VTE prophylaxis in patients with pre-existing coagulation disorders and after severe perioperative bleeding.

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Abstract:
This chapter describes the European Society of Anaesthesiology’s recommendations for venous thromboprophylaxis in patients after severe perioperative bleeding or pre-existing coagulation disorders. Patients with inherited bleeding disorders or pharmacologically induced coagulation disorders are considered. Our recommendations and suggestions for best practice are prescribed at the end of the chapter based on the review of all of the available evidence. The GRADE classification is used. Clinical questions that are commonly posed are addressed such as when and how to alter drug dosage in relation to renal impairment and the role of non-pharmacological prophylaxis is discussed. The role of direct acting oral anticoagulants is reviewed.
1. Guidelines for the prevention of postoperative venous thromboembolism in 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 relative protective effect of the underlying bleeding tendency, is associated with a reduced VTE risk compared with non-haemophilia 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 non-haemophilia patients treated with anticoagulants (2). The incidence of subclinical DVT detected by systematic US-Doppler has also been found to be very low, ranging from 0 to 10 % (3,4).

On the other hand, the risk of bleeding is significant, even when factor concentrate has been carefully managed. In a retrospective evaluation of 72 total knee replacement in 51 haemophilia A and B patients using continuous infusion of factor concentrates and no pharmacological thromboprophylaxis, twenty six haematomas (36.1%) and 2 haemarthroses (2.7%) occurred in 38.8% of cases during the first three 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, FVIII does not reach the high levels of non-haemophilia 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, by contrast with factor IX levels, which are carefully monitored and controlled, postoperative FVIII can reach very high levels in haemophilia B patients. Although it is presently unknown whether these patients are at 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, 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. LMWH would be preferred, as studies testing the direct oral anticoagulants 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 FVIIa has 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 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 FVIII or IX excess is important.

Whilst the presence of inherited thrombophilias has been shown to modify the bleeding phenotype in patients with haemophilia (7,8,9), 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 disease, thrombophilia screening could be considered.

**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 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 FVIII the levels of FVIII will also be impacted. Thrombosis is rare in VWD but according to available data it occurs more frequently than in hemophilia. Most reported cases occurred after orthopaedic surgery (10) and most have been in the presence of additional VTE risk factors (11,12,13). VTE is more prevalent in those with type 1 disease who have received haemostatic therapy (14).

Patients with VWD undergoing major surgery are usually treated with dual concentrates containing FVIII and VWF. The ratio between VWF (VWF:RCo) and FVIII varies among available products, in the
range of 1-2.5 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 FVIII which is beneficial when treating acute bleeds and acute surgery. A secondary rise in FVIII levels occurs with some concentrates after 12-24 hours, in others, a parallel decay over time for VWF and FVIII has been reported. However, infusion of virtually pure VWF will also restore FVIII levels due to binding and stabilization of endogenous FVIII. This will take from 12-24 hours and, in the treatment of acute bleeds and surgery, infusion of exogenous FVIII is sometimes needed. Infusion of VWF will cause a rise in endogenous FVIII level. This, added to infused FVIII may result in supra normal levels, particularly with repeated treatment (15). The half-life is 2-3 fold longer than that seen after replacement for haemophilia (16). Thrombosis has occurred when abnormally high FVIII levels have developed from prolonged factor replacement therapy (17). FVIII levels above 1.5iu/ml have been associated with an approximately five-fold increased risk of venous thrombosis compared to levels below 0.5iu/ml (18,19,20).

For patients with von Willebrand disease receiving factor concentrates replacement therapy, we suggest monitoring factor VII levels and thromboprophylaxis should be considered if any other thrombosis risk factor is present (Grade 2C).

