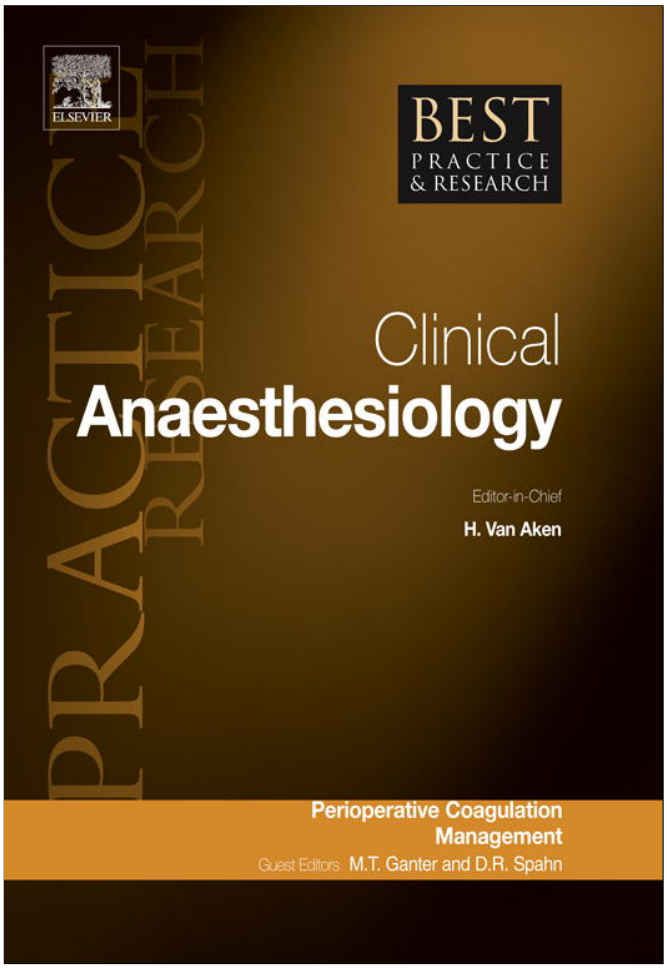

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Hypercoagulability in the perioperative period

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One of the greatest disappointments associated with a successful surgical procedure is a thrombotic or thrombo-embolic complication in the postoperative period. Morbidity and mortality of the perioperative period are related, to a relevant degree, to perioperative thrombo-embolic events. Ranging from simple deep venous thrombosis to pulmonary embolism or arterial thrombosis, this class of complication invariably increases length of hospital stay or may result in mortality. The purpose of this review is to identify the procedures and patient populations noted to have thrombophilia in the postoperative period, link the changes in circulating and *in situ* haematological/biochemical substrates most likely responsible for morbidity, identify the clinical diagnostic modalities that detect recent/impending thrombosis and, lastly, consider the rational therapeutic approaches recommended for minimising postoperative thrombotic complications.

One of the greatest disappointments associated with a successful surgical procedure is a thrombotic or thrombo-embolic complication in the postoperative period. Ranging from simple deep venous thrombosis (DVT) to pulmonary embolism or arterial thrombosis, this class of complication invariably increases the length of hospital stay or may result in mortality. The purpose of this review is to identify the procedures and patient populations noted to have thrombophilia in the postoperative period, link the changes in circulating and *in situ* haematological/biochemical substrates most likely responsible for morbidity, identify the clinical diagnostic modalities that detect recent/impending thrombosis and,

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lastly, consider the rational therapeutic approaches recommended for minimising postoperative thrombotic complications.

Epidemiology of perioperative thrombophilia

Patient and procedural factors

For the purposes of this section, rather than consider the perioperative impact of various inherited thrombophilic disorders (e.g., protein C deficiency and antithrombin deficiency), acquired hypercoagulable disorders are primarily considered. In general, patients who are significantly injured or immobilised are at risk of perioperative thrombotic complications.[1–13] In particular, trauma victims are at significant risk of hypercoagulability based on biochemical (e.g., plasma thrombin–antithrombin complex (TAT) concentration) and thrombelastographic parameters within the first day following injury[1], and may have continued risk of DVT despite prophylaxis.[2–5] Similarly, patients suffering burns are at an increased risk for hypercoagulability and DVT.[6–9] In contrast to trauma and burn victims, healthy patients undergoing orthopaedic procedures acquire postoperative hypercoagulability and thrombophilia[10–13], especially when the lower extremities[11] or shoulder[12] are operated upon. As an additional illustration, patients with solid tumour (e.g., gynaecological or gastrointestinal malignancy) are at risk of hypercoagulability and thrombosis in the perioperative period[14–18], also with thrombelastographic evidence of a prothrombotic state.[16,18] Lastly, as we have recently reported, the introduction of biomaterials exposed to the circulation (e.g., ventricular assist device) can result in hypercoagulability and device thrombo-embolism, in part due to not only enhancement of clot strength[19,20] but also secondary to a systemic hypofibrinolytic state.[20] The biochemical end result in all these scenarios is most likely enhanced regional thrombin generation, clot formation and subsequent propagation, resulting in venous or arterial thrombosis/embolism.

