samples (66.1%), with 39 samples (32.2%) below the target range [230]. In another study of obese subjects (101-165 kg, mean weight 129.6 kg, mean BMI 43) receiving an injection of 75 IU/kg tinzaparin, the mean anti-Xa level was 0.34 IU/mL (95% CI 0.30-0.38) [231]. Tseng *et al.* studied the efficacy of a tinzaparin dose of 75 IU/kg adjusted to actual weight, rounded to the nearest prefilled syringe dose, resulting in a dose of 4500 IU for weights below 110 kg, 10,000 IU for weights between 110 and 159 kg, and 14,000 IU for weights above 160 kg. This strategy proved safe, with a low frequency of VTE and bleeding [207].

Fondaparinux, administered 6 hours postoperatively at a dose of 5 mg once daily, was compared to 4000 IU twice daily enoxaparin in a randomized trial after bariatric surgery (mean BMI of 45 kg/m<sup>2</sup>): the incidences of thrombotic and bleeding complications were not different; however, fondaparinux was more often within the target anti-Xa levels [232].

DOACs are generally not recommended in the early post-bariatric surgery period due to absorption issues, which makes their effectiveness uncertain [233].

In bariatric surgery, the preoperative initiation of pharmacological prophylaxis has been considered. In a small randomized trial, preoperative initiation of prophylaxis was associated with an increase in bleeding events compared to postoperative initiation, although it did reduce the incidence of asymptomatic VTEs [212]. An analysis of a database also showed that preoperative thromboprophylaxis was associated with more transfusions without a reduction in DVT [213]. Given the uncertain benefit-risk ratio of this strategy and by analogy with other surgeries where the benefit of preoperative initiation is not demonstrated [155], it is proposed to start pharmacological prophylaxis postoperatively.

The duration of thromboprophylaxis after bariatric surgery has not been formally evaluated. In 2011, the SFAR recommended a minimum prophylaxis duration of 10 days. The ESA recommends a prophylaxis duration of 10 to 15 days. While the development of ERAS might suggest shortening the duration of prophylaxis, a cohort study conducted between 2003 and 2007 concluded that prophylaxis limited to hospitalization resulted in more VTE than a 10-day prophylaxis [234].

In non-bariatric surgery for obese patients, data are scarce. The analysis of a multicenter database including over 9000 hospitalized patients weighing more than 100 kg showed that enhanced prophylaxis (enoxaparin 4000 IU twice daily or UFH 7500 IU SC thrice daily) was associated with a halving of the VTE risk compared to standard prophylaxis (enoxaparin 4000 IU once daily or UFH 5000 IU SC twice or thrice daily) in patients with a BMI  $\geq 40$  kg/m<sup>2</sup> but not in patients with a BMI  $< 40$  kg/m<sup>2</sup> [222]. Regarding DOAC, in situations where their use is proposed (*e.g.*, lower limb orthopedic surgery), the pharmacokinetics of direct anti-Xa DOAC (apixaban and rivaroxaban) are minimally altered and can be used at usual dosages. The lack of robust data on dabigatran precludes its recommendation. There is very limited experience for BMI  $> 50$  kg/m<sup>2</sup> or weight  $> 150$  kg, and the use of DOAC in this population should only be considered after a careful evaluation of the benefit-risk balance [223,233].

The role of IPC in obese patients is poorly documented. Given that obesity is a VTE risk factor, and by analogy with high thrombotic risk situations (see dedicated section), it is proposed to combine IPC with pharmacological prophylaxis in morbidly obese patients (BMI  $\geq 40$  kg/m<sup>2</sup>) undergoing major surgery. The duration of this combination is not defined, but the use of IPC should not delay the resumption of ambulation. GCS are not indicated (see dedicated section).

For patients weighing between 100 and 150 kg who are not obese but are tall, the prophylaxis regimen is not established: increasing LMWH doses could maintain an anticoagulation level similar to standard-weight patients, but the clinical benefit of this increase is not documented.

In patients with low body weight, it is proposed that doses be reduced to prevent accumulation and bleeding risks. After two injections of enoxaparin 4000 IU, weight  $< 45$  kg was strongly associated with a peak anti-Xa level  $> 0.5$  IU/mL [235], potentially justifying a reduced LMWH dosage (*e.g.*, 2000 IU with enoxaparin) [236,237]. The SmPC for nadroparin suggests dose reduction starting at 50 kg. The SmPC for tinzaparin proposes reducing the dose to 50 IU/kg in very low-weight patients. The SmPC for dalteparin indicates limited experience in patients weighing less than 40 kg. The SmPC for fondaparinux warns of an increased bleeding risk for weights  $< 50$  kg, leading to the recommendation against its use in lower weights.

