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### Regional anaesthesia and anticoagulation

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As the life expectancy of our Western population progressively increases, so does the prevalence of cardiovascular disease and thus the use of antithrombotic drugs. The use of central neuraxial anaesthesia techniques in patients treated with these drugs is a major clinical problem as the presence of an impaired coagulation has been found to be the most important risk factor contributing to the formation of a spinal haematoma. The growing number of case reports of spinal haematoma has led many national societies of anaesthetists to come up with guidelines. This article presents an overview of current guidelines on the use of regional anaesthetic techniques in patients treated with various anticoagulants and also describes a possible strategy to deal with new antithrombotic drugs that have recently been introduced in some countries or will be shortly in others.

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Anaesthetists are often confronted with patients who may benefit from a neuraxial anaesthetic technique and who are also treated with some form of anticoagulant therapy. The number of these patients is growing because of the increasing prevalence of cardiovascular disease in our ageing Western populations and the adoption of our unhealthy Western lifestyle by the emerging economies in Asia and South America. To safely cope with these patients, a number of national associations of anaesthetists have issued practice guidelines on the use of regional anaesthetic techniques in the presence of anti-thrombotics. These guidelines need continuous updating because new anticoagulant drugs are being introduced at regular intervals. In the present article, the risks of regional anaesthesia in anticoagulated patients and existing guidelines are reviewed, and there is special emphasis on new anticoagulants that have recently been introduced or that will shortly become available in most countries.

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## Risk of regional anaesthesia in patients with impaired coagulation status

A spinal haematoma is a rare event that occurs more frequently spontaneously than as a result of neuraxial anaesthesia. Most spontaneous haematomas are idiopathic, but cases related to anticoagulant therapy and vascular malformations represent the second- and third-most common categories.<sup>1</sup> Following neuraxial anaesthesia, the concomitant use of anticoagulants is the risk factor most frequently associated with spinal bleeding.<sup>2,3</sup> Because spinal haematoma is so rare, it is virtually impossible to perform a prospective study to get a more accurate estimate of its incidence. In total, and based on the analysis of case reports, the incidence of a spinal haematoma has been estimated to be 1 in 150 000 and 1 in 220 000 patients after epidural or spinal anaesthesia, respectively.<sup>4</sup> However, there are some indications that the actual incidence might be higher. Horlocker et al. estimated the frequency of spinal haematoma in orthopaedic patients who were treated with enoxaparin to be between 1 in 1000 and 1 in 10 000 neuraxial blockades.<sup>5</sup> Schroeder estimated that the presence of an impaired coagulation increases the bleeding incidence to 1 in 40 800, 1 in 6600 and 1 in 3100 patients following spinal anaesthesia, single-shot epidural anaesthesia and epidural catheter techniques, respectively.<sup>6</sup> A Scandinavian survey covering the incidence of severe neurological complications after central neuraxial blockades between 1990 and 1999 found an incidence of 1 in 3600 female patients undergoing knee arthroplasty under epidural anaesthesia. Although recent case series seem to confirm these higher incidences<sup>7,8</sup>, somewhat more reassuring figures were just published by Cook et al. who reported the results of the third national audit project of the Royal College of Anaesthetists on major complications after central neuraxial block.<sup>9</sup> The authors counted eight vertebral canal haematomas on a total of 707 405 neuraxial blocks, but only five fully met the inclusion criteria. Therefore, the incidence of vertebral canal haematoma can be estimated to be as high as 1 in 88 000 and as low as 1 in 140 000 central neuraxial blocks. Interestingly, the overall incidence of all complications (not only spinal haematoma) was highest after epidural and combined spinal–epidural techniques and in older females and lowest after spinal and caudal approaches and in the paediatric and obstetric population. The low incidence of spinal bleeding in the obstetric population has been shown previously.<sup>10,11</sup>

All drugs or conditions that tamper with coagulation can precipitate a vertebral canal bleeding after central neuraxial anaesthesia, but the compounds most often involved are unfractionated heparin (UH) and low-molecular-weight heparins (LMWHs) alone or in association with acetylsalicylic acid (ASA), non-steroidal anti-inflammatory drugs (NSAIDs) and/or thienopyridines.<sup>12</sup> Other risk factors include bloody, traumatic and/or multiple punctures, osteoporosis with spinal stenosis, Bechterew's disease<sup>13</sup>, the lack of guidelines on the use of central neuraxial techniques in the presence of anticoagulants<sup>10</sup> and advanced age.<sup>9,10</sup> The latter can be explained by the increased occurrence of degenerative spine disorders and renal insufficiency in the elderly. As most anti-thrombotics are eliminated via the kidney, renal insufficiency will prolong and intensify the anticoagulant effects, thereby increasing the haemorrhagic risk if no dose adjustment is performed. Finally, the use of epidural catheters is associated with the highest number of spinal haematomas which will occur, in more than half of the cases, following removal of these catheters.<sup>2,10,12</sup>

All patients should be carefully observed for signs of a developing spinal haematoma after neuraxial blockade or removal of the neuraxial catheter. The patient should be monitored at regular time intervals until a regression of the sensory block by at least two dermatomes or a return of motor function has become apparent. A slow or absent regression of motor and/or sensory block, back pain, urinary retention and the return of sensory and motor deficit after a previous (complete) regression of the block, alone or in combination, suggest a developing spinal haematoma. Further, these monitoring visits should be continued at least for 24 h after removal of the neuraxial catheter.<sup>14</sup> For postoperative analgesia, the use of low concentrations and/or low doses of local anaesthetics and insertion of the epidural catheter at the thoracic level will produce a minimal or absent motor block of the lower limbs and thus facilitate the early detection of a developing haematoma. If there is any doubt, the epidural infusion of local anaesthetics should be stopped immediately to detect any neurological deficit as soon as possible. Both patients and nurses should be taught the signs of a spinal haematoma and instructed to contact an anaesthetist immediately.

When a clinical suspicion of spinal haematoma formation arises, an aggressive diagnostic and therapeutic approach is mandatory. This includes urgent magnetic resonance imaging (MRI), or if MRI

is not available a computed tomography (CT) scan. As a spinal haematoma is a neurosurgical emergency, a protocol should be agreed in advance with the diagnostic imaging service to avoid any delays in the diagnosis. If the diagnosis is confirmed, a decompressive laminectomy should be performed less than 6–12 h after the appearance of the first symptoms of medullary compression to keep the patient's chances of making a complete neurological recovery intact.<sup>2,15</sup>

It is advisable that written protocols are available for the management of suspected cases, covering assessment of motor and sensory function, access to MRI or CT scanning and referral to neurosurgery.<sup>14</sup>

### Guidelines and recommendations

There are virtually no prospective data on the use of central neuraxial anaesthesia techniques in the presence of anti-thrombotic drugs. The majority of the available recommendations and guidelines from national societies of anaesthetists are expert opinions based on large case series, case reports and the pharmacological data of the anticoagulant drugs involved.<sup>16</sup> These guidelines always include: (1) a minimum time interval that should be respected between the last dose of an anticoagulant and insertion of a neuraxial needle/catheter or the removal of that catheter, (2) a minimum time interval that should be respected between the insertion of a neuraxial needle/catheter or the removal of that catheter and the next dose of anticoagulant and (3) minimal values of clotting times necessary for the performance of a neuraxial technique (if applicable). A summary of the recommended time intervals and clotting times can be found in Tables 1 and 2, respectively.

Most of the anticoagulants that are included in these guidelines have been around for some time, and there is a large body of knowledge and experience available. Because the prevalence of cardiovascular disease is increasing globally<sup>17</sup>, the development of new anti-thrombotic drugs has become very important to the pharmaceutical industry and new compounds are being released at an increasing pace. These new compounds often tackle the coagulation process in ways different from the older ones, resulting in a faster onset, longer half-lives and a superior efficacy. Unfortunately, this clinical superiority very often comes at the cost of a somewhat increased tendency to bleed and the impossibility to antagonise the anticoagulant effects. Because they are so new, any experience is lacking and it is difficult to make any statements on the use of central neuraxial anaesthesia in patients treated with these drugs. Recently, Rosencher et al. proposed a management strategy that can be applied when new anticoagulants are used.<sup>18</sup> In brief, the authors propose that the central neuraxial insertion of a needle and/or catheter and the subsequent withdrawal of that catheter should only be performed at least two elimination half-lives after the last dose of an anticoagulant. The next dose of that anticoagulant should only be administered after a time interval that can be obtained by subtracting the time necessary for that specific anticoagulant to reach maximum plasma levels after administration from the time necessary to produce a stable blood clot (i.e. 8 h).

#### *Unfractionated heparin*

Low-dose UH used to be the golden standard in the prophylaxis of venous thrombo-embolism (VTE), but in most countries, it is now replaced by low-dose LMWH. UH produces its anticoagulant effect by combining with antithrombin and inhibiting both factors IIa and Xa equally. The anticoagulant effect is quantified in International Units. Neuraxial techniques are considered safe in the presence of prophylactic doses with UH, always taking into account the patients body weight and kidney function and respecting a minimum time interval of 4 h between the last dose of UH and the subsequent insertion of an epidural/spinal needle (and catheter) or the withdrawal of that catheter.<sup>16</sup>

If UH is administered in therapeutic doses via a continuous intravenous infusion, the time intervals are different. The infusion of heparin should be stopped at least 4 h prior to initiation of neuraxial anaesthesia, but more importantly, a return of normal clotting should be documented via an activated partial thromboplastin time (aPTT) or activated clotting time (ACT). Finally, as UH can cause heparin-induced thrombocytopenia (HIT), a platelet count is recommended if heparin has been administered for at least 5 days.

UH is still the drug of choice when intra-operative intravenous therapeutic heparinisation is needed (e.g., during vascular surgery). In that case, a minimum of 1 h between neuraxial puncture/catheter insertion and the subsequent administration of UH should be respected.<sup>19,20</sup> Catheter removal should

**Table 1**

Summary of recommended minimum time intervals or clotting times before and after central neuraxial needle/catheter insertion and withdrawal of catheters (only valid for patients with normal renal function).

	Before insertion/withdrawal	After insertion/withdrawal
LMWH (prophylactic)	12 h	2–4 h
LMWH (therapeutic)	Platelet count if LMWH > 5 days 24 h	2–4 h
UH (therapeutic)	Platelet count if LMWH > 5 days aPTT or ACT within normal range Platelet count if LMWH > 5 days	1 h
Danaparoid	Neuraxial anaesthesia not to be used	Neuraxial anaesthesia not to be used
Fondaparinux	36 h	12 h
Rivaroxaban <sup>a</sup>	At least 20 h	6 h
Vitamine K antagonists	4–10 days <sup>b</sup> and PT ≥ 50% or INR ≤ 1.4	Immediately
Ticlopidine	10 days	Immediately
Clopidogrel	7 days	Immediately
Prasugrel <sup>a</sup>	At least 7 days	8 h
Eptifibatide/tirofiban	8–10 h and platelet count aPTT or ACT within normal range	2–4 h
Abciximab	24–48 hours and platelet count aPTT or ACT within normal range	2–4 h
Lepirudine	8–10 h aPTT or ECT within normal range	2–4 h
Bivalirudine	8–10 h aPTT or ECT within normal range	2–4 h
Argatroban	4 h PiCT, aPTT, ACT or ECT within normal range	2 h
Dabigatran <sup>a</sup>	Neuraxial anaesthesia contraindicated	Neuraxial anaesthesia contraindicated

<sup>a</sup> No formal guidelines available yet. Time intervals based on the pharmacological properties of the anticoagulant drug or on recommendations by the manufacturer.

<sup>b</sup> Depending on the elimination half-life of the AVK used.

only be considered at least 4 h later and after normalisation of the aPTT or the ACT. Although it may theoretically be safer to postpone surgery for 24 h in case of a bloody puncture, there are no data to support this attitude.

### Low-molecular-weight heparin

LMWHs have become the treatment of choice in both prevention and treatment of VTE because of a higher bioavailability resulting in a superior anticoagulant effect without increasing the bleeding tendency and a greater ease of use without any need to monitor blood clotting. They preferentially inhibit factor Xa formation and their anticoagulant effect is expressed as international units anti-factor Xa activity (IU anti-Xa). LMWHs have a high bioavailability and elimination half-lives ranging from 2 to 6 h and longer, making a once daily administration possible. If creatinine clearance drops below 30 ml min<sup>-1</sup>, the elimination half-life will be doubled.<sup>21</sup> Following subcutaneous administration, peak plasma levels are reached after 4 h and will diminish to 50% of these peak levels about 10–12 h later.

**Table 2**

Laboratory investigations and neuraxial techniques.

	Without problems	After individual evaluation
Prothrombin Time (PT)	> 50% (INR ≤ 1.4)	40–50% (INR 1.41–1.7)
Activated Partial Thromboplastin Time (aPTT)	upper limit of normal <sup>b</sup>	exceeding upper limit of normal by 1–4 sec <sup>b</sup>
Platelet count	>80,000/μl	50,000–80,000/μl

<sup>b</sup> Normal values depend on assay used locally in each hospital

Major neuraxial techniques can be used in the presence of prophylactic doses of LMWH (max. 50 IU anti-Xa  $\text{kg}^{-1}$  per 24 h) if a time interval of 12 h is maintained between the last dose of LMWH and the subsequent insertion of an epidural/spinal needle or catheter and the removal of that same catheter. Higher (intermediate or therapeutic) doses of LMWH will be administered once or twice daily. In that case, the time interval should be doubled: a minimum of 24 h must have elapsed since the last dose of LMWH before a neuraxial puncture can be performed. If the LMWH is administered in a once-daily regimen, the American College of Chest Physicians (ACCP) recommends that the last preoperative dose should only be half the total daily dose.<sup>22</sup>

The next dose of LMWH should only be administered at least 2–4 h after the epidural/spinal puncture or removal of the catheter. Although HIT is less likely to occur after LMWH than after UH, a platelet count is recommended if an LMWH has been used for more than 5 days.

### *Danaparoid*

Danaparoid is a mixture of heparan sulphate, dermatan sulphate and chondroitin sulphate that produces its anti-thrombotic effect via an antithrombin-dependent inhibition of factor Xa.<sup>23</sup> It is marketed as an alternative for LMWH and UH in the prevention and treatment of VTE and pulmonary embolism (PE) in patients with a history of HIT.<sup>24</sup> However, the drug may have a cross-reactivity with heparin-induced antibodies in about 10% of patients. Danaparoid has an elimination half-life of about 25 h and is primarily cleared from the body by the kidneys. Renal insufficiency will therefore cause a significantly prolonged half-life.<sup>25</sup> Despite its long half-life, the drug is administered twice daily. Hence, there will be no trough in the drug's plasma levels, making it virtually impossible to safely perform a neuraxial technique in patients treated with danaparoid.

### *Factor Xa-inhibitors*

#### *Fondaparinux*

Fondaparinux is a synthetic pentasaccharide that selectively inhibits factor Xa. In contrast to the LMWHs, it has no effect on factor IIa. The compound has a bioavailability of almost 100% and an elimination half-life of 18–21 h. As it is mainly removed from the body by the kidneys, the half-life will be prolonged to 36–42 h if the creatinine clearance is inferior to 50  $\text{ml min}^{-1}$ .<sup>26</sup> The use of fondaparinux is not recommended when creatinine clearance falls below 30  $\text{ml min}^{-1}$ . Prophylactic fondaparinux is administered subcutaneously once daily in a dose of 2.5 mg.<sup>27</sup> It is started 6–12 h postoperatively, as the preoperative use may increase the risk of intra-operative bleeding without improving the anti-thrombotic efficacy.<sup>28</sup> Because of the postoperative initiation of the treatment, there is no problem with single-shot neuraxial techniques. However, if a catheter is inserted, it should only be removed in the absence of significant plasma levels of fondaparinux. It is therefore recommended that the removal of such a catheter should only occur under the conditions used in the EXPERT study: maintaining an interval of 36 h after the last dose of fondaparinux.<sup>29</sup> In the presence of an impaired renal function, this delay must be even longer. The next dose of fondaparinux should be administered at least 12 h after catheter removal.

Although there have been a few reports of HIT occurring in patients treated with fondaparinux<sup>30,31</sup>, the ACCP suggests that fondaparinux can be used as an alternative to UH or LMWH in patients with a history of HIT.<sup>32</sup>

#### *Rivaroxaban*

Rivaroxaban (Xarelto<sup>®</sup>) is a selective inhibitor of factor Xa that is administered orally and currently approved for the prevention of deep venous thrombosis after total knee or hip prosthesis surgery. The treatment is initiated 6–8 h after surgery and following administration of a single dose of 10 mg, maximum plasma levels will be reached after 2–4 h. Comparative studies have shown that rivaroxaban is more efficacious than enoxaparin in thromboprophylaxis.<sup>33</sup> However, a recent FDA document also warned against a possible increase in bleeding tendency when compared with enoxaparin.<sup>34</sup> Rivaroxaban has an elimination half-life of 7–11 h that is only minimally influenced by renal function as the drug is eliminated via kidney and liver. Rivaroxaban produces a dose-dependent prolongation of

the aPTT and the HepTest, but they are not recommended by the manufacturer to assess the anticoagulant effect.<sup>35</sup> The prothrombin time (PT) is also influenced by rivaroxaban in a dose-dependent way with a close correlation to plasma concentrations<sup>36</sup>, but the readout for PT is to be done in seconds and not in international normalised ratio (INR). However, routine monitoring is not deemed necessary. As with most new anticoagulants, rivaroxaban cannot be antagonised.

The manufacturer proposes that a time interval of 18–20 h should be respected before the neuraxial catheter is removed. The next dose of rivaroxaban should only be given 6 h after catheter removal. These time intervals correspond to the strategy proposed by Rosencher et al.<sup>18</sup> In case of a bloody puncture, the next administration of rivaroxaban should be postponed for 24 h.<sup>35</sup> Unfortunately, there are no prospective data supporting these recommendations.

### *Direct thrombin inhibitors*

#### *Hirudins: bivalirudin, desirudin and lepirudin*

All hirudins are potent anticoagulants with an essentially irreversible binding to both free and bound thrombin via the active site of thrombin and the fibrinogen-binding site. They are also known as bivalent direct thrombin inhibitors. Originally, hirudins were prepared as unrefined extracts from leeches. Modern hirudins are either recombinants such as lepirudin and desirudin or analogues such as bivalirudin. They are well suited for use in patients with HIT because there is no interaction with platelet factor 4.<sup>37,38</sup> Both lepirudin and desirudin have a half-life of 1.3–2 h, but this half-life increases greatly with the impairment of renal function. Due to their potency and the resulting potential for major bleeding, the anticoagulant effects of the r-hirudins should be closely monitored using the aPTT or the ecarin clotting time (ECT).<sup>39</sup>

Bivalirudin is primarily eliminated from the body by extrarenal mechanisms and has an elimination half-life of 25–30 min.<sup>40,41</sup> The aPTT and the ECT can also be used to monitor bivalirudin activity. Both the r-hirudins and the hirulogs cannot be antagonised<sup>42</sup>, but due to their short half-lives, this is not really an issue. Further, all hirudins are proteins of non-human origin and therefore potentially immunogenic. The immunogenicity seems to increase with the duration of treatment and may increase the anticoagulant effect of the drugs.<sup>43</sup>

There are insufficient data to make any firm recommendations concerning the use of major neuraxial blocking techniques in patients treated with hirudins. However, the pharmacokinetics of the hirudins suggest that epidural and/or spinal needle/catheter insertion or catheter removal should only be performed at least 8–10 h after the last dose and 2–4 h prior to the next administration, and after excluding a remaining anticoagulant effect through the use of the aPTT or the ECT.

#### *Argatroban*

Argatroban is a univalent direct thrombin inhibitor, which is administered intravenously, and binds both free and bound thrombin via reversible binding at the active site of thrombin without any need for anti-thrombin.<sup>44,45</sup> Argatroban has been approved in a number of countries for parenteral use in patients with HIT-associated thrombosis because of the absence of any interaction with platelet factor 4. The anticoagulant effect can be monitored via the prothrombinase-induced clotting time (PiCT), but the ACT, the ECT or the aPTT can also be used.<sup>46</sup> The elimination is independent from renal function and is mainly hepatic with a short half-life of 35–45 min.<sup>47</sup> Because of its short half-life and of its reversible binding to thrombin, the absence of an antagonising drug is not really an issue. In the presence of a normal hepatic function, the aPTT will normalise within 2–4 h after stopping an argatroban infusion.

There is very little known about the use of neuraxial techniques in patients treated with argatroban. If the patient is receiving argatroban for the prevention of deep venous thrombosis because of a history of HIT, epidural and/or spinal needle/catheter insertion or catheter removal should only be performed at least 4 h after the last dose and 2 h prior to the next administration, and after excluding a remaining anticoagulant effect through the use of a PiCT, ACT, aPTT or an ECT. If, on the other hand, the patient is receiving argatroban for therapeutic anticoagulation because of the diagnosis of an acute HIT II, the treatment should not be interrupted because of the high risk of thrombo-embolism. Moreover, an acute HIT is a contraindication to neuraxial blockade.

### *Dabigatran*

Dabigatran (Pradaxa®) is a novel direct thrombin inhibitor that is ingested orally under the form of its prodrug dabigatran etexilate. Dabigatran etexilate is converted by plasma esterases into the active dabigatran. The compound has a long half-life of 12–17 h, is eliminated mainly via the kidney and it cannot be antagonised. Following oral administration, the maximum plasma concentration will be reached after 2–4 h. Recently, dabigatran was approved in a number of countries for the prophylaxis of VTE following elective total hip or knee replacement. Studies have found the drug to have a prophylactic efficacy and bleeding tendency comparable with that of enoxaparin.<sup>48</sup> Treatment is commenced with doses ranging from 75 mg (creatinine clearance 30–50 ml min<sup>-1</sup>) to 110 mg (normal kidney function) 1–4 h after surgery is completed, and repeated every 12 h thereafter. The anticoagulant effect can be quantified using the ECT or the aPTT.<sup>49</sup> As prophylaxis with dabigatran is only started post-operatively, there should be no problem with single-shot neuraxial anaesthesia. However, there is little to no information about the use of indwelling neuraxial catheters as in the few studies with dabigatran in which epidural catheters were used; these were withdrawn at least 4 h before treatment with dabigatran was started. During an ongoing treatment and because of the long half-life and the twice-daily administration, there is no significant trough in the plasma levels that would allow the safe use of neuraxial techniques both with or without catheters. As such, the manufacturer recommends that dabigatran should not be used in patients undergoing anaesthesia with postoperative indwelling epidural catheters and that the first dose of dabigatran be administered at least 2 h after withdrawal of the epidural catheter.<sup>50</sup> However, this may be too short as it will take 8 h for a stable clot to form. As dabigatran will take 2–4 h before reaching maximum plasma levels, it may be advisable to respect a time interval of at least 6 h before administering the first dose of dabigatran. Should dabigatran accidentally be used in a patient with an indwelling neuraxial catheter, then the two half-lives rationale could be applied. Rosencher et al. propose that the catheter should only be withdrawn 36 h after the last dose of dabigatran, while the next dose should be postponed no earlier than 12 h after catheter withdrawal.<sup>18</sup>

### *Vitamin-K-antagonists*

Ongoing treatment with anti-vitamin K agents (AVKs) such as acenocoumarol, phenprocoumon and warfarin is an absolute contraindication for neuraxial anaesthesia. All these drugs cause a deficiency in coagulation factors II, VII, IX and X, which are no longer capable of binding to phospholipid membranes during coagulation. This anticoagulating effect can be effectively reversed by the administration of vitamin K, fresh frozen plasma or Prothrombin–Proconvertin–Stuart Factor–Antihæmophilic Factor B complex (PPSB).

Treatment with AVKs must be stopped, with a delay depending on the half-life of the specific AVK used, prior to any neuraxial anaesthesia technique. Moreover, the INR or PT has to return sufficiently towards their baseline values before any puncture can be performed. Initiation of neuraxial anaesthesia and/or catheter removal should only be performed when the PT is at least at 50% or the INR equal or below 1.4. Caution is necessary when patients treated with AVKs are scheduled for surgery. In most of these cases, the AVKs will be stopped preoperatively and the patients will temporarily be 'bridged' with LMWH or unfractionated heparin.<sup>22</sup> The doses of LMWH or UH used depend on the original indication of the treatment with AVKs and the bleeding risk associated with the planned intervention. In these cases, the previously made recommendations for LMWH or UH do apply.

### *Antiplatelet agents*

#### *Acetylsalicylic acid*

A single dose of ASA produces irreversible inactivation of the cyclo-oxygenase enzyme. After stopping a treatment with ASA, this effect lasts an entire platelet lifetime (i.e., 7–10 days). Further, the overall effect of cyclo-oxygenase inhibition depends on the dose of ASA used. A low dose of ASA (60–300 mg) mainly inhibits thromboxane A<sub>2</sub> (a potent vasoconstrictor and platelet aggregation stimulator) and not so much prostacyclin (a potent vasodilator and platelet aggregation inhibitor). A higher dose of ASA will evenly inhibit both thromboxane A<sub>2</sub> and prostacyclin production.