Aetiology and pathogenesis of perioperative thrombophilia

Enhanced thrombin generation

Relative circulatory stasis following immobilisation coupled with tissue injury is likely responsible for enhanced thrombin generation in several of the aforementioned clinical scenarios.[1,6,7,10,13,16] The biochemical evidence of thrombin generation includes an increase in plasma TAT concentration[1,6] with a concordant decrease in antithrombin activity.[6] Further, an increase in plasma D-dimer concentration[6,7,10,13] is also indicative of a recent thrombin burst and consequent thrombus formation. In the setting of cancer, tissue factor can be expressed by tumour cells at the blood–tumour interface, and subsequently release tissue factor-positive microparticles likely responsible for systemic thrombotic events.[19] An increased propensity to generate thrombin is also noted by enhanced onset (reaction time) and speed of clot formation (angle), as determined by thrombelastography.[1,16,20,21] In sum, regional increases in thrombin generation and/or enhancement of procoagulant potential systemically are observed in the perioperative period.

Hyperfibrinogenaemia

As a response to tumour[18], biomaterials[20,21] or surgical injury[22], circulating fibrinogen concentrations increase and significantly enhance clot strength, as determined by thrombelastography. Thus, even in the presence of relatively normal thrombin generation in an area of flow, stasis or tissue injury may result in an increased risk of thrombosis in the setting of hyperfibrinogenaemia, making elevated fibrinogen concentrations a risk factor for thrombosis in the perioperative period.

Thrombocytosis

Following placement of biomaterials such as that in ventricular assist devices[20,21] or after urological surgery[23], the development of thrombocytosis has been associated with hypercoagulability[20,21] or

clinically apparent thrombotic complications.[21,23] As with hyperfibrinogenaemia, a relative excess and/or activation (in the case of ventricular assist devices) of platelets may prime the circulation to respond excessively to normal or even subnormal generation of thrombin in areas of injury, stasis or on the surface of a biomaterial.

Thrombin-dependent and -independent hypofibrinolysis

As we have recently documented, increased activation of thrombin-activatable fibrinolysis inhibitor (TAFI) via contact activation in patients with ventricular assist devices may result in thrombus formation that is more resistant to fibrinolysis than clots formed by the tissue factor-initiated coagulation.[21] Also of interest, in response to device placement and chronic exposure to biomaterials, it appears that some subpopulations may potentially increase circulating α_2-antiplasmin or decrease plasminogen activity, also resulting in a systemic hypofibrinolytic state.[21] Taken as a whole, patients with mechanical circulation are at risk of both excessively fast and strong thrombus formation on the device, as well as at risk of not being able to disintegrate the thrombus formed with normal engagement of endogenous fibrinolytic processes.

Diagnosis of perioperative thrombophilia

The diagnosis of perioperative thrombosis/thrombo-embolism is typically made based on clinical signs of end-organ ischaemia (e.g., myocardial infarction, pulmonary thrombus and decreased oxygenation) coupled with laboratory evidence of tissue injury (e.g., plasma troponin concentration). When specifically implicating important thrombus formation as the underlying cause, such as the case in DVT and pulmonary embolism, increases in circulating compounds associated with either thrombin generation (e.g., plasma TAT complex concentration[1]) or fibrin degradation from an established clot (e.g., plasma D-dimer concentration[6,7,10,13]) are usually present. While controversy may exist concerning which particular biochemical assessment is the gold standard by which to indentify thrombophilia, the unfortunate circumstance remains that the thrombus has already been formed and perhaps has already caused morbidity. Expressed differently, at present, there are only limited methods to define *a priori* if a particular patient is at risk for the prospective development of thrombophilia in the perioperative period. One such modality is thrombelastography/thromboelastometry (for simplicity, referred to as TEG for the remainder of this work), which is subsequently discussed.

While beyond the scope of the present article, the reader is directed to a recent comprehensive review of the devices and methodology of TEG.[31] The information obtained from using a visco-elastic assessment of thrombus formation (and disintegration) is obtained by measuring the changes in resistance between a cup filled with a sample (either whole blood or plasma) and a pin suspended in the sample. Thus, resistance time relationships are determined, which are then used to grade clot formation that varies from slow-growing and weak to quickly forming and strong.[31] Modifications of TEG methodology include the use of commercially available inhibitors of platelet function to determine the role of platelets in clot formation kinetics and final clot strength.[31] Thus, in the most fundamental terms, TEG allows the clinician/investigator to assess when blood begins to clot, how quickly the clot forms, how strong the clot becomes and how quickly and to what extend the thrombus lyses.

