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REVIEW ARTICLE

Updates in perioperative coagulation: physiology and management of thromboembolism and haemorrhage

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Understanding of blood coagulation has evolved significantly in recent years. Both new coagulation proteins and inhibitors have been found and new interactions among previously known components of the coagulation system have been discovered. This increased knowledge has led to the development of various new diagnostic coagulation tests and promising antithrombotic and haemostatic drugs. Several such agents are currently being introduced into clinical medicine for both the treatment or prophylaxis of thromboembolic disease and for the treatment of bleeding. This review aims to elucidate these new concepts and to outline some consequences for clinical anaesthesia and perioperative medicine.

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The coagulation system: new aspects

The coagulation system is considered by many clinicians to consist just of platelets and clotting factors. For some time, however, it has been recognized that many more cellular and molecular components participate in the coagulation process, thereby forming a multifaceted, well-balanced system called haemostasis. Moreover, the coagulation system is not only made for forming clots but is also involved in a variety of defence systems, including tissue repair, defence against micro-organisms, autoimmune processes, arteriosclerosis, tumour growth and metastasis. The main cellular components of the coagulation systems are platelets, endothelial cells, monocytes and erythrocytes, and the main molecular components are the coagulation factors and inhibitors, fibrinolysis factors and inhibitors, adhesive proteins (e.g. von Willebrand factor, vWF), intercellular proteins, acute-phase proteins, immunoglobulins, calcium ions, phospholipids, prostaglandins and certain cytokines.

Despite this significant diversification, the coagulation proteins are the core components of the haemostatic system, forming a complex interplay that is still not entirely understood. Whereas the classic separation of the coagulation pathway into the extrinsic pathway (initiated by tissue factor) and intrinsic pathway (initiated by contact activation) still has certain validity, the newer time-based structuring provides a much more authentic description of the coagulation process.[25] This involves the following steps (Fig. 1).

(i) Initiation. Tissue factor (TF) expressed by the damaged vascular bed binds FVIIa (which circulates in small quantities), which then triggers coagulation by activating FIX to FIXa and FX to FXa. FXa then binds very rapidly to FII, producing small amounts of thrombin (FIIa). In a much slower reaction, FIXa binds to and activates FX to FXa (3 in Fig. 1). Most coagulation processes *in vivo* are considered to be initiated by tissue factor, whereas the clinical significance of the contact activation (activation of FXII) is still not yet entirely clear. A recent report, however, has shown that RNA from disrupted cells may be the long-sought FXII activator *in vivo*.[72]

(ii) Amplification. Because the amount of thrombin generated at this stage is still too small to activate fibrinogen to fibrin, there are several feedback amplification mechanisms. First, generation of FVIIa is increased by activation of FVII bound to tissue factor by FVIIa, FIXa and FXa. Thrombin then activates the non-enzymatic cofactors FV and FVIII, which accelerate the activation of FII by FXa and of FXa by FIXa, respectively. In a further feedback loop (2 in Fig. 1), thrombin also activates FXI to FXIa, increasing the generation of FIXa.

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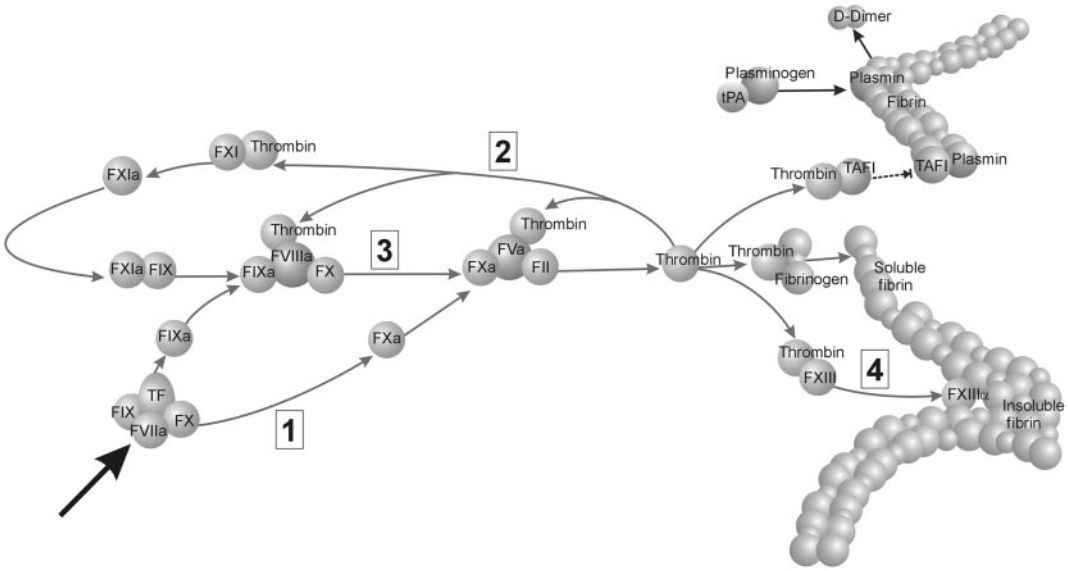

Fig 1 Current model of coagulation and fibrinolysis. *In vivo* the coagulation process is initiated mainly by FVIIa bound to tissue factor (TF; large black arrow), which then activates both FX (1) and FIX (2) (=initiation phase). To increase thrombin generation further, thrombin activates FV, FVIII and FXI in a feedback-loop (3) (=amplification). Continuation of thrombin generation results mainly from the ongoing generation of FXa by FIXa and FVIIIa (=propagation). Maximum thrombin generation occurs only after the formation of fibrin, leading to the formation of FXIIIa, which then crosslinks the fibrin monomers (4) (=stabilization).