There are no data suggesting that anti-platelet therapy with low-dose ASA is associated with an increased risk of spinal haematoma in the presence of a normal platelet count. This is also valid for the combination of low-dose aspirin with dipyridamole. The concomitant administration of ASA with UH has been shown to significantly increase the bleeding risk.<sup>19,20</sup> Whether this is also true for prophylactic doses of LMWH is not known, but a more cautious approach would be to initiate the prophylaxis with LMWHs postoperatively in patients also treated with low-dose ASA<sup>51</sup>, as there does not seem to be a difference in the efficacy of preoperative versus postoperative initiation of thromboprophylaxis with LMWH.<sup>52,53</sup>

### Thienopyridines

Both ticlopidine and clopidogrel are prodrugs that are activated *in vivo* to active metabolites that irreversibly inhibit adenosine diphosphate (ADP)-induced platelet aggregation through interaction with the platelets P2Y<sub>12</sub> receptor and interfering with platelet–fibrinogen binding. This effect cannot be antagonised. Ticlopidine has an elimination half-life of 30–50 h after a single oral dose but up to 96 h after 14 days of repeated dosing. Clopidogrel has an elimination half-life of 120 h, but its active metabolite has a half-life of only 8 h. Because the permanent defect in a platelet protein can only be countered by platelet turnover, the platelet inhibition will persist for 7 and 10 days after clopidogrel and ticlopidine cessation, respectively.

There are no prospective data available that assess the safety of major neuraxial techniques in the presence of a thienopyridine treatment, but a number of spinal haematomas following neuraxial anaesthesia have been described.<sup>12</sup> Therefore, central nerve blocking techniques should be used only if ticlopidine or clopidogrel are no longer active: that is, administration was stopped at least 7 days before for clopidogrel and 10 days before for ticlopidine. This cautious approach is supported by the guidelines of a majority of national associations of anaesthetists.<sup>16</sup> If thienopyridines are used because of the recent implantation of a coronary stent, they should not be stopped only because of the performance of a neuraxial block. In that case, an interdisciplinary approach including the surgeon, the cardiologist and the anaesthetist is mandatory.<sup>54</sup>

Prasugrel is a new oral third-generation thienopyridine that also produces an irreversible inhibition of platelet aggregation, which cannot be antagonised. It is indicated for the prevention of atherothrombotic events in patients with acute coronary syndrome (i.e., unstable angina), non-ST segment elevation myocardial infarction (NSTEMI) or ST segment elevation myocardial infarction (STEMI) undergoing primary or delayed percutaneous coronary intervention (PCI). It is more efficient than clopidogrel in the prevention of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.<sup>55,56</sup> However, the use of prasugrel may be associated with a somewhat higher bleeding tendency. Prasugrel is also an inactive prodrug that is metabolised by the liver into an active metabolite. Compared to clopidogrel, this conversion occurs faster and more efficiently and results in a significantly more active compound.<sup>57</sup> Maximum plasma levels will be reached 30–60 min after oral ingestion. Elimination of the drug occurs mainly via the kidneys with an elimination half-life of about 7.4 h, but following cessation of treatment, the anti-platelet effect will last for several days.<sup>58</sup> As a result, the manufacturer advises that prasugrel be stopped at least 7 days before elective surgery.<sup>59</sup> At this time, there are no data available on the combination of prasugrel with neuraxial anaesthesia techniques but it seems reasonable to assume that, as with surgery, prasugrel treatment should be interrupted at least 7 days prior to neuraxial blockade and/or catheter withdrawal.

### Glycoprotein IIb–IIIa antagonists

The most effective platelet aggregation inhibiting drugs currently available are antagonists of the platelet's glycoprotein IIb–IIIa receptor, which is the final common pathway of platelet aggregation. Drugs belonging to this category are abciximab, eptifibatid and tirofiban. They are all administered intravenously. The anti-platelet effects are reversible, and will disappear about 8 h and 24–48 h after discontinuing eptifibatid/tirofiban and abciximab administration, respectively. In addition, all glycoprotein IIb–IIIa receptor antagonists, but especially abciximab, may cause a profound thrombocytopenia, which may appear within 1–24 h after the first administration.<sup>60,61,62</sup> Finally, these drugs are often combined with UH and/or ASA in an emergency PCI setting. Although the anticoagulant effects can be quantified with the aPTT or the ACT, these tests may not always be a useful indicator of

bleeding risk, as they do not measure platelet function. Platelet function tests are probably a far more effective, although slower, way of assessing platelet aggregation inhibition.<sup>63</sup>

Data assessing the safety of neuraxial techniques in the patients treated with abciximab, eptifibatid and tirofiban are scarce or non-existing. Based on the pharmacological properties of these drugs, epidural and/or spinal needle/catheter insertion or catheter removal should only be performed after full recovery of the platelet aggregation (i.e., 8–10 h or 48 h after the last dose of eptifibatid/tirofiban or abciximab, respectively), and excluding any thrombocytopenia via a recent platelet count.

## Summary

In brief, the performance of central neuraxial anaesthesia in patients on chronic therapy with anticoagulant drugs is an everyday challenge for anaesthetists. Since the end of the 1990s, a number of national associations of anaesthetists have produced guidelines that are updated regularly as the experience with known anti-thrombotics increases and new ones are being introduced. A good knowledge of the current recommendations, the pharmacologic properties (i.e., the elimination half-life, the influence of the individual patient's renal or liver function on the elimination half-life and the time necessary to reach a maximum anticoagulant effect) of the anticoagulant(s) used and of the individual patient's particularities such as weight, renal or hepatic function or the presence and type of coronary stents are all necessary in the safe approach of anticoagulated patients. The ongoing introduction of newer and more efficacious anti-thrombotic drugs makes the challenge even greater as little or no information is available on their use in combination with regional anaesthesia. As a result, well-established and validated guidelines are lacking. When confronted with patients treated with new anti-thrombotics, the knowledge of that specific drug's pharmacologic profile becomes even more important as it is often the only data available that will help to decide whether or not a central neuraxial block is possible or under which circumstances it may be safely performed.

### Practice points

- Anaesthetists should always be aware of any anticoagulant treatment, the pharmacological properties of the anticoagulants used and, if available, of the guidelines relevant for the use of neuraxial anaesthesia techniques in the presence of these specific anticoagulants.
- Anaesthetists should know the indication for a specific anticoagulant treatment.
- An anticoagulant treatment should never be stopped preoperatively, solely for the purpose of a neuraxial anaesthesia technique without considering the indication of the anticoagulant treatment in that specific patient. If stopping the anticoagulant before the intervention results in an increased risk of thrombosis during the perioperative period, then an alternative anaesthesia technique should be considered.
- Anticoagulants that are stopped before the intervention are often 'bridged' by other anticoagulants that do have their own bleeding risk.

### Research agenda

- The ongoing development and introduction of new anti-thrombotics calls for the elaboration of well-established, validated guidelines that are kept up to date to allow a safe perioperative approach of patients treated with these drugs.
- New coagulation assays should be developed that clearly and swiftly quantify the influence of new anti-thrombotics on *in vivo* clot formation.
- New antagonists should be developed that will allow a rapid and safe reversal of new anti-thrombotics in case of an emergency.

## Conflicts of interest

The author has no conflicts of interest.

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# Managing anticoagulated patients during neuraxial anaesthesia

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## Summary

The widespread use of central neuraxial block (CNB) and the prevalence of anticoagulation for different indications have led to an inevitable overlap between the two. The most serious complication of CNB in anticoagulated patients is the risk of spinal/epidural haematoma. Performing CNB in these patients is a complex decision that should take into account the twin risks of bleeding and venous/arterial thrombosis if anticoagulation therapies were to be stopped. Various guidelines have been issued to achieve normal haemostasis and thus allow safe administration of CNB. However, the evidence base for many such recommendations is weak, relying mainly on case reports, small studies and pharmacokinetics of the drugs. Given these limitations it is crucial to fully assess individual risk factors and understand anticoagulant pharmacokinetics in order to appropriately set time intervals for catheter insertion/removal. This paper will review traditional and newer anticoagulation/antiplatelet therapies with a view to improving the management of anticoagulated patients undergoing CNB.

**Keywords:** central neuraxial block, anticoagulation, antiplatelet, spinal epidural haematoma, management.

Neuraxial anaesthesia or central neuraxial block (CNB) in the form of an epidural and/or a spinal block (Fig 1) is increasingly used in various types of surgery to improve pain relief in the perioperative and postoperative periods. The third national audit project of the Royal College of Anaesthetists in the UK estimated that 707 425 CNB procedures are performed annually, of which 41% were epidurals, 46% were spinals, and the rest were combined spinal/epidural and caudal blocks (Cook *et al*, 2009). At the same time, the use of anticoagulant and antiplatelet therapies is also expanding in line with the increasing age of the population. This means that the likelihood of the two occurring together is becoming extremely high. For anaesthetists, one of the main concerns of performing CNB in patients receiving anticoagulation is bleeding into the spinal vertebral canal causing compression

of the theca, which can potentially result in irreversible neurological damage and devastating paraplegia. Although the reported incidence of spinal/epidural haematoma (SEH) to date is relatively low, the clinical severity of its consequences together with the potential costs of subsequent litigation (Cheney *et al*, 1999) and the possibility of under-reporting mean that it is crucial to develop sound strategies for managing anticoagulated patients during CNB.

The most important part of the management process includes individualized preoperative assessment for the risks of thromboembolism in the absence of anticoagulation and SEH. Once the decision to perform CNB has been made, a number of key issues need to be addressed: (i) a schedule for cessation of anticoagulation in order to achieve optimal haemostasis prior to catheter insertion/removal; (ii) a safe interval for initiating thromboprophylaxis postoperatively and (iii) postoperative surveillance for signs of spinal cord compression. Numerous recommendations and guidelines have been issued across Europe and the USA to improve the safety of CNB in anticoagulated patients (Tryba, 1998; Gogarten *et al*, 2003; Horlocker *et al*, 2003; Llau Pitarch *et al*, 2005; Vandermeulen *et al*, 2005; Kozek-Langenecker *et al*, 2005) and recently these guidelines have been compared and reviewed (Gogarten, 2006; Llau *et al*, 2007). Due to differences between Europe and the USA in thromboprophylaxis strategies prior to surgery, there are minor discrepancies amongst them but, by and large, they are similar (Table I). However, one should note that these guidelines were developed not on the basis of large randomized prospective studies but rather from case reports, limited studies of small sample sizes and, more importantly, theoretical knowledge of the pharmacokinetics and pharmacodynamics of each anticoagulant.

More challenges are also emerging as newer and more refined anticoagulant and antiplatelet agents are being licensed and introduced into clinical practice. While these are more effective at reducing the risks of thromboembolism compared with traditional thromboprophylactics, they are characteristically different in terms of half-life and reversibility. Unfortunately, the evidence for the use of these agents during CNB is poor. Hence their administration during CNB would have to depend mainly on understanding of their documented pharmacological properties, previous experience with other anticoagulants and general clinical expertise. In this review we will discuss the management of CNB with reference to the

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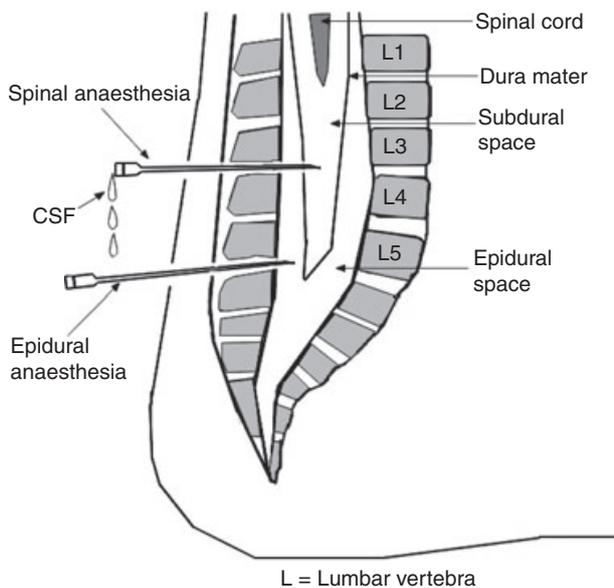


Fig 1. Schematic view of spinal and epidural anaesthesia. CSF, cerebrospinal fluid.

most commonly used anticoagulants/antiplatelet agents in the UK in the light of available data. We will also consider the newer licensed agents, such as dabigatran etexilate (Pradaxa) and rivaroxaban (Xarelto).

### Thromboembolic risk assessment

In order to minimize the risk of the devastating complication of SEH, normal haemostasis is required prior to CNB. For patients receiving anticoagulant/antiplatelet agents, this might come at a cost, as temporary interruption of these therapies can put such patients at increased risk of venous and/or arterial thrombosis, which can be fatal and are associated with serious long-term morbidity and impaired quality of life for patients. Furthermore, the socio-economic burden on the healthcare system created by thromboembolism related mortality and morbidity can be substantial. In the UK, the total cost for the management of venous thromboembolism (VTE) is estimated to be approximately £640 million; an additional £400 million is incurred for the treatment of associated diseases such as venous leg ulcers (House of Commons Health Committee, 2005).

The highest risk for recurrent VTE is within the first 3 months following an acute episode of VTE; in the absence of therapy, the risk of recurrence at 1 and 2 month is 40% and 10%, respectively (Kearon & Hirsh, 1997). Likewise, patients who discontinue clopidogrel prematurely within the first month of having a coronary stent insertion are more likely to die within the year compared with those who continue treatment (7.5% vs. 0.7%,  $P < 0.0001$ ) (Spertus *et al*, 2006). Patients with atrial fibrillation and high CHADS-2 score (congestive heart failure, hypertension, age  $\geq 75$  years, diabetes

mellitus and a history of stroke or transient ischaemic attack) have a high risk of stroke without antithrombotic therapy – the stroke rate per 100 patient-years increases by a factor of 1.5 for each 1-point increase in the CHADS-2 score (Gage *et al*, 2001). Therefore, for these groups of patients, the risk of thromboembolism seems to far outweigh the benefits of CNB and perhaps postponing elective surgery might be more advisable.

A second area of vital concern is the assessment of VTE risk after surgery, particularly when CNB is commonly used, such as in total hip or knee replacement. It was believed that CNB, when compared with general anaesthesia (GA), reduces the odds of VTE by 44% for deep vein thrombosis and 55% for pulmonary embolism after orthopaedic surgery (Rodgers *et al*, 2000). However recent studies using fondaparinux have failed to corroborate this putative advantage (Turpie *et al*, 2003). A combination of several factors like potent new anticoagulant agents, stringent thromboprophylactic protocols, early mobilisation after surgery and better surgical techniques have reduced VTE risk to a level such that the benefit of CNB over GA is rendered negligible in comparison.

In view of the fact that CNB does not obviate the need for thromboprophylaxis after surgery, the question is how soon after surgery should anticoagulation be administered. The use of CNB in patients at high risk of postoperative VTE requires that thromboprophylaxis be delayed after surgery for 12 h in the case of a low molecular weight heparin (LMWH) or 48 h for fondaparinux (Singelyn *et al*, 2007), in order to allow safe removal of the catheter. Without thromboprophylaxis, the VTE risk after orthopaedic surgery can be as high as 40–60% and with prophylaxis this risk reduces overall by 40–80% (Geerts *et al*, 2008). The timing of initiating anticoagulation after surgery is also crucial for optimal and safe thromboprophylaxis; initiation within 2 h of surgery increases the risk of bleeding, while an interval of 6–9 h is deemed effective without posing a significant bleeding risk (Raskob & Hirsh, 2003). Delaying anticoagulation beyond this time, however, will result in suboptimal thromboprophylaxis against VTE. Thus the key issue, and the focus of further studies, is to decide precisely when to initiate thromboprophylaxis after CNB without increasing the risk of either SEH or VTE.

### Individual bleeding risks and general haemostatic requirements during CNB

Abnormal coagulation, whether inherited or acquired, is a major risk factor for SEH during CNB (Vandermeulen *et al*, 1994; Wulf, 1996) and it is generally accepted that CNB is contraindicated in patients with acquired (renal/liver failure, disseminated intravascular coagulation, thrombocytopenia etc.) or congenital bleeding disorders. Bleeding history, clinical examination and drug history remain the best tools for assessing individual bleeding risks prior to surgery; for patients with no bleeding history, routine coagulation screening is not required (Chee *et al*, 2008).

Table I. Comparison of guidelines across countries.

	United States (Horlocker <i>et al</i> , 2003)	Germany (Gogarten <i>et al</i> , 2003)	Spain (Llau Pitarch <i>et al</i> , 2005)	Austria (Kozek-Langenecker <i>et al</i> , 2005)	Belgium (Vandermeulen <i>et al</i> , 2005)
<b>Anticoagulants</b>					
<b>UFH (prophylactic/therapeutic)</b>					
Interval between stopping drug and CIR (h/h)	Not contraindicated/2–4	4/4	4/4	4/4	–/Normal APTT
Interval between CIR and starting drug (h)	1	1	1	1	1
<b>LMWH (prophylactic [once a day]/therapeutic)</b>					
Interval between stopping drug and catheter insertion (h/h)	10–12/24	10–12/24	12/24	12/24	12/24
Interval between catheter insertion and starting drug (h)	6–8	4	6	4	4
Interval between stopping drug and catheter removal (h)	10–12	12	12	–	12*
Interval between catheter removal and starting drug (h)	>2	–	6	4	4
<b>Fondaparinux 2.5 mg once a day</b>					
Interval between catheter insertion and starting drug† (h)	6–8	6–8	6–8	6–8	6–12
Interval between stopping drug and catheter removal (h)	Indwelling catheter is contraindicated	22 h‡/36–42 h§	36	36	36
Interval between catheter removal and starting drug (h)		2–4 h‡/6–12 h§	12	4	12
Stop Aspirin	Not contraindicated	3 d¶	Not contraindicated	2–3 d**	Not contraindicated
Stop Clopidogrel (d)	7	7	7	7	7
Stop Ticlopidine (d)	14	10	10	10	10
Stop Abciximab/Eptifibatide/Tirofiban (h/h/h)	24–48/4–8/4–8	Contraindicated	Not recommended	48/8/8	24–48/8–10/8–10
<b>Oral anticoagulant (warfarin/acenocoumarol)</b>					
INR for performing CNB	INR < 1.5	INR < 1.4	INR < 1.5	INR < 1.4	INR < 1.4

UFH, unfractionated heparin; CIR, catheter insertion/removal; APTT, activated partial thromboplastin time; LMWH, low molecular weight heparin; INR, international normalized ratio; CNB, central neuraxial block.

\*Post CNB procedure only prophylactic dose should be used for as long as neuraxial catheter is maintained.

†Fondaparinux is administered postoperative.

‡Normal renal function.

§Creatinine clearance <50 ml/min.

¶In combination with thromboprophylaxis.

\*\*2 d single-shot atraumatic procedure and 3 d for all other procedures.

The use of concomitant anticoagulant and antiplatelet therapies increases the risk of bleeding during CNB and should be avoided (Horlocker *et al*, 2003). However, when single anticoagulant or antiplatelet agents are administered, CNB is not always contraindicated. In most cases it is sufficient to stop these drugs long enough prior to CNB, to allow normal haemostasis to be restored. For some of these drugs (like warfarin or unfractionated heparin), reliable laboratory tests are available to ascertain the restoration of near-normal haemostasis; however for the majority (like LMWH and antiplatelet agents, among others) this is not the case. Therefore knowledge of their pharmacological properties should help us to estimate the safe period for administering CNB.

The prevailing consensus is that CNB should not be performed in thrombocytopenic patients but none of the guidelines have explicitly addressed the “minimum platelet threshold” for performing CNB. Platelet function is thought to be more important than platelet count alone (Abramovitz & Beilin, 2003) and some authors suggest that a count of  $>50 \times 10^9/l$  is acceptable given normal platelet function, while a count of  $>100 \times 10^9/l$  is acceptable without further assessments (Schindler *et al*, 1990; Douglas, 1991). A report by Owens *et al* (1986) identified 9/33 patients who developed SEH and had thrombocytopenia of  $<50 \times 10^9/l$ ; a recent review concluded that in the absence of other additional risk factors, a platelet count of  $80 \times 10^9/l$  is “safe” for spinal/

epidural blocks and  $40 \times 10^9/l$  for lumbar puncture (LP) (van Veen *et al*, 2009). The British Committee for Standards in Haematology (BCSH) on the use of platelet transfusion recommends that for LP and epidural anaesthesia the platelet count should be raised to at least  $50 \times 10^9/l$  (BCSH, 2003a) whereas the BCSH guidelines on management of immune thrombocytopenia suggests a minimum platelet count of  $80 \times 10^9/l$  (BCSH, 2003b).

### Incidence and risk factors of SEH during CNB

The actual incidence of SEH during CNB cannot be precisely determined due to the rarity of its occurrence which in turn makes large randomized controlled trials difficult to perform. Nonetheless the overall incidence of SEH in patients with normal haemostasis is estimated to be 1:150 000 after epidural block and 1:220 000 after spinal block (Tryba, 1993). These increase to 1:22 000 and 1:32 500 respectively, for patients taking heparin alone and 1:8500 (after epidural) for those taking aspirin and heparin concomitantly (Stafford-Smith, 1996). However, Stafford-Smith (1996) also demonstrated that a bloody procedure still represents the single greatest risk factor for SEH, in both patients with and without abnormal clotting, highlighting the fact that vessel injury rather than anticoagulation is the primary cause of SEH during CNB.

The risk factors for SEH during CNB have been described by several authors (Brem *et al*, 1981; Ruff & Dougherty, 1981; Owens *et al*, 1986; Vandermeulen *et al*, 1994; Wulf, 1996; Horlocker & Wedel, 1998; Moen *et al*, 2004) and are summarized in Table II. The incidence of SEH varies according to the type of surgery, age and sex of patients. For example, the incidence of SEH in obstetric surgery is estimated as 1:200 000 after epidural blockade whereas in elderly females undergoing orthopaedic surgery it can be as high as 1:3600 (Moen *et al*, 2004). The underlying reasons for the increased risk of SEH in elderly females could be due to a combination of: greater frequency of spinal abnormalities like osteoporosis (Moen *et al*, 2004); use of dual antiplatelet/anticoagulant therapies; unrecognized use of non-prescribed aspirin-containing compounds over the counter; or an accumulation of anticoagulant caused by undetectable reduced renal excretion. Among the types of CNB the risk of SEH is highest for indwelling epidural catheters followed by single-shot epidural anaesthesia and then single-shot spinal anaesthesia (Wulf, 1996; Tryba & Wedel, 1997). Removal of an indwelling epidural catheter is as critical as its insertion, as vessel injury may still occur. Severity of the neurological deficit, the size of the SEH and the time between SEH and surgical intervention will affect the outcome (Vandermeulen *et al*, 1994).

It is evident that the presence of multiple risk factors substantially increases the risk of SEH and recent case reports (Table III) demonstrate this, despite safety guidelines having been followed. Thus, in the preoperative period, the impact of risk factors must be properly weighted and assessed before

**Table II.** Risks factors associated with Spinal Epidural Haematoma.

Patients-related
Elderly
Female
Inherited coagulopathy
Acquired coagulopathies (liver/renal failure, malignancy, HELLP syndrome, DIC etc.)
Thrombocytopenia
Spinal abnormalities (spinal bifida/stenosis, spinal tumours, ankylosing spondylitis and osteoporosis)
Procedure-related
Catheter insertion/removal
Traumatic procedure (multiple attempts)
Presence of blood in the catheter during insertion/removal
Indwelling epidural catheter > single-shot epidural block > single-shot spinal block
Drug-related
Anticoagulation/Antiplatelet/Fibrinolytic
Immediate (pre- and post- CNB) anticoagulant administration
Dual anticoagulant/antiplatelet therapies

HELLP, haemolysis, elevated liver enzymes, low platelet count; DIC, disseminated intravascular coagulation, CNB, central neuraxial block.

deciding to use CNB and other forms of anaesthesia should be considered for high risk patients.

### Unfractionated heparin (UFH)

UFH (or 'heparin') achieves its anticoagulant effect by binding to antithrombin and catalysing the inactivation of factors IIa, Xa, IXa and, to a lesser extent, XIa and XIIa. Heparin also binds strongly to a number of plasma proteins including endothelial cells, macrophages and platelet factor 4 which results in its low bioavailability, unpredictable pharmacokinetic and pharmacodynamic properties, and heparin-induced thrombocytopenia (HIT) (Hirsh *et al*, 2008). Therapeutic heparin is monitored by Activated Partial Thromboplastin Time (APTT) whereas prophylactic heparin requires no monitoring (Table IV).

A review of the literature involving >9000 patients who had received CNB in the presence of prophylactic heparin showed no incidences of SEH (Liu & Mulroy, 1998) and the second American Society of Regional Anesthesia (ASRA) guidelines do not regard its use as a contraindication (Horlocker *et al*, 2003). Nonetheless, scattered cases of SEH in the presence of low dose UFH have been reported prior to the second ASRA guidelines (Vandermeulen *et al*, 1994; Sandhu *et al*, 2000; Pay *et al*, 2002) and continue to be reported (Schwarz *et al*, 2004; Christie & McCabe, 2007; Cameron *et al*, 2007).