**FXI deficiency**

FXI levels below 15 iu/ml are known to confer a reduced risk of VTE (21) and ischaemic stroke (22). In contrast, factor FXI above 90th centile confers more than a two-fold increased risk of VTE (23), possibly by sustained thrombin generation and inhibition of fibrinolysis; this has led to the development of FXI inhibitors as antithrombotic agents. Exogenous FXI may have a similar effect (24,25) and patients with FXI deficiency receiving perioperative FXI concentrate are at higher risk of thrombosis, even if factor replacement is managed carefully (26) and thrombotic events, including fatal PEs have been seen even with doses <30u/kg (27,28). The thrombin generation potential varies between the available concentrates (29) but in general doses <20u/kg are effective in achieving haemostasis and the increased risk of thrombosis is less. Fresh frozen plasma is a good source of FXI and can be useful when FXI concentrate is unavailable. Most patients with FXI deficiency have a non-bleeding phenotype and careful assessment is required before planning perioperative management, to avoid unnecessary treatment. Tranexamic acid alone is useful in patients with mild FXI deficiency but has been shown to increase the incidence of postoperative DVT in patients with thrombotic risk factors (30) and should be avoided in patients receiving FXI concentrate, unless unexpected bleeding occurs when the benefits may outweigh the risks (31).
**Factor VII deficiency**

Thromboembolic events have been occasionally described in patients with congenital FVII deficiency, most frequently in patients with associated prothrombotic risk factors (32,33). Surgical procedures, replacement therapy (especially containing activated factors) but also the presence of an antiphospholipid syndrome are frequently associated with these particular 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 F7 mutations. Low FVII coagulant activity levels do not protect against thrombosis. Therefore, peri-operative thrombotic prophylaxis should be relevant for these particular FVII-deficient patients. However, safety, treatment modalities and specific indications of such an antithrombotic prophylaxis remain to be established. As suggested, thromboprophylaxis may be indicated in patients with FVII:C >30% or FVII:C10% to <30% and a history of thrombosis and/or strong risk factors but it is not appropriate for patients with FVII:C<10% (34).

**Fibrinogen disorders**

Hypofibrinogenaemia and dysfibrinogenaemia are associated with thrombosis in 20-30% of cases, which has 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 is insufficient data to recommend a specific perioperative management plan but peak fibrinogen levels of 1.5g/l 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.

**Antithrombin deficiency**

Antithrombin (AT) deficiency is an uncommon autosomal dominant disorder, leaving the affected patients at significantly increased risk for thromboembolism, predominantly in the venous circulation. VTE incidence has been found to be 0.9–2.9% per year, with a recent large prospective study showing an incidence of 1.7% per year (60,61). The initial management of VTE in patients with AT deficiency is similar to that of VTE in any other patient: (i) consideration of thrombolytics; (ii) initial therapy with heparin or fondaparinux; and (iii) transitioning to a vitamin K antagonist (62).
Other rare coagulation disorders

Prothrombin complex concentrates are useful for patients with Factor II deficiency or for Factors X and VII deficiency where specific factor replacement is not available. High and repeated doses have been associated with thrombosis (37) particularly where 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 FXIII concentrate. Platelet function disorders have not been associated with thrombosis except in cases where activated factor VIIa has been used.

2. Guidelines for pharmacologically induced coagulation disorders, patients with a history of heparin-induced thrombocytopenia (HIT), patients after reversal of oral anticoagulation, patients with acquired haemophilia A (AHA) and patients on (dual) anti-platelet therapy (DAPT).

Venous thromboembolism which includes deep venous thrombosis and pulmonary embolism contributes to a high level of morbidity and mortality. There are certain specific subgroups of patient populations that are at higher risk of these complications. Those with coagulation disorders induced by pharmacological agents, those with acquired coagulation disorders such as heparin induced thrombocytopenia and acquired haemophilia A and those who are at special risk by virtue of the medical therapies they are on such as oral anticoagulation that has been reversed, and those on dual anti-platelet therapies.