(iii) Propagation. To maintain continuous thrombin generation, ensuring the formation of a sufficiently large clot, large amounts of FXa are produced by the activation of FX by FIXa and FVIIIa (intrinsic tenase complex). FIXa stems primarily from the activation of FIX by the FVIIa/TF–complex.

(iv) Stabilization. Maximum thrombin generation occurs after the formation of fibrin monomers. Only then is the amount of thrombin high enough to activate FXIII, a transglutaminase, which then cross-links the soluble fibrin monomers to a stable fibrin meshwork. In addition, thrombin then activates the thrombin-activatable-fibrinolysis-inhibitor (TAFI) that protects the clot from fibrinolytic attack.

Surgical procedures often unbalance this elaborate system, leading to a tendency to either thrombosis or bleeding. Besides the operative intervention itself and many well-known clinical risk factors, including immobility, infections, cancer and drugs, there are various other perioperative factors that are increasingly being demonstrated to interfere with the coagulation system, such as hypothermia,[56] metabolic acidosis,[26] volume expanders[49] and extracorporeal circulation.[8] Such perturbation of coagulation can be assessed by various laboratory assays. For example, during the first several hours after surgery there are marked increases in tissue factor, tissue plasminogen activator, plasminogen activator inhibitor-1 (PAI-1) and vWF, leading to a hypercoagulable and hypofibrinolytic state, as evidenced by increased generation of coagulation activation markers, such as thrombin–antithrombin complexes, fibrinopeptide A and many others.[52 57] The levels of these mediators are known to fluctuate rapidly and their degree of perturbation is dependent not only on the type, degree and duration of surgery, but also on the timing of blood collection.

Perioperative thromboembolism

Who needs thromboprophylaxis?

Surgical patients are at risk of developing venous thromboembolism. It is, however, important to recognize that there exist both definable operative procedures and definable groups of patients with significantly higher than normal rates of postoperative thromboembolism. For instance, it has been shown that, without prophylaxis, the incidence of deep vein thrombosis (DVT) is about 14% in gynaecological surgery, 22% in neurosurgery, 26% in abdominal surgery and 45–60% in orthopaedic surgery. In patients with malignancy these rates are markedly higher.[7] Furthermore, as shown in Table 1, there are numerous patient-specific risk factors that also influence the individual risk of thrombosis.

Yet, despite this knowledge and the availability of effective prophylactic methods and consensus guidelines, thromboembolism remains an important problem in surgery. One reason is the low level of implementation of prophylaxis among many clinicians. In several surveys it has been demonstrated that there is still considerable under-use of thromboprophylaxis, because of lack of awareness of the problem of thromboembolism combined with fears of bleeding complications and scepticism about the cost-effectiveness of thromboprophylaxis.[5 14] Decisions about the need for prophylaxis are, as indicated above, further complicated by the wide variation in the risk of thromboembolism according to

Table 1 Patient-specific risk factors influencing the perioperative risk of thrombosis

Clinical risk factors	Drugs	Inherited thrombophilia	Acquired thrombophilia
History of thromboembolism	Oral contraceptives	Activated protein C resistance (FV Leiden mutation)	Antiphospholipid antibody syndrome
Malignancy	Hormone replacement therapy	Prothrombin gene mutation G20210A	Sustained elevated FVIII levels
Age >40 yr		Antithrombin deficiency	
Obesity		Protein C deficiency	
Varicose veins		Protein S deficiency	
Prolonged immobilization		Hyperhomocysteinaemia	
Dehydration			
Heart failure			
Nephrotic syndrome			
Stroke			
Myeloproliferative syndrome			
Behçet's disease			
Pregnancy, puerperium			

Table 2 Risk assessment model (RAM) from the American College of Chest Physicians. Adapted from Samama[88]

Low risk	Moderate risk	High risk	Very high risk
Uncomplicated minor surgery in patients <40 yr with no clinical risk factors	Major and minor surgery in patients 40–60 yr with no clinical risk factors	Major surgery in patients >40 yr who have additional risk factors	Major surgery in patients >40 yr plus previous venous thromboembolic or malignant disease or hypercoagulable state
	Major surgery in patients <40 yr with no additional risk factors		Elective major orthopaedic surgery or hip fracture or stroke or spinal cord injury or multiple trauma
	Minor surgery in patients with risk factors		

the type of operation and patient-specific risk factors.[51] To overcome this problem, a number of risk assessment models (RAMs) have been created to assist physicians in making decisions about whether prophylaxis is needed and which type is required.[20 73 88] An example of an RAM, published by the American College of Chest Physicians,[20] is given in Table 2. Although RAMs have their limitations, such as the lack of extensive validation in various surgical settings and the fact that patients sometimes cannot be categorized, there are many advantages that outweigh these limitations. The major advantages of RAMs are: (i) risk stratification is less likely to be forgotten in the daily routine if each patient has to be categorized before surgery; (ii) important risk factors are more often checked if the physician can follow a checklist; (iii) thromboprophylaxis is less physician-dependent within departments; and (iv) thromboprophylaxis is less under- or overused.

Based on our experience, RAMs can be easily implemented in daily routine and, in addition to the above-mentioned advantages, they produce greater awareness and more discussion about thromboprophylaxis and a greater sense of security among anaesthetists and surgeons.