In contrast to prophylactic heparin, therapeutic heparin is definitively associated with an increased risk of SEH. One prospective study ( $n = 342$ ) compared the incidence of SEH in patients undergoing LP with and without therapeutic intravenous heparin for the treatment of acute cerebral infarct. A 2% incidence of SEH was reported and three main factors

**Table III.** Cases of SEH after spinal/epidural procedure in combination with LMWH from year 2003.

References	Procedures	Age (years) / Sex	Risk factors	Outcome	Anticoagulant
Chan and Bailin (2004)	Lumbar, S	80/F	Concurrent use of aspirin and ketorolac; traumatic and bloody procedure; compression vertebral fracture and osteoporosis	Diagnosis of SEH was made >8 h after symptoms occurred No recovery	Enoxaparin 30 mg BD started 26 h after surgery
Sharma <i>et al</i> (2004)	Thoracic, E	60/F	Aspirin stopped 5 d pre-surgery; traumatized dura from stiff epidural catheter tip	Good recovery after surgery	Enoxaparin 40 mg administered 10 h before catheter insertion
Litz <i>et al</i> (2004)	Lumbar, S	81/F	Clopidogrel stopped 7 d pre-surgery; traumatic and bloody procedure; renal impairment	Partial recovery	Enoxaparin 40 mg 8 and 36 h after lumbar puncture
Ain and Vance (2005)	Lumbar, E	85/F	Warfarin stopped 6 d prior to epidural steroid injection and started on the evening of the injection; renal impairment	Mild residual weakness	Enoxaparin 1 mg/kg (BD) administered >24 h pre procedure and 24 h after procedure
Tam <i>et al</i> (2006)	CSE	80/F	Clopidogrel 7 d prior to surgery and one dose immediately after surgery; renal impairment; spinal abnormality	No neurological improvement despite surgical evacuation	Daltaparin 5000 units given 10 h pre-surgery
Afzal <i>et al</i> (2006)	Lumbar, E	80/M	Ketorolac given immediately post surgery	Urgent surgical treatment. No neurological deficit	Enoxaparin 40 mg administered 20 h after catheter insertion and 12 h prior to catheter removal
Cameron <i>et al</i> (2007)	Lumbar, S	31/F	Malignancy	No adverse outcome	Daltaparin 5000 administered 1 h after catheter removal
Christie and McCabe (2007)	Thoracic, E	Mean age 72/2F	Bloody tap; spinal abnormality; malignancy	Diagnostic delays leading to adverse neurological outcome	Enoxaparin 20 mg administered 10 h before and 9 h after catheter insertion
Xu <i>et al</i> (2009)	Lumbar, E	78/F	Warfarin and aspirin stopped 6 d pre-intrathecal steroid injection; INR normal prior to procedure	Full recovery	Enoxaparin (1 mg/kg) administered 30 h pre and post procedure

SEH, spinal/epidural haematoma; LMWH, low molecular weight heparin; INR, International Normalized Ratio; S, spinal; F, female; BD, twice a day; E, epidural; CSE, combined spinal and epidural; M, male; CNB, central neuraxial block.

**Table IV.** Mode of action, pharmacokinetic properties and reversal of anticoagulant drugs.

Name of drugs	Target	$T_{max}$ (h)	Half-life (h)	Excretion	Monitoring	Antidote
Intravenous UFH (Hirsh <i>et al</i> , 2008)	Ila, Xa, IXa and XIa	Immediate	Dose-dependent Range 30–90 min	Saturable* and non saturable (renal)	APTT (therapeutic range 1.5–2)	Protamine sulphate
LMWH (Hirsh <i>et al</i> , 2008)	Xa and Ila	3–5	3–6	Renal	Anti Xa†	Protamine sulphate partially
Fondaparinux (Hirsh <i>et al</i> , 2008)	Indirect Xa	1–2	17–21	Renal	Anti Xa†	None
Rivaroxaban (Kubitza <i>et al</i> , 2005)	Xa	3–4	5–9	Renal and gut	PT/APTT and HepTest†	None
Dabigatran (Baetz & Spinler, 2008)	Ila	0.5–2	12–17	Renal (80%)	PT, ecarin clotting time†	None

UFH, unfractionated heparin; APTT, activated partial thromboplastin time; LMWH, low molecular weight heparin; PT, prothrombin time.

\*Saturable phase is via binding to endothelial cell receptors and macrophages (large proportion).

†Routine monitoring is not recommended.

for the increased risk were identified: (i) the initiation of heparin within 1 h of procedure; (ii) concomitant use of aspirin at the time of the LP and (iii) traumatic procedure (Ruff & Dougherty, 1981). Based on this data and that from Tryba (1993), the incidence of SEH with UFH following CNB was calculated to be 34.9-fold higher after traumatic LP *versus* non-traumatic LP and 11.6-fold higher if heparin was administered <1 h, compared with >1 h after (Stafford-Smith, 1996). Other studies have shown that CNB can be performed safely in patients who will subsequently receive therapeutic heparin if: there is careful patient selection; CNB is performed at the time of nadir activity of heparin; concomitant use of anticoagulation is avoided prior to CNB and administration of heparin is delayed until at least 60 min after the procedure (Rao & El-Etr, 1981; Baron *et al*, 1987).

Recently two cases of epidural haematoma have been reported in association with therapeutic UFH and CNB (Rosen *et al*, 2004; Davignon *et al*, 2008). One was the first ever reported case of SEH in cardiac surgery, involving an 18-years-old man who received thoracic epidural anaesthesia for aortic valve replacement surgery and at the time of the catheter removal he was fully anticoagulated with heparin, had received a thrombolytic drug (alteplase) and was possibly thrombocytopenic (Rosen *et al*, 2004). In an editorial Chaney (2005) questioned the benefits of CNB in cardiac surgery and advised that both bleeding and thrombotic risks after CNB are not negligible and should be assessed carefully in such patients.

Patients receiving UFH should have an APTT checked prior to catheter insertion/removal; CNB should be performed only when the APTT has normalized (Vandermeulen *et al*, 1994; Tryba, 1998). If UFH has been administered for >4 d, a platelet count should be checked prior to CNB to exclude HIT (Tryba, 1998). The insertion/removal of the catheter should be performed at least 4 h after therapeutic/prophylactic UFH had ceased and the next dose should be administered no sooner than 1 h after catheter insertion/removal (Table I). The question as to whether to proceed with or abort surgery after a bloody tap remains unanswered, as no controlled studies have addressed this issue. If a traumatic neuraxial procedure occurs, a delay of 6 and 12 h is presently recommended in Spain and Germany respectively (Gogarten *et al*, 2003; Llau *et al*, 2007).

### Low molecular Weight Heparin (LMWH)

LMWHs comprise of fragments of UFH and depending on the depolymerization process, different preparations, such as enoxaparin, tinzaparin or dalteparin, are generated. Although these are biochemically and pharmacologically different, their clinical efficacy in the prevention of VTE after surgery is similar (White & Ginsberg, 2003). Most of the data we have on the incidence of SEH during CNB involving LMWH relates to enoxaparin, but these should be treated as indicative for the different LMWH preparations (Tryba, 1998).

LMWHs have greater inhibitory activity against factor Xa than thrombin (IIa) and, being smaller molecules than UFH, they bind less tightly to endothelium, platelet factor 4 and other heparin-binding plasma proteins. Hence they have better bioavailability, less HIT complications and better anticoagulant response predictability, rendering laboratory monitoring unnecessary in most instances (Hirsh *et al*, 2008) (Table IV). LMWH is excreted via the renal route and is therefore contraindicated in patients with a creatinine clearance of <30 ml/min. Monitoring with anti Xa activity is not a reliable indicator of bleeding and is not routinely recommended unless patients are pregnant, obese or have severe renal impairment (Baglin *et al*, 2006a). In the UK, LMWHs have almost completely replaced UFH and are now the treatment of choice for the prevention and treatment of VTE and the treatment of acute coronary syndrome.

The use of prophylactic LMWH in patients undergoing CNB had been adopted in Europe since 1987. Enoxaparin, at a dose of 20 or 40 mg once a day, was initiated 12 h before surgery. To prevent the occurrence of SEH with the use of LMWH during CNB, practice recommendations were issued, advising that neuraxial catheter insertion/removal should be delayed for at least 10–12 h after the last dose of prophylactic LMWH with the subsequent dose given no sooner than 8–12 h after catheter insertion (Vandermeulen *et al*, 1994; Tryba, 1993). Early reviews involving >10 000 patients and pharmaceutical data of several million patients showed that CNB in combination with LMWH, using European regimes was safe with only one case of SEH being reported (Bergqvist *et al*, 1992, 1993).

In North America the story was different. Enoxaparin was introduced in May 1993 without any specific recommendation regarding the timing of CNB and it was administered immediately postoperatively at a dose of 30 mg twice daily. Within 5 years of its introduction, the Food and Drug Administration (FDA) had received reports of 43 patients who had undergone CNB and developed SEH after receiving enoxaparin (Wysowski *et al*, 1998). The FDA issued a public health advisory warning in December 1997 and instructed all the LMWH manufacturers to issue a “black-box” warning of this potential complication in their product sheets (Lumpkin, 1998). In 1998 the first sets of practice guidelines were issued following the ASRA consensus conference (Enneking & Benzon, 1998; Urmev & Rowlingson, 1998; Rosenquist & Brown, 1998; Liu & Mulroy, 1998; Horlocker & Wedel, 1998) and in May 2003 these guidelines were updated further in order to improve the safety of patients undergoing CNB in the presence of anticoagulant agents (Horlocker *et al*, 2003).

By 1998, a total of 13 cases of SEH associated with the use of LMWH had been reported in Europe whereas in the USA this number had reached 60 (Horlocker *et al*, 2003). The reasons for this discrepancy between the two continents were believed to be mainly due to the USA having: (i) a higher total daily dose of LMWH; (ii) more frequent dosages, leading possibly to higher trough levels of LMWH during catheter insertion/

removal; (iii) a lack of practical guidelines regarding timings of CNB and administration of LMWH and (iv) more epidurals being performed (Tryba & Wedel, 1997; Horlocker *et al*, 2003). Using statistical analysis, Schroeder (1998) calculated the incidence of SEH with LMWH in the USA to be 1:40 000 after spinal anaesthesia and 1:3100 after indwelling epidural catheter in female orthopaedic patients. Subsequently, in Sweden, Moen *et al* (2004), reported a similar incidence of SEH (1:3600) after epidural blocks amongst elderly females undergoing orthopaedic surgery. It would seem that SEH following LMWH under the European regime is not as rare as once thought and it is possible that cases of SEH may be under-reported.

Examination of the 40 cases of SEH in combination with LMWH in the USA (Horlocker & Wedel, 1998) and 33 cases in Sweden (Moen *et al*, 2004) identified the main risk factors to be: female orthopaedic patients; advanced age (>70 years); epidural techniques more than spinal; concomitant use of LMWH with other anticoagulants/antiplatelets; traumatic procedure and most importantly, insufficient intervals between cessation/initiation of LMWH and CNB. Since 2003, when the second ASRA consensus was published, we know of at least 10 cases of SEH reported in the English literature related to the combination of spinal/epidural procedures and LMWH (Table III). The risk factors are largely identical to those previously mentioned. Five additional cases of epidural haematomas were reported by the third national audit project of the Royal College of Anaesthetists in the UK amongst 97 925 epidural blocks; however we do not know whether these involved the use of any anticoagulants (Cook *et al*, 2009).

Patients receiving LMWH preoperatively have altered coagulation status and this worsens when renal impairment is present or other anticoagulant/antiplatelet therapies are concomitantly administered prior to CNB. Platelet count should be checked prior to catheter insertion/removal on patients who have received LMWH for >4 d, in order to rule out the small risk of HIT (Keeling *et al*, 2006). An interval of at least 12 h should be respected for once daily prophylactic dose of LMWH before insertion of the catheter to ensure that trough levels are achieved. Indwelling catheters can be maintained after CNB but removal of the catheter should be performed no sooner than 12 h after the last dose of LMWH (Table I). The recommendations on the timing of LMWH following catheter insertion vary slightly across countries, with Germany, Austria and Belgium recommending an interval of 4 h while Spain and the USA recommend a 6- to 8-h interval.

For therapeutic doses of LMWH (i.e. enoxaparin 1 mg/kg twice a day or 1.5 mg/kg once a day), a 24-h delay should be maintained before the catheter is inserted and removal of the catheter should occur at least 12 h after the last dose of LMWH. In the event of bloody procedure during catheter insertion, the initiation of LMWH should be delayed for 24 h postoperatively (Horlocker *et al*, 2003).

## Fondaparinux

Fondaparinux is a synthetic indirect inhibitor of factor Xa which has a half-life of 17–21 h (Table IV). A meta-analysis of phase III clinical trials in orthopaedic surgeries showed that fondaparinux, when compared to LMWH, was more effective in VTE prevention and when given >6 h after surgery the risks of bleeding were similar (Turpie *et al*, 2002). In the UK fondaparinux is licensed for thromboprophylaxis after major orthopaedic surgery (NICE, 2007). Fondaparinux is excreted via the renal tract and therefore is contraindicated in patients with a creatinine clearance of <30 ml/min.

In the initial dose ranging study, one case of SEH was reported in a patient receiving 6 mg of Fondaparinux, who had undergone multiple traumatic neuraxial procedures (Turpie *et al*, 2001). Thus, in subsequent studies fondaparinux was strictly controlled during CNB, allowing only single-shot techniques and excluding patients with a prolonged indwelling catheter or who have had bloody tap or difficult procedures (e.g. >2 attempts). No further neuraxial haematomas occurred (Turpie, 2005). The use of fondaparinux in combination with continuous catheter techniques was later investigated in the EXPERT study ( $n = 1553$ ) in patients undergoing major orthopaedic surgery (Singelyn *et al*, 2007). Again, no incidents of SEH were reported. Fondaparinux was initiated between 6 and 12 h after surgery in 95% of the patients. To permit the safe removal of the neuraxial catheter the second dose of fondaparinux was skipped and the catheter was removed 36 h after the first dose. The subsequent dose of fondaparinux was given 12 h after catheter removal, thus allowing a window period of 48 h between the first two injections. The rate of symptomatic VTE at 4–6 weeks after surgery in the EXPERT study was similar in patients with and without a neuraxial catheter [0.8% vs. 1.1% respectively, odd ratio 0.79 (95% confidence interval 0.42–1.49)].

As fondaparinux is only started 6–8 h after surgery, there is agreement amongst countries that single-shot neuraxial techniques, preoperatively, should not pose any problems. The situation however is not as clear when a postoperative indwelling catheter is left *in situ* in combination with fondaparinux; in the USA this combination is not recommended (Horlocker *et al*, 2003) whereas in Europe the interval used in the EXPERT study is recommended (Table I).

## Oral anticoagulants

### *Coumarin derivatives (warfarin)*

Warfarin inhibits the synthesis and vitamin K-dependent post-translational gamma carboxylation of clotting factors II, VII, IX, X, as well as Proteins C, S and Z. The prothrombin time (PT) or international normalized ratio (INR) is the most commonly used test to monitor warfarin and it reflects the plasma activities of three of the four clotting factors (II, VII and X). Because factor VII has the shortest half-life (about

6 h), the initial increase in the INR when warfarin is started is reflective of factor VII activity. However the therapeutic effect of warfarin is most dependent on the reduction of factor II and X, which have relatively longer half-lives (60–72 h and 24–36 h, respectively). Conversely, after stopping warfarin, factor II is the slowest to normalize (Ansell *et al*, 2008). The complete and immediate reversal of warfarin can be achieved with clotting factor concentrates (Makris *et al*, 1997) and vitamin K (Watson *et al*, 2001).

Several studies have investigated the administration of oral anticoagulation prior to and after the CNB. Odoom and Sih (1983) found no cases of SEH in 1000 epidural blocks performed in 950 patients undergoing vascular surgery who had received preoperative oral anticoagulation and intraoperative heparin. They excluded patients with thrombocytopenia, coagulopathies or those who were receiving preoperative aspirin or heparin. The partial thromboplastin time test prior to surgery was abnormally prolonged. Three other retrospective studies, involving >11 800 patients undergoing orthopaedic surgery, examined the incidence of SEH after the removal of the catheter in patients receiving continuous epidural anesthesia/analgesia in the presence of low dose warfarin (Horlocker *et al*, 1994; Wu & Perkins, 1996; Parvizi *et al*, 2007). Warfarin was administered either the night before surgery (Wu & Perkins, 1996) or on the day of the surgery (Horlocker *et al*, 1994; Parvizi *et al*, 2007). The mean INR on the day of the catheter removal was between 1.4–1.54. No cases of SEH were reported. All authors concluded that controlled oral anticoagulation can be co-administered safely with CNB as long as there is careful patient selection, close monitoring of anticoagulation and extreme vigilance for signs of SEH after catheter removal (Wu & Perkins, 1996; Horlocker *et al*, 1994; Parvizi *et al*, 2007). However it should be noted that patients only received low dose warfarin (c.5 mg) for thromboprophylaxis, which achieved subtherapeutic levels of anticoagulation. In the UK, warfarin has been replaced by LMWH for both short term surgical and medical thromboprophylaxis but remains in use for: (i) treatment and/or recurrence of VTE and (ii) prevention of thromboembolism in patients with atrial fibrillation or mechanical heart valves. For these applications, therapeutic levels of anticoagulation (INR range 2–3.5) are required (Baglin *et al*, 2006b).

To date, no studies have evaluated the therapeutic and chronic use of oral anticoagulation with CNB and several guidelines contraindicate such a use (Tryba, 1998; Vandermeulen *et al*, 2005; Horlocker *et al*, 2003). Patients receiving chronic oral anticoagulation (warfarin), and who are in the intermediate and high risk group of developing thromboembolism (i.e. mechanical mitral/aortic valve, AF with congestive cardiac failure, etc.), should stop warfarin 4–5 d prior to CNB and “bridging therapy” with LMWH or UFH should be initiated (Kearon & Hirsh, 1997; Heit, 2001). The INR should be checked prior to CNB in all patients. An INR of <1.4 prior to catheter manipulation is recommended by most guidelines except for Spain and ASRA, which recommend an INR of <1.5 (Table I).

Two cases of SEH have occurred after epidural steroid injections despite stopping warfarin at least 5 d before (Ain & Vance, 2005; Xu *et al*, 2009). Both were elderly females who had received therapeutic doses of enoxaparin once warfarin was stopped. One also had renal impairment (Ain & Vance, 2005).

## New oral anticoagulants

The limitations of the current anticoagulants have led to the development of newer agents whose target is more refined and the need for monitoring is not required due to their predictable dose-response relationship. Recently dabigatran etexilate and rivaroxaban have successfully undergone NICE technology appraisals (NICE, 2008, 2009) for thromboprophylaxis following major orthopaedic surgery and will be discussed in more detail.

### Dabigatran

Dabigatran etexilate is an oral direct thrombin inhibitor that is rapidly converted to its active form, dabigatran. After multiple drug administrations dabigatran’s half-life ranges from 12–17 h and the peak plasma concentration occurs within 0.5–2 h (Table IV). A linear relationship is seen between dabigatran etexilate concentration and the ecarin clotting time and INR (Baetz & Spinler, 2008). The dose of dabigatran etexilate for thromboprophylaxis is 220 mg once daily, being administered initially as a half dose of 110 mg, 1–4 h after surgery.

### Rivaroxaban

Rivaroxaban, an oral direct Xa inhibitor, reversibly blocks the free factor Xa and clot-associated factor Xa. It has an oral bioavailability of 80–100% and the maximum plasma level is reached after 3–4 h. Its terminal half-life is 5–9 h. Rivaroxaban prolongs both PT and APTT dose-dependently (Kubitza *et al*, 2005) (Table IV). The established prophylactic dose for rivaroxaban is 10 mg once daily, with the first dose administered 6–8 h after surgery.

Another direct oral factor Xa inhibitor is Apixaban, which has shown promise in prophylaxis and treatment of VTE (Lassen *et al*, 2007; Buller *et al*, 2008). Further studies of its use for VTE thromboprophylaxis are ongoing.

### The use of new oral anticoagulants during CNB

There has been no case of SEH reported with the use of dabigatran etexilate or rivaroxaban during CNB. Based on previous experience with other anticoagulant agents like fondaparinux (Singelyn *et al*, 2007) and the pharmacological profile of the new anticoagulant agents, Rosencher *et al* (2007) in their review proposed that: (i) removal of the catheter must be delayed by an interval of at least two half-

lives (i.e. <25% of the drug remains active) after the prophylactic anticoagulant has been administered and (ii) the next dose must be delayed by a period equal to: [time needed for an initial platelet plug to solidify into a stable clot (8 h)] – [ $T_{\max}$  of the drug] (Fig 2).

Based on this proposal, they speculated that with rivaroxaban, the catheter should not be removed for at least 20 h after the previous dose and the next dose should be given no sooner than 6 h after catheter removal (Rosencher *et al*, 2007). This is also in accordance with the manufacturer's recommendation (emc.medicines.org.uk/medicine/21265/SPC). However, in the case of dabigatran, Rosencher's proposal and the manufacturer's recommendation are substantially different. The manufacturer does not recommend that dabigatran etexilate be started at all in patients who have a postoperative indwelling epidural catheter, and a minimum of 2 h must pass between catheter removal and the first dose of dabigatran (emc.medicines.org.uk/medicine/20760). In contrast, Rosencher *et al* (2007) do not rule out its use in patients with postoperative indwelling catheter; they propose that catheter should not be removed until 36 h (two half-lives) have elapsed from the previous dose and the subsequent dose be given no sooner than 12 h after catheter removal. Given the lack of evidence on the use of these agents with postoperative indwelling catheters, it is difficult to provide definite recommendations until further studies are performed to evaluate their use in such cases. Another recent review has issued recommendations on the use of new anticoagulants during CNB and these are based on the pharmacological profiles of the new agents (Llau & Ferrandis, 2009).

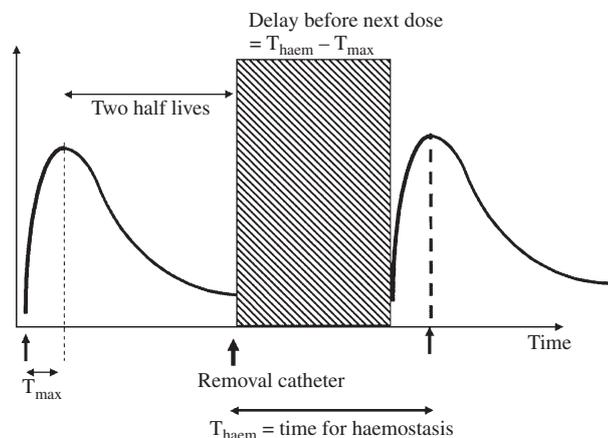


Fig. 2. Suggested strategy for prophylactic anticoagulant drugs and catheter removal. Reproduced from: Rosencher, N., Bonnet, M.P., & Sessler, D.I. (2007) Selected new antithrombotic agents and neuraxial anaesthesia for major orthopaedic surgery: management strategies. *Anaesthesia*, **62**, 1154–1160. With permission of Wiley-Blackwell.  $T_{\text{haem}}$  = time needed for an initial platelet plug to solidify into a stable clot (8 h);  $T_{\text{max}}$  = time to reach maximal anticoagulant activity. For example: half-life of fondaparinux is 17 h and  $T_{\text{max}}$  is 1 h; therefore delay catheter removal for at least 36 h (two half-lives) and the next dose should be given at least 7 h after catheter removal.

## Anti-platelet agents

### Non steroidal anti-inflammatory drug (NSAID)

Aspirin, the most commonly used NSAID for the primary prevention of cardiovascular and cerebrovascular diseases, is a cyclo-oxygenase 1 (COX-1) inhibitor that irreversibly inhibits platelet function, thus prolonging bleeding time for the entire lifetime of the platelet (7–10 d). Other COX-1 inhibitors, such as naproxen, ibuprofen and diclofenac, act as reversible prostaglandin synthesis inhibitors that have short half lives and cause transient and incomplete platelet dysfunction in the vast majority of patients.

Several studies have demonstrated the relative safety of CNB in the presence of aspirin or other NSAID therapies. Two prospective studies involving close to 2000 patients (Horlocker *et al*, 1995, 2002) and one retrospective ( $n = 805$ ) study (Horlocker *et al*, 1990) examined the effect of anti-platelet drugs (mostly aspirin) during CNB and reported no incidence of SEH postoperatively even though blood was noted in 22% of patients during catheter insertion in one study (Horlocker *et al*, 1995). Aspirin was taken preoperatively by 39% of patients in two studies (Horlocker *et al*, 1990, 1995) and 15% of patients in the third (Horlocker *et al*, 2002). All of these support the use of CNB in patients taking aspirin. However, the statement made by Horlocker *et al* (1995) that “preoperative antiplatelet therapy does not increase the risk of SEH associated with CNB” has been questioned (Maclean, 1995; Urmev & Rowlingson, 1998) on the basis that the number of patients studied is short of the 150 000–200 000 required to produce results of sufficient statistical power (Tryba, 1993).

Several case reports of SEH during CNB in combination with aspirin or other COX-1 inhibitor NSAID have been published (Ruff & Dougherty, 1981; Owens *et al*, 1986; Vandermeulen *et al*, 1994; Urmev & Rowlingson, 1998; Litz *et al*, 2001; Afzal *et al*, 2006; Cameron *et al*, 2007). In most of these cases the concomitant use of NSAID with heparin or other antiplatelets had been a major implicating risk factor for SEH. Most guidelines do not contraindicate the use of aspirin alone prior to CNB (Table I); however if thromboprophylaxis with heparin is started preoperatively, a 2–3 d aspirin-free period prior to CNB is recommended in Germany and Belgium to reduce the risk of SEH (Gogarten, 2006; Kozek-Langenecker *et al*, 2005).

### ADP receptor antagonists (clopidogrel and ticlopidine)

Clopidogrel and ticlopidine are thienopyridines that specifically and irreversibly block platelet P2Y<sub>12</sub> ADP receptors, causing impairment of both the primary and secondary phases of platelet aggregation. Platelet function is restored to normal when clopidogrel is stopped for 7 d and ticlopidine for 10–14 d (Patrono *et al*, 2004). Due to the side-effects of aplastic anaemia and thrombotic thrombocytopenic purpura,

ticlopidine has been replaced by clopidogrel in most instances. The European Society of Cardiology recommends that the duration of “double” antiplatelet therapy with aspirin and clopidogrel should be for 9–12 months following non ST-elevation acute coronary syndrome and 6–12 months after drug eluting stent to avoid late vessel thrombosis (Silber *et al*, 2005). This means that more patients are now receiving “dual” antiplatelet therapy.