Heparin induced thrombocytopenia

Wiegele et al (46) presented a case reporting that administration of LMWH may result in HIT-II despite previous uneventful exposure after eight days. (45) report a retrospective study of 22 patients treated with a DOAC and argatroban followed up for 19 months. All patients tolerated DOAC and normalised platelet counts but 6 patients had died of non-thrombotic causes by 19 months. They concluded that a short course of argatroban followed by a DOAC is safe and effective. (44) in a review of orthopaedic and oncological resection surgery concluded that aspirin appears as effective as LMWH prophylaxis and may reduce bleeding risk and extended prophylaxis up to four weeks post surgery reduces VTE episodes. (40) however in a systematic review were unable to recommend the use of DOAC for the treatment of HIT.
Reversal of DOACs – direct oral anticoagulants (eg dabigatran and idarucizumab)

Non-vitamin K oral anticoagulants (DOACs) have been proven to be at least as effective as VKA with similar or lower rates of bleeding and fewer drug and food interactions (47,48). In addition, they have a more predictable anticoagulant effect, allowing a fixed dose regimen and obviating the need for routine anticoagulation monitoring. DOACs include the direct thrombin inhibitor dabigatran and the factor Xa inhibitors, namely rivaroxaban, apixaban and edoxaban.

Shulman and colleagues (47) in a randomized, double-blind, non-inferiority trial involving patients with acute VTE first compared dabigatran (150 mg twice daily) with warfarin (INR 2-3), observing that dabigatran was as effective as warfarin, having a similar safety profile. DOACs have been repeatedly observed successful in VTE prophylaxis and treatment, non-valvular AF, electrical cardioversion, and pre-procedural anticoagulation for catheter ablation of AF (47-56).

However, a major concern regarding DOACs was the lack of a readily available antidote to reverse their anticoagulation effect in case of life-threatening bleeding or need for emergent surgery. Although, coagulation factor concentrates can be used in patients with haemophilia and to reverse the effect of VKAs but, in DOAC-treated patients, results are inconsistent and could potentially have prothrombotic effects. Phase III clinical trials of recombinant modified factor Xa (andexanet alfa) are ongoing and a humanized antibody fragment directed against dabigatran called idarucizumab is now available. Idarucizumab is a monoclonal antibody fragment that binds dabigatran with high affinity in a 1:1 molar ratio. Glund and colleagues [57] recently performed a randomized, placebo-controlled, double-blind, proof-of-concept phase 1 study investigating the safety, tolerability, and efficacy of increasing doses of idarucizumab for the reversal of anticoagulant effects of dabigatran.

Idarucizumab was associated with immediate, complete, and sustained reversal of dabigatran-induced anticoagulation; no unexpected or clinically relevant safety concerns were observed. Consonant results were also observed by the prospective cohort study REVERSE-DA trial of Pollack and co-workers [58]. Similarly, andexanet alfa designed to reverse the anticoagulant effects of factor Xa inhibitors, has been proved effective in reversing the anticoagulant activity of apixaban and rivaroxaban within minutes after administration [59].

The timing of when to start prophylaxis therapy after reversal is important. VTE can arise because the timing of the start of therapeutic re-anticoagulation is delayed, or that prophylactic VTE therapy is not started in error or early enough.
**Acquired haemophilia A**

Analysis of pooled data from published series of hemophilia patients undergoing arthroplasty showed an estimated incidence of symptomatic VTE of 0.5% (1) reviewed 42 patients who underwent 71 hip or knee replacements over 39 years. 6 cases (10.5%; 57 with available data) used sequential intermittent compression devices and 2 (2.8%) postoperatively received low-molecular-weight heparin. One patient (1.4%) who received low-molecular-weight heparin had a symptomatic, lower-extremity, deep venous thrombosis 10 days after hip replacement for traumatic fracture. None of the other 70 surgical cases had symptomatic VTE within 3 months after the procedure.

