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GUIDELINES

European guidelines on perioperative venous thromboembolism prophylaxis

Patients with preexisting coagulation disorders and after severe perioperative bleeding

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In patients with inherited bleeding disorders undergoing surgery, we recommend assessment of individual risk for venous thromboembolism, taking into account the nature of the surgery and anaesthetic, type and severity of bleeding disorder, age, BMI, history of thrombosis, the presence of malignancy and other high-risk comorbidities. Venous thromboembolism risk should be balanced against the increased bleeding risk associated with anticoagulant use in patients with known bleeding disorders (Grade 1C). In these patients undergoing major surgery, we recommend against routine postoperative use of pharmacological thromboprophylaxis, especially for patients with haemophilia A and B (Grade 1B). Glomerular filtration rate should be assessed before initiation of each direct oral anticoagulant, and also at least once a year or more frequently as needed, such as postoperatively before the resumption of therapeutic direct oral anticoagulant administration, when it is suspected that renal function could decline or deteriorate (Grade 1C). Reduced dosages of low molecular weight heparins may be used relatively safely during transient severe ($<50 \times 10^9 l^{-1}$) thrombocytopaenia (Grade 2C). Monitoring of anti-Xa levels may be used to adjust the doses of low molecular weight heparin in patients with moderate or severe thrombocytopaenia (Grade 2C). The delay between major gastrointestinal bleeding and resuming warfarin should be at least 7 days (Grade 2C). For patients at a high risk of thromboembolism and with a high bleeding risk after surgery, we consider that administering a reduced dose of direct oral anticoagulant on the evening after surgery and on the following day (first postoperative day) after surgery is a good practice (Grade 2B).

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

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

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

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

Introduction

Patients with acquired or inherited coagulation disorders are often very difficult to manage as far as venous thromboembolism prophylaxis is concerned. An optimal balance between the thrombotic and the bleeding risks has to be found. Timing to stop or to restart prophylaxis and doses of antithrombotic and haemostatic agents are complicated issues that have not been addressed in detail by the most recent guidelines. In this chapter, three haematologists (CH, SP, FM) and two anaesthesiologists (AA, SKL) have scrutinised the literature and proposed some recommendations.

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Patients with inherited bleeding disorders

Haemophilia

Postoperative venous thrombosis is rare amongst patients with haemophilia. The higher requirement for joint replacement surgery, due to the long-term consequences of acute haemarthroses, is associated with a younger age at surgery and this, combined with the relatively protective effect of the underlying bleeding tendency, is associated with a reduced risk of venous thromboembolism (VTE) compared with nonhaemophilia individuals. The estimated risk of symptomatic VTE in haemophilia patients undergoing joint arthroplasty and receiving no pharmacological thromboprophylaxis is 0.5%,[1] approximately half that of nonhaemophilia patients treated with anticoagulants.[2] The incidence of subclinical deep venous thrombosis (DVT) detected by systematic ultrasound-Doppler has also been found to be very low, ranging from 0 to 10%.[3,4]

However, the risk of bleeding is significant, even when factor concentrate has been carefully managed. In a retrospective evaluation of 72 total knee replacements in 51 haemophilia A and B patients using continuous infusion of factor concentrates and no pharmacological thromboprophylaxis, 26 haematomas (36.1%) and two haemarthroses (2.7%) occurred in 38.8% of cases during the first 3 postoperative weeks.[5]

Thus, for the majority of patients with haemophilia, the risk of thrombosis is outweighed by the increased risk of bleeding associated with the use of anticoagulants. Furthermore, although factor levels are 'normalised' for the perioperative period, it is likely that for patients with haemophilia A, factor VIII does not reach the high levels of nonhaemophilia patients.[6] The protection against VTE afforded by the clotting factor deficiency in patients with haemophilia A may not be applicable to patients with haemophilia B undergoing major surgery. Indeed, in contrast with factor IX levels, which are carefully monitored and controlled, postoperative factor VIII can reach very high levels in haemophilia B patients. Although it is currently unknown whether these patients are at a higher risk of VTE, thromboprophylaxis is more likely to be warranted in patients with haemophilia B than haemophilia A. As the number of elderly patients with haemophilia increases, the risk factors for VTE increase.