Antithrombotic regimens

Low-molecular weight heparin (LMWH) is the gold standard in surgical thromboprophylaxis. As has been shown in a direct comparison of several studies using different prophylaxis regimens in hip replacement patients, LMWH, hirudin and adjusted-dose unfractionated heparin (UFH) led to the highest risk reduction.[20] Whereas hirudin is associated with an unacceptably high rate of bleeding complications and adjusted-dose UFH is laborious and requires more than one injection per day (or an infusion), LMWH has no such disadvantage and is easy to use as a once-per-day injection without the necessity of monitoring. It is notable that the greatest reduction in the risk of thrombosis has been found in patients with high-risk operations and/or important personal risk factors.[60 61] Although the currently available LMWHs, including certoparin, dalteparin, enoxaparin, nadroparin, tinzaparin and reviparin, differ in their pharmacokinetic properties, there is no evidence so far that any one of these products offers more or less protection from thromboembolism. In addition, none of the different LMWHs has been found to be especially useful or disadvantageous for specific patient groups (e.g. renal or liver insufficiency, heparin-induced thrombocytopenia) despite the different pharmacology of the various LMWHs.

There are at least three prophylactic LMWH regimens in use in patients undergoing high-risk operations (Table 3).[33] In Europe, prophylaxis is traditionally started 12 h before surgery, whereas in North America it is initiated 12–48 h after surgery. The third regimen starts prophylaxis either more than 12 h before or 12 h after surgery. LMWH prophylaxis

Table 3 Current established LMWH regimens for perioperative thromboprophylaxis. *Where no regimen is shown, the corresponding indication has not been specifically tested with the corresponding LMWH. Usually, the regimen stated under general surgery is then used

	Dalteparin	**Enoxaparin**	**Nadroparin**	**Tinzaparin**	**Certoparin**	**Danaparoid**
General surgery (moderate risk)	2500 U s.c. 1–2 h preop and once daily postop	20 mg s.c. 1–2 h preop and once daily postop	2850 U s.c. 2–4 h preop and once daily postop	3500 U s.c. 2 h preop and once daily postop	3000 U s.c. 1–2 h preop and once daily postop	*
General surgery (high risk)	5000 U s.c. 8–12 h preop and once daily postop	40 mg s.c. 1–2 h preop and once daily postop or 30 mg s.c. every 12 h starting 8–12 h postop	*	*	*	750 U s.c. 1–4 h preop and every 12 h postop
Orthopaedic surgery	5000 U s.c. 8–12 h preop and once daily 12–24 h postop or 2500 U s.c. 6–8 h postop, then 5000 U s.c. once daily	40 mg s.c. 1–2 h preop and once daily postop or 30 mg s.c. every 12 h starting 8–12 h postop	38 U kg^{-1} s.c. 12 h preop and once daily on postop days 1, 2, and 3; then increase to 57 U kg^{-1} s.c. once daily	4500 U s.c. 12 h preop and once daily postop or 75 U kg^{-1} s.c. once daily starting 12–24 h postop	*	750 U s.c. 1–4 h preop and every 12 h postop
Major trauma	*	30 mg s.c. every 12 h starting 12–36 h after injury if haemostatically stable	*	*	*	*
Acute spinal injury	*	30 mg s.c. every 12 h	*	*	*	*

s.c.=subcutaneous.

is started before surgery on the basis of previous observations that surgical interventions led to activation of coagulation, probably promoting the generation of thrombi.[21] Unfortunately, the optimal regimen is uncertain because direct comparisons between these regimens with sufficiently large sample sizes are not available. A recent analysis of pooled data from several studies using either pre- or postoperative prophylaxis, however, has shown that there is no convincing evidence that starting prophylaxis before surgery is associated with a lower incidence of venous thromboembolism than starting after surgery.[100]

An increasing body of literature, generally examining hip replacement patients as a risk model, shows a significant incidence of DVT developing only weeks after hospital discharge.[77] In particular, a recent epidemiological study of 19 586 patients with hip arthroplasty has shown that 76% of patients suffering from symptomatic thrombosis experienced these events only after hospital discharge (median time 17 days).[110] Whereas the overall frequency of symptomatic thromboses was 2.8%, the rate of venographic thromboses found in intervention studies is as high as 20%. With regard to possible complications, such as pulmonary embolism and post-thrombotic syndrome, asymptomatic thrombosis can be considered to be clinically significant. However, whether extended thromboprophylaxis should be given to all patients routinely after high-risk surgery is still a matter of debate. Results of several studies using LMWH for 4–6 weeks after major orthopaedic surgery have shown that the rate of venographic thromboses can be reduced by more than 50%.[77 110] Coumarins, though cheaper, do not seem to offer the same degree of protection.[16 91] Results of a recent systematic review of all available studies supported the need for extended out-of-hospital prophylaxis in patients undergoing arthroplasty surgery.[46] It should be noted, however, that the true benefit of treating asymptomatic, venographic thromboses is not yet clear and data about cost-effectiveness are still lacking.

New antithrombotic drugs

There are many new anticoagulant drugs under investigation that target novel sites in the coagulation pathway, including tissue-factor/FVIIa, FVa and FVIIIa, FIXa, FXa, FXIIIa, PAI-1 and thrombin.[108] Only a few of them, however, have recently entered or will soon enter the market. One such new anticoagulant is fondaparinux (Arixtra®), a synthetic molecule that is structurally and functionally like heparin, consisting of five saccharide units (pentasaccharide). Like heparin, it binds and activates antithrombin but inhibits only FXa and not thrombin.[19] Fondaparinux is being tested extensively in large phase 3 trials in patients undergoing major orthopaedic surgery. These trials have revealed that fondaparinux 2.5 mg once daily, starting 6 h after surgery, gives a clear benefit compared with enoxaparin.[103] In particular, the overall incidence of venous thromboembolism up to day 11 was reduced from 13.7% (371 of 2703 patients) in the enoxaparin group to 6.8% (182 of 2682 patients) in the fondaparinux group, with a common odds reduction of 55.2% in favour of fondaparinux. It should be noted that in some studies the postoperative interval before starting with the first dose was considerably different between the enoxaparin and fondaparinux groups (12–24 *vs* 6 h). In addition, although the endpoints of these studies were venographic thromboses, there was no benefit of fondaparinux over enoxaparin with regard to the frequency of symptomatic DVT. It will be interesting to see the results of studies using fondaparinux for other prophylactic indications.