(42) conducted a retrospective study of patients with haemophilia undergoing THR/TKR. There were 23 patients with hemophilia, 18 (78%) with hemophilia A and 5 (22%) with hemophilia B, who underwent high-risk surgeries (39% THR and 61% TKA). The VTE prophylaxis included sequential compression device, 12 (52%), and prophylactic enoxaparin, 1 (4%). Ten (43%) patients did not receive VTE prophylaxis. At 1-year follow-up, they did not find any evidence of clinical VTE in their patients (41) suggest that in the majority of the patients the use of graduated compression stockings and early mobilization can be sufficient to prevent venous thromboembolism.

**Dual anti platelet therapy**

(Knight, Klaskala et al. (39) assessed 5294 acute coronary syndrome patients looking at factors associated with dual antiplatelet therapy and anticoagulation. DAP was less likely in those who were receiving anticoagulation (P<0.0001) although of those that had a VTE history 40% were on anticoagulants on discharge. 923 had atrial fibrillation and 337 had a history of venous thromboembolism; these patients had increased use of anticoagulants (29% and 40%, respectively). Post discharge use of anticoagulation was rare. The role of DAP and the direct factor Xa inhibitors in ACS is still being evaluated.

3. How and when should renal function be followed in patients with pre-existing coagulation disorders and after severe bleeding?

The kidney only synthesises urokinase and thus, plays a minor role in haemostasis. Determination of renal function is important in patients receiving oral and parenteral anticoagulants.

Although there is a need for an eGFR evaluation, there is still a lack of knowledge regarding which
method of renal function evaluation is best appropriate in patients with anticoagulants. Serum creatinine, for instance, is inaccurate to estimate the degree of renal failure especially in the elderly (62,63). There are currently 4 ways to estimate renal function and eGFR: Cockcroft and Gault formula (CG), 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 (64-68). The limitations of CG equation are well known: failure to normalize for body surface area along with a lack of validation in a broad sample of patients with chronic kidney disease (69). The CG formula is also influenced by body weight and body mass index (BMI) while MDRD and CKD-EPI equations are adjusted for body surface area (68-69). However, the CG formula had the greatest accuracy for patients who are underweight (68). The CG formula calculated with the ideal body weight (IBW) improves the classification of renal impairment among older adults(70).

The HAS-BLED score (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) which includes the renal function is a score to predict major bleeding in anticoagulated AF patients (95-96).

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

Glomerular filtration rate (eGFR) should be assessed before each DOAC’s initiation, also at least once year or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (Grade 1C) (71). 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 >75–80 years (especially if the patient is on dabigatran or edoxaban), or in frail patients(72). The proposed recheck interval is creatinine clearance value divided by 10 (CrCl/10) if the CrCl is lower than 60 ml/min or more frequently if indicated. A recent observational study on 162 patients with NVAF after hospitalization for acute decompensated heart failure (ADHF) showed that up to two-thirds of patients experienced a variation of more than 20% in CrCl over 6 months and these changes should be taken into account for dose adjustment of DOACs (73).

This is of particular importance as the risk of major bleeding and ischemic stroke may be highly correlated to plasma DOAC concentrations (74). Of note, in the XANTUS study, a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation, 34.4% had no baseline assessment of the renal function (75). Pilot phase 3 studies of DOACs used the CG formula to estimate kidney function for patient’s inclusion, to elaborate drug dosing guidelines and to evaluate impact of renal function on bleeding and thrombotic risk (76-79). In a frail
(i.e BMI) and older population, it seems more safe to use the CG formula which underestimates GFR than another equation which overestimates GFR and risk to misclassify DOAC dose adaptation as demonstrated by Hellden A et al (80). This correlates to results of several other studies suggesting that use of the MDRD equation for drug dosing often yields higher doses than does CG equation, especially with narrow therapeutic window range drugs and high-risk subgroups, such as the elderly (81-86).

In conclusion, to date, there is no optimal GFR estimation’s equation. All formulas have their limitations. Regulatory authorities have to set up guidelines for kidney function estimation in clinical trial and to promote the use of the best appropriate GFR equation for drug dosing. The US Food and Drug Administration (FDA) recently endorsed the use of more contemporary means for estimating GFR (69).