When assessing hypercoagulability with TEG, it has been discerned that clot strength (platelet mediated and fibrinogen mediated) is associated most strongly with hypercoagulable states and clinical thrombophilia.[18,20–22,24–30] However, these and other investigations have noted that decreased time to onset of clotting and increased speed of clot formation are also associated with hypercoagulable states and history of thrombophilia.[22,25,26,28,29] It is not surprising that such heterogeneity in TEG data and thrombophilia has been documented, as the biochemical and cellular aetiology of thrombophilic disorders are diverse. For example, one would expect excess circulating tissue factor activity (as in patients with malignancy) to primarily enhance the onset of coagulation, but perhaps not increase final clot strength, as has been previously demonstrated *in vitro*.[32] By contrast, in the setting of mechanical circulation, both marked increases in circulating fibrinogen concentration and platelet activation/thrombocytosis may not markedly diminish the time to onset of coagulation, but rather instead significantly increase the speed of clot formation and final clot strength.[20,21] Thus, the aetiological

diversity of thrombophilia has resulted in different patterns of TEG-based definitions of hypercoagulability, making therapeutic decision making difficult.

As has been recently reviewed[29], TEG has been reported to be 0–100% sensitive and 62–92% specific for predicting postoperative thrombo-embolic complications. The primary problems with using TEG include: (1) no standardisation for the use of activators for specific clinical situations (e.g., tissue factor activation for *in vivo* embolic events and contact activators (kaolin) for biomaterial-associated thrombosis); (2) no well-accepted adoption of the generation of 95% confidence intervals for TEG parameter values from normal subjects with various activators; and (3) no large clinical studies wherein populations at risk for perioperative hypercoagulability and thrombophilia are assessed with TEG using standardised, situation-specific activators to compare patient results to normal 95% confidence interval values. There are also potentially important differences in TEG parameters within the same blood sample, depending on the machine and activator used.[33] Taken as a whole, until a concerted effort is made across institutions to establish a TEG-based database of normal subject values that are consistent with regard to sample type, activator and particular machine, the ability to predict thrombophilia in populations at risk based on TEG-predicated hypercoagulability will be elusive.

Given the aforementioned background concerning the epidemiology, aetiology and biochemical basis for perioperative hypercoagulability and thrombophilia, it is fitting to consider at length pharmacological and mechanical thromboprophylaxis.

Indication for venous thrombo-embolism (VTE) preventive measures

The indication for VTE preventive measures should be evaluated in all patients foreseen to undergo a surgical intervention. Thrombotic risk needs to be balanced against bleeding risk (Table 1).[34] Both of these risks can be evaluated by patient history and in part by laboratory examinations. Prior thrombo-embolic events in the patient and first-degree family members and the presence of known risk factors for VTE are relevant for the correct management. Accepted risk factors for VTE are listed in. VTE occurring in the presence of an acquired risk factor is considered provoked. When VTE occurs in the absence of an acquired risk factor, it is considered idiopathic. Bleeding risk can be related to the patient or to the intervention. Bleeding risk related to the patient should ideally be evaluated using a standardised and validated questionnaire, and that related to the planned intervention can vary from hospital to hospital and should be adjusted to local characteristics.

Indication for preventive measures can be evaluated on an individualised basis using risk assessment models that incorporate the above-mentioned elements. To date, no such model has been

Table 1
VTE risk factors.

Modifiable	Non-modifiable
Surgery	Increasing age
Trauma Immobility (lower extremity parsis)	Sex
Cancer active or occult	Factor V Leiden (RR
Cancer therapy	Prothrombinmutation G20210A
Venous compression	hereditary antithrombin deficiency
Previous VTE	hereditary protein S deficiency
Pregnancy and postpartum period (6 weeks)	hereditary protein C deficiency
Estrogen containing oral contraceptives or hormone replacement	
Selective estrogen receptor modulators	
Erythropoiesis stimulating agents	
Acute medical illness	
Inflammatory bowel disease	
Nephrotic syndrome	
Paroxysmal nocturnal hemoglobinuria	
Obesity	
Central venous catheterization	
Antiphosphopholid antibody syndrome	

Adapted from.[35]

Table 2
Caption should read: Levels of Thromboembolism Risk and Recommended Thromboprophylaxis in Hospitalized Patients. Adapted from [35].