For DOACs, the SmPC for apixaban and rivaroxaban state that no dosage adjustment is necessary for low body weight. The SmPC for dabigatran notes that available data are limited.

### 13. Pediatric surgery

The incidence of VTE in the perioperative period is lower in the pediatric population than in adults [238]. This is likely due to differences in the hemostatic balance in children and the absence of acquired VTE risk factors or those related to certain pathologies and/or treatments [239,240]. The increased VTE risk during adolescence is correlated with the maturation of the hemostatic system, which becomes similar to that of adults [241]. Numerous observational studies report an increased VTE risk around the age of 14, generally corresponding to puberty [242,243]. Other risk factors that increase the incidence of VTE in children and adolescents are quite classic, though inconsistently reported in studies (neoplasia, estrogen treatment, inflammatory diseases, obesity, severe dehydration, trauma, congenital thrombophilia, smoking, surgery duration, intensive care unit admission, *etc.*) [240].

Moreover, the bleeding risk associated with anticoagulation (prophylactic or therapeutic) in children is significant: between 0.4% and 3% for major bleeding, and up to 21% for minor bleeding [244].

Several similar thrombotic risk assessment models have been published [245–249]. All these models consider the child's age (> 13 or 14 years) and VTE risk factors commonly found in adults. When the number of VTE risk factors is low (low to moderate VTE risk), non-pharmacological prevention methods are generally used: hydration, early ambulation, and possibly IPC (if size and weight are appropriate). When the number of risk factors is high (at least 4 to 6, according to the studies), pharmacological prophylaxis is used, most often with LMWH at preventive doses. For children under 40 kg around puberty or the age of 14 years, the dosage regimens for LMWH have not been evaluated. The proposed regimens usually include 50 IU/kg/day of enoxaparin administered in one or two daily injections and 50 IU/kg of tinzaparin in a single injection [249].

By mid-2024, DOACs do not have marketing authorization for primary prevention in pediatrics, and the published data are scarce.

#### 14. Patients in intensive care unit

Outside of intensive care units (ICU), venous thromboprophylaxis is recommended for patients with acute medical conditions resulting in reduced mobility or those undergoing major surgical interventions. Intensive care combines the most severe forms of these two situations, with a 60% increased risk for VTE, corresponding to a VTE incidence of 10-20% without prophylaxis [250,251].

Pharmacological prophylaxis is recommended as first-line therapy. In ICU, only UFH and LMWH are easily usable and have been evaluated in randomized trials. The longer half-life and/or absence of specific antagonists make the use of DOAC and fondaparinux less practical. In a meta-analysis of 5 studies comparing LMWH and UFH in ICU [250], the use of LMWH was associated with fewer VTE without an increased risk of bleeding (Table 1). This meta-analysis also confirmed the lower risk of HIT with LMWH. Therefore, LMWH has a more favorable benefit-risk profile than UFH in ICU.

**Table 1:** Network Meta-analysis comparing LMWH and UFH for thromboprophylaxis in ICU [250][2].

| Events         | Number of studies | Number of patients | Odds-ratio (IC95%) |
|----------------|-------------------|--------------------|--------------------|
| DVT            | 6                 | 5645               | 0,78 (0.65 – 0.95) |
| PE             | 3                 | 4447               | 0.67 (0.36 – 1.22) |
| Major bleeding | 4                 | 1002               | 1.71 (0.49 – 5.95) |
| HIT            | 3                 | 4447               | 0.38 (0.15 – 0.98) |
| Mortality      | 2                 | 1408               | 0.90 (0.68 – 1.18) |

LMWHs are eliminated by the kidney (see dedicated section); thus, their use in severe renal impairment (eGFR between 15 and 30 mL/min/1.73 m<sup>2</sup>) carries a risk of accumulation. Dalteparin, along with tinzaparin, is one of the LMWH with the highest molecular weight, its elimination is less influenced by renal function. A subgroup analysis of the PROTECT study, which compared dalteparin and UFH for thromboprophylaxis in ICU patients (Table 2), did not observe an increased bleeding risk with dalteparin treatment in patients with an eGFR < 30 mL/min/1.73 m<sup>2</sup> [197]. The use of LMWH in cases of severe renal impairment aligns with recent modifications to their marketing authorization and requires adjustments to dosing regimens (see dedicated section). In all cases, end-stage kidney disease remains a contraindication for LMWH, requiring the use of UFH.