Finally, in the lack of consensus, the use of the CG method to evaluate the renal function of patients with DOAC is suggested (Grade 2C) (87-89).

DOACs should be resumed postoperatively when haemostasis has been achieved. The timing of the first postoperative dose of the DOACs differed among the DOACs and does not depend on the renal function.

Acceptable efficacy and safety can be achieved when appropriate first dose of anticoagulant is given at least 6 hours after surgery (117). When the risk of postoperative bleeding is higher than the risk of thromboembolic event, the full dose anticoagulation might be resumed 48 or 72 hours after the procedure (118-119) (Grade 2B). For patients at high risk for 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 (118-119) (Grade 2B).

**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 (90-92). The analysis of the AURICULA registry (AF patients on warfarin treatment) suggested that the monitoring of renal function should be implemented in clinical practice in AF patients (93). A recent multicentre prospective observational study including 4,093 patients ≥80 years naïve to VKA compared the ability of the CG, MDRD and CKD-EPI formulas to predict the bleeding risk. They concluded that although the different available equations yield different eGFR, all appear to similarly predict the risk of major bleeding (94).
In conclusion, to evaluate the renal function for all anticoagulants, the use of the CG equation may also be suggested for VKA patients (Grade 2C).

**Low molecular weight heparins**

The risk of bleeding complications with LMWH is higher in patients with impaired renal function (99-101). Therefore, renal function should be measured in case of severe bleeding of a patient receiving low molecular weight heparin (Grade 1C).

A retrospective single centre showed in a cohort of 413 consecutive patients undergoing hip fracture surgery, that moderate renal impairment that was an independent factor associated with transfusion, with both CG and MDRD formulas (102). CG may be preferred to MDRD to avoid overestimation of renal function (Grade 2C) (103).

There is an inverse relationship between CrCl and anti-Xa levels (99,104-105). 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) (106-110).

**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 (112-114). NICE Guidelines recommend ordering renal function tests depending on the severity of surgery and the ASA Grade (Table 2).

The risk index of Kheterpal et al. is useful for the identification of patients at risk for postoperative renal impairment (grade: 2B). (2) Calculated GFR is superior to serum creatinine for the identification of patients with pre-existing renal impairment (Grade 2B). (3) Urine output should be monitored carefully throughout the perioperative phase and adequate fluid management provided in order to avoid worsening of pre-existing renal failure for patients at risk for postoperative renal impairment (Grade: 2C) (115).
<table>
<thead>
<tr>
<th>Year</th>
<th>Equation Type</th>
<th>Formula</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>CKD-EPI creatinine equation</td>
<td>( 141 \times \min(\text{Scr}/k, 1)^a \times \max(\text{Scr}/k, 1^{1.129} \times 0.993^{\text{Age}} \times 1.018 \times \text{if female}) \times 1.159 \times \text{if black} )</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Where Scr is serum creatinine (in mg/dl), k is 0.7 for females and 0.9 for males, a is _0.329 for females and _0.411 for males, min is the minimum of Scr/ k or 1, and max is the maximum of Scr/ k or 1.</td>
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<td></td>
<td>MDRD eGFR (mL/min/1.73 m^2)</td>
<td>( 186 \times [\text{serum creatinine (mg/dl)}]^{1.154} \times [\text{age}]^{0.203} \times (0.742 \times \text{if female}) \times (1.212 \times \text{if black}) )</td>
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<tr>
<td></td>
<td>Cockcroft and Gault formula</td>
<td>( \frac{\text{(140-age) \times \text{weight (kg)}}}{\text{72 \times \text{creatinine (mg/dl)}}} \times 0.85 \times \text{if woman} )</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>CKD-EPI cystatin C equation</td>
<td>( 133 \times \min(\text{SCysC}/0.8, 1)^{-0.449} \times \max(\text{SCysC}/0.8, 1)^{1.328} \times 0.996^{\text{Age}} \times 0.932 \times \text{if female} )</td>
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<tr>
<td></td>
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<td>Where SCysC is serum cystatin C (in mg/l), min indicates the minimum of SCysC/0.8 or 1, and max indicates the maximum of SCysC/0.8 or 1.</td>
<td></td>
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</tbody>
</table>
|          | Cockcroft and Gault formula with ideal body weight | IBW for men = 50 + 0.9 x [length (in cm) – 152]  
IBW for women= 45.5 + 0.9 x [length (in cm) – 152] |