A detailed risk analysis for each individual patient is warranted. The following factors could affect the decision to provide pharmacological thromboprophylaxis: personal or family history of VTE, known thrombophilia, active cancer, mild haemophilia, history of major bleeding or haemophilia B (in association with other risk factors). Although this option has so far not been validated, if pharmacological thromboprophylaxis in patients with haemophilia undergoing major surgery is deemed necessary, it should be restricted to the first few postoperative days as long as there is still high factor substitution therapy and complete correction of the clotting factor deficiency. Low molecular weight heparins (LMWHs) would be preferred, as studies testing the direct oral anticoagulants (DOACs) have excluded patients with inherited bleeding disorders. The long half-life of warfarin makes it contraindicated in this patient group.

Surgery in patients with inhibitors is particularly challenging, with higher bleeding risks and higher thrombotic risks posed by bypassing agents. Activated prothrombin complex concentrates used concomitantly with recombinant factor VIIa have a particularly high risk of VTE and should be avoided.

High endogenous factor VIII and IX levels are associated with a heightened VTE risk and it is reasonable to assume that excessive use of exogenous factor carries the same level of risk. Indeed, anecdotal reports of VTE in patients with haemophilia are often associated with elevated levels. Therefore, avoidance of factors VIII or IX excess is important.

Although the presence of inherited thrombophilias has been shown to modify the bleeding phenotype in patients with haemophilia,[7–9] the effect may be small in those with no personal or family history of thrombosis and does not justify routine thrombophilia screening prior to surgery. In patients with a personal or family history of VTE, thrombophilia screening could be considered.

Von Willebrand disease

Von Willebrand disease (VWD) is classified into distinctly different forms with a broad spectrum of laboratory findings and clinical phenotypes. Type 1 VWD has a reduced level of von Willebrand factor (VWF), Type 2 has a qualitative abnormality of VWF and Type 3 is virtually lacking VWF in plasma and platelets. As VWF serves as a carrier of factor VIII, the levels of factor VIII will also be impacted. Thrombosis is rare in VWD, but according to available data, it occurs more frequently than in haemophilia. Most reported cases occurred after orthopaedic surgery[10] and most have been in the presence of additional VTE risk factors[11,12]; VTE is more prevalent in those with type 1 disease who have received haemostatic therapy.[13]

Patients with VWD undergoing major surgery are usually treated with dual concentrates containing factor VIII and VWF. The ratio between VWF (VWF:RCo) and factor VIII varies among available products, in the range of 1 to 2.5 for most concentrates and much higher for a purified VWF concentrate. Infusion with the first group of concentrates provides an immediate rise in VWF and factor VIII, which is beneficial when treating acute bleeds and acute surgery. A secondary rise in factor VIII levels occurs with some concentrates after 12 to 24 h; in others, a parallel decay over time for VWF and factor VIII has been reported. However, infusion of virtually pure VWF will also restore factor VIII levels due to binding and

stabilisation of endogenous factor VIII. This will take from 12 to 24 h, and in the treatment of acute bleeds and surgery, infusion of exogenous factor VIII is sometimes needed. Infusion of VWF will cause a rise in endogenous factor VIII level. This, added to infused factor VIII, may result in supranormal levels, particularly with repeated treatment.[14] The half-life is two to three-fold longer than that seen after replacement for haemophilia.[15] Thrombosis has occurred when abnormally high factor VIII levels have developed from prolonged factor replacement therapy.[16] Factor VIII levels above 1.5 IU ml^{-1} have been associated with an approximately five-fold increased risk of venous thrombosis compared with levels below 0.5 IU ml^{-1}.[17–19]

For patients with VWD receiving factor concentrate replacement therapy, we suggest that monitoring factor VIII levels and thromboprophylaxis should be considered if any other thrombosis risk factor is present (Grade 2C).

Factor XI deficiency

Factor XI levels below 15 IU ml^{-1} are known to confer a reduced risk of VTE[20] and ischaemic stroke.[21] In contrast, factor XI concentrations above the 90th centile confer more than a two-fold increased risk of VTE,[22] possibly by sustained thrombin generation and inhibition of fibrinolysis; this has led to the development of factor XI inhibitors as antithrombotic agents. Exogenous factor XI may have a similar effect[23,24]; patients with factor XI deficiency receiving perioperative factor XI concentrate are at a higher risk of thrombosis, even if factor replacement is managed carefully,[25] and thrombotic events, including fatal pulmonary embolism, have been seen[26,27] even with doses less than 30 IU kg^{-1}. The thrombin generation potential varies between the available concentrates,[28] but in general, doses less than 20 IU kg^{-1} are effective in achieving haemostasis and the increased risk of thrombosis is less. Fresh frozen plasma is a good source of factor XI and can be useful when factor XI concentrate is unavailable. Most patients with factor XI deficiency have a nonbleeding phenotype and careful assessment is required before planning perioperative management to avoid unnecessary treatment. Tranexamic acid alone is useful in patients with mild factor XI deficiency but has been shown to increase the incidence of postoperative DVT in patients with thrombotic risk factors[29] and should be avoided in patients receiving factor XI concentrate unless unexpected bleeding occurs, when the benefits may outweigh the risks.[30]