Another new anticoagulant agent is melagatran (Exanta®), a non-covalent, synthetic, direct thrombin inhibitor. Interestingly, it is also available in an oral preparation (ximelagatran) with very predictable and reproducible pharmacokinetic and pharmacodynamic profiles.[53] Besides oral administration, melagatran has a number of benefits, including rapid onset of action, lack of drug–food interactions, and no requirement for routine blood coagulation monitoring. Both drug forms have been tested in two large trials as prophylactic treatment in major orthopaedic surgery.[27 29] In one study, melagatran was tested against dalteparin (both drugs given before surgery followed by ximelagatran), while in the other study ximelagatran was tested against warfarin (both started after surgery). The studies concluded that both regimens (subcutaneous melagatran followed by oral ximelagatran and oral ximelagatran alone) were safe, well tolerated and as effective as the other regimen tested. Although registration of (xi)melagatran has already been filed in several countries, some open questions need to be clarified. For instance, there is at present no drug available to antagonize the effect of melagatran. Furthermore, the prothrombin time (PT) does not seem to be an adequate test to measure melagatran activity (if necessary), as the same melagatran concentration has been found to be associated with widely varying PT/international normalized ratio (INR) results depending on the specific assay used.[68]

Thromboprophylaxis in patients undergoing regional anaesthesia

Neuraxial anaesthesia and analgesia provide excellent postoperative analgesia and allow early mobility after major surgery.[9 44 76 84] In addition, there is a considerable group of patients who wish to stay awake during surgery. Epidural anaesthesia and analgesia are therefore used frequently in many centres, although a true outcome benefit in terms of mortality or major organ dysfunction could not be confirmed in two recent large-scale prospective randomized studies, with the exception of reduced pulmonary complications.[76 84]

The most feared complication of neuraxial anaesthesia is epidural haematoma, which has potentially devastating neurological complications. As more and more patients are treated with drugs interfering with blood coagulation or platelet function, the anaesthetist is frequently faced

with the problem of whether neuraxial anaesthesia is still an option or whether such co-medication means it is contraindicated (Table 4). Several US and European societies have issued guidelines on locoregional anaesthesia in patients treated with heparin, oral anticoagulation, drugs interfering with platelet function, and other drugs used for thromboprophylaxis.[35 44 89]

These guidelines are similar[9 35 44] in the following respects:

Admitting that data are incomplete and, in the case of the newer antiplatelet and antithrombotic drugs, virtually non-existent. This applies equally to drug combinations.

Regarding the risk of epidural haematoma during placement and removal of an epidural catheter to be similar and therefore applying the same rules.

Considering the risk of peripheral nerve and plexus blocks to be smaller than the risk of epidural analgesia.

Suggesting the use of low concentrations of local anaesthetics in combination with opioids (and epinephrine).

Monitoring the patient after surgery to detect paralysis suggestive of an early epidural haematoma.

Not discussing whether stopping antiplatelet or anticoagulation therapy is advisable just to allow neuraxial anaesthesia or analgesia to be instituted, given the fact that stopping such therapy *per se* may result in major complications,[22 48 89] possibly linked to postoperative hypercoagulability.[43 90]

Reproducing and commenting on these guidelines is beyond the scope of this review, but the essential aspects are summarized in Table 5. Many centres have established local guidelines pending evidence-based national guidelines (particularly regarding issues not fully covered, such as drug combinations, including the addition of heparin to antiplatelet drug therapy).

Table 4 Contraindications to neuraxial anaesthesia and analgesia. *As most PT reagents are very sensitive to FVII deficiency, the INR is often determined by the FVII level. Therefore, the cut-off level of the INR that constitutes a contraindication for neuraxial anaesthesia can vary according to whether the course of the INR is increasing or decreasing. If the INR is increasing, the cut-off level would be INR>1.5 (FVII levels are mostly about 40%). If the INR is decreasing (e.g. after ceasing coumarin therapy), the cut-off level would be INR>1.2

Prothrombin time (PT)	INR>1.5*
APTT	>40 s
Platelet count	<50 000 μl^{-1}

Management of patients on oral anticoagulants

Perioperative management of patients on regular oral anticoagulants is guided by the risk of thromboembolism and the bleeding associated with different anticoagulant strategies. While the risk of haemorrhage depends mainly on the site and type of surgery, the risk of thromboembolism depends on the indication for regular oral anticoagulation (arterial or venous prophylaxis), how long ago the patient had a thrombosis, and on the type of surgery.[55] Based on these variables, the

Table 5 Precautions for neuraxial anaesthesia or analgesia in patients taking anticoagulant drugs. Recommended minimum delay between last dose and placement or removal of epidural catheter and minimum delay after placement or removal of epidural catheter and subsequent dosing of the drug (modified according to references 33, 38, 105 and 106). The first number represents these authors' recommendations; recommendations also found in the literature are in parentheses. *With the twice-daily US dosing regimen, the first dose is usually given 12–24 h after surgery, and removal of the epidural catheter is recommended before initiation of thromboprophylaxis. If the epidural catheter is left in place during thromboprophylaxis with the twice-daily low molecular weight heparin dose, a 24-h delay between the last heparin dose and removal of the epidural catheter is recommended.[105] **Combination with other drugs influencing the coagulation system including prophylactic heparin may be dangerous[38]