### Table 2: Recommendations to order renal function tests for specific surgery grades (minor, intermediate, and major or complex) and ASA grades

<table>
<thead>
<tr>
<th>Surgery Grade</th>
<th>ASA 1</th>
<th>ASA 2</th>
<th>ASA 3 or 4</th>
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<tr>
<td>Minor surgery</td>
<td>Not routinely</td>
<td>Not routinely</td>
<td>Consider in people at risk of AKI*</td>
</tr>
<tr>
<td>Intermediate surgery</td>
<td>Not routinely</td>
<td>Consider in people at risk of AKI²</td>
<td>YES</td>
</tr>
<tr>
<td>Major or complex surgery</td>
<td>Consider in people at risk of AKI</td>
<td>YES</td>
<td>YES</td>
</tr>
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</table>

* AKI: Acute Kidney Injury
4. Which lab tests are indicated to exclude persistence of acquired perioperative coagulopathy before VTE prophylaxis?

Phase 3 trials with vitamin K antagonists (VKAs), low-molecular weight heparin (LMWH), fondaparinux and direct oral anticoagulants 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 (121-140). Lab 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 (i.e. factor XIII, fibrinolysis etc.) (141). 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 direct oral anticoagulants (142-147). 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 clinical relevant dabigatran level (148-149). Specific assays should be used to exclude the present of relevant anti-Xa drug levels (146-147).

Finally, standard laboratory tests (aPTT, PT, fibrinogen and bleeding time) have poor negative and positive predictive values of bleeding risks during a surgical intervention or other invasive procedure (150).

The ability of thrombin generation and fibrin clot formation are independently reduced in acquired dilutional coagulopathy (151-152).

5. Should we adapt the LMWH dosage depending on the platelet count?

There is limited data in the literature regarding anticoagulant treatment during severe thrombocytopenia. The safety and efficacy of LMWHs during thrombocytopenia should be evaluated further, in larger clinical studies involving more patients with severe thrombocytopenia.

Three clinical trials studied the interest of LMWHs for prophylaxis of hepatic veno-occlusive disease in patients who underwent bone marrow transplantation (157-159). They showed that these patients may benefit from a reduced dose of LMWHs (157-159). Regarding haematological malignancies,
current evidence includes several case series (160-162) totalling 19 patients and a retrospective analysis of 126 patients (163). These data suggest reduced dosages of low molecular weight heparins may be used relatively safely during transient severe (<50 G/L) thrombocytopenia (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 thrombocytopenia. They made the following suggestions based on the exclusion criteria in clinical trials (164). This proposal can be extended to haematological patients.

In cancer patients or patients with haematological disorders and thrombocytopenia, full doses of anticoagulant can be used for the treatment of established venous thromboembolism if the platelet count is > 50 G/L and there is no evidence of bleeding; for patients with a platelet count below 50 G/L, 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 (165-167). Since every LMWH is different, LMWHs monitoring requires calibration towards the specific LMWH used for therapy (168). Other limitations of anti-Xa activity measurement include an inter-assay variability (169-170), inter-laboratory variation (171) and poor correlation to antithrombotic efficacy (172).

6. When do we start VTE prophylaxis 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 (174-182)

Resuming warfarin following gastrointestinal (GI) bleeding is associated with lower risk for thromboembolism and decreased mortality. Resuming warfarin has not been associated with a
significant increase of the risk of recurrent GI bleeding. Resuming warfarin therapy should be considered for most patients following resolution of GI 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., mechanical heart valves) may benefit from resuming warfarin therapy despite ongoing risk for recurrent GI 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, where the risk of thromboembolism could be higher than the risk of haemorrhage.