No studies have evaluated the use of thienopyridines during CNB. Three cases of SEH associated with CNB and clopidogrel have been reported despite clopidogrel being stopped 7 d prior, as recommended by most guidelines (Litz *et al*, 2004; Tam *et al*, 2006; Christie & McCabe, 2007). Risk factors, namely renal impairment, traumatic procedure and spinal abnormality, were also present (Litz *et al*, 2004; Tam *et al*, 2006).

In the preoperative period, all patients receiving antiplatelet therapy should be assessed for risks of SEH against the risks of arterial thrombosis from the discontinuation of these agents. Based on the pharmacological aspects of both drugs, the safety interval for performing CNB from most guidelines is recommended as 7 d after the last dose of clopidogrel and 10–14 d after ticlopidine (Table I).

#### Glycoprotein (GP) IIb/IIIa antagonists

GP IIb/IIIa antagonists include abciximab, eptifibatid and tirofiban. They bind to platelet GP IIb/IIIa receptors causing rapid inhibition of platelet aggregation when administered intravenously. Abciximab, the most frequently used drug of this class, has a plasma half-life of 12 h and complete platelet recovery occurs 48 h after discontinuing the drug. The effect of eptifibatid and tirofiban on platelet recovery ranges from 4–8 h after stopping these drugs (Patrono *et al*, 2004). There are no studies or known case reports of SEH occurring during CNB with these agents. Most guidelines do not advise their use during CNB as most patients would also have received a combination of aspirin, clopidogrel and/or heparin. If GP IIb/IIIa antagonists have been administered, the platelet count should always be checked prior to CNB as these agents can cause profound thrombocytopenia (Patrono *et al*, 2004). CNB should not be performed until platelet function has recovered (48 h for abciximab and 8 h for eptifibatid/tirofiban).

#### Postoperative management of SEH

Although back pain is reported to be the most common and earliest symptom of SEH (Kreppel *et al*, 2003), most patients have instead reported sensory-motor deficit of the lower limbs or bowel and bladder dysfunction (Vandermeulen *et al*, 1994; Horlocker & Wedel, 1998; Moen *et al*, 2004). The onset of symptoms ranges from 15 h to 3 d after the initiation of heparin (Vandermeulen *et al*, 1994; Horlocker & Wedel, 1998) and the investigation of choice for diagnosing SEH is Magnetic Resonance Imaging (MRI) (Larsson *et al*, 1988).

The ultimate treatment is emergency surgical decompression by laminectomy.

Local written guidelines regarding the use of CNB in patients with altered coagulation should be in place in all hospitals (SIGN 2002). Neurological observation should be performed every 4 h (Meikle *et al*, 2008) and continue for at least 24 h after catheter removal (Horlocker *et al*, 2003). Any motor or sensory deficit that develops during CNB, in the absence of a recent local anaesthetic bolus, should be treated as indicative of SEH and the epidural infusion should be stopped immediately (Meikle *et al*, 2008). If there is no recovery of neurological symptoms within 4 h an urgent MRI should be performed (Christie & McCabe, 2007) and ideally surgery should take place within 8–12 h of developing symptoms in order to improve the chances of recovery (Vandermeulen *et al*, 1994; Lawton *et al*, 1995).

#### Conclusion

The key issue in the management of anticoagulated patients during CNB is how to balance the risk of VTE on the one hand and the risk of SEH on the other (Table V). If CNB is to be performed one must ensure that (i) near-normal haemostasis is restored prior to catheter insertion/removal and (ii) post-CNB anticoagulation is carried out neither too early nor too

**Table V.** Summary of management of anticoagulated patients during CNB.

1. Individual assessment for the risks of venous/arterial thrombosis against the benefit of CNB
2. Individual assessment for bleeding risk prior to CNB
3. Avoid multiple anticoagulant/antiplatelet therapies prior to CNB
4. Ensure normal haemostasis prior to catheter insertion/removal
5. Respect time interval for cessation (initiation) of anticoagulants prior to (after) catheter insertion/removal
  - a) UFH (prophylactic and therapeutic)
    - Stop 4 h prior to catheter insertion/removal
    - Restart at least 1 h after catheter insertion/removal
  - b) LMWH
    - Stop 12/24 h (prophylactic/therapeutic respectively) prior to catheter insertion
    - Restart at least 4 h after catheter insertion/removal
  - c) Fondaparinux
    - Start 6–8 h after catheter insertion
    - Stop 36 h prior to catheter removal
    - Restart 12 h after catheter removal
  - d) Warfarin
    - Stop 4–5 d prior to catheter insertion and perform CNB if INR < 1.4
  - e) Antiplatelets
    - Aspirin on its own is not contraindicated
    - Stop Clopidogrel/Ticlopidine/Abciximab/Tirofiban and Eptifibatid for 7 d/14 d/48 h/8 h/8 h respectively, prior to CNB
6. Close neurological monitoring for signs of SEH after CNB

CNB, central neuraxial block; UFH, unfractionated heparin; h, hours; LMWH, low molecular weight heparin; d, days; INR, international normalized ratio; SEH, spinal epidural haematoma.

late, so as to avoid SEH and suboptimal thromboprophylaxis, respectively. Paying attention to: the recommended time intervals for the cessation/initiation of the anticoagulants; careful patient selection; individual risk assessment and pharmacological knowledge of the anticoagulant agents are all crucial factors in the safe administration of CNB. These elements, taken together, constitute an integrated strategy for improving patient management during CNB.

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## COMMENTARY

# Perioperative management of antithrombotic therapy: lifting the fog

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The perioperative management of patients who are receiving an antithrombotic drug, typically a vitamin K antagonist (VKA) or aspirin with/without clopidogrel, can be aptly described as foggy. Questions about the risks and benefits to patients with different management strategies abound, definitive answers about such risks and benefits are few, and uncertainty dominates. The fog surrounding best practices for perioperative anticoagulation is likely to frustrate clinicians, perhaps leading some to consider this clinical problem as being of peripheral interest and destined to be obviated by emerging alternatives to VKAs. It is a more central issue, however, for many front-line clinicians, whether general practitioners dealing with patients who need dental extraction or anesthetists who are planning spinal anesthesia prior to major surgery. Of the more than two million people in North America who are receiving long-term therapy with a VKA, a considerable proportion will require its temporary interruption [1]. This number is likely to increase, as is the number of persons who are receiving long-term anticoagulants and such patients are those most likely to require a surgical or other procedure.

To establish best practices for VKA-treated patients who require perioperative VKA interruption for an elective surgical or other procedure, a two-pronged strategy is required. One approach consists of randomized trials, which aim to address big-picture questions, such as what is the optimal heparin bridging strategy after surgery, and should heparin bridging be given at all during interruption of a VKA? The other approach consists of observational studies, which aim to study individual procedures and to determine how perioperative anticoagulation should be tailored to fit that procedure.

In this issue of the *Journal of Thrombosis and Haemostasis*, Witt *et al.* [2] have adopted the second approach to focus on anticoagulant management around polypectomy. Their work

has helped to enrich a sparse but burgeoning literature that is assessing perioperative anticoagulation in individual but common procedures, such as dental extraction and related procedures, cataract removal, and pacemaker or defibrillator implantation [3–5].

Gastrointestinal endoscopic procedures are among the commonest procedures that VKA-treated patients undergo. They can be classified as interventional (e.g. gastric or colonic polypectomy, sphincterotomy, esophageal stricture dilatation, percutaneous gastrostomy), which have a high (1–6%) risk for bleeding, or diagnostic (e.g. endoscopy and biopsy, cholangiopancreatography), which have a low (< 1%) risk for bleeding [6].

In managing VKA-treated patients who require polypectomy (or any other non-surgical or surgical procedure for that matter), there are three principal management options. The first is to continue the VKA without interruption, although most clinicians will adjust the dose downwards so that the International Normalized Ratio is targeted to 2.0–2.5 at the time of a minor procedure and to 1.5–1.9 at the time of a more extensive procedure. The second approach is to stop the VKA 4–6 days preprocedure and resume it on the evening of or day after the procedure. The third approach involves stopping the VKA and administering a short-acting heparin, typically low molecular weight heparin, before and after surgery during the 8–10 days when the anticoagulant effect of VKA recedes and is restored; this is referred to as 'bridging anticoagulation'. Finally, there are variations on these approaches, such as 'one-tailed bridging', when a heparin is given before but not after surgery or when a VKA is resumed with a loading (double the usual) dose during the first two postoperative days.

The study by Witt *et al.*, although not determining which of these approaches to take, is an important step towards defining polypectomy-specific risks and alerting clinicians as to the possible perils with perioperative anticoagulant management. The investigators assembled two cohorts: 425 VKA-treated patients and 800 age-matched non-anticoagulated patients, all of whom had elective colon polypectomy. The principal finding

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that VKA-treated patients had an 11-fold higher risk for postprocedure bleeding than the non-anticoagulant group (2.6% vs. 0.2%) is surprising, especially as VKA-treated patients received standardized perioperative management, which included stopping the VKA 4 days before the procedure and, if heparin bridging was administered, giving the last preprocedure dose 24 h beforehand and the first postprocedure dose on the next day [7]. Moreover, the bleeds were serious, as most required urgent colonoscopy to stop bleeding, typically from an ulcerated polyp stalk. Only two predictors of bleeding were identified, consisting of VKA use and removal of multiple polyps, neither of which is a modifiable risk factor. Thromboembolic events were rare, occurring in < 0.5% of both groups, and the study was underpowered to detect an effect (if any) of perioperative interventions such as heparin bridging to prevent thromboembolism.

Although the study could not provide a definitive polypectomy-specific perioperative anticoagulation strategy, there are some things that clinicians can do to minimize perioperative bleeding in such patients. First, consider stopping the use of drugs that may affect hemostasis. Witt found that patients with coronary artery disease, in whom aspirin is often coadministered with a VKA [8], were at higher risk for bleeding. Although evidence is lacking that aspirin, on its own, increases postpolypectomy bleeding, it may do so in the setting of coadministered VKA therapy [9]. Second, consider delaying the resumption of (or avoiding altogether) postprocedure bridging. Witt found a higher proportion of bridged patients than of non-bridged patients who bled (5.6% vs. 2.0%) and, although the difference was not statistically significant, it is plausible that 18–24 h postpolypectomy may be too early for resumption of therapeutic-dose heparin bridging [7]. Third, consider how hemostasis is achieved after a procedure. After a polyp is transected with a snare device, an eschar forms at the base of the stalk that subsequently dislodges, leaving a stump that may be still oozing blood. If this 'scab' dislodges at a time when there is a therapeutic level of anticoagulation, 3–4 days postpolypectomy, one would expect anticoagulant-potentiated bleeding [10]. This lends further support for delayed resumption of VKAs after polypectomy and, in patients who are bridged, delayed resumption of heparin, perhaps for 72 h after the procedure. Finally, ask your proceduralist colleague to consider ways of minimizing bleeding. Although electrocautery of the polyp stalk blood vessels ('hot snare') did not appear to decrease bleeding in Witt's study, as it may in fact promote ulceration and subsequent bleeding, perhaps another intervention, such as endoscopic clips applied to the transected stalk, which are typically retained for weeks, can prevent bleeding in patients who are at increased risk for bleeding or in whom heparin bridging is planned [11].

At this point, many readers may be concerned that the aforementioned measures to reduce postpolypectomy bleeding can even be suggested on the basis of what are inferences or weak (Grade 2C) evidence. It is acknowledged that additional research, preferably through well-designed observational stud-

ies, is needed to determine best practices in VKA-treated patients who are having polypectomies. Waiting for randomized trials to provide definitive answers in such patients, although ideal, is unrealistic, given that several interventions can be potentially tested to minimize bleeding (four were proposed earlier), and undertaking separate trials to address each of these is impracticable. Furthermore, although new oral direct thrombin and anti-factor Xa inhibitors will address many of the drawbacks of VKAs, perioperative management will remain problematic, owing to drug pharmacokinetic properties that vary with age and renal function, and uncertainty about ways of measuring these drugs' anticoagulant effect perioperatively using readily available laboratory tests [12].

With regard to defining best practices for perioperative anticoagulant management, work is in progress with studies such as PERIOP-2 [13] and BRIDGE [14], large randomized trials that are aimed at defining the role of low molecular weight heparin bridging in patients who require VKA interruption before surgery on a broader scale. Studies such as those by Witt *et al.*, although smaller in scope and with a lower ranking on the evidence hierarchy, are of integral importance to the practicing clinician, as they help to define risks around a procedure and to guide current management. In future, such observational studies will also help clinicians to apply the results of ongoing and future randomized trials to individual patients. Ultimately, the collective objective of such work is to help lift the fog that surrounds perioperative anticoagulant management and improve patient care.

### Acknowledgements

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The author states that he has no conflict of interest.

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## Management of Excessive Perioperative Bleeding & Clotting

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### Assessment of coagulation <sup>(1)</sup>

#### Inherited Bleeding Disorders

- a. Von Willebrand's disease (vWD)
- b. Haemophilia
- c. Thrombocytopenia <sup>(2)</sup>

#### Acquired Bleeding disorders <sup>(3,4)</sup>

**iatrogenic** due to absolute or relative overdoses of:

Drug	Reversal
a. Warfarin	Vit K, Haemosolvex®, Plasma
b. Non-selective NSAIDs	Platelets
c. Heparin	Protamine.
d. Factor Xa inhibitors <sup>(5)</sup> Low molecular weight heparins (LMWHs) Fondaparinux Oral rivaroxaban	Partial with protamine Nil Specific
e. Factor IIa inhibitors <sup>(5)</sup> Oral dabigatran IV argatroban / hirudin [not available in SA]	Nil Specific

#### Trauma / Sepsis

- a. **Increased consumption** –Disseminated intravascular coagulation DIC <sup>(6)</sup>.
- b. **Dilution** – exacerbated by the deadly triad of trauma: coagulopathy, hypothermia and acidosis <sup>(7)</sup>.

#### Elective Screening for bleeding disorders <sup>(8)</sup>:

##### Qualitative tests

Factor deficiencies

- a. aPTT vWD; ↓Factors VIII, IX & XI
- b. PT / INR ↓Vit K, Mild liver dysfunction, ↓Factor VII
- c. Both prolonged ↓↓ Vit K, Sever liver dysfunction. ↓ Factors II, V, X

##### Quantitative tests

Substrate deficiency (↓synthesis / ↑consumption)

- d. Fibrinogen
- e. Platelets

### Functional tests

- f. High shear / Arterial / Platelet: Platelet Function Analyser (PFA)  
g. Low shear / Venous / Cascade: Thromboelastogram (TEG) / Automated; ROTEG / ROTEM

### Emergency Screening for bleeding disorders <sup>(10)</sup>

#### Investigation

Platelets to  $>50 \times 10^9$

aPTT  $> 2.5 \times$  control

Fibrinogen

<1:

1-2:

>2:

#### Intervention

Platelet transfusion

Check fibrinogen

Cryoprecipitate

Plasma (FDP / FFP)

Tranexamic acid [rFVIIa]

### Excessive clotting

**Acquired thrombophilias** <sup>(10)</sup> are due to changes in the vessel wall blood components and/or flow.

The most important individual components include:

1. **Smoking**
2. **Oestrogen**
3. **Malignancy**
4. **Previous Thrombosis**
5. **Immobilisation**
6. **Other: Diabetes; Sepsis; Trauma; ↑Cell / Factor synthesis**

The American College of Chest Physicians (ACCP) <sup>(10)</sup> approach, endorsed by an expert panel in South Africa <sup>(11)</sup>, is to subdivide patients presenting for surgery into three risk groups – low, intermediate and high. The surgical procedures patients will undergo can be classified in the same way providing a 3x3 table (below) from healthy patients undergoing minor surgery who are at low risk of VTE to patients at high risk of thrombosis undergoing major surgery who will require pharmacological prophylaxis to prevent fatal VTE.

## Surgical Procedure

	<b>Minor</b> Eye Body surface	<b>Intermediate</b> Upper abdominal, Thoracic	<b>Major</b> Pelvic, Hip Leg
<b>Thrombotic Risk</b>			
<b>Low</b> Age <60 Mobile No significant Comorbidities	Mobilisation	Mobilisation Mechanical	Mobilisation Mechanical Pharmacological
<b>Intermediate</b> Age > 60 Limited mobility Well controlled Comorbidities	Mobilisation	Mobilisation Mechanical Pharmacological	Mobilisation Mechanical Pharmacological
<b>High</b> Age > 60 Immobile Poorly controlled Comorbidities	Mechanical Pharmacological Extended duration	Mechanical Pharmacological Extended duration	Mechanical Pharmacological Extended duration & Dose

VTE prophylaxis may be simplified by using this table

		<b>Risk of Bleeding</b>	
		<b>Low</b>	<b>High</b>
<b>Risk of Thrombosis</b>	<b>Low</b>	LMWH	UFH
	<b>High</b>	LMWH + ICD	ICD Add LMWH With ↓ Risk

Excessive clotting is dangerous in the presence of risk factors including <sup>(12)</sup>:

1. Previous DVT
2. Mechanical Heart valves
3. Atrial fibrillation where risk is further subdivided by the CHADS score:

Condition	Points
C Congestive heart failure	1
H Hypertension: BP above 140/90 mmHg (Or controlled on medication)	1
A Age $\geq 75$ years	1
D Diabetes Mellitus	1
S2 Prior Stroke or TIA	2
Risk: Low 0      Intermediate 1-2      High $>2$	

### LMWH (Enoxaparin) Regimes <sup>(12)</sup>

Standard Prophylaxis:	0.5mg/kg	Daily	DVT / VTE prophylaxis
Extended Prophylaxis	0.5mg/kg	BD	Previous VTE / AF (CHADS $>0$ ) Mech Valve
Therapy (Thrombolytic)	1mg/kg	BD	Current VTE / ACS

### Excessive clotting on therapeutic anticoagulation

#### Congenital thrombophilias <sup>(13)</sup>

The commonest inherited thrombophilias are **Activated protein C resistance**, **Factor V Leiden** and the inappropriately named **Lupus Anticoagulant** or **Antiphospholipid Antibody**. Less common are deficiencies of protein C and S and mutations of prothrombin and fibrinogen.

#### Platelets:

- i. **Thrombotic thrombocytopenic purpura (TTP)** arise from an imbalance between vWF and the enzyme ADAMTS13. Early plasmapheresis reduces mortality from  $>90\%$  to  $<10\%$  so a patient presenting with a fever and thrombocytopenia should be referred to a centre that can deliver plasmapheresis as soon as possible.
- i. **HIT Heparin induced thrombocytopenia (HIT)**  
Arises 5-14 days after the initiation of heparin therapy due to antibodies that activate platelet factor 4 (PF-4) or heparin resulting in thrombosis with a falling platelet count. The incidence is highest with unfractionated heparin but can occur with LMWH.

#### Management

- i. **Mechanical** - The major problem with lower limb DVT is fatal or disabling pulmonary embolisation. This may be prevented by the deployment of an inferior vena cava filter, which can be permanent or retrievable.
- ii. **Pharmacological** – heparin is ineffective and needs to be withdrawn in HIT. The most effective anticoagulants are the direct thrombin inhibitors hirudin and argatroban (neither available in SA) and dabigatran (only available in an oral formulation).

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1

### Principles of perioperative coagulopathy

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**Keywords:**

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coagulation factors  
fibrinogen  
platelets  
intravenous fluids  
acidosis  
hypothermia  
coagulation tests  
viscoelastic methods

Perioperative coagulopathy impacts on patient outcome by influencing final blood loss and transfusion requirements. The recognition of pre-existing disturbances and the basic understanding of the principles of and dynamic changes of haemostasis during surgery are pre-conditions for safe patient management. The newly developed cellular model of coagulation facilitates the understanding of coagulation, thereby underscoring the importance of the tissue factor-bearing cell and the activated platelet. Amount of blood loss as well as amount and type of fluids used are the main factors involved in the development of dilutional coagulopathy, which is the most frequently observed cause of coagulopathy in the otherwise healthy surgical patient. Recent data from studies using viscoelastic coagulation studies confirm the central role of fibrinogen in stable clot formation and provide essential knowledge about its changes during blood loss and fluid administration. Besides early decrease in clot firmness during mild-to-moderate dilution, profound dilution results in a critical decrease in thrombin generation as well as a reduction in numbers and function of platelets. Although our knowledge of perioperative coagulopathy has dramatically increased over the past few years, several questions such as critical thresholds for fibrinogen, platelets, impact of FXIII and TAFI remain unanswered and need to be investigated further.

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Since the late 1980s, there has been consistent growth in the evidence showing that allogeneic blood transfusions frequently needed in surgical patients are associated with considerable adverse effects. Besides the nowadays small risk of transmitting infectious diseases, transfusion-induced

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immunomodulation and its consequences such as increased risk for infection, persistent microchimaerism and recurrence of cancer remain even today serious side effects, as well as transfusion-related circulatory overload (TACO) and lung injury (TRALI).<sup>1–4</sup> Because the competence of the haemostatic system contributes substantially to final blood loss and transfusion requirements, knowledge of the underlying mechanisms of coagulopathy is an important factor for successfully employing concepts aimed at minimising patient exposure to allogeneic blood transfusion. Importantly, surgical patients are not only prone to develop coagulopathic bleeding, but they are also at risk for thrombosis, especially in the postoperative period.<sup>5</sup> Defining risk profiles or discussing the need for postoperative thrombosis prophylaxis is, however, beyond the scope of this article.

Disruption of endothelium and exposure of tissue factor and collagen to the blood stream initiate a complex process starting with platelet adhesion and leading to the localised formation of a stable clot within a few minutes. Keeping in mind the complexity of the system and of control mechanisms, many anaesthetists view haemostasis as a highly sophisticated black box, impossible to understand. By discussing simplified models of haemostasis and the commonly observed pattern of changes, the present review intends to encourage anaesthetists to acquire a basic understanding of the dynamic changes of haemostasis as generally occurring during surgery.

## **Preoperative evaluation**

### *Patients' history and physical examination*

Pre-existing bleeding disorders most frequently result from disturbed platelet function or von Willebrand disease Type I (vWD).<sup>6</sup> These are overlooked if the results of platelet count and routine coagulation tests are used to assess haemostasis only. Many platelet disorders result from anti-platelet medication or co-existing diseases and are sufficiently characterised, while diagnostic assessment of hereditary platelet disorders can be difficult.<sup>7</sup> Moreover, to confirm or exclude the various types of vWD, time-consuming specific laboratory tests may be needed and, thus, intra-operative diagnosis in the acutely bleeding patient is not feasible.<sup>8</sup> Therefore, patients' history (including the patients' and the families' bleeding history) and a careful preoperative physical examination are essential for timely detection of patients susceptible to pre-existing haemorrhagic disorders.<sup>9</sup> However, mild coagulation factor deficiencies and platelet dysfunction can be aggravated by surgical trauma and fluid administration, thus, first manifesting themselves during surgery.

### *Co-existing diseases susceptible for concomitant haemorrhagic disorders*

Co-existing diseases such as severe infection/sepsis, hepatic or renal insufficiency, amyloidosis, thyroid dysfunction, connective tissue disease, immunologic, myeloproliferative and neoplastic diseases or cardiovascular diseases with turbulent circulation should alert the anaesthetist to the possible presence of disseminated intravascular coagulation (DIC), imbalances in fibrinolysis, thrombocytopenia/thrombocytopeny, coagulation factor deficiencies or acquired von Willebrand syndrome.<sup>10</sup> Among these, diagnosis of acquired von Willebrand syndrome is challenging because it requires sophisticated laboratory tests in the presence of severe bleeding that persists until specific treatment is administered.<sup>11,12</sup> Acquired von Willebrand syndrome is categorised as type 1 (qualitative lack of vWF) or more commonly as type 2 disorder, which refers to a reduction in the high-molecular-weight von Willebrand factor multimers (HMW:vWF) and a decrease in platelet-dependent functions. The underlying aetiologies include auto-antibodies to vWF, adsorption of vWF into tumour cells or activated platelets, increased proteolysis and mechanical destruction of HMW:vWF multimers under high shear stress.

### *Standard laboratory screening*

Although routine coagulation tests for prothrombin time (PT) and activated partial thromboplastin time (aPTT) show poor correlation with bleeding risk, they are traditionally performed preoperatively.<sup>13,14</sup> Routine coagulation tests show good reproducibility and are useful to guide therapy with

oral anticoagulants or unfractionated heparin. These tests were initially developed to detect and differentiate the deficiency of coagulation factors of the intrinsic or extrinsic pathway with high sensitivity. Importantly, they do not reflect anticoagulatory proteins, vWD (except types with decreased FVIII) or deficiency of FXIII. However, only a few patients will exhibit congenital coagulation factor deficiency. Haemophilia A, B and von vWD represent 95–97% of all congenital deficiencies of coagulation factors, while the remaining defects are very rare.<sup>15</sup>

Usually these patients have shown bleeding symptoms since early childhood, and diagnosis is established and treatment already predetermined by a haematologist. Of course, patients with end-stage liver disease or those receiving oral anticoagulants, unfractionated heparin or exhibiting vitamin K deficiency will present with pathological PT or aPTT values. Associated with severe bleeding, an acquired coagulation factor deficiency can result from antibodies directed against individual coagulation factors.<sup>16</sup> Acquired coagulation factor deficiency should be suspected in patients with unexplained pathological results for PT or aPTT, history of previous exposure to fibrin glue or spontaneous soft-tissue or retroperitoneal haematoma. Diagnosis is confirmed by plasma change tests, low concentration of a single coagulation factor and detection of the specific inhibitor. Lastly, among the preoperatively assessed laboratory parameters, fibrinogen concentration is of interest because patients showing low initial fibrinogen concentrations are prone to develop fibrinogen deficiency already at much smaller blood loss volumes than are patients with initially high fibrinogen levels.<sup>17</sup>

Besides impairment of platelet function, thrombocytopenia may be present. In general, thrombocytopenia may result from decreased synthesis or increased consumption. However, thrombocytopenia is most frequently acquired and associated with immunological and infectious diseases, radiation, bone-marrow disease, uraemia, liver disease, medication, transfusion, vWD Type IIB or disseminated intravascular coagulation.<sup>10</sup>

### Basic understanding of the clotting process

The basic pre-conditions for clot formation are physiological milieu, highly effective activators and accelerators, localising matrix, sufficient substrate and stabilising factors (Fig. 1). In addition, clot formation overshoot is prevented by several limiting control mechanisms and the activity of the counterbalancing fibrinolytic system.