**Table 2:** Results of the subgroup analysis of the PROTECT study comparing dalteparin and UFH for thromboprophylaxis in ICU, according to renal function

|                                 |                | Dalteparin | UFH    | Hazard Ratio (IC85%) |
|---------------------------------|----------------|------------|--------|----------------------|
| Severe Renal impairment (n=590) | VTE            | 10.0 %     | 6.4 %  | 1.87 (0.96 – 3.63)   |
|                                 | Major bleeding | 8.9 %      | 11.0 % | 0.89 (0.51 – 1.53)   |

Standard doses of LMWH used in medical or surgical settings may be ineffective in the ICU for the most severe, most inflammatory patients, or in cases of obesity [252][4]. Higher dosing regimens have been proposed in ICU, adjusted for body weight or BMI. The COVID pandemic allowed for the evaluation of these higher doses [253]. Recommendations from the GIHP supported this approach without increased bleeding risk [254,255], but they did not demonstrate clinical superiority over standard dosing regimens [249,253,256]. Monitoring of anti-Xa level

to adjust LMWH doses is often discussed; however, this strategy has not yet shown its clinical benefit [257].

Regarding mechanical prophylaxis, GCS have not shown efficacy in ICU and can cause skin lesions [258]. Therefore, it is no longer indicated in this setting. Few studies have evaluated the use of IPC, and a meta-analysis shows that IPC use in ICU reduces the risk of VTE compared to patients without thromboprophylaxis (Table 3) [171]. IPC should be proposed when pharmacological prophylaxis cannot be prescribed due to a high bleeding risk. On the other hand, adding IPC to pharmacological prophylaxis has not shown additional benefit compared to pharmacological prophylaxis alone [171]. This strategy might be reserved for patients at very high VTE risk: severely injured patients or major cancer surgery [168,259,260].

**Table 3:** Results of a meta-analysis of studies evaluating IPC in ICU [12]

|                                    | Events | n studies / n patients | Risk ratio (IC95%) |
|------------------------------------|--------|------------------------|--------------------|
| IPC vs. control                    | VTE    | 4 / 1120               | 0.35 (0.18 -0.68)  |
|                                    | PE     | 2 / 402                | 0.17 (0.06-0.50)   |
|                                    |        |                        |                    |
| IPC + heparin<br>vs. Heparin alone | VTE    | 4 / 2777               | 0.55 (0.24-1.27)   |
|                                    | PE     | 3 / 2661               | 0.72 (0.31-1.69)   |

## 15. Tranexamic acid and regimens of perioperative venous thromboprophylaxis

The administration of tranexamic acid (TXA) to reduce bleeding and transfusion requirements is supported by high-level evidence in high-bleeding risk surgery and trauma [261–268]. TXA does not increase the risk for perioperative VTE: randomized trials [261,263–268] and meta-analyses [262,269] have shown that TXA does not increase the incidence of VTE after general, orthopedic, or cardiac surgery, vaginal or cesarean delivery, postpartum hemorrhage, severe trauma, or traumatic brain injury. Double-blind randomization ensured that pharmacological prophylaxis protocols (indication, drug choice, initiation timing, duration) were not altered by TXA [261,263–268]. Furthermore, when the initiation of thromboprophylaxis with DOAC is delayed until the day after major orthopedic surgery, TXA administration does not increase the frequency of VTE [262]. When TXA is prescribed for congenital bleeding disorders such as hemophilia or platelet dysfunction, the indication for venous thromboprophylaxis is discussed on a case-by-case basis.