	Minimum delay between last dose and placement or removal of epidural catheter	Minimum delay after placement or removal of epidural catheter and subsequent dosing
Heparin		
Unfractionated heparin	4 h (2–4 h)	1 h (0.5–1 h)
Low molecular weight heparin	12 h (10–12 h)*	4 h (2–12 h)
ADP receptor antagonists		
Clopidrogel (Plavix®)	⩾7 days (7 to >7 days)	Immediately
Ticlopidin (Ticlid®) (no longer on the market)	⩾10 days (10–14 days)	Immediately
COX inhibitors		
Non-selective, NSAIDs	0 day (0–2 days)**	Immediately
COX-2-selective (Rofecoxib, Vioxx®; Celecoxib, Celebrex®)	0 day (0 day)	Immediately
GPIIb/IIIa antagonists		
Abciximab (ReoPro®)	2 days (contraindicated)	4 h (2–4 h)
Tirofiban (Aggrastat®)	1 day (contraindicated)	4 h (2–4 h)
Eptifibatid (Integrilin®)	1 day (contraindicated)	4 h (2–4 h)
Vitamin K antagonists	(See Table 4)	Immediately
Aspirin (60–325 mg/day)	0 day (0–2 days)**	Immediately
Fondaparinux (Arixtra®)	No epidural catheter recommended (not recommended to 24 h)	No epidural catheter recommended (not recommended to 6 h)
Melagatran, ximelagatran (Exanta®)	12 h (8–10 h)	4 h (2–4 h)

physician needs to determine for each patient the length of the perioperative anticoagulant-free window and the indication, type and dose of an alternative anticoagulant given after discontinuing and before resuming oral anticoagulation. Principally, in patients at high risk of thromboembolism, the anticoagulant-free window should be as short as possible, and during the time from stopping them to resuming coumarins an alternative anticoagulant should be given at a therapeutic or high prophylactic dose. In this situation, intravenous UFH is most useful as it can be given up to 2–4 h before surgery, can be easily monitored, and can be restarted soon after surgery with slowly increasing doses. LMWHs are less useful because of their long half-life and the limited possibility of antagonizing their anticoagulant effect. In patients at low risk of thromboembolism, the oral anticoagulant-free window can be longer and an alternative anticoagulant, if necessary at all, can be given in prophylactic doses.[54] In these cases, LMWHs may be preferred. Classification of patients into groups at high and low risk of thromboembolism, as shown in Table 6, is based mainly on the chronic, not necessarily perioperative, risk of recurrence, and is thus somewhat arbitrary.

There is no strict rule as to when coumarins should be stopped before surgery, as this decision depends on several factors, including the degree of anticoagulation, the type of coumarin, the indication, the time between hospital admission and surgery, and whether UFH can be administered intravenously. Spontaneous normalization of the INR takes about 4 days before surgery in patients with an INR between 2 and 3 who are taking warfarin.[109] Vitamin K takes at least 24 h to fully antagonize oral anticoagulation. If urgent reversal of oral anticoagulation is needed, treatment includes infusion of fresh frozen plasma (FFP) or prothrombin complex concentrate. With both FFP and prothrombin complex concentrate, elevated INR values can be lowered within minutes. Prothrombin complex concentrate, however, is increasingly being used because the effect is more reliable and less volume overload occurs than with FFP.[66] A recent report has shown that recombinant, activated FVIIa (rFVIIa; NovoSeven®) can also lower INR values quickly and effectively.[96] This treatment, however, should be considered only if severe bleeding occurs.

Perioperative haemorrhage

Predictability of bleeding

Some bleeding is due to insufficient or ineffective local surgical haemostasis and a certain percentage of procedures are accompanied by a degree of haemorrhage that is deemed to be excessive. In a large meta-analysis of more than 50 studies of DVT prophylaxis with heparin, it was noted that among the 7486 controls given placebo, 3.3% were considered to have bled excessively and that 0.1% died as a result of haemorrhage.[23] Is it possible to identify such patients before surgery? Even in the 1980s, several studies had clearly demonstrated that no coagulation test, including PT, aPTT and bleeding time, is capable of providing this information.[85 102] Newer studies have substantiated these findings.[92] New test systems, such as the platelet function analyser PFA-100, which tests the adhesion and aggregation capability of platelets in flowing whole blood, are of limited value in predicting bleeding. Two recent studies found no significant correlation between the calculated intra- and postoperative blood loss and PFA-100 values in patients undergoing cardiac surgery.[28 59] Somewhat better performance was found for thrombelastography, with a negative predictive value for postoperative bleeding after cardiac surgery of >80%, particularly when it was combined with PFA-100 measurements.[15] In particular, the angle alpha was the best predictor and, in combination with the adenosine diphosphate PFA test, the predictive accuracy was further increased, although the positive predictive value was small (41%). The best method to determine haemorrhagic risk with surgery is an adequate history and physical examination. This important message is based on several large trials

Table 6 Recommended management of patients on regular oral anticoagulants

	Risk factors	Regimen
Low risk	No history of thromboembolism. Last venous thromboembolic episode >3 months. Last arterial thromboembolic event >1 month. Mechanical heart valve without previous thromboembolic event. No permanent patient-specific risk factors (e.g. cancer, thrombophilia, immobilization etc.)	*Preoperative*. Stop coumarins 3–5 days before surgery. If INR<2 start LMWH or UFH at prophylactic doses until surgery (time between last heparin injection and surgery depends on dose and type of heparin) *Postoperative*. Give LMWH or UFH starting 12–24 h after surgery at prophylactic doses until INR>2. Start coumarins within 24–48 h after surgery
High risk	Last venous thromboembolic episode <3 months. Last arterial thromboembolic event <1 month. Mechanical heart valve with previous thromboembolic events. Atrial fibrillation. Permanent patient-specific risk factors (e.g. cancer, thrombophilia, immobilization etc.)	*Preoperative.* Stop coumarins 3–5 days before surgery. If INR<2 start UFH i.v. at therapeutic doses until 4–6 h before surgery. Alternatively, LMWH can be given at therapeutic doses; last injection must be ⩾24 h before surgery *Postoperative*. 8–12 h after surgery start UFH i.v. (or LMWH s.c.) at increasing doses until therapeutic level is reached, continue until INR>2. Start coumarins within 24–48 h after surgery