The several steps of the complex coagulation cascade cited in every textbook describe the initiation of coagulation as it occurs in test tubes and are thus useful in explaining how coagulation tests work. By contrast, the newly developed cellular model of coagulation<sup>18</sup> enables a better understanding of the clotting process as it occurs *in vivo* (Fig. 2).

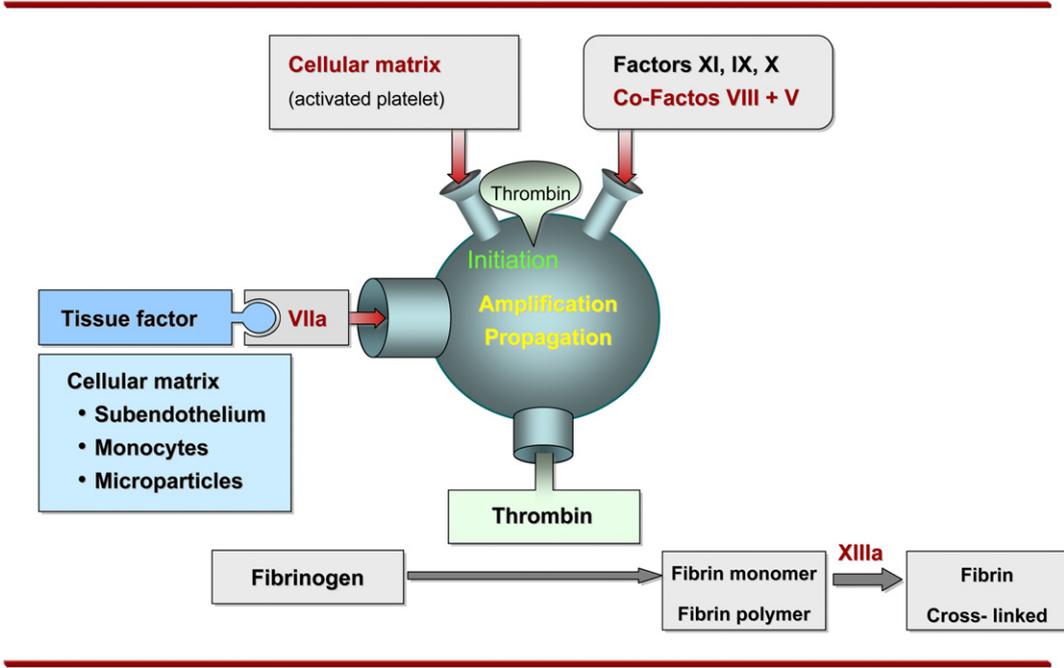
Although closely linked, primary and secondary haemostases are separately discerned for didactic reasons.

#### Primary haemostasis

Simply stated, exposure of subendothelial collagen initiates platelet spreading, platelet adhesion and shape change, platelet granule secretion and initial platelet aggregation. These initial steps are facilitated by the bridging activity of vWF, the binding of fibrinogen to platelet glycoprotein receptors (GPIIb/IIIa) and the small amount of thrombin, which is built up during the initiation of coagulation.

#### Secondary haemostasis: thrombin and clot formation

During initiation of coagulation, the exposed tissue factor (TF) and circulating FVIIa form the TF/FVIIa complex (Fig. 2). This complex results in the formation of coagulation factors FVa and FXa and leads to conversion of prothrombin to thrombin in small amounts. During amplification and propagation of coagulation, this initial thrombin activates adherent platelets, facilitating platelet granule release and binding of coagulation factors, fibrinogen and Ca<sup>++</sup>. In addition, initial thrombin enables formation of FVIIIa, promoting more FXa formation. In parallel, thrombin-induced FXIa activates FIXa, which, in turn, increases FXa formation. Lastly, thrombin activates FVa and, in the presence of FXa and



**Fig. 1.** The thrombin "reactor". Tissue factor-bearing cells expose tissue factor to the blood stream, resulting in complex formation with circulating VIIa. By activating factors X and V a small amount of thrombin is formed. This initial thrombin activates platelets and factors XI, IX, X and co-factors VIII and V resulting in a thrombin burst necessary for cleavage of fibrinogen. The formed fibrin monomers polymerize spontaneously and are finally cross-linked by means of XIIIa.

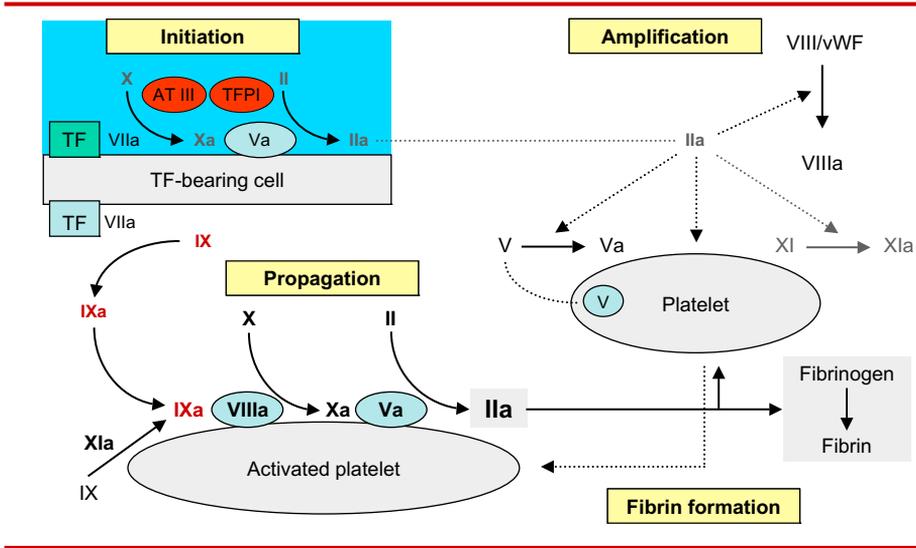


Fig. 2. The cellular model of coagulation according to M. Hoffman, Blood Reviews 17: S1–S5; 2003.

$\text{Ca}^{++}$  bound to the surface of activated platelets, large amounts of prothrombin are rapidly converted to thrombin (thrombin burst).<sup>18</sup>

Most thrombin is formed during clot formation.<sup>19</sup> Every activated platelet exposes several thousand glycoprotein receptors (GPIIb/IIIa) for effective binding of fibrinogen and thus primary platelet aggregation. Following sufficient thrombin generation, fibrinogen is cleaved and the resulting fibrin monomers spontaneously polymerise to form uncross-linked fibrin. In fibrinogen knockout mice, afibrinogenemia results in formation of unstable platelet plugs that are dislocated by shear forces and, thus, are able to cause paradoxical arterial thrombosis.<sup>20</sup> Frequently overlooked, the final stability of the formed platelet/fibrin clot determines effective cessation of bleeding. The main stabilising factors are the thrombin-induced factors FXIIIa and thrombin-activatable fibrinolysis inhibitor (TAFIa).<sup>21</sup> FXIIIa stabilises the clot by catalysing fibrin cross-linking (cross-linked fibrin) and incorporating anti-fibrinolytic proteins into the clot. TAFIa decreases fibrinolysis by reducing fibrin's binding sites for plasminogen and tissue plasminogen activator (t-PA).

#### Control mechanisms for overt coagulation activation (Fig. 3)

Broadly speaking, initial thrombin formation is limited by tissue factor pathway inhibitor (TFPI) and antithrombin (AT), which neutralise TF/FVIIa complex, FXa and thrombin. Endogenous heparin sulphate or exogenous heparin serve as co-factors for AT by increasing the speed of reaction dramatically. Interestingly, thrombin is also bound to the formed fibrin; thus, excessive thrombin levels are limited by intact fibrin formation (antithrombin I).<sup>22</sup>

Binding of thrombin to endothelial thrombomodulin (TM) decreases the various pro-coagulant effects of thrombin and activates circulating protein C to activated protein C (aPC). aPC and its co-factor free protein S (PS) slow thrombin formation by inactivating the thrombin-accelerating co-factors FVIIIa and FVa (Fig 3 VIIIi, Vi).

#### Fibrinolytic system

Activation of circulating plasminogen to plasmin by t-PA, urokinase (u-PA), FXIIa or kallikrein results in proteolytic lysis of cross-linked fibrin, formation of D-dimers and even defibrination in severe

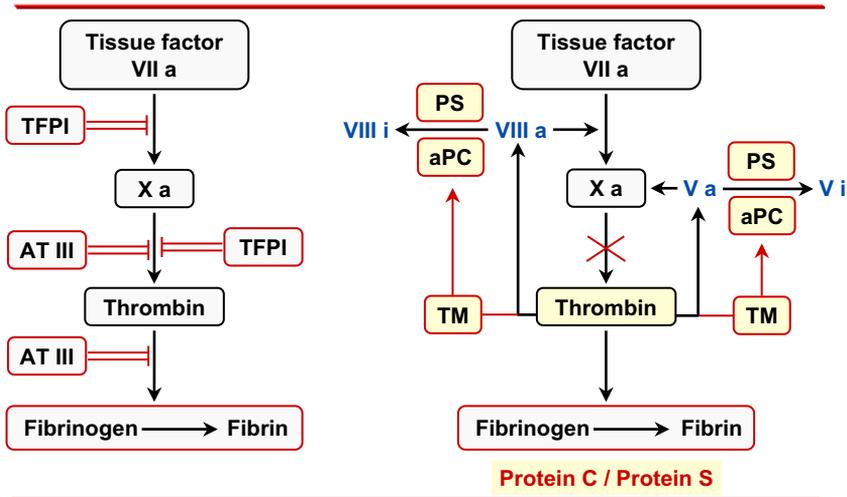


Fig. 3. Control of thrombin formation.

cases of hyperfibrinolysis due to plasmin's ability to also degrade fibrinogen. However, neutralising systems usually prevent the development of this severe hyperfibrinolysis. They consist of  $\alpha$ -anti-plasmin-mediated binding of free plasmin and plasmin activator inhibitor (PAI), which inactivates plasminogen activators and the activity of the mentioned clot stabilising factors FXIIIa and TAFIa.

In summary, thrombin is the key enzymatic motor of the clot formation process and fibrinogen is the major substrate during clotting, while platelets are the localising matrix, contribute to thrombin formation and are also a necessary substrate. To arrest bleeding the formation of a stable fibrin clot is the *sine qua non*. Even the highest and sustained thrombin burst is wasted if insufficient substrate is available, as demonstrated *in vitro* and *in vivo* during administration of rFVIIa.<sup>23,24</sup>

### Basic understanding of increased intra-operative bleeding

Increased bleeding can be localised or systemic, and the main underlying problem can be surgical or related to impaired haemostasis. However, major surgical bleeding will quickly be accompanied by impaired haemostasis, as will moderate or occult continuous bleeding, albeit more slowly. During coagulopathic bleeding, the main underlying mechanism might be related to impairment of primary haemostasis, thrombin generation, deficiency/malfunction of substrates, decreased resistance to fibrinolysis or presence of hyperfibrinolysis. Furthermore, surgically induced endothelial lesions and influx of coagulation activating substances and microparticles activate coagulation and fibrinolysis, resulting in consumption of platelets and fibrinogen and increase of D-dimers. However, in the otherwise healthy surgical patient, activation of coagulation is mainly localised, which is in contrast to the clinical picture of disseminated intravascular coagulation (DIC). The coagulation system is closely linked to the inflammatory system. Therefore, patients presenting with infection, systemic inflammatory syndrome or severe sepsis show a completely different pathology, which is mentioned in a simplified manner here. In these patients, some of the haemostasis players are up-regulated while others are down-regulated.<sup>25</sup> The resulting haemostatic competence changes dynamically with the stage of the underlying disease, varying from activated hypercoagulable states with diffuse microvascular thrombosis to consumptive hypocoagulability.

It is well known that patients on continuous anti-platelet medication show increased transfusion requirements and CPB-induced platelet dysfunction is a recognised factor that contributes to blood loss

during and after cardiac surgery.<sup>26</sup> However, the question as to whether relevant platelet dysfunction occurs during other types of surgery remains to be answered. The platelets' contribution to haemostatic competence, management of patients under anti-platelet therapy, as well as the special features of the coagulopathy of trauma are discussed as specific topics in this issue.

## Dilutional coagulopathy

Dilutional coagulopathy mainly results from the synergistically and commonly combined effects of blood loss and fluid administration, leading to decreased quantity and quality of substrates, altered balance of activators and anticoagulants and probably reduced clot stability.

### Substrate deficiency

Platelets and fibrinogen determine clot firmness, which is also influenced by FXIII. Clinical studies clearly showed that severe thrombocytopenia usually develops in the late course of blood loss (>150% of blood volume), that fibrinogen deficiency develops far before critical levels of other coagulation factors occur (>200% of blood volume) and that low fibrinogen concentrations and platelet counts are the most sensitive predictor of diffuse microvascular bleeding.<sup>27,28</sup> The fact that fibrinogen is the first factor to reach critical levels is explained by the large amounts needed for clot formation (Table 1), the limited increase in fibrinogen synthesis and the simultaneously increased fibrinogen breakdown during blood loss.<sup>29</sup> Hiippala and co-workers first described in 1995 that during blood loss, fibrinogen concentrations become critically low (<1 g l<sup>-1</sup>) after a median blood loss of more than 100% of the calculated blood volume.<sup>30</sup> However, all investigated patients showed high normal preoperative fibrinogen levels and several also exhibited supra-normal levels. By contrast, the study by McLoughlin investigating patients with borderline fibrinogen levels found critical fibrinogen concentrations already at a blood loss of about 50% of their blood volume.<sup>31</sup> The assumption that initial fibrinogen concentration determines the percentage of lost blood volume at which a critically reduced concentration occurs was confirmed by a mathematical model that was also validated by patient data.<sup>17</sup> Most textbooks and review articles cite a fibrinogen value below 1 g l<sup>-1</sup> as critical with regard to increased bleeding.<sup>32,33</sup> However, this figure refers to the findings of a small, old study in which all of four patients developed profuse microvascular bleeding and concomitantly showed fibrinogen values below 0.8 g l<sup>-1</sup>.<sup>28</sup> Considering fibrinogen's significance for clot firmness, scepticism arises as to whether a threshold of fibrinogen concentration set at one-third of normal enables sufficient clot formation in surgical patients.<sup>34</sup> Indeed, data from patients

**Table 1**

Physiological concentrations of coagulation factors and their half-life.

Coagulation factor	Plasma concentration (mg/L)	Half-life (hours)
II	48–123	48–123
VII	0.5	3–4
IX	4	18–30
X	10	38
V	4–14	4–36
VIII	0.15	8–12
XI	2–7	60–80
XII	15–47	40–50
vWF	5–10	6–12
XIII	2	192
Fibrinogen	2000–4000	72
AT	0.15–0.39	70
PC	2–6	6–8
PS	20–25	24–58
TFPI	0.06–0.180	1.5

Adopted from Barthels M, Poliwoda H. Gerinnungsanalysen. 6th edn; pp 245–325. Stuttgart New York: Georg Thieme Verlag 1998.

undergoing neurosurgery, cardiac surgery or exhibiting peripartur bleeding clearly show increased blood loss when fibrinogen concentration drops below  $2 \text{ g l}^{-1}$ .<sup>35–38</sup> Interestingly, this was the same threshold found to be associated with significant increase in clot firmness *in vitro*.<sup>39</sup> Fibrinogen measurements are poorly standardised, especially at the very low and the very high levels, and are influenced by the presence of colloids and fibrin-degradation products and do not necessarily correlate with fibrin polymerisation.<sup>40–42</sup> Therefore, the establishment of a critical functional threshold for fibrinogen/fibrin polymerisation might be more useful. Our own clinical experience shows that diffuse microvascular bleeding appears when fibrin polymerisation (measured by the viscoelastic ROTEM technique) drops below a MCF of 7 mm in a FibTEM test, a value that usually corresponds to a fibrinogen concentration of  $1.5 \text{ g l}^{-1}$ .<sup>42,43</sup> This clinical experience has been recently confirmed by results of a study conducted in women developing postpartum haemorrhage.<sup>44</sup> It should be noted that fibrinogen concentrations are increased in elderly patients and those with inflammation, malignant disease and in various other conditions. In these patients, huge blood loss can be tolerated until fibrinogen becomes critically low.

As with fibrinogen, the critical threshold for platelet numbers in surgical patients are currently not known and refer mainly to consensus statements or expert opinions.<sup>32</sup> A recent experimental study showed that high-dose fibrinogen compensated for reduced clot firmness during thrombocytopenia and also slowed blood loss resulting from inflicted liver injury.<sup>45</sup> Furthermore, data from Lang and co-workers indicate that fibrinogen increases clot strength independently of platelet count.<sup>46</sup> Therefore, the actual relationship between the two substrates might be more important than the concentration of fibrinogen or platelet counts alone and the functionality of platelets seems to be more relevant than numbers of platelets. As FXIII is also involved in clot firmness, variability of clot firmness further increases, which might explain the difficulties in establishing clear thresholds for single components such as fibrinogen or FXIII in surgical patients. Interestingly, Gerlach found the highest incidence of re-bleeding and need for revisions in neurosurgical patients when all three determinates of clot firmness, that is, fibrinogen, FXIII and platelets, were decreased, although the decrease was moderate for each of these factors.<sup>35</sup>

### Activator deficiency

The observations that pro-coagulant coagulation factors are commonly critically reduced in the late stages of blood loss only<sup>28,30,42,43</sup> might be explained by the facts that they are needed at low concentrations (Table 1), are decreased through blood loss and dilution but, as enzymes, are not consumed by the reaction they promote. In addition, the only coagulation factor needed at a relatively high concentration is prothrombin and its concentration shows a linear relationship to thrombin generation.<sup>47</sup> Prothrombin is usually present at relatively high plasma levels and also shows a relatively long-lasting half-life (Table 1). By contrast, small concentrations of other coagulation factors are needed for sufficient thrombin generation.<sup>48</sup> FVIII deficiency rarely occurs because of endothelial release and the acute phase response, and FV is stored in platelet granules in a quantity of up to 20% of plasma concentrations. Interestingly, the decrease in concentrations of coagulation factors is not uniform during surgery. In patients undergoing cardiac surgery, Davidson observed that factors FII and FX decreased significantly more than did factors FV and FVII, while FVIII did not change at all.<sup>49</sup> In that study, a more than 50% reduction in thrombin generation (endogenous thrombin potential; ETP) was associated with increased bleeding and was mainly governed by FII and FX levels, a finding also observed in patients undergoing various types of surgery.<sup>50</sup> Importantly, thrombin generation not only depends on sufficient pro-coagulant factors and co-factors, but also on the activity of the counterbalancing factors.<sup>51</sup> As these factors also decrease during blood loss and fluid administration, thrombin generation may remain sufficient, as shown in surgical patients by Horne and co-workers, although concentrations of pro-coagulants were reduced to some extent.<sup>52</sup> The even mild decrease in several coagulation factors is sensitively detected by standard coagulation tests that soon show pathological values, especially when more than one single factor is decreased<sup>53</sup>; but these tests do not reflect the activity of anticoagulatory proteins and thus the system's balance.

### *Impaired clot stability, hyperfibrinolysis*

Although patients with congenital FXIII deficiency usually show spontaneous bleeding at levels below 4%, increased postoperative or unexpected intra-operative bleeding has been observed in surgical patients already at levels below 60%.<sup>21,35,54,55</sup> *In vitro* data show that with FXIII concentrations below 60%, clot firmness decreases and profoundly at concentrations below 30%.<sup>56</sup> Unfortunately, at this time, the dynamics of TAFI in surgical patients and its impact on bleeding tendency are largely unknown and the results of clinical studies need to be awaited.

Hyperfibrinolysis occurs rarely in surgical patients except in those on cardiopulmonary bypass and during liver transplantation. Furthermore, hyperfibrinolysis may be present in obstetrics, severely traumatised patients and patients undergoing urological procedures. The degree and speed of clot dissolution can vary, and slight or late lysis can resolve spontaneously or proceed to hyperfibrinolysis with complete clot dissolution within a few minutes. As a consequence severe bleeding arises, which, if not treated with anti-fibrinolytics, readily culminates in a profound deficiency of all players in the coagulation system. Interestingly, Tanaka found *in vitro* that, during induced hyperfibrinolysis, the addition of rFVIIa increased lysis of the clot in the absence of anti-fibrinolytics.<sup>23</sup>

### *The need for monitoring*

The amount of blood loss at which the above-mentioned specific deficiencies need to be watched out for varies considerably in the individual patient; it strongly depends on the patient's blood volume and initial haemostatic competence, which is highly variable.<sup>57</sup> Furthermore, surgical factors (cardiopulmonary bypass, vascular surgery, large tissue trauma, bleeding from spongiosal bone surfaces and obstetric bleeding), the type and amount of fluid used and alterations in the physiological milieu influence speed of development and type of mainly underlying deficiencies. Notably, deficiency of substrate, impairment of thrombin generation or increased fibrinolysis can occur independently or consecutively.<sup>50</sup> Thus, a monitoring that ideally displays the actual balance of all haemostasis players and one that quickly allows differential diagnosis of main deficiencies is undoubtedly helpful for safe patient management.

### *Specific effects of intravenous fluids*

During considerable blood loss, on the one hand, the disadvantages that fluids have on haemostasis are far outweighed by their beneficial effect on the circulatory system. On the other hand, patients showing minor blood loss but receiving inappropriately large amounts of fluids may suffer iatrogenic coagulopathy.<sup>58</sup> Besides, the more pronounced volume-expansion colloids exert specific effects on the activity of vWF and the clot formation process. Experimental data also show that effects seen after 0.9% NaCl solution differ from that following Ringer's lactated solution.

### *Colloids*

A huge number of investigations have clearly demonstrated that colloids impair clot formation to a larger extent than do crystalloids.<sup>42,59–61</sup> In summary, the most pronounced effects are shown with dextrans (which are not further discussed here), followed by differently prepared hydroxyethyl starch solutions (HESs), gelatines and albumin. Regarding the various HES preparations, increased molecular weight (MW) and degree of substitution are thought to correlate with increased side effects on haemostasis including expression of platelet glycoprotein receptors and coating of platelets.<sup>62</sup> However, other studies show that increasing MW mainly influences intravascular half-life, while no differences were found for clot formation, PT, aPTT or vWF.<sup>63,64</sup> The induction of a von Willebrand-like syndrome has been observed in patients receiving HES solutions, and a significant decrease in von Willebrand Ristocetin activity (localised at the high molecular part of the vWF, permits platelet adhesion to the endothelium and between each other) was also observed following infusion of gelatine.<sup>65,66</sup> However, it can be assumed that, in most surgical patients, these effects are minor when using the rapidly degradable new HES solution at recommended doses. By contrast, in patients showing borderline vWF

activity or repeatedly receiving highly substituted high-molecular-weight HES over several days, severe bleeding can be provoked.<sup>67</sup> Although gelatin, HES130/0.4 and HES 200/0.5 showed no influence on endogenous release of molecular markers of fibrinolysis *in vivo*, a decreased resistance of clots to fibrinolysis has been observed with colloids *in vitro*.<sup>68,69</sup> This might refer to colloid-associated interference with FXIII or to the fact that weaker clots dissolve faster.<sup>70,71</sup>

### Crystalloids

Some data indicate slight hypercoagulability during moderate dilution using 0.9% NaCl as compared with colloid solution, and imbalances in AT levels were assumed to explain these findings.<sup>72</sup> However, these hypotheses could not be confirmed in orthopaedic patients.<sup>42,61</sup> More clinically relevant, the administration of large amounts of 0.9% NaCl may result in the development of dilutional acidosis and diminished thrombin formation. Until now, only experimental data show decreased thrombin generation, impairment of clot formation and blood loss to be greater following 0.9% NaCl than Ringer's lactated solution.<sup>73,74</sup> *In vitro* data also show that hypertonic solutions significantly affect platelet aggregation and coagulation while in pigs, clot formation was better maintained with a single dose of hypertonic saline–HES solution as compared with gelatine or isotonic HES solution administered at commonly used amounts.<sup>75</sup>

### Laboratory findings during dilutional coagulopathy

Irrespective of the type of fluid used, standard coagulation tests have been shown to become pathological soon, and with colloids, this effect is more pronounced.<sup>42</sup>

Mild dilution mainly results in reduction of clot firmness, being significantly larger with colloids as with crystalloids, and delayed initiation of coagulation occurs only with profound dilution (>50%).<sup>51,63,76</sup> A disturbance in fibrinogen/fibrin polymerisation as the possible underlying mechanism for decreased clot firmness was firstly suspected by results of a study conducted in orthopaedic patients<sup>51</sup> and later confirmed by further clinical data.<sup>42,77</sup> After 30–40% dilution, these studies showed a decrease in fibrinogen concentration, colloid-induced decreased clot firmness but sufficient platelet numbers and sustained thrombin formation. Furthermore, both studies show improved clot firmness with *in vivo* and *ex vivo* fibrinogen supplementation but no effect of platelets or FXIII when added *ex vivo*.<sup>77</sup> However, the study of Mittermayr<sup>42</sup> showed that the correlation between fibrinogen concentration and measured polymerisation disappeared, and improvement of polymerisation was less in patients receiving HES than in those receiving gelatine, a finding also made in previous *in vitro* studies.<sup>78</sup> These data suggest that besides provoking acquired fibrinogen deficiency, HES solutions interfere with fibrinogen/fibrin polymerisation by a yet unknown mechanism.