## 16. Laboratory testing during venous pharmacological prophylaxis

### 16.1 Measuring the level of anticoagulation

The term anticoagulation level, although imperfect, is used for anti-Xa level of UFH and LMWH and for DOAC and fondaparinux concentration values. The term "monitoring" is not used as it would imply multiple determinations in the same patient to adjust the administration modality of the anticoagulant. The experts aimed to address five questions:

- (i) Is anticoagulation level predictive of VTE and bleeding events during thromboprophylaxis with LMWH?
- (ii) Does LMWH dose adjustment based on anti-Xa level reduce VTE without increasing the risk of bleeding?
- (iii) Are there specific populations (elderly, extreme weights, renal impairment) for whom anticoagulation level determination has prognostic value?
- (iv) What is the analytical precision of anticoagulation level based on anti-Xa measurement, particularly for the low values observed in thromboprophylaxis?
- (v) Is there a benefit to measuring the level of anticoagulation during thromboprophylaxis with UFH, fondaparinux, or DOACs?

In surgery, data on anti-Xa levels during LMWH prophylaxis are mainly observational. After TKA, anti-Xa level  $>0.2$  IU/mL 12 hours after enoxaparin 4000 or 6000 IU/day (measured on postoperative days 1, 3, and 6) was associated with a higher frequency of bleeding events, whereas anti-Xa level  $<0.1$  IU/mL was associated with VTE [270]. In hepatobiliary and pancreatic surgery, a peak anti-Xa level  $<0.2$  IU/mL was associated with a higher frequency of VTE [271]. After abdominal cancer surgery, an anti-Xa level between 0.2 and 0.4 IU/mL was associated with a lower frequency of VTE [272]. However, dose adjustment of enoxaparin by increments of 1000 IU based on peak anti-Xa level was not associated with a reduction in VTE after pancreatic surgery [273]. In plastic surgery, a peak anti-Xa level  $<0.3$  IU/mL after 4000 IU/day of enoxaparin was associated with an excess VTE [274]. In neurosurgery, "supraprophylactic" anti-Xa level (defined by a peak  $>0.5$  IU/mL) with 4000 IU/day of enoxaparin was associated with a higher frequency of bleeding events compared to prophylactic level defined by the range 0.2–0.4 IU/mL [275]. A meta-analysis of 9 studies (including one

randomized study of 985 patients undergoing plastic, thoracic, colorectal, or orthopedic surgery) found an association between peak anti-Xa level  $<0.3$  IU/mL (for administration of 4000 IU/day enoxaparin) or  $<0.2$  IU/mL (for regimens with enoxaparin twice daily) and VTE [276]. In trauma, injury severity and obesity were associated with "subprophylactic" anti-Xa levels ( $<0.2$  IU/mL) [277]. A meta-analysis of 24 observational studies totaling 7276 patients found a lower frequency of symptomatic VTE when peak anti-Xa level was  $>0.2$  IU/mL or  $>0.1$  IU/mL at trough (before the next injection), but when LMWH dose was adjusted to reach these anti-Xa levels, there was no decrease in VTE [278]. Another meta-analysis, including 15 observational studies (10,348 patients) found a lower frequency of VTE when the dose of enoxaparin was adjusted (by increments of 1000 IU of enoxaparin) to anti-Xa level without a difference in bleeding events [279]. This second meta-analysis, which included asymptomatic VTE, relied partly on unpublished data and highlighted the heterogeneity of the included populations, ultrasound screening practices, and targeted anti-Xa level; thus, the level of evidence is very low. Furthermore, all dose adjustment approaches based on anti-Xa level were compared to a regimen using 3000 IU enoxaparin administered every 12 hours (commonly used in North America), making it difficult to extrapolate to once-daily dosing regimens used in Europe.

#### Specific populations:

- Advanced age alone is not associated with the accumulation of prophylactic enoxaparin in a medical-surgical population [280].
- A weight  $< 45$  kg has been strongly associated with a peak anti-Xa level  $> 0.5$  IU/mL [235], which may justify a reduced LMWH dose (2000 or 3000 IU enoxaparin) [236]. In bariatric surgery, a weight  $> 150$  kg was associated with a peak anti-Xa level  $< 0.2$  IU/mL after 4000 IU of enoxaparin [225]. These two small-scale studies did not observe an association between anti-Xa level and thrombotic or bleeding events.
- Severe renal impairment leads to the accumulation of LMWH and justifies dose adjustment (see dedicated section).