Factor VII deficiency

Thromboembolic events have been described occasionally in patients with congenital factor VII deficiency, most frequently in patients with associated prothrombotic risk factors.[31,32] Not only surgical procedures and replacement therapy (especially containing activated factors)[31,32] but also the presence of an antiphospholipid syndrome are frequently associated with these thrombotic events. Some genetic variants (R304Q and A294V) encoding for residues located at the two extremities of a β-strand B2 critical for tissue factor binding are more frequently associated with thrombotic events than other equally frequent factor VII mutations. Low factor VII coagulant activity levels do not protect against thrombosis. Therefore, perioperative thrombotic prophylaxis should be relevant for these factor VII deficient patients. However, safety, treatment modalities and specific indications of such antithrombotic prophylaxis remain to be established. As suggested, thromboprophylaxis may be indicated in patients with factor VII:C more than 30% or factor VII:C 10 to less than 30% and a history of thrombosis and/or strong risk factors, but it is not appropriate for patients with factor VII:C less than 10%.[33,34]

Fibrinogen disorders

Hypofibrinogenaemia and dysfibrinogenaemia are associated with thrombosis in 20 to 30% of cases, and there is an even higher prevalence in afibrinogenaemia.[35] Thromboembolism may occur spontaneously or in association with fibrinogen substitution therapy and friable platelet-rich thrombi may embolise readily, particularly in patients with afibrinogenaemia. There are insufficient data to recommend a specific perioperative management plan, but peak fibrinogen levels of 1.5 g l^{-1} have been reported for major surgery.[36] Continuous infusion may be helpful in maintaining a steady normal range of fibrinogen and simultaneous LMWH thromboprophylaxis may be considered. Prothrombin complex concentrates should not be used in these patients.[37]

Other rare coagulation disorders

Prothrombin complex concentrates are useful for patients with factor II deficiency or for factors X and VII deficiency in whom specific factor replacement is not available. High and repeated doses have been associated with thrombosis[37] particularly when there are additional risk factors. Thrombotic events have not been observed with high-purity factor X replacement therapy. Factor XIII deficiency has been associated with thrombosis with and without replacement therapy and care should be taken to avoid excessive use of factor XIII concentrate. Platelet function disorders have not been associated with thrombosis except in cases wherein activated factor VIIa has been used.

How and when should renal function be monitored in patients with preexisting coagulation disorders and after severe bleeding?

Determination of renal function is important in patients receiving oral and parenteral anticoagulants. Although there is a need for an estimated glomerular filtration rate (eGFR) evaluation, there is still a lack of knowledge regarding which method of renal function evaluation is

most appropriate in patients with anticoagulants. Serum creatinine concentration, for instance, is inaccurate to estimate the degree of renal failure especially in the elderly.[38,39] There are currently four ways to estimate renal function and eGFR: Cockcroft and Gault formula, Modification of Diet in Renal Disease Study (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Cystatin-C (Table 1). CKD-EPI creatinine seems to have superior accuracy.[40] The limitations of the Cockcroft and Gault equation are well known: failure to normalise for body surface area along with a lack of validation in a broad sample of patients with chronic kidney disease.[41] The Cockcroft and Gault formula is also influenced by body weight and BMI, while MDRD and CKD-EPI equations are adjusted for body surface area.[41,42] However, the Cockcroft and Gault formula has the greatest accuracy for patients who are underweight.[42] The Cockcroft and Gault formula calculated with the ideal body weight (IBW) improves the classification of renal impairment among older adults.[43] The HAS-BLED score (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalised ratio, elderly, drugs/alcohol concomitantly), which includes the renal function, is a score to predict major bleeding in anticoagulated patients with atrial fibrillation.[44,45]