In summary, administration of intravenous fluids diminishes the concentration of activators/anti-coagulants and the substrate fibrinogen by expanding plasma volume. More specifically, artificial colloids further impair the process of fibrinogen/fibrin polymerisation. Mild-to-moderate dilution mainly affects clot strength while thrombin generation is maintained until profound dilution.

### Alterations in the physiological milieu

Besides optimal pH value and body temperature, adequate quantities of ionised calcium and even red cells are necessary pre-conditions for optimal coagulation and clot formation. Hypothermia and acidosis are usually prevented during elective surgery by appropriate fluid management and use of pre-warmed fluids and warming systems. Nevertheless, intra-operatively decreased calcium may also result from citrate overload associated with blood transfusion or be a consequence of colloid administration. In addition, the justified restrictive use of red cell transfusion and compensation of blood loss through volume administration promotes the decrease of concentrations of coagulation factors and fibrinogen by the consequently increased plasma volume. Furthermore, the attenuation of the direct and indirect influence of red cells on haemostasis<sup>79</sup> needs to be accepted. These facts might explain why the development of coagulopathy and the need for treatment can occur much earlier nowadays

than described in older studies that used whole blood (containing stable coagulation factors) and higher transfusion triggers.

The mechanisms of hypothermia, acidosis and hypocalcaemia on haemostasis were recently described in detail in an excellent review and will only be summarised here.<sup>80</sup>

Basically, hypothermia decreases fibrinogen synthesis<sup>81</sup>, the activity of the various proteases<sup>82</sup> and also the functionality of platelets at temperatures <35 °C.<sup>83</sup> By contrast, deep hypothermia can be accompanied by accelerated microthrombosis caused by increased GPIIb/IIIa activation.<sup>84</sup>

Since the pH optimum for thrombin generation is in the alkali range, a reduction in pH towards 7.1 nearly halves thrombin generation and even diminishes the efficacy of rFVIIa by TF-dependent and -independent formation of FXa.<sup>82</sup> Besides reduced thrombin generation, an experimental model found fibrinogen concentration and platelet numbers at pH 7.1 to be reduced by about 30% and 50%, respectively; speed and quality of clot formation were consequently decreased.<sup>85</sup> Interestingly, despite persisting acidosis, spontaneous recovery of thrombin formation was observed in that study after infusing animals with Ringer's lactated solution, while no effects on thrombin generation occurred after pH correction to 7.4 using sodium bicarbonate. In addition, correction of acidosis did not influence low platelet numbers or low fibrinogen concentrations, suggesting increased consumption of fibrinogen and platelets triggered by acidosis.

Positively charged Ca<sup>++</sup> ions play a pivotal role during coagulation, and these were formerly known as the coagulation factor FIV. Ca<sup>++</sup> ions facilitate the assembly of coagulation factors on the platelet surface, increase the resistance of the formed fibrin, influence its polymerisation and are needed for normal platelet function.<sup>80</sup>

In brief, perioperative coagulopathy can result from pre-existing deficiencies/malfunction of coagulation factors and platelets (hereditary, iatrogenic and acquired), which should be diagnosed preoperatively to plan appropriate management. Nevertheless, the most frequently occurring problem in patients undergoing extensive or long-lasting surgery is the development of dilutional coagulopathy. Dilutional coagulopathy results from blood loss, consumption and dilution of fibrinogen, coagulation factors and platelets and is aggravated by hyperfibrinolysis, hypothermia, acidosis and hypocalcaemia, which, however, are rare during elective surgery. The impact of dilutional coagulopathy varies with the amount of blood loss and amount and type of fluid used. Studies using viscoelastic methods clearly show that clot firmness diminishes first, mainly caused by decreased fibrinogen concentrations and disturbance of polymerisation. Development of critical thrombocytopenia and deficiency of thrombin formation usually occur only in the late stages of blood loss with profound dilution. This general pattern is modified by factors unique to the patient and specific surgical conditions. Importantly, coagulopathy increases blood loss, transfusion requirements and the need for surgical re-exploration, factors that are associated with increased costs, morbidity and mortality.<sup>1–5</sup> A basic understanding of haemostasis and adequate monitoring are pre-conditions for limiting blood loss, and also for avoiding unnecessary transfusion or hypercoagulability, which puts patients at risk for thrombosis.

### Practice points

1. Basic understanding of haemostasis facilitates timely recognition of deficiencies that need to be corrected to avoid increased blood loss.
2. Because marked inter-patient differences exist, patients should be monitored and treated accordingly.
3. The balance between activators and natural anticoagulants dictates thrombin formation, which is the key motor of coagulation. Deficiency of thrombin formation usually occurs only in the late stages of blood loss, but can be accelerated in an unphysiological milieu.
4. Clot formation is a pre-condition for arresting bleeding, and all the thrombin formed is wasted if sufficient substrates, fibrinogen and platelets are not available.
5. Besides clot formation, clot stability is important and is governed by factors FXIII, TAFI and the activity of the fibrinolytic system. Importantly, these are not reflected by PT or aPTT results.

## Research agenda

Clinical research is warranted to the following:

1. Identify clear thresholds for critical fibrinogen concentration and polymerisation as well as for platelet numbers.
2. Investigate changes of platelet function generally occurring during surgery.
3. Evaluate dynamics of FXIII concentrations and TAFIa formation in surgical patients and their association with blood loss.

## Conflict of interest

Over the past 5 years, Petra Innerhofer has received educational grants or honoraria for consulting and lecturing, expenses for travel and hotel accommodations and partial support for conducting studies (without any exertion of influence on her study design, statistics or manuscript preparation) from the following companies:

Abbott GmbH (Vienna, Austria), Baxter GmbH (Vienna, Austria), B. Braun Melsungen GmbH (Melsungen, Germany), CSL Behring GmbH (Marburg, Germany), Fresenius Kabi GmbH (Graz, Austria), Novo Nordisk A/S (Bagsvaerd, Denmark), Octapharma AG (Vienna, Austria) and Pentapharm GmbH (Munich, Germany).

In the past 5 years and related to the topic addressed in this article, Joachim Kienast has received educational grants or honoraria for consulting or lecturing, costs incurring for travel and hotel accommodations from the following company: CSL Behring GmbH (Marburg, Germany).

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# Novel Oral Anticoagulants

## *Implications in the Perioperative Setting*

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### ABSTRACT

Patients undergoing surgery receive anticoagulation for perioperative thromboprophylaxis or ischemic cardiovascular disease. Because anticoagulants may also potentiate bleeding, clinicians need to understand the implications of anticoagulation in perioperative and postoperative patient management. Many newer anticoagulants that are now available or are in clinical development do not require routine coagulation monitoring, have more predictable dose responses, and have fewer interactions with other drugs and food. The most advanced oral anticoagulants in clinical development are the direct factor Xa inhibitors rivaroxaban and apixaban, and the direct thrombin inhibitor dabigatran etexilate. These agents have been evaluated in the postoperative setting in patients undergoing total hip- or knee-replacement surgery with promising results, and it remains to be seen whether these results will translate into other surgical settings. The impact of the new agents will be influenced by the balance between efficacy and safety, improved convenience, and potential cost-effectiveness benefits.

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**S**URGICAL patients are increasingly receiving anticoagulation for perioperative thromboprophylaxis and as therapy for ischemic cardiovascular disease. Patients with atrial fibrillation, prosthetic valves, or coronary artery disease are also at risk for thrombosis and so may be receiving anticoagulation therapy when they present for surgery. All therapies that prevent clot growth or formation in pathologic states also interfere with normal hemostasis. As a result, patients often present for surgery with an acquired hemostatic imbalance because of preexisting preoperative anticoagulation.

Under physiologic conditions, there is a complex and delicate equilibrium between vascular endothelial cells, platelets, coagulation factors, natural inhibitors of coagulation, and the fibrinolytic system.<sup>1</sup> After vascular injury, surgical or trauma patients also develop additional acquired procoagulant changes that alter this complex balance.<sup>1</sup> Hemostasis is far more complex than the simplified coagulation cascade of intrinsic and extrinsic hemostatic activation taught in medical school, and clinicians are often presented with patients receiving one or more anticoagulation therapies. Multiple therapies are currently in use, and newer therapies are approved in other countries and are in development in North America. Because anticoagulants may also potentiate bleeding, it is important that clinicians understand the implications of perioperative and postoperative therapy for thromboembolic disease on the patient. Furthermore, with the introduction of low-molecular-weight heparin (LMWH), there were initial concerns regarding the management of regional anesthesia in patients on LMWH therapy, because standard coagulation assays were not appropriate to monitor its effects.<sup>2</sup> This review discusses the established therapies and novel anticoagulant agents for the prevention of venous thromboembolism (VTE) in the perioperative and postoperative management of surgical patients. The review will focus on anticoagulant agents without discussion of antiplatelet agents.

### VTE after Surgery

Venous thromboembolism comprises deep vein thrombosis and pulmonary embolism (PE), which are potentially life threatening but often preventable conditions. PE, the most

life-threatening manifestation of VTE, occurs in 1.7% of patients without *versus* 0.9% of patients with thromboembolic prophylaxis.<sup>3</sup> Approximately 10% of all cases of PE are rapidly fatal,<sup>4</sup> and VTE may be associated with long-term clinical consequences such as pulmonary hypertension, post-thrombotic syndrome, and recurrent thromboembolic events. There is also a significant healthcare resource burden associated with VTE.<sup>5–7</sup>

Nearly 65% of surgical patients are at risk of VTE according to the American College of Chest Physicians (ACCP) criteria.<sup>8</sup> Because thrombus formation is triggered by vascular trauma and venous stasis,<sup>9</sup> major surgery and postoperative immobility increase the risk of developing VTE.<sup>9,10</sup> In addition to the nonsurgical risk factors for VTE, such as increasing age or body mass index, or a history of VTE, perioperative risk factors include the type and duration of surgery, the type of anesthetic used, the degree and duration of immobility, and the occurrence of dehydration or sepsis.<sup>11</sup> The risk of VTE varies depending on the type of surgery; without thromboprophylaxis, the risk of deep vein thrombosis in most general, open gynecologic or urologic surgery patients is 10–40%, which rises to 40–80% in patients undergoing major orthopedic surgery.<sup>12</sup> The effectiveness of thromboprophylaxis for the prevention of postoperative VTE has consistently been demonstrated in clinical trials.<sup>12</sup> The internationally recognized guidelines produced by the ACCP and other national guidelines recommend the use of anticoagulants after most types of major surgery.<sup>12,13</sup>§,|| The difference in the risk of VTE is reflected in the varying proportion of patients receiving ACCP-recommended prophylaxis between different types of surgery, as demonstrated in the ENDORSE (Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting) study; 88% of patients undergoing hip or knee replacement were receiving prophylaxis, compared with 69% of those undergoing colorectal surgery and 50% of those undergoing urologic surgery.<sup>8</sup> For surgical patients at low risk of VTE, early mobilization may be sufficient to prevent VTE. Patients at moderate or high risk, or those who are likely to have extended periods of immobilization, require thromboprophylaxis to prevent VTE. However, thromboprophylaxis after certain types of surgery, such as vascular, gynecologic, and urologic,<sup>12</sup> lack clinical trial or prospective data to make appropriate recommendations, or recommendations are based on limited data.

§ National Institute for Health and Clinical Excellence. Venous thromboembolism—reducing the risk. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. Available at: <http://guidance.nice.org.uk/CG92>. Accessed April 28, 2010.

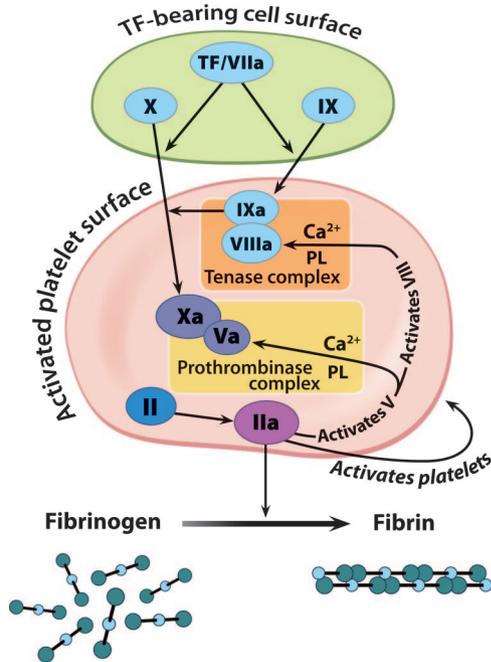
|| American Academy of Orthopaedic Surgeons. Clinical guideline on prevention of symptomatic pulmonary embolism in patients undergoing total hip or knee arthroplasty. Available at: [http://www.aaos.org/Research/guidelines/PE\\_guideline.pdf](http://www.aaos.org/Research/guidelines/PE_guideline.pdf). Accessed January 11, 2010.

The levels of recommendations made by the ACCP are based on an evaluation of benefit *versus* harm, burden, and cost. Strong (grade 1) recommendations are made if there is confidence that benefits do or do not outweigh harm, burden, and cost. If the magnitude of the benefits and risks is less certain, the weaker (grade 2) recommendations are made. Grade 1 recommendations can be applied to most patients; the application of grade 2 suggestions requires further evaluation of individual patient and resource requirements. The quality of the supporting randomized control trial evidence for these recommendations is graded as high (A), moderate (B), or low (C) quality, depending on factors such as the design and conduct of the trial and the precision and consistency of results.<sup>14</sup>

Patients undergoing major orthopedic surgery—hip or knee arthroplasty—are at significantly increased risk of developing VTE compared with patients undergoing other types of surgery.<sup>12,15</sup> The most recent ACCP guidelines recommend routine use of LMWH, fondaparinux, or a dose-adjusted vitamin K antagonist (VKA) for the prevention of VTE in all patients undergoing total hip or knee replacement or hip fracture surgery (grade 1A).<sup>12</sup> Thromboprophylaxis after these procedures is generally well accepted; however, adherence to guidelines with respect to start time, duration, and intensity of therapy is relatively low.<sup>16</sup> In addition, a significant proportion of venous thromboembolic events occur after discharge from hospital,<sup>15,17</sup> highlighting the importance of an appropriate duration of prophylaxis in these patients.

There are few prospective studies in patients undergoing thoracic surgery.<sup>12</sup> However, VTE is not an uncommon complication in these patients, in that approximately 5% of patients develop postoperative PE,<sup>18</sup> and approximately 1.3% develop fatal PE.<sup>18,19</sup> Data from one study found that PE was the second most frequent reason for early postoperative death after lung resection,<sup>19</sup> a finding that may also be related to the high incidence of atrial fibrillation that can occur.<sup>20</sup> In addition, patients undergoing thoracic surgery are likely to have other underlying risk factors for VTE such as cancer or delayed mobilization.<sup>12</sup> Despite the lack of data regarding the risk of VTE in these patients, the ACCP recommends that physicians consider the use of LMWH, low-dose unfractionated heparin (UFH), or fondaparinux after thoracic surgery (grade 1C).<sup>12</sup>

The risk of VTE after cardiac surgery is based on retrospective studies with variable results. The incidence of postoperative PE is reported at between 0.75% and 10%.<sup>21</sup> Cardiac surgery patients are at high risk for developing both atrial fibrillation<sup>22</sup> and heparin-induced thrombocytopenia (HIT; a well-described prothrombotic adverse drug reaction),<sup>23,24</sup> which increase the risk of arterial and venous thrombosis.<sup>25,26</sup> Additional factors for the risk of VTE associated with cardiac surgery may not be due to the procedure *per se*<sup>15</sup> but to underlying patient characteristics, including preexisting atrial fibrillation, heart failure, valvular heart disease, prior myocardial infarctions, and the underlying disease



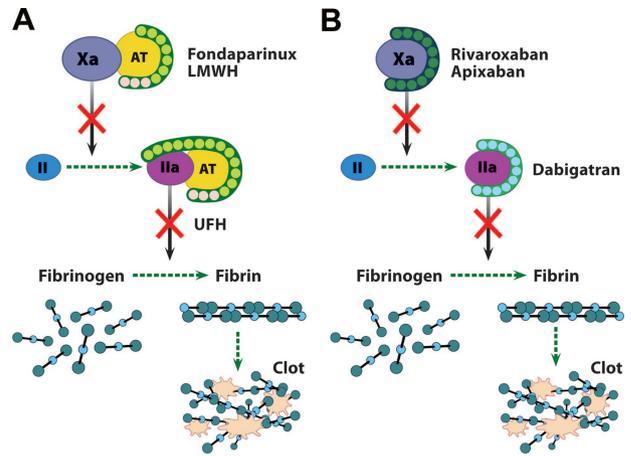
**Fig. 1.** The coagulation cascade. TF = tissue factor; PL = phospholipids.

state. It is estimated, based on extrapolated data, that 1,100–1,300 deaths occur in the United States each year as a result of VTE after coronary artery bypass grafting.<sup>27</sup> Although asymptomatic VTE occurs frequently,<sup>28</sup> symptomatic VTE can also go undetected after cardiac surgery, because symptoms—such as shortness of breath and leg discomfort or swelling—may be attributed to the expected consequences of the preexisting conditions or surgery (*i.e.*, saphenous vein harvest).<sup>27</sup>

The overall risk of clinically important VTE may be relatively low after coronary artery bypass grafting, but patients often require anticoagulation because of unstable angina or the presence of other risk factors.<sup>12</sup> Despite limited evidence, the ACCP recommends thromboprophylaxis with LMWH, UFH, or optimally used bilateral intermittent pneumatic compression or graduated compression stockings, to provide early thromboprophylaxis in patients who may have a more complicated postoperative course than usual (grade 1C).<sup>12</sup> They recommend the use of LMWH over low-dose UFH (grade 2B) based on the fact that LMWH is associated with a lower risk of HIT compared with UFH.<sup>12</sup>

**Current Options for Thromboprophylaxis**

The mainstay of anticoagulant drugs—the heparins—target two major components of the coagulation cascade, factor Xa and thrombin, as shown in figures 1 and 2A. Classically, the coagulation cascade *in vitro* comprises two pathways: the intrinsic coagulation pathway, which is initiated when contact is made between blood and exposed negatively charged surfaces (exposed as a result of tissue damage), and the ex-



**Fig. 2.** The primary mechanism of action of the established anticoagulants (unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], and fondaparinux) via antithrombin-dependent binding (A) and the new anticoagulants (rivaroxaban, apixaban, and dabigatran etexilate) via antithrombin-independent binding (B). UFH also inactivates factors Xa, IXa, XIa, and XII via antithrombin, but to a lesser extent than inactivation of thrombin. LMWH also inactivates thrombin via antithrombin, but to a lesser extent than inactivation of factor Xa. AT = antithrombin.

trinsic coagulation pathway, which is initiated upon vascular injury and exposure of tissue factor. These two pathways converge at the point where factor X is activated to factor Xa. The activation of factor X is catalyzed by factor IXa, through interaction with the protein cofactor VIIIa (intrinsic tenase) or by tissue factor and factor VIIa (extrinsic tenase; fig. 1). Factor Xa activates prothrombin to thrombin, which then activates factors XI, VIII, and V, amplifying the cascade. Thrombin converts soluble fibrinogen to fibrin and activates factor XIII to XIIIa, which cross-links fibrin polymers, solidifying the clot (fig. 1). However, a cell-based model of hemostasis is a better method of understanding the complex interactions of procoagulant and anticoagulant factors, the critical role of tissue factor, and the role of hemostatic-vascular interactions in hemostasis.<sup>29–31</sup>

**UFH and LMWH**

UFH and LMWHs are widely used but are also associated with a number of limitations.<sup>32</sup> UFH inactivates both thrombin and factor Xa, catalyzed by binding to antithrombin (also called antithrombin III), whereas LMWH—also by binding to antithrombin—has a selective inhibitory effect on factor Xa (fig. 2A).<sup>32</sup> One advantage of UFH is that it can be completely neutralized with protamine sulfate—unlike LMWHs.<sup>32</sup> UFH requires regular coagulation monitoring, dose adjustments, and potential monitoring for HIT.<sup>32</sup> LMWH requires parenteral administration but monitoring is not required in patients with normal renal function (table 1). However, its half-life is prolonged in patients with renal dysfunction, therefore monitoring and/or dose reduction is recommended in these patients.<sup>32</sup>

**Table 1.** Properties of the Established Anticoagulants Used in the Surgical Setting

	LMWH	VKAs	Fondaparinux
Bioavailability, %	~90	~100	100
Half-life, h	3–6	36–42	17–21
Elimination	Renal	Renal	Renal
Management with anesthesia	<ul style="list-style-type: none"> <li>• Preoperative LMWH:               <ul style="list-style-type: none"> <li>- Low dose: needle placement at least 10–12 h after last dose</li> <li>- High dose: needle placement 24 h after last dose</li> <li>- Neuraxial techniques should be avoided in patients administered LMWH 2 h preoperatively</li> </ul> </li> <li>• Postoperative LMWH:               <ul style="list-style-type: none"> <li>- Twice-daily dose: Initiate 24 h after surgery. Remove catheter 2 h before first dose</li> <li>- Once-daily dose: Initiate 6–8 h after surgery. May leave catheter in. Remove catheter 10–12 h after last dose. Resume therapy 2 h after catheter removed</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• If prophylactic dose of warfarin is given &gt;24 h before surgery, check INR measurements before initiating neuraxial anesthesia</li> <li>• Remove neuraxial catheters at INR &lt;1.5</li> </ul>	<ul style="list-style-type: none"> <li>• Atraumatic needle placement and avoidance of indwelling catheters recommended</li> <li>• Postoperative therapy with indwelling catheter:               <ul style="list-style-type: none"> <li>- Initiate therapy 6–8 h after surgery</li> <li>- Remove catheter 36 h after last dose</li> <li>- Resume therapy 12 h after catheter removed</li> </ul> </li> </ul>
Monitoring required	No	Yes	No
Food/drug interactions	None reported	Multiple	None
Immunogenicity	Can induce immune-mediated platelet activation. Risk of HIT	Low risk of HIT	Low risk of HIT

HIT = heparin-induced thrombocytopenia; INR = international normalized ratio; LMWH = low-molecular-weight heparin; VKA = vitamin K antagonist.

### Fondaparinux

Fondaparinux is a synthetic pentasaccharide that binds to antithrombin, producing a conformational change at the reactive site of antithrombin, to selectively inhibit factor Xa by mechanisms identical to LMWHs, but without affecting thrombin activity (fig. 2A).<sup>32</sup> Fondaparinux also inhibits free factor Xa, but not factor Xa bound to the prothrombinase complex.<sup>33</sup> It is administered by subcutaneous injection and has a longer half-life than LMWHs, requiring a once-daily dose (table 1).<sup>32</sup> The risk of HIT is relatively low.<sup>34</sup> Fondaparinux does not require routine coagulation monitoring, except in patients with renal dysfunction, because fondaparinux is primarily eliminated renally (table 1).<sup>33</sup> There are no currently available reversal agents for fondaparinux, although partial reversal has been described.<sup>35</sup>

### VKAs

VKAs, of which warfarin is the most frequently used, interfere with the posttranslational carboxylation of coagulation factors II, VII, IX, and X, and other coagulation proteins,

resulting in a reduced coagulant effect.<sup>36</sup> Warfarin has unpredictable pharmacodynamic, pharmacokinetic and pharmacogenetic properties, causing major variability in patients' dose responses (table 1).<sup>36</sup> Initiating VKA therapy requires frequent therapeutic monitoring and dose adjustments using the international normalized ratio (INR), based on the prothrombin time.<sup>36</sup> Administration of vitamin K is recommended to reverse a mildly increased INR. Prothrombin complex concentrates are recommended for reversal in cases of life-threatening bleeding or intracranial hemorrhage<sup>36,37</sup>; however, fresh frozen plasma is still used if prothrombin complex concentrates are not available. Off-label use of recombinant factor VIIa has also been reported to reverse the INR effect.