Category	DVT risk in the absence of prophylaxis	Suggested thrombopropyhalxis options
Low risk	<10%	No specific prophylaxis early ambulation
Moderate risk	10–40%	UFH, LMWH, Fondaparinux
High risk	40–80%	UFH, LMWH, Fondaparinux
Med or high AND high bleeding risk	10–80%	Mechanical prophylaxis

formally validated. The American College of Chest Physician guideline (ACCP-GL) 2008 proposes four surgical risk categories and assigns each the appropriate interventional strategy (Table 2).[35]

Modality of VTE prevention

Once the indication for VTE preventive measures has been established, there are two principal modalities to choose from: mechanical VTE prophylaxis and pharmaceutical VTE prophylaxis. Mechanical forms of VTE prophylaxis include intermittent pneumatic compression and compression stockings. This form of VTE prevention is considered generally less efficient than pharmacologic intervention. Mechanical forms can be considered in all risk settings as adjunctive measures; however, cost-efficiency considerations need to be made. ACCP-GL has recommended them only in the high-risk setting with an additional bleeding risk.[35]

Initiation of pharmacologic prophylaxis

Whether to start pharmacologic VTE prophylaxis before or after a surgical intervention has been and still remains a matter of debate.[36] Different strategies have been adopted in different geographic regions and also for different drugs. In North America, VTE prophylaxis is generally initiated post-operatively, while pharmacologic prophylaxis is usually started preoperatively in Europe. The newer drugs including fondaparinux and the direct anti-Xa and direct anti-IIa have received or have requested registration for postoperative initiation.

Agents used for pharmacologic prophylaxis

Agents used for pharmacologic prophylaxis can be categorised according to their mode of action. Indirect anticoagulants inhibit coagulation through an intermediary protein and by themselves do not exert an inhibitory effect on coagulation. Direct anticoagulants bind directly to the active centre of their target, thereby inhibiting the proteolytic activity of serine proteases such as FIIa (thrombin) or FXa (Fig. 1). While indirect anticoagulants such as heparins interact and inhibit free FIIa and free FXa, the newer direct inhibitors interact and inhibit both free and protein-bound coagulation factors.

Indirect anticoagulants

Indirect anticoagulants commonly used in clinical practice include unfractionated heparin (UFH), fractionated forms of heparins called low-molecular-weight heparins (LMWH) and the synthetic pentasaccharide, fondaparinux (Table 3). The active principle common to these drugs is a sequence of five sugars that permits binding to antithrombin (AT) (Fig. 2 and Fig. 3). Only molecules that contain this specific pentasaccharide have an anticoagulant effect. AT is a natural inhibitor of thrombin (FIIa), FXa and some other coagulation factors. *In vivo*, the interaction of AT and an activated coagulation factor is so slow that no biologically relevant anticoagulant effect results. In the presence of heparins or fondaparinux, which have binding sites for both AT and the target coagulation factor, the above-described interaction of AT with the active centre of the target coagulation factor (CF) is accelerated 700-fold. This results in a covalent link being formed between the AT molecule and the active centre

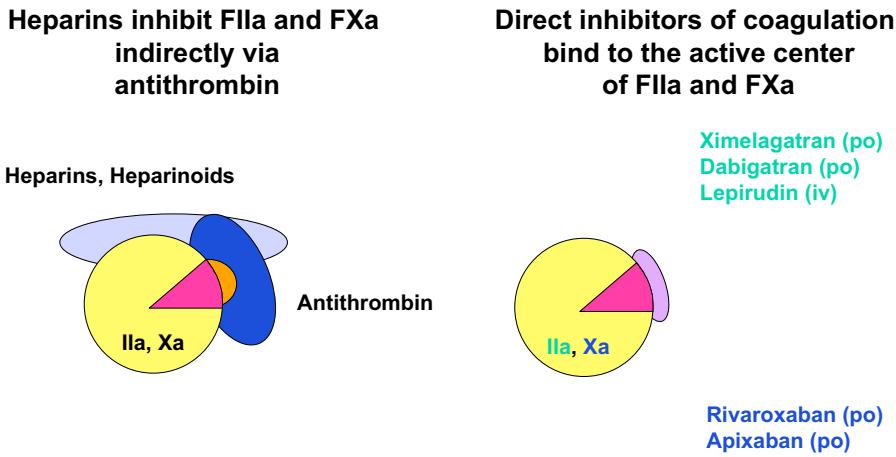

Fig. 1. Indirect and direct inhibitors of coagulation. Heparins (light blue) are indirect inhibitors of coagulation as they do not interact with the active site of the activated coagulation factor (depicted by the red triangle in the yellow circle). In the absence of heparin the physiologic coagulation inhibitor antithrombin (dark blue) and activated coagulation factors IIa or Xa interact only very slowly. This interaction is increased approximately 700-fold in the presence of heparin, which has binding sites for both antithrombin (see pentasaccharide) and the activated coagulation factor.[46] The novel direct inhibitors of factor IIa and factor Xa are small molecules (purple) that are specific for and bind to the active site of their respective target. Rivaroxaban and Dabigatran have FDA or EMEA approval for perioperative prophylaxis in hip and knee surgery. Ximelagatran was withdrawn from the market. For Apixaban phase 3 data has recently been published. Molecules depicted in blue target factor Xa while those in green target factor IIa.