Direct oral anticoagulants (dabigatran, rivaroxaban, apixaban and edoxaban)

eGFR should be assessed before initiation of any DOACs, and at least once a year, or more frequently as needed in certain clinical situations when it is suspected that renal function could decline or deteriorate (Grade 1C).[46] The updated European Heart Rhythm Association (EHRA) practical guide on the use of DOACs in patients suggests that renal function should be checked 6-monthly for patients more than 75 to 80 years of age (especially if the patient is on dabigatran or edoxaban), or in frail patients.[46] The proposed recheck interval is creatinine clearance value divided by 10 (CrCl/10) if the CrCl is lower than 60 ml min^{-1} or more frequently if indicated. Pilot phase 3 studies of DOACs used the Cockcroft and Gault formula to estimate kidney function for patients' inclusion, to elaborate drug dosing guidelines and to evaluate the impact of renal function on bleeding and thrombotic risk.[47–50] In a frail (i.e. low BMI) and older population, it seems safer to use the Cockcroft and Gault formula that underestimates GFR than another equation that overestimates GFR and risks misclassifying DOAC dose adaptation as demonstrated by Hellden *et al.*[51] This correlates with results of several other studies suggesting that use of the MDRD equation for drug dosing often yields higher doses than does the Cockcroft and Gault equation, especially with narrow therapeutic window range drugs and high-risk subgroups, such as the elderly.[52,53] In conclusion, to date, there is no optimal GFR estimation equation. All formulae have their limitations. Regulatory authorities have to set up guidelines for kidney function estimation in clinical trials and to promote the use of the most appropriate GFR equation for drug dosing. Finally, in the lack of consensus, the use of the Cockcroft and Gault method to evaluate renal function of patients with DOAC is suggested (Grade 2C).[54–56]

DOACs should be resumed postoperatively when haemostasis has been achieved. The timing of the first postoperative dose of different DOACs differs and does not depend on renal function. Acceptable efficacy and safety can be achieved when an appropriate first dose of anticoagulant is given at least 6 h after surgery.[57] When the risk of postoperative bleeding is higher than the risk of thromboembolic events, the full-dose anticoagulation might be resumed 48 or 72 h after the procedure (Grade 2B).[58] For patients at a high risk of thromboembolism and with a high bleeding risk after surgery, consider administering a reduced dose of DOAC on the evening after surgery and on the following day (first postoperative day) after surgery (Grade 2B).[58]

Vitamin K antagonists

Renal failure is considered as a risk factor for bleeding and is included in several models of stratification of bleeding risk and clinical practice guidelines.[59–61]

Table 1 Validated equations allowing estimation of renal function

2009 CKD-EPI creatinine equation	$141 \times \min(SCr/k, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age}$ [x1.018 if female] [x1.159 if black]
	Where SCr is serum creatinine (in mg dl^{-1}), κ is 0.7 for women and 0.9 for men, a is -0.329 for women and -0.411 for men, min is the minimum of SCr/κ or 1, and max is the maximum of SCr/κ or 1.
MDRD eGFR (ml min^{-1} per 1.73 m^2)	$186 \times$ [serum creatinine (mg dl)]$^{-1.154} \times$ (age)$^{-0.203} \times$ (0.742 if female) $\times$ (1.212 if black)
Cockcroft and Gault formula	[(140-age) $\times$ weight (kg)]/(72 $\times$ creatinine (mg dl^{-1}))(x 0.85 if woman)
2012 CKD-EPI cystatin C equation	$133 \times \min(SCysC/0.8, 1)^{-0.499} \times \max(SCysC/0.8, 1)^{-1.328} \times 0.996^{Age}$ [x 0.932 if female]
	Where SCysC is serum cystatin C (in mg l^{-1}), min indicates the minimum of SCysC/0.8 or 1, and max indicates the maximum of SCysC/0.8 or 1.
Cockcroft and Gault formula with ideal body weight (IBW)	IBW for men = 50 + 0.9 $\times$ [length (in cm) − 152]
	IBW for women = 45.5 + 0.9 $\times$ [length (in cm) − 152]

Analysis of the AURICULA registry (patients with atrial fibrillation on warfarin treatment) suggested that monitoring of renal function should be implemented in clinical practice in patients with atrial fibrillation.[62] A recent multicentre prospective observational study including 4093 patients aged at least 80 years naive to vitamin K antagonists (VKAs) compared the ability of the Cockcroft and Gault, MDRD and CKD-EPI formulae to predict the bleeding risk. They concluded that although the different available equations yield different eGFRs, all appear to predict the risk of major bleeding similarly.[63] In conclusion, to evaluate renal function for all anticoagulants, the use of the Cockcroft and Gault equation may also be suggested for VKA patients (Grade 2C).