### The Use of Anticoagulants and Neuraxial Anesthesia

Anticoagulant use with neuraxial anesthesia, including spinal/epidural puncture, can increase the risk of epidural or

spinal hematoma, which can lead to permanent paralysis. The risk of epidural hematoma with neuraxial anesthesia is increased 15-fold with the use of anticoagulant therapy without appropriate precautions.<sup>38</sup> This risk can be further increased with the use of postoperative indwelling epidural catheters. It is critical, therefore, to ensure that anticoagulated patients under anesthesia are appropriately and correctly managed, particularly with the continuing development of new, potentially more potent anticoagulants. The risk of hematoma associated with a specific anticoagulant is difficult to accurately assess because the low incidence of hematoma (one epidural hematoma per 150,000 epidural injections)<sup>38</sup> means that prospective randomized trials are not possible.<sup>39</sup> It is difficult, therefore, to assess the best strategy to balance the risk of hematoma with effective thromboprophylaxis.<sup>38</sup> Several national guidelines have been developed based on case reports and the pharmacokinetic properties of the relevant agents,<sup>38,40</sup> and recommendations are therefore drug specific. Patient management is based on appropriate timing of needle placement and catheter removal relative to the timing of anticoagulant drug administration, to ensure that drug concentration is at its lowest.<sup>39</sup> Delaying the initiation of anticoagulation after surgery can further reduce the risk of hematoma.<sup>38</sup> With all anticoagulants, the risk of hematoma is increased with concomitant use of medications such as nonsteroidal antiinflammatory drugs, clopidogrel, or other anticoagulants, therefore, management of patients taking these medications requires caution. In addition, all patients undergoing neuraxial anesthesia should be monitored for signs of neurologic impairment to enable prompt intervention.<sup>38,39</sup>

### UFH

The consensus statement from the American Society of Regional Anesthesia and Pain Medicine (ASRA) on regional anesthesia in the anticoagulated patient bases its recommendations for UFH on the initial recommendations established 20 yr ago, supported by reviews of case series and case reports of spinal hematoma.<sup>39</sup> ASRA recommends that UFH administration be delayed for 1 h after needle placement. Indwelling neuraxial catheters should be removed 2–4 h after the last UFH dose, and the next dose should be given 1 h after catheter removal. Patients should be carefully monitored for any signs of hematoma (table 1).<sup>39</sup>

### LMWH

**Preoperative LMWH.** Pharmacokinetic studies of the LMWH enoxaparin demonstrated that after a single bolus administration of 40 mg, anti-Xa activity had nearly returned to baseline after 12 h (in patients with normal renal function).<sup>40</sup> To ensure that trough levels are achieved, ASRA recommends that needle placement should occur at least 10–12 h after the last dose of LMWH<sup>39</sup>; most European guidelines recommend a delay of at least 12 h, but a delay of 20 h is recommended by French guidelines.<sup>38</sup> ASRA recommends that needle placement occur at least 24 h after the last

dose if a higher dose of LMWH is used (such as 1 mg/kg enoxaparin every 12 h or 1.5 mg/kg daily).<sup>39</sup> Neuraxial techniques should be avoided in patients administered LMWH 2 h preoperatively, because needle placement would occur during peak anticoagulant activity (table 1).<sup>39</sup>

**Postoperative LMWH.** The management of anesthesia with postoperative LMWH is based on the dosing regimen used. Twice-daily dosing may be associated with an increased risk of spinal hematoma.<sup>39</sup> The ASRA guidelines recommend that the first dose be administered no earlier than 24 h postoperatively, regardless of anesthetic technique, and only in the presence of adequate (surgical) hemostasis. Indwelling catheters should be removed before initiation of LMWH therapy. If a continuous technique is selected, the epidural catheter may be left indwelling overnight and removed the following day, with the first dose of LMWH administered at least 2 h after catheter removal.<sup>39</sup> For once-per-day dosing, as used in the European Union (EU), the first postoperative LMWH dose should be administered 6–8 h postoperatively. The second postoperative dose should occur no sooner than 24 h after the first dose.<sup>39</sup> Indwelling neuraxial catheters may be safely maintained but the catheter should be removed a minimum of 10–12 h after the last dose of LMWH according to ASRA<sup>39</sup> (this recommendation differs between countries, as described previously). Subsequent dosing should occur a minimum of 2 h after catheter removal according to the ASRA guidelines,<sup>39</sup> but European guidelines recommend a 4–6 h delay.<sup>38</sup>

### Fondaparinux

It is recommended that fondaparinux be started between 6 and 8 h after the end of surgery.<sup>38</sup> Indwelling epidural catheters should not be removed until 36 h (at least two half-lives) after the previous dose, and the next dose should not be given until 12 h after catheter removal (a more convenient time point than that suggested by the pharmacokinetics of the drug). The 48-h window required between two injections of fondaparinux is achieved by skipping one injection.<sup>38</sup> In the EXPERT (Evaluation of ariXtra for the Prevention of vEnous thromboembolism in daily pracTice) study, this regimen was shown to allow safe catheter removal without affecting the thromboprophylaxis efficacy. In patients receiving 2.5 mg fondaparinux daily for 3–5 weeks after major orthopedic surgery, the rate of symptomatic VTE was similar in patients with and without catheters, and no neuraxial hematomas were reported.<sup>41</sup> Although the risk of spinal hematoma is unknown, spinal hematoma has been reported in association with the use of fondaparinux.<sup>39</sup> Patients receiving fondaparinux with neuraxial anesthesia and postoperative indwelling epidural catheters should be closely monitored for signs and symptoms of neurologic impairment (table 1).<sup>38</sup>

### VKAs

The anesthetic management of patients receiving warfarin, either as a long-term therapy or as thromboprophylaxis perioperatively, has been controversial. The ASRA consensus

statement bases its recommendations on drug pharmacology, the clinical relevance of vitamin K coagulation factor levels, and case reports of spinal hematoma.<sup>39</sup> For patients who require long-term anticoagulation, VKA therapy should ideally be stopped 4–5 days before surgery, and the INR should be measured before initiation of neuraxial block. For patients receiving a prophylactic dose of warfarin more than 24 h before surgery, INR measurements should be checked before initiating neuraxial anesthesia. Neuraxial catheters should be removed when the INR is less than 1.5 (table 1)<sup>39</sup>; this value was derived from studies that correlate hemostasis with clotting factor activity levels greater than 40%.<sup>39</sup>

## Reversing the Effects of Anticoagulation

Anticoagulation is associated with an increased risk of bleeding, particularly after surgery, and clinicians must consider the risks and benefits of therapy in individual patients. The risk of experiencing a bleeding event is related to the intensity of the anticoagulant effect and the length of therapy (VKAs), the dosage used (UFH and LMWH), and underlying patient characteristics.<sup>42</sup> Patients may also experience bleeding events as a result of overdose. In the event of a bleeding episode, agents that are able to reverse the effects of anticoagulation may be required. In addition, patients receiving anticoagulants may suffer a major trauma or require emergency surgery for which rapid reversal of the effects of anticoagulation will be required. UFH can be rapidly and completely neutralized with protamine sulfate; LMWHs can be partially neutralized by protamine sulfate.<sup>32</sup> For patients receiving VKA therapy with serious or life-threatening bleeding, the ACCP recommends infusion of vitamin K supplemented with either fresh frozen plasma, prothrombin complex concentrate, or recombinant factor VIIa (rFVIIa).<sup>36</sup>

## New Options for Thromboprophylaxis

Because of specific limitations of the currently available anticoagulant agents, there has been a long-standing need for more convenient, effective anticoagulant therapies for clinical management of VTE, especially in the era of minimizing hospital stay after surgery. Newer agents may have an important impact on perioperative and postoperative care and patient management. Most current anticoagulant agents require parenteral administration, whereas VKAs have a slow onset, marked variability in effect, and need frequent coagulation monitoring. By targeting specific components of the coagulation cascade, the new small-molecule anticoagulants in development should have a more predictable pharmacologic profile and dose response than untargeted agents, potentially eliminating the requirement for routine coagulation monitoring.<sup>43</sup>

Oral inhibitors of factor Xa and thrombin are among the newer agents currently in development or under consideration by North American regulatory agencies. Factor Xa is an attractive target as the rate-limiting factor in the generation and amplification of thrombin.<sup>44</sup> Thrombin also has a piv-

otal role in hemostasis, converting soluble fibrinogen to fibrin, activating factors V, VIII, and XI (which generate more thrombin), and activating platelets (fig. 1).<sup>45</sup> Although there is considerable debate regarding the best target for anticoagulation, both of these types of inhibitor have been extensively studied in large randomized clinical studies. One theory is that factor Xa inhibition may cause less bleeding than direct inhibition of thrombin because residual thrombin can still be activated by critical feedback processes.<sup>44</sup> Because the coagulation cascade is an amplification pathway, one molecule of factor Xa catalyzes the formation of almost 1,000 thrombin molecules.<sup>44</sup> There are several new parenteral and oral agents in various stages of development that directly or indirectly inhibit factor Xa or thrombin.

## New Anticoagulants and Neuraxial Anesthesia

As with the established anticoagulants, the management of patients with new anticoagulants and neuraxial anesthesia will be based on the pharmacokinetic properties of the anticoagulant. Needle or catheter placement and removal should be timed to take place when anticoagulant concentrations are at their lowest, and patients should be monitored closely for signs of hematoma in the initial days after catheter removal. Rosencher *et al.*<sup>38</sup> suggest allowing at least two half-lives (for the specific anticoagulant) to pass before catheter removal, at which point only 25% of the drug remains active. Allowing a longer interval would only slightly reduce the drug concentration, because elimination slows after this point.<sup>38</sup> The risk of the residual anticoagulant activity and neuraxial hematoma needs to be weighed against the risk of VTE. They suggest that anticoagulation should be restarted after 8 h minus the time to reach maximum activity ( $T_{max}$ ), on the basis of the fact that it takes 8 h to establish a stable clot but allowing time for the peak of anticoagulation to be reached.<sup>38</sup> Although this approach does not guarantee extremely low anticoagulant levels over the entire time interval indicated, it is suggested that this is a reasonable compromise between the risk of bleeding and the risk of VTE.<sup>38</sup> In the following section, specific recommendations are outlined according to the manufacturers' instructions, where available, for managing each agent when used with neuraxial anesthesia.

## Factor Xa Inhibitors

### Indirect Factor Xa Inhibitors

**Idraparinux and Idrabiotaparinux.** The synthetic pentasaccharide idraparinux is a chemically modified version of fondaparinux that inhibits factor Xa through binding to antithrombin, but its affinity for antithrombin is 34-fold greater than that of fondaparinux. Because of this high affinity, it has a half-life of ~80 h, making once-weekly dosing feasible.<sup>46,47</sup> However, because there is no antidote, this long half-life may be problematic if bleeding occurs or urgent surgery is required.<sup>47</sup> Idraparinux is administered subcutaneously and does not require routine coagulation monitor-

ing.<sup>47</sup> In patients with deep vein thrombosis, idraparinus demonstrated efficacy similar to that of standard therapy but was less efficacious than standard therapy in patients with PE.<sup>48</sup> Idraparinus was effective in preventing recurrent VTE for 6 months but increased the risk of major bleeding compared with standard therapy.<sup>49</sup> In the Amadeus trial, idraparinus demonstrated similar efficacy for the prevention of stroke in patients with atrial fibrillation but significantly increased the risk of bleeding compared with VKAs, and the study was discontinued.<sup>50</sup> A biotinylated version of idraparinus (idrabioparinus) has subsequently been developed that has a specific neutralizing agent; it also can be administered once per week.<sup>51</sup> There are no further trials planned with either idraparinus or idrabioparinus.

**Danaparoid Sodium.** Danaparoid sodium is a subcutaneous, low-molecular-weight heparinoid with a long half-life<sup>32,52</sup> that, like LMWH, requires antithrombin to inactivate factor Xa. Although approved for HIT in several countries other than the United States, it was initially approved to prevent postoperative VTE but is more expensive than LMWHs, so it is no longer marketed in this indication.<sup>32,52</sup> Danaparoid is seldom used.<sup>32,52</sup>

### Direct Factor Xa Inhibitors

**Rivaroxaban.** Rivaroxaban is an oral, direct factor Xa inhibitor with more than 10,000-fold greater selectivity for factor Xa than for other related serine proteases.<sup>53</sup> In contrast to LMWH and similar agents, rivaroxaban does not require antithrombin as a cofactor.<sup>54</sup> Direct factor Xa inhibitors, including rivaroxaban, can inhibit free factor Xa, clot-bound factor Xa, and factor Xa bound to the prothrombinase complex (fig. 2B),<sup>44,55</sup> unlike indirect factor Xa inhibitors, such as fondaparinux, which are unable to inhibit factor Xa within the prothrombinase complex. Rivaroxaban is also a non-heparin-like molecule that may be suitable for the management of patients with HIT.<sup>56</sup> It has an oral bioavailability of 80–100% (for a 10-mg dose),<sup>#</sup> and approximately two-thirds of the administered dose undergoes metabolic degradation in the liver.<sup>57</sup> Of this, half is excreted *via* the kidneys and half *via* the fecal route. The remaining third is eliminated as unchanged drug in the urine (table 2).<sup>57</sup>

Rivaroxaban has been approved in the EU, Canada, and several other countries for the prevention of VTE in adult patients after elective hip- or knee-replacement surgery, based on the results of the extensive phase III RECORD (REGulation of Coagulation in ORthopaedic surgery to prevent Deep vein thrombosis and pulmonary embolism) program. The program included more than 12,500 patients in four trials comparing once-daily rivaroxaban with either 40 mg enoxaparin once daily (the regimen approved in the EU) or 30 mg enoxaparin twice daily (a regimen approved in the

United States in patients undergoing total hip- or knee-replacement surgery). In all four trials, rivaroxaban therapy demonstrated superiority to the enoxaparin regimens tested for the prevention of VTE, without a significant increase in the rate of major bleeding (table 3).<sup>58–61</sup> In a pooled analysis of these studies, rivaroxaban regimens significantly reduced the incidence of the composite of symptomatic VTE and death compared with enoxaparin regimens.<sup>62</sup>

When used with neuraxial anesthesia for total hip- or knee-replacement surgery, an epidural catheter should not be removed earlier than 18 h after the last administration of rivaroxaban, and the next rivaroxaban dose should be administered no earlier than 6 h after the removal of the catheter (table 2).# Rivaroxaban is not recommended in patients undergoing total hip- or knee-replacement surgery who have creatinine clearance (CrCl) rates of <15 ml/min and may be used with caution in patients with CrCl of 15–29 ml/min. No dose adjustment is necessary in patients with mild (CrCl 50–80 ml/min) or moderate (CrCl 30–49 ml/min) renal impairment.# Rivaroxaban is contraindicated in patients undergoing hip- or knee-replacement surgery who have hepatic disease associated with coagulopathy and clinically relevant bleeding risk. It may be used with caution in patients with cirrhosis who have moderate hepatic impairment (Child–Pugh B) if not associated with coagulopathy. No dose adjustment is necessary in patients with other hepatic diseases or those aged over 65 yr.# Rivaroxaban is metabolized *via* cytochrome P3A4 (CYP3A4), cytochrome P2J2, and cytochrome P450-independent mechanisms and is a substrate of the transporter proteins P-glycoprotein (P-gp) and the breast cancer resistance protein. Its use is therefore not recommended in patients undergoing total hip- or knee-replacement surgery who are receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp, such as ketoconazole, itraconazole, voriconazole, posaconazole, and ritonavir.# Fluconazole can be coadministered with caution. Moderate inhibitors of CYP3A4 and P-gp (such as erythromycin), and strong inhibitors of either CYP3A4 or P-gp (such as clarithromycin) can be used. Strong CYP3A4 inducers (such as phenytoin, carbamazepine, and phenobarbital) should be coadministered with caution.# In studies in healthy subjects, no clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was coadministered with acetylsalicylic acid or clopidogrel, although an increase in bleeding time was observed with clopidogrel in some subjects.<sup>63,64</sup> Patients undergoing total hip or knee replacement who are receiving rivaroxaban can concomitantly receive nonsteroidal antiinflammatory drugs and platelet aggregation inhibitors, but care should be taken because of the increased risk of bleeding. Care should also be taken if patients are to receive other anticoagulants.# There is no antidote to reverse the anticoagulant effect of rivaroxaban, and standard methods should be used to control bleeding events should they occur.# Discontinuation or delaying the next dose may be sufficient, because rivaroxaban has a half-life of 7–11 h. Other strategies include mechanical

# Xarelto®. Summary of product characteristics—EU. Bayer Health-Care. Available at: [http://www.xarelto.com/html/downloads/Xarelto\\_Summary\\_of\\_Product\\_Characteristics\\_May2009.pdf](http://www.xarelto.com/html/downloads/Xarelto_Summary_of_Product_Characteristics_May2009.pdf). Accessed March 29, 2010.

**Table 2.** Properties of the New Oral Anticoagulants for Potential Use in the Surgical Setting

	Apixaban	Rivaroxaban	Dabigatran
Target	Factor Xa	Factor Xa	Thrombin
Bioavailability, %	34–88*	80–100	6.5
Half-life, h	8–11 with twice-daily dosing	7–11	12–14 (healthy subjects)
Dosing for thromboprophylaxis after THR or TKR	Twice daily†	<ul style="list-style-type: none"> <li>Initiate (full dose) 6–10 h after surgery (provided hemostasis has been established)</li> <li>Once daily, fixed dose (10 mg)</li> </ul>	<ul style="list-style-type: none"> <li>Initiate with half the daily dose (single 110-mg capsule) within 1–4 h of surgery; continue with full 220-mg dose (two 110-mg capsules) once daily thereafter</li> <li>Fixed dosing</li> </ul>
Dosing in special populations after THR or TKR	—	<ul style="list-style-type: none"> <li>CrCl &lt;15 ml/min: not recommended</li> <li>CrCl 15–29 ml/min: use with caution</li> <li>CrCl 30–49 ml/min: no dose adjustment</li> <li>Hepatic disease associated with coagulopathy and clinically relevant bleeding risk: not recommended</li> <li>Cirrhotic patients with moderate hepatic impairment not associated with coagulopathy: use with caution</li> <li>Other hepatic diseases: no dose adjustment</li> <li>Age over 65 yr: no dose adjustment</li> </ul>	<ul style="list-style-type: none"> <li>CrCl &lt;30 ml/min: not recommended</li> <li>CrCl 30–50 ml/min: reduced dose (150 mg od [two 75-mg capsules])</li> <li>Hepatic impairment (elevated liver enzymes at &gt;2× ULN): not recommended</li> <li>Age over 75 yr: reduced dose (150 mg od [two 75-mg capsules])</li> </ul>
Elimination	Fecal, 56%; renal, ~25%	<ul style="list-style-type: none"> <li>Approximately one-third excreted as unchanged active substance in urine</li> <li>Of the two-thirds metabolized, half is renally, and half is eliminated via hepatobiliary route in feces</li> </ul>	Renal (85% after i.v. administration)
Management with anesthesia	No information available	Neuraxial anesthesia: epidural catheter should not be removed earlier than 18 h after the last dose; next dose no earlier than 6 h after catheter removal	<ul style="list-style-type: none"> <li>Not recommended in patients undergoing anesthesia with postoperative indwelling epidural catheters</li> <li>First dose should occur a minimum of 2 h after catheter removal</li> </ul>
Monitoring required	No	No	No
Antidote available	No	No	No
Drug interactions	Minimal, but no recommendations yet available	<ul style="list-style-type: none"> <li>Not recommended: Potent inhibitors of CYP3A4 or P-gp (e.g., ketoconazole, itraconazole, voriconazole, posaconazole, HIV protease inhibitors)</li> <li>Use with caution: Fluconazole; strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital)</li> <li>Use with care: NSAIDs; PAIs; other anticoagulants</li> </ul>	<ul style="list-style-type: none"> <li>Dose adjustment required: amiodarone (a P-gp inhibitor)</li> <li>Not recommended: quinidine; other anticoagulants; certain antiplatelet agents (GPIIb/IIIa receptor antagonists, clopidogrel, ticlopidine, dextran, and sulfipyrazone)</li> <li>Use with caution: Strong P-gp inhibitors (e.g. verapamil, clarithromycin); potent P-gp inducers (e.g. rifampicin, St John's wort)</li> <li>Use with care: NSAIDs</li> </ul>
Immunogenicity	No information available	Not immunogenic for HIT antibodies	No information available

\* Animal studies. † Not yet approved in any country.

CrCl = creatinine clearance; CYP3A4 = cytochrome P450 3A4; HIT = heparin-induced thrombocytopenia; HIV = human immunodeficiency virus; i.v. = intravenous; NSAID = non-steroidal anti-inflammatory drug; od = once daily; PAI = platelet aggregation inhibitor; P-gp = P-glycoprotein; THR = total hip replacement; TKR = total knee replacement; ULN = upper limit of normal.

**Table 3.** Phase III Trial Results for Dabigatran, Rivaroxaban, and Apixaban after Total Hip- or Knee-Replacement Surgery

	Duration of Therapy	Primary Efficacy Endpoint*		Major Bleeding†	
		% (n/N)	p-Value for Difference from Enoxaparin	% (n/N)	p-Value for Difference from Enoxaparin
<b>Dabigatran</b>					
RE-NOVATE (THR), N = 3,494	28–35 days	—	—	—	—
Dabigatran 220 mg od	—	6.0 (53/880)	<0.0001	2.0 (23/1,146)	—
Dabigatran 150 mg od	—	8.6 (75/874)	<0.0001	1.3 (15/1,163)	—
Enoxaparin 40 mg od	—	6.7 (60/897)	—	1.6 (18/1,154)	—
RE-MOBILIZE (TKR), N = 2,615	12–15 days	—	—	—	—
Dabigatran 220 mg od	—	31.1 (188/604)	0.0234	0.6 (5/857)	—
Dabigatran 150 mg od	—	33.7 (219/649)	0.0009	0.6 (5/871)	—
Enoxaparin 30 mg bid	—	25.3 (163/643)	—	1.4 (12/868)	—
RE-MODEL (TKR), N = 2,101	6–10 days	—	—	—	—
Dabigatran 220 mg od	—	36.4 (183/503)	0.0003	1.5 (10/679)	—
Dabigatran 150 mg od	—	40.5 (213/526)	0.017	1.3 (9/703)	—
Enoxaparin 40 mg od	—	37.7 (193/512)	—	1.3 (9/694)	—
<b>Rivaroxaban</b>					
RECORD1 (THR), N = 4,541	31–39 days	—	—	—	—
Rivaroxaban 10 mg od	—	1.1 (18/1,595)	<0.001	0.3 (6/2,209)	0.18
Enoxaparin 40 mg od	—	3.7 (58/1,558)	—	0.1 (2/2,224)	—
RECORD2 (THR), N = 2,509	—	—	—	—	—
Rivaroxaban 10 mg od	31–39 days	2.0 (17/864)	<0.0001	<0.1 (1/1,228)	—
Enoxaparin 40 mg od	10–14 days	9.3 (81/869)	—	<0.1 (1/1,229)	—
	(with placebo for 31–39 days)				
RECORD3 (TKR), N = 2,531	10–14 days	—	—	—	—
Rivaroxaban 10 mg od	—	9.6 (79/824)	<0.001	0.6 (7/1,220)	0.77
Enoxaparin 40 mg od	—	18.9 (166/878)	—	0.5 (6/1,239)	—
RECORD4 (TKR), N = 3,148	10–14 days	—	—	—	—
Rivaroxaban 10 mg od	—	6.9 (67/965)	0.0118	0.7 (10/1,526)	0.1096
Enoxaparin 30 mg bid	—	10.1 (97/959)	—	0.3 (4/1,508)	—
<b>Apixaban</b>					
ADVANCE-1 (TKR), N = 3,195	10–14 days	—	—	—	—
Apixaban 2.5 mg bid	—	9.0 (104/1,157)	0.06	0.7 (11/1,596)	0.05
Enoxaparin 30 mg bid	—	8.8 (100/1,130)	—	1.4 (22/1,588)	—
ADVANCE-2 (TKR), N = 3,057	10–14 days	—	—	—	—
Apixaban 2.5 mg bid	—	15.1 (147/976)	<0.001	—	—
Enoxaparin 40 mg od	—	24.4 (243/997)	—	—	—

\* Composite of any deep vein thrombosis, pulmonary embolism, and death from any cause. † Different definitions of major bleeding were used in each study program.

bid = twice daily; n = number of patients in which the particular outcome occurred; N = total number of patients in the group; od = once daily; RECORD = REgulation of Coagulation in ORthopaedic surgery to prevent Deep vein thrombosis and pulmonary embolism; THR = total hip replacement; TKR = total knee replacement.

compression, surgical interventions, fluid replacement and hemodynamic support, or transfusions. If these methods are unable to control a bleeding episode, rFVIIa may be considered, but this recommendation is based on data from preclinical studies. In these studies, rFVIIa partially reversed the

anticoagulant effects of rivaroxaban in *in vitro* and primate models.<sup>65,66</sup> The activated prothrombin complex concentrate factor VIII inhibitor bypassing activity (FEIBA) has also demonstrated ability to partially neutralize the effect of high-dose rivaroxaban in studies in baboons and rats.<sup>66,67</sup> The

prothrombin complex concentrate Beriplex<sup>®</sup> (CSL Behring, Marburg, Germany) was also able to reverse effects of high-dose rivaroxaban in rats, and plasma-derived and recombinant factor Xa have also demonstrated potential as antidotes for factor Xa inhibitors.<sup>68–70</sup> There is, however, no clinical data for the use of these agents in patients receiving rivaroxaban. Although routine monitoring is not required, several clotting assays have been investigated for their potential to monitor levels of rivaroxaban should this be required in the event of an overdose, for example. These preliminary tests indicate that prothrombin time (using a rivaroxaban calibrator), dilute Russell's viper venom test, one-step PiCT<sup>®</sup> (Pentapharm, Basel, Switzerland), and HepTest<sup>®</sup> (American Diagnostica, Stamford, CT) assays seem to be the most useful.<sup>71</sup> However, commercially available prothrombin time tests should not be used for factor Xa inhibitors; for rivaroxaban, prothrombin time assay results should be expressed in rivaroxaban plasma concentration in micrograms per milliliter with calibrated plasma concentrations.<sup>71</sup> Factor Xa chromogenic assays may also be a useful measure of rivaroxaban activity in human plasma, using rivaroxaban as a calibrator.<sup>71,72</sup>

Rivaroxaban is also under investigation for the treatment of VTE and the prevention of recurrent VTE in the phase III EINSTEIN program (table 4). The EINSTEIN Extension study assessed the relative efficacy and safety of rivaroxaban *versus* placebo in patients who had completed 6 or 12 months of anticoagulant treatment for an acute episode of VTE. Rivaroxaban (20 mg once daily) was associated with an 82% relative risk reduction in the recurrence of VTE and a low incidence of major bleeding (0.7% in the rivaroxaban group, 0% with placebo).<sup>\*\*</sup> A phase II study of rivaroxaban in patients with acute coronary syndrome (ACS) identified tolerable doses, which will be investigated in phase III trials.<sup>73</sup> Other ongoing studies are shown in table 4. Overall, rivaroxaban represents one of the first new oral anticoagulant agents to be approved in different markets.