of the CF. The inactive covalently linked AT–CF complex then dissociates away from the indirect coagulation inhibitor, permitting repeated interactions of the inhibitor with free AT and free activated CF. Thrombin exists in a free circulating form and clot-bound forms, where it is commonly associated with fibrinogen and/or fibrin. Indirect coagulation inhibitors only inhibit free thrombin or free FXa, whereas clot- or protein-bound forms are not accessible for inhibition due to the molecule size of the involved (Fig. 3).

Vitamin K antagonists (VKAs) such as warfarin (commonly used in North America), acenocoumarol and phenprocoumon (the latter two are commonly used in Europe) are indirect anticoagulants that exhibit their inhibitory activity, not through interaction with the active site of its target. VKAs modify the membrane-binding domains (the so-called gla domains) of the vitamin-K-dependent proteins (such as FII, FVII, FIX and FX as well as protein C and protein S). VKA inhibit a post-translational modification of these proteins, rendering them less capable or incapable of interacting with activated membranes. Diminished co-localisation of non-post-translationally modified CF, in turn, leads to coagulation inhibition that can be quantitated by the prothrombin time or the international normalised ratio (INR).

Direct anticoagulants

Direct anticoagulants in clinical use today target the active centre of activated CF. Chemical engineering has permitted the design of small molecules capable of efficiently inhibiting specific targets such as thrombin (Dabigatran) and FXa (Rivaroxaban and Apixaban). In contrast to heparins, which only interact with free thrombin or free FXa, the direct inhibitors are capable of inhibiting free and protein-bound activated CF.

Table 3
Overview of indirect anticoagulants.

	UFH	Dalteparine	Tinzaparine	Enoxaparine	Nadroparine	Fondaparinux
MW (kDa)	15 (3–30)	5.6	4.5	4.5	4.3	1.7
antiXa:anti IIa	1:1	2.1:1	1.9:1	2.8:1	2.5–4:1	>100:1
$t_{1/2}$	0.6–1	2.8–3.8	3.4–4.1	3.5–4.1	3.5	17–21
peak (h)	3	2.8–4	3.2	2.7–3.5	3	3

Molecular weight (MW), half life (t1/2), time to peak plasma level after sc injection in hours (peak (h)); data based on manufacturers data.[46,47]