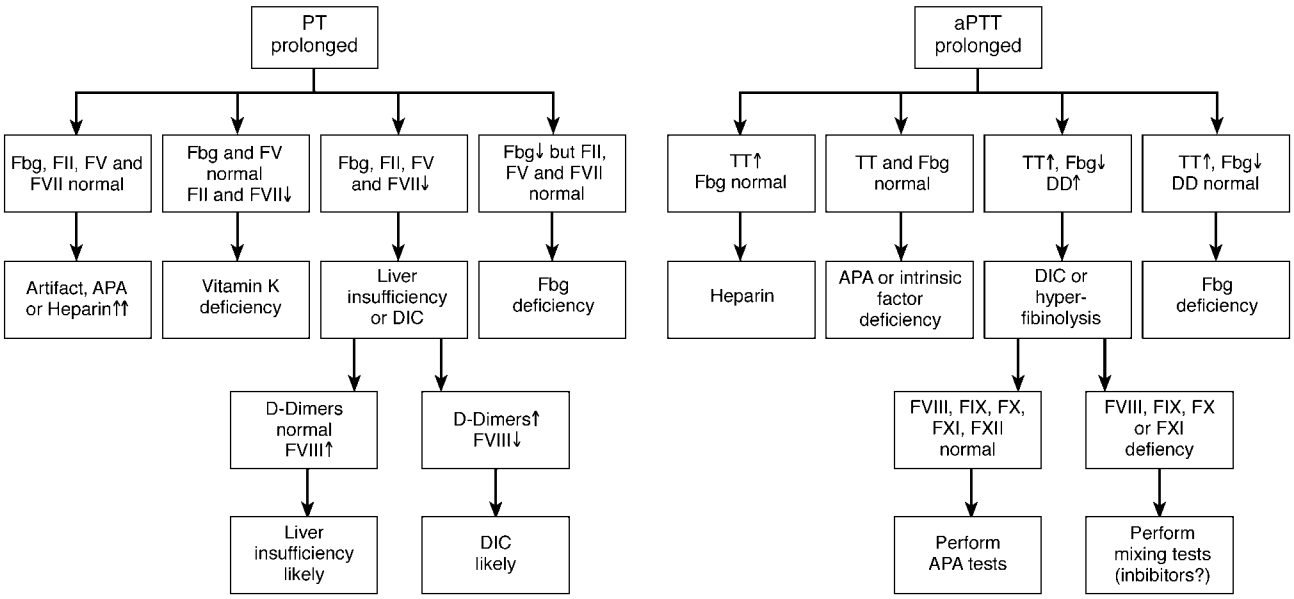

Fig 2 Laboratory evaluation of a prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT). Antiphospholipid antibody (APA) tests, as mentioned in the aPTT tree, may include lupus anticoagulants, anticardiolipin antibodies and anti-β_2-GPI antibodies. Clotting mixing tests are performed to detect acquired neutralizing antibodies (inhibitors) to single coagulation factors. DD=D-dimers; DIC=disseminated intravascular coagulation; Fbg=fibrinogen; TT=thrombin time.

showing that patients with a definite or suspicious history of bleeding are more likely to bleed during surgery than patients with a negative history.[23 45 92] However, the bleeding history may be misleading in patients who have never been exposed to surgery or trauma, or if the interviewer fails to ask the appropriate questions.

Nevertheless, preoperative laboratory testing, including PT, aPTT, platelet count and even larger batteries of tests, have become routine in most institutions. The physician's sense of security and the perceived protection from legal liability may be the driving forces. As a substantial percentage of all unexpected abnormalities detected by preoperative laboratory tests are ignored, liability would be even greater in such cases.[37 92] Thus, despite the importance of a bleeding history, the ideal strategy in predicting perioperative haemorrhage using coagulation tests remains unknown.

Assessment of the bleeding patient

Surgery or major trauma is the ultimate test of the haemostatic system. Patients who have never bled to any significant degree can bleed excessively during surgery. Rapid and appropriate diagnostics to detect a possible underlying haemostatic defect, either inherited or acquired, are of pre-eminent importance. A haemostatic defect should always be considered if bleeding occurs simultaneously at multiple sites, presents as slow oozing from a non-identifiable source, or is delayed after initially adequate haemostasis. Bleeding from a single site or sudden onset of massive bleeding is probably due to a local structural defect. Assessment of a patient with a suspected coagulation defect should always include a thorough re-evaluation of his or her history, determination of any drugs given before surgery, including crystalloids, colloids and blood products, and a physical examination to determine the type and location of the bleeding. Initial laboratory evaluation should cover the entire range of possible coagulation defects, including clotting factor deficiencies, thrombocytopenia (and if possible thrombocytopathia), hyperfibrinolysis, and disseminated intravascular coagulation (DIC). Figure 2 gives a brief overview of how to proceed if prolongation of either the PT or aPTT occurs.

Transfusion therapy: evidence and guidelines

Transfusion of blood products is associated with various risks.[1 39 97] Restricted use is therefore advisable[39] but under-transfusion also needs to be avoided.[105] Guidelines have been issued by a variety of societies and expert panels.[1 4 24 95 99] This review focuses on FFP and platelet transfusions. Guidelines for red blood cell transfusions[1 4 24 95 98 99] are beyond the scope of this article.