Low molecular weight heparins

The risk of bleeding complications with LMWHs is higher in patients with impaired renal function.[64–66] Therefore, renal function should be measured in case of severe bleeding in a patient receiving LMWH (Grade 1C). A retrospective single centre showed in a cohort of 413 consecutive patients undergoing hip fracture surgery that moderate renal impairment was an independent factor associated with transfusion, with both Cockcroft and Gault and MDRD formulae.[67] Cockcroft and Gault may be preferred to MDRD to avoid overestimation of renal function (Grade 2C).[68] There is an inverse relationship between CrCl and anti-Xa levels.[65,69] However, it is still debated whether there is a clear benefit in anti-Xa monitoring regarding LMWH efficacy and safety outcomes, especially in patients with renal impairment (Grade 2C).[70–74]

Perioperative setting

Clinical characteristics to consider before ordering renal function tests include likely perioperative therapies, endocrine disorders, risk of renal dysfunction and use of certain medications or alternative therapies.[75,76] The UK National Institute for Health and Care Excellence (NICE) guidelines recommend ordering renal function tests depending on the severity of surgery and the American Society of Anesthesiologists' (ASA) physical status grade (Table 2). The risk index of Kheterpal *et al.*[77] is useful for identification of patients at risk of postoperative renal impairment (Grade 2B). Calculated GFR is superior to serum creatinine for the identification of patients with preexisting renal impairment (Grade 2B).[78] Urine output should be monitored carefully throughout the perioperative phase and adequate fluid management provided in order to avoid worsening of preexisting renal failure for patients at risk of postoperative renal impairment (Grade 2C).[79]

Which laboratory tests are indicated to exclude persistence of acquired perioperative coagulopathy before venous thromboembolism prophylaxis?

Phase 3 trials with VKAs, LMWH, fondaparinux and DOACs were performed for VTE prevention in high-risk surgical patients. The results of these trials provided information about the relationship between the first perioperative dose and both safety and efficacy of anticoagulant prophylaxis.[80–96] Laboratory tests were not included in these studies to guide the timing of the first perioperative dose.

In addition, standard laboratory global tests [activated partial thromboplastin time (aPTT) and prothrombin time (PT)] are not sensitive to all acquired and hereditary factor defects (factor XIII, fibrinolysis and so on).[97] This sensitivity is also variable according to the reagent. The sensitivity to temperature, pH, anticoagulants, lupus anticoagulants and C-reactive protein should also be considered.

A normal aPTT and/or PT do not exclude the presence of therapeutic levels of DOACs.[98–103] As a result, a specific test does not allow the timing of the start of VTE prophylaxis to be determined. A normal thrombin time excludes a clinically relevant dabigatran level.[104,105] Specific assays should be used to exclude the presence of relevant anti-Xa drug levels.

Finally, standard laboratory tests (aPTT, PT, fibrinogen and bleeding time) have poor negative and positive predictive values for bleeding risks during a surgical intervention or other invasive procedure.[106]

Should we adapt low molecular weight heparins dosage depending on the platelet count?

There are limited data in the literature regarding anticoagulant treatment during severe thrombocytopaenia. The safety and efficacy of LMWHs during thrombocytopaenia should be evaluated further, in larger clinical studies

Table 2 Recommendations to order renal function tests for specific surgery grades (minor, intermediate and major or complex) and American Society of Anesthesiologists grades

	ASA 1	ASA 2	ASA 3 or 4
Minor surgery	Not routinely	Not routinely	Consider in people at risk of AKI
Intermediate surgery	Not routinely	Consider in people at risk of AKI	Yes
Major or complex surgery	Consider in people at risk of AKI	Yes	Yes

AKI, acute kidney injury; ASA, American Society of Anesthesiologists' physical status grade.

involving more patients with severe thrombocytopaenia. Three clinical trials studied the use of LMWHs for prophylaxis of hepatic veno-occlusive disease in patients who underwent bone marrow transplantation.[107–109] They showed that these patients may benefit from a reduced dose of LMWHs. Regarding haematological malignancies, current evidence[110–112] includes several case series totalling 19 patients and a retrospective analysis of 126 patients.[113] These data suggest that reduced doses of LMWHs may be used relatively safely during transient severe ($<50 \times 10^9$ l^{-1}) thrombocytopaenia (Grade 2C).