The delay between major GI bleeding and warfarin resuming should be at least 7 days (Grade 2C). Warfarin restarting after 7 days of interruption is associated with improved survival and decreased thromboembolism without increased risk of GI bleeding after 7 days of interruption. An ongoing clinical trial is evaluating the risk and/or benefit of early versus late resumption of anticoagulation in patients with major non-trauma-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 (ICH) during the perioperative period (183-226)**

The decision on resuming anticoagulation should be based on the evaluation on 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 ICH, the risks of haematoma growth or recurrent ICH and thromboembolic events.

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 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 ≥ 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) will be completed. 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 with data for DOACs for which there are no published data for the moment.

Cardiac tamponade (227)
In case of cardiac tamponade (CT) complicating catheter ablation of atrial fibrillation (AF), it seems to be effective and safe to resume anticoagulation therapy 12 hours after removal of the drainage catheter. This may help to prevent thromboembolic events following catheter ablation of AF.

Direct oral anticoagulants
There is 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 (228). However, the absence of reversal agents makes the patient care difficult in case of ICH. There is a new specific antagonist available for dabigatran known as idarucizumab which warrants further studies. Several ongoing clinical trials will address this important clinical question.

6. What is the place for non-pharmacological means of VTE prophylaxis (in the early postoperative phase) in this special group of patients? (229-234)
See recommendations at end of chapter.

Recommendations:
We recommend against routine postoperative use of pharmacological thromboprophylaxis for patients with haemophilia A and B undergoing major surgery (Grade 1B).

We recommend that patients with haemophilia undergoing surgery, should be individually risk assessed for VTE, taking into account the nature of the surgery and anaesthetic, type and severity of haemophilia, age, body mass index, 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).

We suggest that patients should be encouraged to achieve their ideal body weight prior to surgery to minimise thrombotic and bleeding risks (Grade C).

We suggest that all patients undergoing major surgery should have mechanical thromboprophylaxis, with antiembolic stockings and/or pneumatic compression devices continued postoperatively (Grade 2C).

If the balance of risks favours pharmacological thromboprophylaxis, we suggest 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 0.6-1.0 iu/ml (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 3-5 days, to guide treatment and avoid wide fluctuations in factor levels (Grade 1C).

We recommend that, for major surgery, factor levels of 0.8-1.0 iu/ml should be aimed for and not be allowed to fall below 0.5iu/ml or rise above 1.5iu/ml in the postoperative period (Grade 1B).

We recommend against routine thrombophilia screening for patients with haemophilia undergoing surgery (Grade 1C).
We recommend that patients with VWD undergoing surgery are individually risk assessed for VTE, considering the nature of the surgery and anaesthetic, haemostatic management, age, BMI, thrombotic history, hormone therapy and the presence of malignancy and other high risk comorbidities. (Grade 1C).

We recommend patients treated with factor concentrate in the perioperative and postoperative period should have both FVIII and VWF levels monitored to avoid excessive rise in factor levels and accumulation of FVIII. We recommend checking levels 12 hourly for the first 24 hours after major surgery and daily thereafter (Grade 1B).

We recommend the use of factor concentrate with the highest ratio between VWF:RCo and FVIII:C should be considered, to minimise risk of FVIII accumulation (Grade 1C).

We recommend that for patients with FXI deficiency, bleeding phenotype and risks are carefully assessed, to avoid unnecessary treatment (Grade 1C).

We recommend that use of FXI concentrate is kept to a minimum to avoid increasing the thrombotic risk (Grade 1C).

We recommend that all patients receiving FXI concentrate have mechanical thromboprophylactic measures (Grade 1C) and suggest that they are considered for pharmacological thromboprophylaxis (Grade 2C).