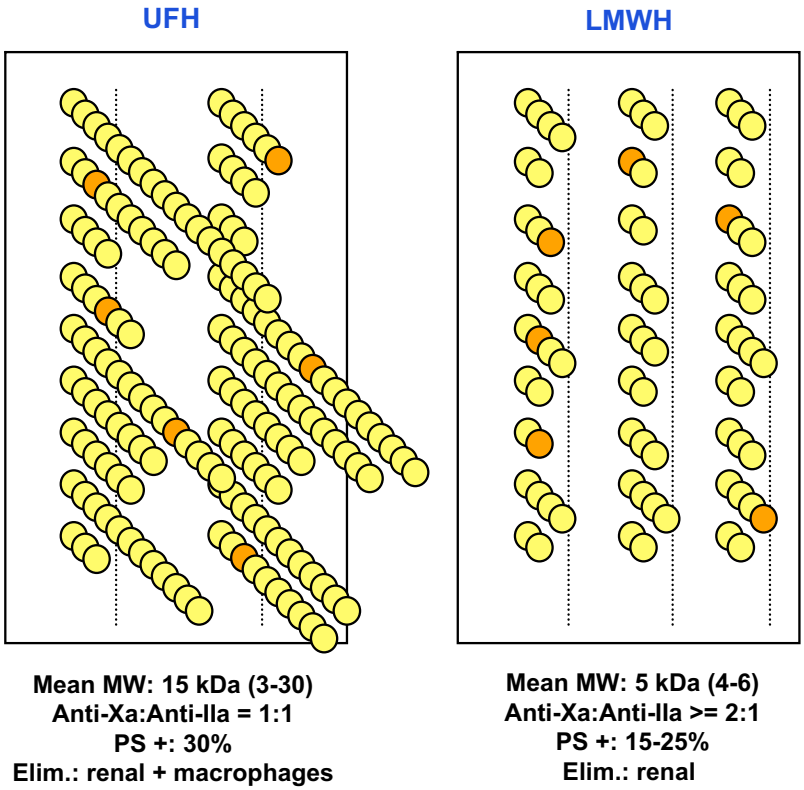

Fig. 2. Unfractionated vs. fractionated heparins. Unfractionated heparins are a mixture of molecules of varying molecular weight. Each yellow or orange circle represent 5 monosaccharid units. The anticoagulant effect of a particular heparin molecule depends on the presence of at least one characteristic pentasacharide sequence (PS) that is capable of interacting with and activating antithrombin. This pentasacharide sequence is depicted in orange. All molecules that do not contain an orange circle thus do not express anticoagulant activity. Molecules of at least 18 monosaccharide units (3–4 circles) are required for heparins to bind to and potentially inhibit factor IIa. Factor Xa inhibition by heparin is not size dependent – both short and long molecules containing the PS sequence will inhibit factor Xa. The ratio of short (<=4 circles) to longer molecules of any heparin preparation determines the ratio of antixa to antiy IIa activity. For unfractionated heparins this ratio is 1: 1, while it is 2–4: 1 for LMWH (2:1 for LMWH with higher mean molecular weights and 4: 1 for LMWH with lower mean molecular weights). Next to the anti Xa to anti IIa ratio molecule size also plays a role in heparin elimination. Heparin preparations with large molecules are cleared both renally as well as by the reticuloendothelial system; small molecules are only cleared renally. Adapted from.[46]

Duration of pharmacologic prophylaxis

In general, perioperative pharmacologic VTE prophylaxis is prescribed for 7–10 days or until the patient has regained full ambulatory status. ACCP-GL give general recommendations for the duration of prophylaxis.[35] The guidelines provided by the SFAR give more detailed information for the various fields and types of surgery.[37]

Operations or contexts associated with a very high or prolonged VTE risk mandate the so-called prolonged prophylaxis. ACCP-GL propose prolonged prophylaxis (>10 days, for up to 35 days) with a grade 1A recommendation for hip-fracture surgery. In patients after neurosurgery, trauma-surgery and neuro-rehabilitation prophylaxis is recommended until discharge or ambulation.[37] There are data suggesting that prolonged prophylaxis (at least 1 month) should be prescribed in patients with major abdominal and pelvic (including cancer) surgery.[38]

Intensity and administration of anticoagulation

There are three levels of anticoagulation that are relevant in this context: no anticoagulation, prophylactic dosing and therapeutic dosing.

No anticoagulation is indicated in the low-risk category, which the ACCP defines by a DVT risk without prophylaxis of <10%. This category includes minor surgery in mobile patients and fully mobile

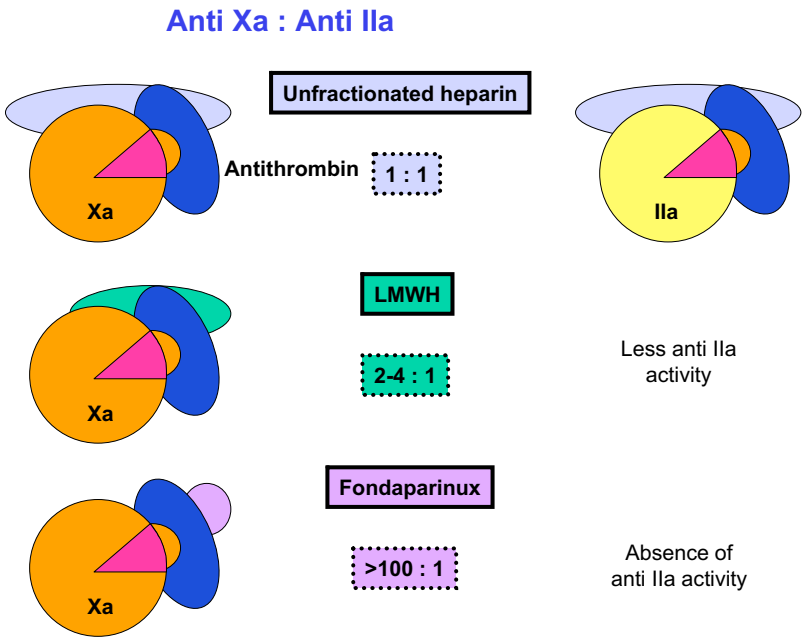

Fig. 3. Anti Xa: anti IIa ratio. Due to the relative abundance of short and long molecules in UFH have a anti Xa to anti IIa ratio of 1:1, while LMWH have reduced relative IIa activity anti Xa: anti IIa = 2–4: 1. Fondaparinux being a pentasacharide only has anti Xa activity. Antithrombin is depicted in blue, UFH in blue, LMWH in green and Fondaparinux in purple.

medical patients. All other patients with the only exception of those with high VTE risk AND high bleeding risk should receive pharmacologic thromboprophylaxis. Pharmacologic thromboprophylaxis is contraindicated in actively bleeding patients, patients with a perceived high bleeding risk or other medical contraindications. In case of contraindication for pharmacologic prophylaxis, mechanical methods of thromboprophylaxis with proven efficacy should be evaluated. The ACCP recommends:

Prophylactic-level anticoagulation

Validated and recommended regimes of prophylactically dosed pharmacologic thromboprophylaxis include the options listed in Table 4.