Concerning cancer patients, an international consensus working group of experts has recently performed a systematic review using the GRADE system. They found no study for the treatment and prophylaxis of VTE in cancer patients with thrombocytopaenia. They made the following suggestions based on the exclusion criteria in clinical trials. This proposal can be extended to haematological patients.

In cancer patients or patients with haematological disorders and thrombocytopaenia, full doses of anticoagulant can be used for the treatment of established VTE if the platelet count is more than 50×10^9 l^{-1} and there is no evidence of bleeding; for patients with a platelet count below 50×10^9 l^{-1}, decisions on treatment and dosage should be made on a case-by-case basis with the utmost caution (Grade 2C).

It is recommended to monitor the intensity of anticoagulation by the measurement of peak anti-Xa activity levels with various target ranges depending on the LMWH preparation and the frequency of dosing.[65,70,114] As every LMWH is different, LMWH monitoring requires calibration towards the specific LMWH used for therapy.[115] Other limitations of anti-Xa activity measurement include inter-assay variability,[116,117] inter-laboratory variation[118] and poor correlation to antithrombotic efficacy.[119]

When should venous thromboembolism prophylaxis be started and at which dose in patients with severe intraoperative bleeding?

There are few data regarding the outcomes of restarting anticoagulation in patients who develop severe bleeding.[1] Thus, there is still a need for randomised controlled trials on restarting oral anticoagulation and the risk of stroke and recurrent bleeding after severe bleeding.

Warfarin

Gastrointestinal bleeding

Resuming warfarin following gastrointestinal bleeding is associated with a lower risk of thromboembolism and decreased mortality. [120–128] Resuming warfarin has not been associated with a significant increase of the risk of recurrent gastrointestinal bleeding. Resuming warfarin therapy should be considered for most patients following resolution of gastrointestinal bleeding (Grade 1C). It is more difficult to decide to resume warfarin therapy when the bleeding source cannot be identified or cannot be definitively treated.

Patients with a high thrombotic risk (e.g. those with mechanical heart valves) may benefit from resuming warfarin therapy despite an ongoing risk of recurrent gastrointestinal bleeding (Grade 2C). It appears pertinent to propose anticoagulant treatment withdrawal for as short a period as possible only in situations involving a high risk of thrombosis, wherein the risk of thromboembolism could be higher than the risk of haemorrhage.

The delay between major gastrointestinal bleeding and warfarin resuming should be at least 7 days (Grade 2C). Restarting warfarin after 7 days of interruption is associated with improved survival and decreased thromboembolism without an increased risk of gastrointestinal bleeding. An ongoing clinical trial is evaluating the risk and/or benefit of early versus late resumption of anticoagulation in patients with major nontrauma-related haemorrhage occurring while receiving anticoagulant treatment for a high risk of thrombosis (NCT02091479).

In all these groups of patients, no evidence could be found on the timing of restarting VTE thromboprophylaxis and this highlights the need for future studies on this specific question.

Intracranial haemorrhage during the perioperative period

The decision on resuming anticoagulation should be based on the evaluation of the indication for anticoagulation, the treatment history with warfarin, any possible precipitating risk factors for the haemorrhage, the condition of the patient, the location of intracranial haemorrhage (ICH), the risks of haematoma growth or recurrent ICH and thromboembolic events.[63,129–169]

ICH location and the risk for ischaemic cerebrovascular events seem to be the key factors in the assessment of the risk/benefit balance before restarting anticoagulation after ICH. Patients with lobar haemorrhage or cerebral amyloid angiopathy remain at a higher risk for anticoagulant-related ICH recurrence than thromboembolic events and therefore would be best managed without anticoagulants. Patients with deep hemispheric ICH and a CHA2DS2-VASc at least 5 may receive net benefit from restarting anticoagulation. Currently available data regarding the timing of resuming are contradictory. Delays of warfarin reintroduction from 7 days to 30 weeks have been suggested.

Patients with a history of ICH have an increased risk of recurrent ICH when treated with VKA anticoagulation. All patients with a history of ICH thus require a careful

evaluation of their thromboembolic risk to estimate the clinical benefit of (re)starting anticoagulation with VKAs.