We suggest tranexamic acid alone is useful for patients with mild FXI deficiency but should not be given as haemostatic prophylaxis to patients receiving FXI concentrate (Grade 2C).

We recommend that all patients with FVII deficiency have mechanical thromboprophylactic measures (Grade 1C) and suggest they are considered for pharmacological thromboprophylaxis if they have associated risk factors (Grade 2C).

We recommend careful assessment of bleeding and thrombotic risks and management influenced by the predominant clinical phenotype (Grade 1C).
We suggest that for major surgery, fibrinogen levels should be closely monitored aiming to maintain levels 1-1.5g/l for 10-14 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).

We suggest that in patients with antithrombin deficiency, consideration is given to thrombolytics, initial therapy with heparin and the use of vitamin K antagonists. 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).

We recommend VTE prophylaxis in patients with HIT (GRADE 1C).

We suggest the use of argatroban (followed by a DOAC) for VTE prophylaxis in HIT (GRADE 2C).

We recommend VTE prophylaxis after reversal of oral anticoagulants (GRADE 1C).

Start of VTE prophylaxis may be considered 6 h after reversal or after bleeding stop and continued until resumption of oral anticoagulation (GRADE 2C).

We suggest VTE prophylaxis in patients with acquired haemophilia A or on dual antiplatelet therapy according to thrombotic risk factors (GRADE 2C).

Pharmacological VTE prophylaxis is not suited for replacing antiplatelet activity (GRADE C).

LMWH (at prophylactic doses) is not recommended for bridging DOAC perioperatively (GRADE 2B).

Glomerular filtration rate (eGFR) should be assessed before each DOAC’s initiation, also at least once year or more frequently as needed such as postoperatively before the resumption of therapeutic DOAC administration, when it is suspected that the renal function could decline or deteriorate (Grade 1C).

The use of the CG 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).

We suggest assessing anti-Xa monitoring in patients with renal impairment in order to detect accumulation (Grade 2C).

Urine output should be monitored carefully throughout the perioperative phase and adequate fluid management provided in order to avoid worsening of pre-existing renal failure for patients at risk for postoperative renal impairment (Grade 2C).

Clinical exclusion of signs of postoperative bleeding are more relevant for postponing the commencement of VTE prophylaxis rather than relying on any specific lab 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 G/L) thrombocytopenia (Grade 2C).

Monitoring anti-Xa level may be used to adjust the doses of LMWH in patients with moderate or severe thrombocytopenia (5) (Grade 2C).

In cancer patients or patients with haematological disorders and mild thrombocytopenia (platelet count > 80 G/L, pharmacological prophylaxis may be used; if the platelet count is below 80 G/L, pharmacological prophylaxis may only be considered on a case-by-case basis and careful monitoring is recommended (Grade 2C).

Resuming warfarin therapy should be considered for most patients following resolution of GI bleeding (Grade 1C).
Patients with a high thrombotic risk (e.g. mechanical heart valves) may benefit from resuming warfarin therapy despite ongoing risk for recurrent GI bleeding (Grade 2C).

Patients with a HAS-BLED score lower than the CHADS₂ score may benefit from earlier resuming (Grade 2C).

The delay between major GI bleeding and warfarin resuming should be at least 7 days (Grade 2C).

We suggest International Normalized Ratio at the time of bleeding should be considered to resume anticoagulation (Grade 2C).

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.

We can find no evidence to inform us about the timing and dose of restarting prophylaxis in this group of patients and this merits further studies in this arena.

We suggest International Normalized Ratio at the time of bleeding may also be considered to resume anticoagulation (Grade 2C).

We suggest resuming anticoagulant therapy 12 hours after removal of drains in cases of cardiac tamponade (Grade C).

In patients after major intraoperative bleeding we suggest using mechanical prophylaxis over no prophylaxis early postoperatively (Grade 2C).

When the risk of bleeding diminishes, pharmacologic 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, the full dose anticoagulation may be resumed 48 or 72 hours after the procedure (Grade 2B).

For patients at high risk for 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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