FFP and platelet transfusions are relatively frequently associated with side-effects such as febrile, non-haemolytic and allergic transfusion reactions, bacterial contamination, and transfusion-related acute lung injury.[6 39 69 75 94] Such products should be restricted to situations in which their efficacy has been documented. However, there is amazingly little scientific information available concerning the clinical efficacy of FFP and platelet transfusions.[1 93] The few existing guidelines consist more of expert opinion than of scientific evidence.

Anaesthetists[1] and oncologists[93] have issued guidelines for platelet transfusion. According to these guidelines, prophylactic platelet transfusions are indicated in leukaemia patients

at platelet counts <10 000 μl^{-1} in the absence of fever, heparin treatment or active minor bleeding (although lower, safe thresholds have been described by Gmür and colleagues)[34 87] and with platelet counts <20 000 μl^{-1} in the presence of such risk factors.[93] For major surgery, platelet transfusions are recommended to maintain platelet counts above 50 000 μl^{-1}, particularly if microvascular bleeding occurs.[1 93] Minor surgery, however, can be performed without platelet transfusion in patients with a platelet count <50 000 μl^{-1}.[58] In certain situations in which platelet dysfunction may be present, such as after cardiopulmonary bypass, and when the consequences of bleeding might be devastating, such as in neurosurgery, maintaining platelet counts between 50 000 and 100 000 μl^{-1} may be necessary. Only with severe platelet dysfunction will platelet counts >100 000 μl^{-1} require transfusion.

Transfusion of FFP is considered to be indicated in the following situations: urgent reversal of anticoagulation induced by vitamin K antagonists (besides the use of prothrombin complex concentrates), microvascular bleeding in the presence of an elevated PT (INR >1.6) or aPTT (>1.5 times normal) and microvascular bleeding in patients transfused with >1 blood volume when PT and aPTT are unavailable.[1 81] In contrast, FFP transfusions are contraindicated as volume replacement.[1 81] Hopefully, the strict use of such guidelines will decrease the number of inappropriate FFP transfusions.[65]

Red blood cell transfusions have also been advocated to improve blood coagulation.[82 104 105] It is unlikely, however, that reduction of the haematocrit alone compromises blood coagulation significantly. We have shown that decreasing the haematocrit gradually from 40% to 10%, thereby maintaining platelet count and coagulation factors at normal levels, does not compromise blood coagulation in any way, as assessed by thrombelastography.[47]

Haemostatic drug therapy

Besides transfusion therapy, treatment of bleeding is often supplemented with one or more haemostatic drugs. However, most of these drugs are substitutes for single or combined clotting factors, which do not induce coagulation but only replenish absent or diminished coagulation factors. This is important, as coagulation factor concentrates such as fibrinogen, prothrombin complex concentrate and vWF concentrate are too often administered in an attempt to improve coagulation, even though there is no deficiency of the relevant clotting factor. Although it has long been known that further elevation of above-normal levels of a single coagulation factor, e.g. FVIII or FIX, leads to more effective *in vitro* coagulation, as evidenced by a shortened coagulation time,[32 58] there is no evidence that this occurs *in vivo* or stops bleeding. Apart from the vast experience and evidence of the efficacy of coagulation factor concentrates in the treatment of hereditary coagulation factor deficiencies such as haemophilia, afibrinogenaemia and vWF disease, there is only sparse evidence of the efficacy of these concentrates in patients with surgical bleeding.[10 11 13 64] On the basis of these considerations and the fact that the minimal concentration of a specific coagulation factor required for normal haemostasis is known from *in vitro* experiments, it seems reasonable to administer coagulation factor concentrates only in cases in which a deficiency of the corresponding factor has been demonstrated. To clarify the appropriate use of coagulation factor concentrates in surgery, however, randomized trials are needed.

Other widely used haemostatic drugs are antifibrinolytic agents, including tranexamic acid, aminocaproic acid and aprotinin, which inhibit the activation of plasminogen and the activity of plasmin, respectively.[107] As shown in several randomized, placebo-controlled studies, both aprotinin and tranexamic acid can significantly reduce blood loss in cardiac surgery when used prophylactically.[17 62 71 78] Whether these results translate into a better overall outcome and justify routine use in all patients with cardiac surgery, however, is still debated.

Prophylactic use of antifibrinolytics, mainly aprotinin, in liver transplantation has also revealed encouraging results.[80 83] The blood-sparing effect of aprotinin was found to be significant during the post-reperfusion period, suggesting that inhibition of reperfusion-associated hyperfibrinolysis is related to its efficacy. With the currently available knowledge, aprotinin seems to effectively reduce blood loss during orthotopic liver transplantation regardless of the indication.[79] In major orthopaedic surgery, mainly joint replacement surgery, the use of antifibrinolytics has revealed conflicting results, making their widespread use as routine medication to reduce blood loss unlikely.[3 38 50 106]

Apart from their positive effects in prophylaxis, antifibrinolytics have shown limited benefits so far in stopping bleeding episodes. Significant efficacy has been found only in primary menorrhagia and in gastrointestinal and urogenital bleeding.[67] This may be explained by the fact that mucous membranes are rich in fibrinolytic substances. In old uncontrolled studies, aprotinin was been associated with an increased rate of thrombotic complications, including myocardial infarction and pulmonary embolism, in patients undergoing cardiac surgery. Although such adverse effects have also been reported more recently,[36] randomized, controlled studies have so far failed to demonstrate a significant increase in thrombotic complications in patients treated with aprotinin.[17 50]