Hopefully, the level of evidence will increase when the ongoing RESTART trial (www.RESTARTtrial.org) has been completed. The RESTART trial is a randomised controlled trial for adults surviving spontaneous intracerebral haemorrhage who had taken an antithrombotic drug (i.e. anticoagulant or antiplatelet medication) for the prevention of vaso-occlusive disease before the ICH. This trial will also provide data for DOACs, for which there are no published data for the moment.

Cardiac tamponade

In case of cardiac tamponade complicating catheter ablation of atrial fibrillation, it seems to be effective and well tolerated to resume anticoagulation therapy 12 h after removal of the drainage catheter.[170] This may help to prevent thromboembolic events following catheter ablation of atrial fibrillation.

Direct oral anticoagulants

There are no data available concerning the outcomes of restarting anticoagulation in patients who develop severe bleeding while anticoagulated with DOACs (dabigatran, rivaroxaban, apixaban and edoxaban). These new drugs reduce the risk of ICH.[171] However, the absence of reversal agents makes patient care difficult in case of ICH. There is a new specific antagonist available for dabigatran known as idarucizumab,[172] which warrants further studies. The complete results of the REVERSE AD trial were presented at the American Heart Association congress in December 2016. Two groups of patients on dabigatran were included, 298 patients in group A who had serious bleeding, and 196 patients in group B who required an urgent procedure. The dilute thrombin time normalised within 4 h in 235 out of 238 patients (98.7%) in group A and 141 out of 143 patients (98.6%) in group B. Clinical outcomes, considered only as secondary endpoints, were assessed by the treating clinician. It is important to note that the median time to the cessation of bleeding in group A was 3.5 h for gastrointestinal bleeds and 4.5 h for nongastrointestinal and non-ICH bleeds after idarucizumab administration. The authors admitted that this endpoint was difficult to assess in many patients, such as those with intracranial or retroperitoneal bleeding.

Andexanet alpha is the antidote for anti-Xa inhibitors.[173,174] Recently, results from the phase III trial, the 'Prospective, Open-Label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor Who Have Acute Major Bleeding' (ClinicalTrials.gov number, NCT02329327) have been published. The authors evaluated 67 patients with acute major bleeding within 18 h of the last factor Xa inhibitor administration. Rates of excellent or good efficacy occurred in 84% of cases for gastrointestinal bleeding and 80% for intracranial bleeding. Finally, 18% of patients had an ischaemic event during the 30-day follow-up period after the infusion of andexanet. Only 27% of patients resumed anticoagulant therapy within 30 days after acute major bleeding. Birocchi *et al.*[175] have asked recently if resuming anticoagulant therapy soon after effective haemostasis could reduce thrombotic events.

Recommendations

- In patients with inherited bleeding disorders undergoing surgery, we recommend assessment of individual risk of VTE, taking into account the nature of the surgery and anaesthetic, type and severity of haemophilia, age, BMI, history of thrombosis and the presence of malignancy and other high-risk comorbidities. VTE risk should be balanced against the increased bleeding risk associated with anticoagulant use in patients with haemophilia (Grade 1C).
- For the perioperative management of patients with inherited bleeding disorders, we suggest liaison with haematologists to guide treatment (Grade 2C).
- We suggest that, if factor replacement therapy is required for perioperative haemostasis, excess use should be avoided and factor levels carefully monitored (Grade 2C).
- In patients with inherited bleeding disorders undergoing major surgery, we suggest mechanical thromboprophylaxis (Grade 2C), especially in factor VII deficiency (Grade 1C).
- In patients with inherited bleeding disorders undergoing major surgery, we recommend against routine postoperative use of pharmacological thromboprophylaxis, especially for patients with haemophilia A or B (Grade 1B).
- If the balance of risks favours pharmacological thromboprophylaxis, we suggest that low molecular weight heparin should be administered as for patients without haemophilia undergoing the same surgery, and factor VIII/IX levels should be maintained at 0.6 to 1.0 IU ml^{-1} (Grade 2C).
- In haemophilia patients with inhibitors, we suggest against the use of pharmacological thromboprophylaxis (Grade 2C).
- We recommend that patients with haemophilia who require perioperative factor concentrate are monitored with daily factor levels for the first 3 to 5 days to guide treatment and avoid wide fluctuations in factor levels (Grade 1C).
- We recommend that, for major surgery, factor levels of 0.8 to 1.0 IU ml^{-1} should be aimed for and not be allowed to fall below 0.5 IU ml^{-1} or rise above 1.5 IU ml^{-1} in the postoperative period (Grade 1B).
- In general, we recommend against routine thrombophilia screening for patients with haemophilia undergoing surgery (Grade 1C).