#### Limitations of anti-Xa-based anticoagulation measurement

- Various parameters contribute to the variability of plasma LMWH levels measured by anti-Xa chromogenic assays (methods currently used in France). The heterogeneity of anti-Xa assays (analyzers and reagents) is well established for UFH [281,282], but less documented for LMWH, for which laboratory monitoring indications are rare. The influence of the reagent and tube type (citrate alone or CTAD mixture) on the anti-Xa levels should be more limited for LMWH than for UFH due to the shorter heparin chains thus the lower capacity to bind to plasma proteins other than antithrombin. An appropriate LMWH calibrator should be used [283]. Comparative studies of anti-Xa reagents have been conducted in patients receiving therapeutic doses of LMWH, and the difference between two tests performed with different reagents could reach 0.12 IU/mL [284–286].
- External quality assessment (EQA) programs, which send the same samples to laboratories to compare results, have reported high coefficients of variation (CVs) of 12-33% for samples containing LMWH levels  $< 0.35$  IU/mL, whereas a CV below 10% should be achieved [287]. EQA programs rarely provide samples with LMWH anti-Xa levels  $< 0.3$  IU/mL. Additionally, the limit of quantification (the lowest value that can be measured with an acceptable CV) varies depending on the analyzers and reagents; it must be determined by each laboratory and will condition the laboratory's ability to report results for low values between the limit of quantification (around 0.1 IU/mL) and 0.3 IU/mL.

- These arguments suggest caution in using the anti-Xa assay, and it is important not to apply conclusions from a published study to local practice if the anti-Xa assay in the study differs from that used locally.
- For anti-Xa DOAC, clinical studies did not include laboratory monitoring [52]. Moreover, the broad therapeutic window of DOAC argues against laboratory testing.

During thromboprophylaxis with enoxaparin administered once daily, observed peak anti-Xa levels (sample taken at 4 hours after at least 3 injections) frequently range from 0.2 to 0.5 IU/mL, with a potential influence from the anti-Xa assay used (often not detailed in the literature). Existing data mainly concern enoxaparin administered twice daily, with fewer studies on dalteparin and tinzaparin. While some observational studies have found an association between anti-Xa level and postoperative VTE and bleeding events, no randomized trial has demonstrated the benefit of adjusting LMWH dosage based on anti-Xa level to reduce these complications. Such an approach may be ineffective (due to the variability among anti-Xa assays, measurement imprecision for low anti-Xa values, and the time required to adjust the dosage, with samples taken at a minimum of three days of treatment), costly, and complex to implement (samples taken 4 hours after LMWH injection, outside usual sampling times; a significant number of patients is already discharged by day 3). When facing a bleeding event, determining anti-Xa level can document potential accumulation or overdose and estimate the contribution of the anticoagulant to bleeding (likely negligible if anti-Xa level is below 0.2 IU/mL). Institutional protocols for managing thromboprophylaxis should define the rare indications for anti-Xa assay and consider the type of LMWH, dosing regimen (once or twice daily), and the analyzer/reagent system used.

For UFH, fondaparinux, and DOACs at prophylactic doses, there is no evidence showing a clinical benefit to routine measurement of anticoagulation levels. Therefore, no recommendation was possible. However, this measurement can guide management in case of bleeding with suspected overdose.

## **16.2. Platelet count monitoring and risk of heparin-induced thrombocytopenia (HIT)**

The recommendations are those of SFAR-GIHP-GFHT [198]. The rationale is based on observational studies. Patients receiving postoperative thromboprophylaxis (including after cesarean section) have an intermediate risk of HIT (0.1 to 1%) with LMWH and a high risk (> 1%) with UFH [288,289]. HIT typically occurs between 4 to 14 days after the initiation of heparin treatment, rarely after 15 days, and exceptionally after 1 month [290]. HIT can occur earlier if there has been heparin exposure within the previous 3 months [291]. The incidence and severity of thrombotic complications during HIT appear to be inversely associated with the earliness of HIT treatment [292,293].

The use of a decision-making algorithm based on the clinical probability assessment of HIT and validated laboratory tests likely limits the risk of overdiagnosis associated with monitoring of platelet counts [52].

## 17. Postoperative distal deep vein thrombosis

This section aims to determine whether the diagnosis of distal deep vein thrombosis (dDVT) modifies thromboprophylaxis regimen and to define the situations in which this pharmaceutical prophylaxis should only be extended without switching to anticoagulant treatment.

The management of postoperative isolated distal deep vein thromboses (dDVT) is debated, both in terms of the indication for anticoagulant treatment, its intensity (prophylactic or therapeutic), and its duration, as studies are few and provide low levels of evidence.