Desmopressin is an analogue of arginine vasopressin and induces release of vWF from the vascular endothelium, thereby elevating both vWF and FVIII in the circulation. Desmopressin has been shown to be effective in treating bleeding in patients with congenital, mild haemophilia A and vWF disease type 1.[67] To reduce blood loss during surgery in patients with otherwise normal haemostasis, desmopressin proved to be less effective. In a meta-analysis of 17 trials in 1171 patients, investigating desmopressin as prophylactic treatment in cardiac surgery, desmopressin

reduced blood loss by only 9%, which was considered not to be clinically relevant.[18] Newer studies have confirmed these observations, stating that, despite improvement in platelet function, desmopressin does not seem to have obvious beneficial effects on postoperative haemostasis in patients without any bleeding disorder who are undergoing elective cardiac surgery.[74] Whether a subgroup of patients on preoperative aspirin benefit from desmopressin needs to be investigated further. Moreover, in a comprehensive review analysing 14 randomized trials of 1034 adult patients scheduled for varying non-urgent surgery, the authors found that there is no convincing evidence that desmopressin minimizes perioperative the allogeneic red blood cell transfusion requirement in patients who do not have congenital bleeding disorders. This suggests that there is no benefit in using desmopressin as a means of minimizing perioperative allogeneic red blood cell transfusion.[41] All in all, it seems evident that desmopressin primarily provides benefits in patients with mild congenital haemophilia A or vWF disease.

rFV11a

Although not yet approved for indications other than bleeding in haemophiliacs with antibodies, rFVIIa (NovoSeven®) may be the ultimate haemostatic drug. rFVIIa is so far the only haemostatic drug that not only replaces a missing factor but actively initiates and promotes the coagulation process. This is a novel and very promising strategy to treat haemorrhagic diseases. The haemostatic effect of rFVIIa depends on its property of binding to TF and activated platelets, thereby rapidly activating FII to thrombin and FX to FXa respectively.[31 70 86] The result is a local thrombin burst that enables feedback activation of intrinsic coagulation factors, the activation of more platelets, and finally the generation of fibrin. A major advantage of rFVIIa is that this procoagulant effect does not occur systemically in the circulation but is limited to the site where the vessel injury occurred. In about 300 case reports and small series of patients with severe, life-threatening bleeding, rFVIIa has proved to be a very potent haemostatic drug, whatever the cause of the bleeding.[2 42] For instance, rFVIIa has been used successfully in patients with coumarin-induced bleeding, upper gastrointestinal bleeding, severe thrombocytopenia and thrombocytopathia and in patients with severe haemorrhage from trauma, neurosurgery, cardiac surgery and obstetric surgery. So far, there is only one randomized, controlled study of rFVIIa evaluating its prophylactic effect in patients undergoing retropubic prostatectomy.[30] The study showed that, with one dose of rFVIIa 40 $\mu g\ kg^{-1}$ given during surgery, transfusion frequency could be reduced from 58% in the placebo group to 0% in the rFVIIa group. Preliminary results from new studies evaluating the efficacy of rFVIIa in patients undergoing hepatectomy and patients suffering from severe upper gastrointestinal bleeding have similarly shown that blood loss can be reduced remarkably with rFVIIa.[63] However, detailed data have not yet been published. In addition, large, randomized studies in patients with severe trauma, liver transplantation and intracerebral haemorrhage are continuing. They will provide more information to clarify the uncertainties regarding its indications, optimal dose regimen, the optimal timing, the influence of the platelet count, and its cost-effectiveness.

Emerging challenges

A challenging and growing problem in surgery is the increased use of new, non-antagonizable anticoagulants such as fondaparinux (Arixtra®), (xi)melagatran (Exanta®) and recombinant nematode anticoagulant protein c2 (NAPc2), a FVIIa/TF inhibitor. Although in several non-clinical reports rFVIIa has been shown to partly reverse the anticoagulant effect of fondaparinux and NAPc2,[12 63] it remains unclear whether rFVIIa is really effective in clinical situations and whether it can be used routinely in view of its high cost. Another non-antagonizable anticoagulant is recombinant activated protein C (drotrecogin alpha, Xigris®) which is currently approved only in patients with severe sepsis. Although situations where patients receiving this drug need surgery may occur only rarely, their management will be challenging. Bleeding is the most common adverse reaction associated with Xigris therapy. In the PROWESS sepsis trial, serious bleeding events were observed in 3.5% of Xigris-treated and 2.0% of placebo-treated patients during the 28-day study period.[10] Because the risk of bleeding may be increased significantly in patients with risk factors for bleeding, the manufacturer recommends that Xigris should not be used with concurrent heparin therapy, platelet counts $<30\,000\ \mu l^{-1}$ and INR>3.0. In cases of bleeding, the infusion should be stopped immediately. As there is no known antidote for Xigris and effective antihaemorrhagic strategies are not known, administration of rFVIIa could theoretically be considered. However, because Xigris is administered to patients with sepsis, the often concomitant DIC may limit the use of rFVIIa.

Summary

Today's understanding of coagulation is time-based (Fig. 1). At the site of injury, tissue factor is expressed and binds to FVIIa, which circulates in minute quantities in its activated form, activating small quantities of FXa, which produces small amounts of thrombin (FIIa). By several positive feedback-loops, the generation of thrombin is amplified and propagated. When thrombin generation is maximal, fibrin monomers are formed.

Indications and thromboprophylaxis regimens are reviewed (Tables 1–3), including the use of recently introduced drugs such as fondaparinux and (xi)melagatran. The impact of such treatment on patients undergoing regional anaesthesia (Tables 4 and 5) are outlined. Diagnostic procedures (Fig. 2, Table 6) and treatment regimens for patients with pre-existing or intraoperative coagulation defects are increasingly challenging and these are discussed in detail.

Addendum

A haemostatic (procoagulant) therapy using recombinant factor VIIa may be beneficial following major trauma. Preliminary results of a large pivotal phase II multi-centre study in 280 trauma patients have recently been reported (http://www.novonordisk.com/). Patients treated with recombinant factor VIIa received less red blood cell transfusions, had fewer complications and spent less time in intensive care units. Severe adverse events including thrombo-embolic complications were equal in both groups.

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