- We recommend that patients treated with factor concentrate in the perioperative and postoperative period should have both factor VIII and von Willebrand factor levels monitored to avoid an excessive rise in factor levels and accumulation of factor VIII. We recommend checking levels 12-hourly for the first 24 h after major surgery and daily thereafter (Grade 1B).
- We recommend that the use of factor concentrate with the highest ratio between vWF:RCo and factor VIII:C should be considered, to minimise risk of factor VIII accumulation (Grade 1C).
- We recommend that the use of factor XI concentrate is kept to a minimum to avoid increasing the thrombotic risk (Grade 1C).
- We recommend that all patients receiving factor XI concentrate have mechanical thromboprophylactic measures (Grade 1C) and suggest that they are considered for pharmacological thromboprophylaxis (Grade 2C).
- We suggest that tranexamic acid alone is useful for patients with mild factor XI deficiency but should not be given as haemostatic prophylaxis to patients receiving factor XI concentrate (Grade 2C).
- In patients with factor VII deficiency, we suggest that they are considered for pharmacological thromboprophylaxis if they have associated risk factors (Grade 2C).
- We suggest that for major surgery, fibrinogen levels should be closely monitored aiming to maintain levels 1 to 1.5 $g\,l^{-1}$ for 10 to 14 days postoperatively (Grade 2C).
- Perioperative management may require simultaneous use of fibrinogen concentrate and low molecular weight heparin, depending on the clinical phenotype (Grade 2C).
- Glomerular filtration rate (eGFR) should be assessed before any direct oral anticoagulant (DOAC) is initiated, and at least once yearly or more frequently as needed, such as postoperatively before the resumption of therapeutic DOAC administration, when it is suspected that renal function could decline or deteriorate (Grade 1C).
- The use of the Cockroft–Gault method to evaluate renal function of patients with DOAC is suggested (Grade 2C).
- We suggest that anti-Xa levels may be measured in cases of severe bleeding in patients with renal impairment receiving low molecular weight heparin (Grade 1C).
- Clinical exclusion of signs of postoperative bleeding is more relevant for postponing the commencement of VTE prophylaxis rather than relying on any specific laboratory tests (Grade 2C).
- We suggest against the systematic use of standard laboratory tests to exclude persistence of acquired perioperative coagulopathy before VTE prophylaxis (Grade 2C).
- Reduced dosages of low molecular weight heparins may be used relatively safely during transient severe ($<50 \times 10^9\ l^{-1}$) thrombocytopaenia (Grade 2C).
- Monitoring anti-Xa level may be used to adjust the doses of low molecular weight heparin in patients with moderate or severe thrombocytopaenia (Grade 2C).
- In cancer patients or patients with haematological disorders and mild thrombocytopaenia (platelet count $>80 \times 10^9\ l^{-1}$), pharmacological prophylaxis may be used; if the platelet count is below $80 \times 10^9\ l^{-1}$, pharmacological prophylaxis may only be considered on a case-by-case basis and careful monitoring is recommended (Grade 2C).
- Patients with a high thrombotic risk (e.g. mechanical heart valves) may benefit from resuming warfarin therapy despite ongoing risk for recurrent gastrointestinal bleeding (Grade 2C).
- Patients with a HAS-BLED score lower than the $CHADS_2$ score may benefit from earlier resumption (Grade 2C).
- The delay between major gastrointestinal bleeding and warfarin resumption should be at least 7 days (Grade 2C).
- We suggest international normalised ratio (INR) at the time of bleeding may also be considered to resume anticoagulation (Grade 2C).
- We suggest resuming anticoagulant therapy 12 h after removal of drains in cases of cardiac tamponade (Grade C).
- When the risk of bleeding diminishes, pharmacological VTE prophylaxis may be initiated depending on thrombotic risk factors (Grade 2C).
- We recommend that when the risk of postoperative bleeding is higher than the risk of thromboembolic event, full-dose anticoagulation may be resumed 48 or 72 h after the procedure (Grade 2B).
- For patients at a high risk of thromboembolism and with a high bleeding risk after surgery, we consider that administering a reduced dose of DOAC on the evening after surgery and on the following day (first postoperative day) after surgery is good practice (Grade 2B).

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