### Definition of isolated dDVT

Isolated dDVT of the lower limbs are anatomically defined as thromboses below the popliteal vein, without extension to the proximal veins or associated pulmonary embolism. The distal deep veins include the tibial veins (anterior and posterior), the fibular veins, and the muscular veins (soleal, gastrocnemius). dDVT account for up to half of all diagnosed DVT [294].

dDVT share the same risk factors as proximal DVT (pDVT), but some factors, particularly the postoperative context, are more significant (OR 1.8, 95%CI 1.3-2.5, distal vs. proximal) [295–297]. dDVT are frequently observed after trauma or lower limb surgery, but also after abdominal or pelvic surgery and potentially after any type of surgery [298]. Systematic screening one week after TKA reveals dDVT in 33 to 46% of cases [299,300]. They are most often asymptomatic.

### Can patients at higher risk of proximal extension or pulmonary embolism (PE) be identified?

The risk associated with dDVT is proximal extension and PE. This risk is low, but various risk factors have been identified. These include factors related to the thrombosis, such as the observation of more than one thrombosed vein or bilateral dDVT, and patient-related factors such as personal history of VTE, active cancer, a persistent risk factor, and the accumulation of patient-related risk factors [301–306]. dDVT in the venous trunks and muscular dDVT have the same progression profile [301,307].

### What is the risk of proximal extension or PE from an isolated dDVT?

In the absence of any anticoagulation, the rate of symptomatic PE is < 1% [307,308], and the rate of proximal extension varies between studies, ranging from 5 to 10% [309,310] and up to 20% in a series with a significant proportion of cancer patients [311]. After surgery, the risk of extension appears to be similar. For instance, after TKA, a proximal extension was reported for 3.5% of dDVT diagnosed at day 7, at the end of short-duration thromboprophylaxis [300].

With pharmacological prophylaxis, the risk of proximal extension or PE from dDVT has been estimated between 3 and 10%, mainly from registries in heterogeneous populations, not systematically postoperative ones [312]. The PROTHEGE trial specifically assessed the evolution of postoperative dDVT in patients receiving LMWH thromboprophylaxis, but it did not compare it to therapeutic treatment [300]. In this study, 878 patients receiving prophylactic LMWH following TKA had a venous CUS on day 7. Those presenting with proximal DVT (n=21) were excluded from the study. The others (negative CUS or dDVT) were randomized to either short-term thromboprophylaxis, totaling 10 days, or extended thromboprophylaxis, lasting 35 days, with a control venous ultrasound on day 35. Among patients with dDVT on day 7, 7.8% in the short-term thromboprophylaxis group and 2.8% ( $p=0.067$ ) in the extended thromboprophylaxis group experienced a proximal or symptomatic VTE or bleeding, while rates of extension or recurrence (including distal) were 14.8% and 4.5%, respectively ( $p<0.001$ ). These results suggest that in the absence of risk factors for extension, continuing

thromboprophylaxis up to 35 days reduces complications from dDVT compared to short-term thromboprophylaxis.

### **Bleeding risk and anticoagulant treatment of dDVT**

Therapeutic anticoagulation for dDVT increases the risk of bleeding complications. In the randomized CACTUS trial, administering nadroparin at a therapeutic dose for six weeks increased major and clinically significant bleeding complications compared to placebo among patients at low bleeding risk since they were non-surgical or non-cancer patients [307]. An analysis from a registry of 697 patients with dDVT, of which 39% were postoperative patients and 19% were trauma patients, showed that therapeutic anticoagulation was associated with more clinically significant bleeding (8.6% vs. 2.2%, OR=4.87, 95% CI 1.37-17.3), particularly in postoperative patients [313].

However, prophylactic treatment might be associated with lower bleeding risk: in the PROTHEGE trial, only 1/144 (0.7%) of patients with dDVT on day 7 who received extended thromboprophylaxis for 35 days experienced major bleeding [300].

For patients with isolated dDVT and contraindications to anticoagulants, clinical and echo-Doppler monitoring is an option. Two randomized trials [309,311] showed that when there is suspicion of a first DVT (40% after surgery or trauma [300]), serial proximal CUS repeated after one week (which does not detect dDVT), was as safe in terms of thromboembolic risk at 3 months as complete CUS (which leads to diagnosing and treating both dDVT and proximal DVT). These results suggest that dDVT can be left untreated, provided that there is clinical monitoring and a repeated ultrasound after one week to look for potential extension. Beyond two weeks, the risk of extension appears to be low [314].