Therapeutic-level anticoagulation

In the context of VTE prevention, VKAs are indicated in high-risk situations such as hip and knee replacement or hip fracture surgery. For these indications, they need to be prescribed with a target INR of 2.0–3.0. This INR corresponds to a therapeutic level of anticoagulation. Alternatives to VKA in these three indications include LMWH, fondaparinux and new direct anticoagulants. These drugs are prescribed at a 'prophylactic' dosing level and thus discussed above. Low-dose (at a prophylactic level) VKA trials have been performed but, to date, no low-dose regimen has been validated in the perioperative setting.

Table 4
Approved prophylactic regimens for the perioperative setting.

Modality	Dose	AntiXa: Anti IIa	Inhibition
LD–UFH	5000 IU 2–3x/d sc	1:1	Indirect
LMWH	As recommended	2:1: – 4:1	Indirect
Fondaparinux	2.5 mg sc/d	Xa selective	Indirect
Rivaroxaban	10 mg po/d	Xa selective	Direct
Dabigatran	110 or 220 mg po/d	IIa selective	Direct

Bridging anticoagulation

There are also patients who have therapeutic anticoagulation prior to surgery and in whom this degree of anticoagulation needs to maintained or re-established perioperatively. The three most frequent indications for therapeutic anticoagulation affect approximately 1% of the general population. They are VTE, atrial fibrillation and mechanical heart valves. These three, as well as any other indications for therapeutic-level anticoagulation, need to be specifically managed in the perioperative setting. Detailed perioperative bridging strategies[39] go beyond the scope of this review but some general remarks shall suffice. Preoperatively, a thorough evaluation of bleeding risk related to the patient and to the procedure should be performed. Bleeding risk needs to be counterbalanced against thrombotic risk linked to cessation of anticoagulation in the particular patient.

In patients with low personal bleeding risk in whom a procedure with a low bleeding risk is foreseen, one can consider continuing anticoagulation without 'bridging'. Examples of such low bleeding risk procedures include dental extractions or cataract surgery. In patients where bridging (temporal cessation of therapeutic-level anticoagulation) is performed, VKA should be re-initiated postoperatively as soon as possible as they take several days to reach steady-state levels. When VKAs have not raised the INR into the therapeutic range on at least two subsequent samplings, concomitant alternative anticoagulation using UFH or LMWH or another registered anticoagulant is indicated. By the rule of thumb, we do not start UFH or LMWH before 6–12 hours postoperatively. Bleeding is regularly re-assessed postoperatively and anticoagulant therapy only initiated in the absence of active bleeding. Typically – provided active bleeding has been ruled out – a prophylactic dose of either UFH or LMWH is prescribed for the first night. In patients in whom severe renal insufficiency is unlikely to occur, we prefer LMWH over UFH, because of the given dose–response effect and the reduced rate of heparin-induced thrombocytopenia. For LMWH, on day 1 postoperatively, we often prescribe either a prophylactic or half therapeutic dose (depending on the body weight of the patient and bleeding status) twice daily (morning and evening). If no bleeding complications occur by then, we prescribe a single, full-therapeutic dose as of day 2 postoperatively. The main exceptions are patients with mechanical heart valves, in whom twice-daily application of LMWH is absolutely indicated.

Factors influencing dosage of pharmacologic VTE prophylaxis

There are several factors that may influence the dose of pharmacologic VTE prophylaxis, including individualised risk category, body weight or body mass index, renal insufficiency and platelet count.[40]

Low-risk surgical interventions require a lower dose of prophylaxis than moderate- and high-risk interventions. The 2004 ACCP-GL specified the appropriate LMWH as $<$3400 IU for low-risk interventions and $>$3400 for others; the current GL specifies "that clinicians follow the manufacturer suggested dosing guidelines."[35,41]

Clinical studies have reported weights from $>$40 kg up to a maximum reported weight of 196 kg.[42–44] Many studies, however, excluded patients of $>$150–160 kg. There is thus little, if any, evidence for dosing at the extremes of body weight. Most authors agree that body mass index is a better parameter for dose adaptation. For patients with a BMI $>$40, a recent review suggests to increase the VTE prophylactic dose used. The utility and validity of peak antiXa levels are debated; the data regarding target anti-Xa levels are discussed in the monitoring section subsequently.