### **Management of dDVT**

The management of isolated postoperative dDVT is widely debated, particularly regarding the intensity of anticoagulation. The decision to use therapeutic anticoagulation should consider the risk of extension of the dDVT, dependent on the characteristics of the thrombosis itself and the patient, as well as the postoperative bleeding risk.

A randomized trial conducted after THA or TKA showed that systematic screening of dDVT by CUS and their treatment did not reduce the rate of proximal DVT and PE on day 35 [315] but increased major bleeding. Thus, systematic screening and treatment are not recommended.

In the meta-analysis by Franco *et al.* [316], prophylactic treatment of dDVT (OR=0.54, 95% CI 0.30-0.99) was as effective in terms of recurrence of VTE as therapeutic treatment (OR=0.51, 95% CI 0.29-0.91) compared to no treatment. Overall, these data suggest that in the absence of risk factors for extension, an approach by "extended thromboprophylaxis" may be appropriate in the postoperative context. The presence of risk factors for extension warrants discussion of therapeutic treatment.

The duration of therapeutic anticoagulation for dDVT is still a matter of debate as published studies have not included surgical patients. In the DURAC trial, a 6-week treatment for dDVT was associated with more thromboembolic recurrences at 2 years, although not statistically significant, compared to 6 months (11.4% vs. 5.8%, n.s.) [317]. Conversely, in the DOTAVK trial, a 6-week anticoagulant treatment after a first episode of dDVT not related to cancer did not expose to an increased thromboembolic risk at 15 months (2.0% vs. 3.4%, n.s.) compared to a 3-month treatment and had a better bleeding risk profile (1.0% vs. 3.4%, n.s.) [318]. The RIDTS trial compared 6 weeks to 3 months of treatment with rivaroxaban 20 mg/day for isolated symptomatic dDVT. Extending the treatment to 3 months allowed a reduction in VTE

recurrences (11% vs. 19%, RR=0.59, 95% CI 0.36-0.95), mainly dDVT, particularly recurrence in the same vein. This effect was not found in case of provoked dDVT (RR=0.47, 95% CI 0.15-1.45), but the sample size was small [319].

Regarding the choice of anticoagulant, the RIETE registry showed that treatment of dDVT with rivaroxaban was as effective and safe as treatment with LMWH/VKA [320].

### Conflicts of interest

Pierre Albaladejo: Bayer Healthcare, BMS-Pfizer, Sanofi

Normand Blais: None

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Anne Godier: Aguetant, Alexion, Bayer Healthcare, BMS-Pfizer, Boehringer Ingelheim, Sanofi, CSL Behring, LFB, Octapharma, Stago, Viartis

Alexandre Godon: BMS-Pfizer, LFB, Sanofi

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Grégoire Le Gal: BMS, Inari, Leo Pharma, Pfizer, Sanofi

Alexandre Mansour: i-SEP, LFB, Aguetant, Viartis et Pfizer

Anne-Céline Martin: Abbott, Bayer Healthcare, BMS-Pfizer, Boehringer Ingelheim, Novartis

Mikael Mazighi: Boehringer, Novartis, Novonordisk, Acticor, Astra Zeneca

Patrick Mismetti: Aspen, Leo Pharma, Sanofi, Pfizer

Pierre-Emmanuel Morange : BMS, Pfizer, Sanofi

Serge Motte: Bayer Healthcare, BMS-Pfizer, Leo Pharma, Viartis

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Jean-François Schved: pas de lien d'intérêt

Pierre Sié: pas de lien d'intérêt

Sophie Susen: CorWave, Roche-Chugai, Stago, Biomarin, Bioverativ, CSL Behring, LFB, Novo-Nordisk, Sanofi, Shire/Takeda, Siemens Healthinners, Stago and Sobi

Charles Tacquard: Sanofi, BMS Pfizer

Pierre-Marie Roy: Aspen, Bayer Health Care, Boehringer-Ingelheim, Sanofi-Aventis, Pfizer, Bristol Myers Squibb, LFB, Viatris

Marie-Antoinette Sevestre: BMS Pfizer, Leo Pharma, Viatris, Novartis

André Vincentelli: None

Paul Zufferey: Sanofi Aventis

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