Renal function may mandate dose adaptations for indirect anticoagulants particularly for LMWHs. The dosing of low-dose UH does not need to be adapted in case of renal failure. The situation is different for LMWHs and particularly for the pentasaccharide, fondaparinux. Larger heparin molecules are cleared both renally and by the reticulo-endothelial system, whereas small heparin molecules are only cleared renally. Thus, they may accumulate depending on severity of renal failure, molecular weight of the heparin in question, dosing and the duration of therapy. Based on a review of the available data, no dose adaptation is proposed for dalteparine and tinzaparine in patients with severe renal failure treated for up to 10 days at prophylactic doses. However, dose adaptation is proposed for the enoxparine b.i.d. regimen (30 mg b.i.d. sc/d) commonly used in North America.[40]

Low platelet count is a further reason to modify or omit pharmacologic VTE prophylaxis. Futhermore, validated data in this domain are rare. In a study where therapeutically dosed LMWH were

investigated, Lee et al. suggested not to give LMWH to patients with platelet counts below 50 G l^{-1}.[43] By analogy, one can postulate that above 50 G l^{-1} level, it is safe to prescribe prophylactically dosed LMWH. For values above 20 and below 50 G l^{-1}, one can consider prophylaxis based on an individualised risk/benefit evaluation. For platelet counts below 20 G l^{-1}, many authors would omit pharmacologic prophylaxis.

Monitoring of prophylactic anticoagulation

Monitoring is necessary when a medication does not have a predictable dose–response effect in individual patients. After a given dose, a test that correlates with the anticoagulant effect of the drug is performed, and the subsequent doses of the medication are prescribed in function of the observed test results. VKAs at therapeutic doses can be monitored using the INR. For therapeutic anticoagulation, target INR classically is 2.0–3.0. Treatment with UH can be monitored using tests sensitive to the inhibitory action on FIIa, such as the activated partial thromboplastin time (aPTT) or the thrombin time. At prophylactic doses, UFH generally does not or only minimally alters PTT and thrombin time. UFH's inhibitory effect on FXa can be assayed using FXa-specific substrates, which when cleaved by FXa generate a cleavage product that absorbs light at a given wavelength. In the presence of heparin these substrates are not cleaved, permitting their absolute quantisation based on the extinction curves.

LMWH, fondaparinux and also the new direct anti-Xa and anti-IIa do not require monitoring as they possess the advantage of having a predictable dose–response effect. Under certain conditions, such as very high or low body weight, renal failure or when re-absorption of the drug is being questioned, one may want to quantitate the circulating levels of the drug in question. For medications with an anti-Xa effect such as LMWH, fondaparinux and oral anti-Xa, the anti-Xa activity is an adequate approach. Data regarding target anti-Xa levels, for instance, for LMWH is scarce. The ACCP-GL do not give target levels. Based on individually different anti-Xa:anti-IIa ratios of the different LMWH on the market, each LMWH will have its own target range. The Nutescu paper summarises published data and gives a target anti-Xa of 0.001–0.25 for moderate-risk patients (2500 IU dalteparine) and 0.2–0.5 for high-risk patients treated with dalteparine 5000 IU and 0.5–1.2 for patients receiving exoxaparine 30 mg b.i.d.[40] The drugs' manufacturers can further provide data from the phase II and phase III trials that were performed.

Subcutaneously (sc) applied anticoagulants, in general, share one common time-to-peak levels. For UFH, LMWH and fondaprinux applied sc, peak levels are reached after 3–5 h. At our institution, the peak levels are measured uniformly at 4 h after application. ICU patients deserve special consideration as diminished cutaneous circulation (induced by concomitant catecholamine treatment) or generalised oedema may retard or abolish re-adsorption of sc applied anticoagulants.[45]

Research agenda

- Perioperative hypercoagulability and thrombophilia are important clinical problems, significantly contributing to the cost of health care as well as adding to patient morbidity and mortality.
- Future investigation must focus on improving the capacity to prospectively identify patients at risk with presently available conventional and visco-elastic measures of haemostasis and fibrinolytic resistance.
- This goal can be achieved by continued innovation with regard to both modifications of methods such as TEG (e.g., identification of excess tissue factor) and the establishment of perioperative database registries of patient populations at risk using standardised methods such as TEG.
- Lastly, using this paradigm, rational therapeutic interventions can be employed, with ongoing clinical and laboratory surveillance either supporting or refuting the efficacy of a particular mechanical/pharmacological strategy to decrease perioperative hypercoagulability/thrombophilia.

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