**Apixaban.** Apixaban is another oral, direct factor Xa inhibitor with good bioavailability, low potential for drug–drug interactions, and a half-life of approximately 12 h (table 2).<sup>74</sup> It has a high affinity for factor Xa and inhibits free factor Xa, factor Xa in the prothrombinase complex, and factor Xa bound to platelets (fig. 2B).<sup>74,75</sup> In animal studies, apixaban has a bioavailability of 34–88%.<sup>75</sup> In humans, it is eliminated *via* multiple pathways, predominantly *via* the fecal route (56%), with 25–29% of the recovered dose eliminated *via* urinary excretion.<sup>74</sup> Concomitant administration of apixaban and platelet inhibitors has only been studied in animal arterial thrombosis models. Apixaban in combination with acetylsalicylic acid or acetylsalicylic acid plus clopi-

dogrel demonstrated enhanced antithrombotic efficacy without excessive increases in bleeding time and will be investigated further in clinical trials.<sup>76</sup> Preliminary *in vitro* studies indicate that metabolic drug–drug interaction potential between apixaban and coadministered cytochrome P450 substrates or inhibitors is minimal, indicating that dose adjustments may not be required.<sup>77</sup> Although routine monitoring is not required, there are limited data available regarding effective methods of monitoring the effect of apixaban should this be required. An anti-Xa assay has demonstrated potential for predicting apixaban plasma concentration,<sup>78</sup> but apixaban produces only modest changes in INR and activated partial thromboplastin time, so these tests are not thought to be useful for monitoring.<sup>75</sup> There is no specific antidote for apixaban, and there is currently no information available on studies of potential reversal agents, except for preclinical studies of plasma-derived and recombinant factor Xa, which showed dose-dependent reversal of the anticoagulant effect of apixaban.<sup>69,70</sup>

Apixaban, administered twice daily, has been evaluated for the prevention of VTE after total knee-replacement surgery in two phase III studies. In the ADVANCE-1 study, apixaban failed to meet the noninferiority criteria compared with 30 mg enoxaparin twice daily for the prevention of VTE. However, apixaban was associated with lower rates of clinically relevant bleeding and had an adverse event profile similar to that of enoxaparin (table 3).<sup>79</sup> In ADVANCE-2, apixaban was more effective than 40 mg enoxaparin once daily for the prevention of VTE and was associated with a lower risk of major and clinically relevant bleeding (table 3).<sup>80</sup> ADVANCE-3 is ongoing and will compare apixaban with 40 mg enoxaparin once daily after total hip-replacement surgery (table 4). In a phase II placebo-controlled study, apixaban was evaluated for the prevention of acute ischemic and safety events in patients with ACS on antiplatelet therapy (APPRAISE). Apixaban for 6 months was associated with a dose-related increase in major or clinically relevant nonmajor bleeding and lower rates of ischemic events compared with placebo. The two higher-dose apixaban arms were discontinued because of excess total bleeding.<sup>81</sup> Ongoing clinical trials of apixaban are shown in table 4.

**Other Direct Factor Xa Inhibitors under Investigation.** Several other direct factor Xa inhibitors have been studied, including YM150, which has completed studies in patients undergoing total hip replacement (ONYX and ONYX-2),<sup>82,83</sup> and phase II studies evaluating the efficacy and safety of once- and twice-daily dosing after knee replacement (PEARL and PEARL-1; table 4). Further studies are currently ongoing (table 4). Another oral, direct factor Xa inhibitor in phase II/phase III development is DU-176b (edoxaban), which inhibits both free and prothrombinase-bound factor Xa. DU-176b reduced the incidence of VTE after total knee replacement without increasing the risk of major or clinically relevant bleeding. It is noteworthy that this is the only placebo-controlled study conducted with one of the newer oral anticoagulants, and the rate of major bleeding in the placebo

\*\* Buller HR, on behalf of the Einstein investigators: Once-daily oral rivaroxaban versus placebo in the long-term prevention of recurrent symptomatic venous thromboembolism. The Einstein-Extension study. December 8, 2009. Available at: <http://ash.confex.com/ash/2009/webprogram/Paper25669.html>. Accessed January 11, 2010.

**Table 4.** Key Ongoing Clinical Trials of New Anticoagulant Agents\*

Trial Name	Purpose of Investigation
Dabigatran etexilate RE-NOVATE II	Dabigatran etexilate for extended thromboprophylaxis compared with enoxaparin after THR (NCT00657150)
RE-MEDY	Placebo-controlled trial of long-term therapy with dabigatran etexilate for the prevention of recurrent VTE (NCT00329238)
RE-COVER, RE-COVER II	Dabigatran etexilate compared with warfarin for the 6-month treatment of acute symptomatic VTE (NCT00680186)
RE-SONATE	Dabigatran etexilate in the long-term prevention of recurrent symptomatic VTE (NCT00558259)
RELY-ABLE	Long-term safety of dabigatran etexilate for the prevention of stroke in patients with AF (NCT00808067)
Rivaroxaban EINSTEIN PE	Rivaroxaban compared with enoxaparin plus a VKA for 3, 6, or 12 months' treatment in patients with confirmed acute symptomatic PE with or without symptomatic DVT (NCT00439777)
EINSTEIN DVT	Rivaroxaban compared with enoxaparin plus a VKA for 3, 6, or 12 months' treatment in patients with confirmed acute symptomatic DVT without symptomatic PE (NCT00440193)
ROCKET AF (Rivaroxaban Once daily, oral, direct Factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation)	Rivaroxaban compared with warfarin for the prevention of stroke in patients with AF (NCT00403767)
ATLAS ACS TIMI 51 (Anti-Xa Therapy to Lower cardiovascular events in addition to Aspirin with or without thienopyridine therapy in Subjects with Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction 51)	Rivaroxaban in addition to ASA with/without thienopyridine therapy to reduce the risk of cardiovascular events in patients with ACS (NCT00809965)
MAGELLAN (Multicenter, rAndomized, parallel Group Efficacy superiority study in hospitalized medically ill patients comparing rivaroxaban with enoxaparin)	Rivaroxaban compared with enoxaparin for the prevention of VTE in hospitalized medically ill patients (NCT00571649)
Apixaban ARISTOTLE (Apixaban for Reduction In STroke and Other Thromboembolic Events in atrial fibrillation)	Apixaban compared with warfarin for the prevention of stroke in patients with AF (NCT00412984)
AVERROES	Apixaban compared with antiplatelet therapy for the prevention of stroke prevention in patients with AF unable to take warfarin (NCT00496769)
ADOPT	Apixaban compared with enoxaparin for the prevention of VTE in hospitalized medically ill patients (NCT00457002).
AMPLIFY	Apixaban compared with enoxaparin plus a VKA for the treatment and secondary prevention of VTE (NCT00643201)
ADVANCE-3	Apixaban compared with enoxaparin 40 mg once daily for the prevention of VTE after THR
YM150 PEARL, PEARL-1	YM150 compared with enoxaparin for the prevention of VTE in patients undergoing elective TKR (NCT00408239, NCT00595426)
ONYX-3	YM150 compared with enoxaparin in subjects undergoing THR (NCT00902928)
OPAL-2	Safety of YM150 compared with warfarin in patients with AF (NCT00938730)
n.a.	YM150 for the prevention of VTE in patients undergoing hip fracture surgery or surgery in the lower extremities (NCT00937911)
n.a.	YM150 compared with mechanical prophylaxis for the prevention of VTE in patients undergoing major abdominal surgery (NCT00942435)

*(continued)*

Table 4. Continued

Trial Name	Purpose of Investigation
DU-176b (edoxaban) n.a.	DU-176b compared with dalteparin for the prevention of VTE in patients undergoing THR (NCT00398216)
n.a.	DU-176b for the prevention of VTE in patients undergoing THR (NCT00107900)
n.a.	DU-176b compared with warfarin for the prevention of stroke in patients with AF (NCT00806624, NCT00781391, NCT00504556)
Betrixaban EXPLORE-Xa	Betrixaban compared with warfarin for the prevention of stroke in patients with AF (NCT00742859)
Otamixaban SEPIA-ACS1	Otamixaban compared with unfractionated heparin and eptifibatide in patients with non-ST elevation ACS (NCT00317395)
Odiparcil n.a.	Odiparcil for the prevention of VTE after TKR (NCT00041509)
n.a.	Pharmacokinetic/pharmacodynamic study of odiparcil with ASA in patients with AF with low or intermediate risk of stroke (NCT00240643)

\* <http://clinicaltrials.gov>. Accessed 18 April 2010.

ACS = acute coronary syndrome; AF = atrial fibrillation; ASA = acetylsalicylic acid; DVT = deep vein thrombosis; n.a. = not applicable; PE = pulmonary embolism; THR = total hip replacement; TKR = total knee replacement; VKA = vitamin K antagonist; VTE = venous thromboembolism.

group was higher than the rate seen with a 5-mg dose of DU-176b.<sup>84</sup> Two studies evaluating DU-176b for the prevention of VTE after hip-replacement surgery have been completed, but no data are currently available (table 4). A dose-finding study in patients with atrial fibrillation found two doses of DU-176b with safety profiles similar to standard therapy,<sup>85</sup> and additional efficacy and safety studies are ongoing (table 4).

An additional oral, direct factor Xa inhibitor, betrixaban, is also in phase II development and has been evaluated after total knee replacement in patients in the United States and Canada.<sup>86</sup> Additional studies include the EXPLORE-Xa study, which will compare the efficacy and safety of three doses of betrixaban with warfarin for the prevention of stroke in patients with atrial fibrillation (table 4). Eribaxaban (PD0348292) has been evaluated in patients undergoing total knee replacement and demonstrated a significant dose response for efficacy, and a trend for an increase in bleeding, although this was not significant.<sup>87</sup> Otamixaban is another noncompetitive, direct inhibitor of factor Xa that is given parenterally and has a half-life of 1.5–2 h.<sup>88,89</sup> It has been evaluated in a phase II dose-ranging study of patients undergoing percutaneous coronary intervention (PCI), in which it demonstrated a positive risk–benefit profile compared with UFH.<sup>89</sup> Further studies, such as the SEPIA-ACS1 study (table 4), will help to determine the potential role of otamixa-

ban in ACS; no studies of this agent in the postoperative setting are currently under way.

### Direct Thrombin Inhibitors

**Ximelagatran.** Ximelagatran, a prodrug of the active metabolite melagatran, is an oral, direct thrombin inhibitor.<sup>43</sup> Initially approved and marketed in the EU for the prevention of VTE after total hip- and knee-replacement surgery in 2004, it also demonstrated potential for preventing thromboembolic events after myocardial infarction and in patients with atrial fibrillation.<sup>90–94</sup> However, it was withdrawn from the market in 2006 because of concerns over potential liver toxicity. Ximelagatran provided proof of principle that direct inhibition of thrombin was an effective mode of action for new anticoagulants.

**Dabigatran Etexilate.** Dabigatran etexilate is an oral, direct thrombin inhibitor (fig. 2B) in advanced clinical development, with a rapid onset of action, no reported drug or food interactions, and no requirement for routine coagulation monitoring (table 2).<sup>95,96</sup> Dabigatran has a half-life of 12–14 h (in healthy subjects) and a bioavailability of 6.5%.†† Unchanged dabigatran is predominantly excreted *via* the kidneys, with approximately 80% of an intravenous dose excreted unchanged in the urine. Dabigatran has been approved in the EU, Canada, and several other countries for the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip- or knee-replacement surgery. In this indication, it is not recommended for use in patients with severe renal impairment, or hepatic impairment (increased liver enzymes at more than

†† Pradaxa® prescribing information. Boehringer-Ingelheim. Available at: [http://www.pradaxa.com/Include/media/pdf/Pradaxa\\_SPC\\_EMEA.pdf](http://www.pradaxa.com/Include/media/pdf/Pradaxa_SPC_EMEA.pdf). Accessed March 29, 2010.

two times the upper limit of the normal range). A reduced dose is recommended in patients with moderate renal impairment (CrCl 30–50 ml/min) or aged more than 75 yr.†† The cytochrome P450 system has a limited role in the metabolism of dabigatran; therefore, drugs metabolized by this system have low potential for clinically relevant interactions and are not contraindicated.†† Dabigatran is a substrate of P-gp, so when used with amiodarone (a P-gp inhibitor) in patients undergoing total hip- or knee-replacement surgery, the dabigatran dose should be reduced to 150 mg once daily.†† The P-gp inhibitor quinidine is contraindicated, and strong P-gp inhibitors (such as verapamil and clarithromycin) should be coadministered with caution. Caution is also advised for concomitant use of potent P-gp inducers such as rifampicin or St. John's wort. No clinically relevant interaction between digoxin (a substrate of P-gp) and dabigatran was observed in studies in healthy subjects, and digoxin is not contraindicated.†† Although delayed absorption of dabigatran was reported when coadministered with proton pump inhibitors, no effect on bleeding or efficacy was observed in clinical trials.†† Dabigatran is not recommended for concomitant use with other anticoagulants and certain antiplatelet agents (GPIIb/IIIa receptor antagonists, clopidogrel, ticlopidine, dextran, and sulfapyrazole).†† In phase III trials in patients undergoing total hip- or knee-replacement surgery, concomitant use with acetylsalicylic acid and nonsteroidal antiinflammatory drugs demonstrated a safety profile similar to that of enoxaparin, a standard of care,<sup>97</sup> but it is advised to monitor patients receiving dabigatran with nonsteroidal antiinflammatory drugs closely for signs of bleeding.†† Dabigatran is not recommended in patients undergoing anesthesia with postoperative indwelling epidural catheters for total hip- or knee-replacement surgery. Administration of the first dose should occur a minimum of 2 h after the catheter is removed, and patients should be observed for neurologic signs and symptoms.<sup>98</sup>

There is no specific antidote to reverse the effect of dabigatran.†† *In vitro* studies showed that rFVIIa is not able to reverse the effects of thrombin inhibitors,<sup>65</sup> but there is limited information available regarding the effects of other potential reversal agents. Routine coagulation monitoring is not required, and there are difficulties in measuring the anticoagulant effect of dabigatran using standard clotting assays, should this be needed. The effect on activated partial thromboplastin time is not dose dependent, and the sensitivity of INR assays is too low (as for all direct thrombin inhibitors). The thrombin time assay responds in a linear fashion, but lacks standardization and may be too sensitive for clinically relevant plasma concentrations. Ecarin clotting time seems to be the most accurate assay<sup>95</sup> but is not widely available. In the phase III clinical program, dabigatran etexilate administered once daily demonstrated efficacy and safety similar to that of 40 mg enoxaparin once daily for the prevention of VTE after total hip- or knee-replacement surgery (RE-MODEL, RE-NOVATE; table 3).<sup>99,100</sup> However, compared with the North American enoxaparin regimen of

30 mg twice daily, dabigatran failed to meet the noninferiority criteria for efficacy (RE-MOBILIZE; table 3).<sup>101</sup> It has demonstrated efficacy superior to that of dose-adjusted warfarin for the prevention of stroke in patients with atrial fibrillation, with a similar rate of major bleeding (RE-LY).<sup>102</sup> Dabigatran 150 mg twice daily demonstrated noninferiority to dose-adjusted warfarin (INR 2.0–3.0) for the 6-month treatment of acute symptomatic VTE (RE-COVER).<sup>103</sup> An additional study will evaluate further the efficacy and safety of dabigatran compared with warfarin for the 6-month treatment of acute symptomatic VTE (RE-COVER II; table 4). Other ongoing clinical studies are listed in table 4.

**Parenteral Agents.** Bivalirudin is a parenteral, bivalent direct thrombin inhibitor that, unlike heparin, inhibits both free and fibrin-bound thrombin and has low immunogenic potential.<sup>104</sup> It is an oligopeptide of hirudin, and its affinity for thrombin is intermediate between hirudin and argatroban (see paragraphs 3–5 of this section).<sup>104</sup> It has a rapid onset of action and is predominantly metabolized *via* proteolysis with subsequent renal excretion.<sup>104</sup> Bivalirudin is approved for use in patients with unstable angina who are undergoing percutaneous transluminal coronary angioplasty or for the treatment of patients with, or at risk for, HIT or HIT and thrombosis syndrome undergoing PCI. It is also indicated for PCI with provisional use of glycoprotein IIb/IIIa antagonist therapy.<sup>104</sup> In these indications, bivalirudin is intended for concomitant use with acetylsalicylic acid.<sup>105</sup> In patients with moderate- or high-risk ACS undergoing invasive treatment with glycoprotein IIb/IIIa inhibitors, bivalirudin was associated with similar rates of ischemia and significantly lower rates of bleeding compared with heparin.<sup>106</sup> In patients with ST-elevation myocardial infarction undergoing primary PCI, anticoagulation with bivalirudin alone significantly reduced 30-day rates of major bleeding and net adverse clinical events (major bleeding or major adverse cardiovascular events, including death, reinfarction, target-vessel revascularization for ischemia, and stroke) compared with heparin plus glycoprotein IIb/IIIa inhibitors.<sup>107,108</sup>

Bivalirudin is the most extensively studied agent in patients requiring cardiac surgery who are HIT positive,<sup>109–111</sup> although it is not formally approved in this setting. Prospective studies have compared bivalirudin with heparin in patients without HIT who are undergoing cardiac surgery with or without cardiopulmonary bypass.<sup>109,112–114</sup> Bivalirudin dosing for off-pump cardiac surgery is similar to that used in PCI, as listed in table 5. Standard activated clotting times are used to monitor its anticoagulant effects.

Lepirudin and desirudin are recombinant hirudins, synthetic analogs of hirudin manufactured by recombinant DNA technology. Lepirudin is approved for use in patients with HIT and associated thromboembolic disease to prevent further thromboembolic complications.<sup>26,115</sup> Lepirudin was initially reported for cardiac surgery and cardiopulmonary bypass; however, bleeding was a major problem.<sup>116–118</sup> HIT patients receiving lepirudin generate antibodies and require close monitoring (using activated partial thromboplastin

**Table 5.** Bivalirudin Dosing in Cardiac Surgery

	Percutaneous Coronary Intervention <sup>104</sup>	Off Pump <sup>110,112,113</sup>	On Pump <sup>111,114</sup>
Initial bolus dose, mg/kg i.v.	0.75	0.75	1.0 (Priming dose of 50 mg added to the priming solution of the cardiopulmonary bypass reservoir)
Initial infusion rate, mg/kg/h	1.75	1.75	2.5
Target ACT, s	—	>300	2.5× baseline
Additional bolus dose, mg/kg	0.3	0.1–0.5 or increased infusion rate	0.1–0.5

ACT = activated clotting time; i.v. = intravenous.

time) to avoid bleeding complications.<sup>119</sup> In patients with renal dysfunction, the drug may have a prolonged half-life.<sup>120</sup> No agents are currently available for reversing these direct thrombin inhibitors.

Desirudin (recombinant hirudin) is approved for use in the EU and now in the United States for the prevention of VTE after total hip- or knee-replacement surgery as a twice-daily subcutaneous dose, with the first dose given before surgery.<sup>121</sup> It reduced the risk of VTE after total hip replacement compared with enoxaparin, with a bleeding risk similar to that of enoxaparin despite the administration of desirudin immediately before surgery (compared with enoxaparin administration the night before),<sup>122,123</sup> and has demonstrated favorable efficacy and safety compared with heparin in patients with stable angina who are undergoing percutaneous transluminal coronary angioplasty.<sup>124</sup> It has also shown potential for the prevention of myocardial infarction in patients with ACS.<sup>125</sup> Antigenicity and anaphylaxis are also reported, although the risk of hypersensitivity to desirudin seems to be relatively low. Because desirudin is primarily eliminated by the kidneys, patients with moderate or mild-to-moderate renal impairment, and those receiving concomitant oral anticoagulant therapy, require monitoring using activated partial thromboplastin time.<sup>121</sup>

Argatroban is an injectable, synthetic, univalent direct thrombin inhibitor indicated for prophylaxis or treatment of thrombosis in patients with or at risk for HIT who are undergoing PCI.<sup>126–129</sup> Patients with HIT are likely to have reduced renal function; a potential advantage of argatroban is that, unlike bivalirudin and lepirudin, it is hepatically eliminated, so no dose adjustments are required in patients with renal impairment.<sup>130</sup> Because lepirudin is renally eliminated and bivalirudin is partially (approximately 20%) renally eliminated,<sup>104</sup> their use may require dose adjustment in renally impaired patients to avoid accumulation. In addition, unlike the use of lepirudin,<sup>119</sup> no antibodies that alter the anticoagulant activity of argatroban have been detected after prolonged or repeated use of argatroban.<sup>131</sup> Monitoring of argatroban is with the use of activated partial thromboplastin time, with a therapeutic goal of 1.5–3.0 times baseline values. The context-sensitive half-life of argatroban is 46 min, and no reversal agents are currently available.<sup>132</sup>

### Other Novel Agents in Early-phase Development

Odiparcil is an oral, indirect thrombin inhibitor in phase II development that exerts its anticoagulant effect through activation of antithrombin II (heparin cofactor II), a natural anticoagulant.<sup>133</sup> A study investigating odiparcil for the prevention of thromboembolism after total knee replacement has recently been completed (TEMPEST [ThromboEMbolism Prevention Efficacy and Safety Trial]); other ongoing trials are listed in table 4.

RB006 is a direct factor IXa inhibitor that is currently in early development as part of the REG1 anticoagulation system, which also comprises its antidote, RB007.<sup>134</sup> RB006 elicits its anticoagulant effect by selectively inhibiting the factor VIIIa/IXa-catalyzed activation of factor X.<sup>134</sup> It has demonstrated anticoagulant and antithrombotic activity in preclinical studies, and phase II dose-ranging studies are currently being conducted. A safety study of the REG1 anticoagulation system has recently been completed in which it was compared with UFH in subjects undergoing elective PCI after pretreatment with clopidogrel and acetylsalicylic acid.<sup>135</sup> A phase II comparison with heparin in subjects with ACS (RADAR), is currently ongoing. TTP889 is an oral inhibitor of factor IX in phase II clinical development that demonstrated antithrombotic potential in early studies. However, in a recent exploratory study in hip fracture patients, TTP889 started after 5–9 days of standard VTE prophylaxis was not effective in reducing thromboembolism compared with placebo.<sup>136</sup> Further studies of different doses and in different indications are warranted to assess the full potential of this agent.

Recombinant human soluble thrombomodulin (ART-123) is composed of the active extracellular domain of thrombomodulin, a thrombin receptor on the endothelial cell surface. It binds to thrombin to inactivate coagulation, and the thrombin–ART-123 complex activates protein C to produce activated protein C. Activated protein C, in the presence of protein S, inactivates factor VIIIa and factor Va, inhibiting further thrombin formation.<sup>137</sup> In a dose-ranging study in patients undergoing hip replacement surgery, ART-123 demonstrated efficacy for the prevention of VTE,<sup>137</sup> but further clinical studies are required to determine its potential for VTE prevention. It has also demonstrated potential in the

treatment of patients with disseminated intravascular coagulation associated with hematologic malignancy or infection compared with heparin, an established treatment method.<sup>138</sup>

SR123781A is the first synthetic hexadecasaccharide that inhibits both factor Xa and thrombin *via* antithrombin binding without binding to PF4.<sup>139</sup> It therefore maintains all the antithrombotic properties of heparin without the risk of developing HIT. It is an injectable agent and has demonstrated antithrombotic activity in preclinical studies.<sup>140</sup> In a dose-ranging study (DRIVE [Dose Ranging Study in Elective Total Hip Replacement Surgery]) in patients undergoing total hip replacement, a statistically significant dose–response effect was observed with SR123781A for both efficacy and safety outcomes.<sup>141</sup> A phase II study (SHINE) in patients with ACS has been completed, but no results are available to date.

## Summary

Clinicians need to be aware of new and emerging anticoagulants in development that have the potential to improve the efficacy, safety, and convenience of perioperative and postoperative anticoagulant management. The extent to which new anticoagulants will be applied into therapeutic algorithms will depend on the balance between efficacy and safety, the ease of administration and management, as well as pharmacoeconomic considerations. The new oral agents will potentially be more convenient to use in the perioperative and postoperative periods compared with the established injectable agents, helping to improve adherence to the guideline recommendations, particularly after hospital discharge. Because the new agents do not require routine coagulation monitoring, they carry an important practical advantage over warfarin and other VKAs that require frequent INR testing. The new agents have more predictable dose responses, fewer interactions with other drugs and food, and will not require dose adjustments based on age, weight, or renal function. Of the newer oral drugs, the agents most advanced in clinical development are the direct factor Xa inhibitors rivaroxaban and apixaban and the direct thrombin inhibitor dabigatran etexilate. Rivaroxaban and dabigatran are approved in the EU for the prevention of VTE in adult patients undergoing elective total hip- or knee-replacement surgery but are not approved in the United States for any indication. Apixaban is not yet approved in any country for any indication. These agents have been evaluated in the postoperative setting in patients undergoing total hip- or knee-replacement surgery, with promising results, and it remains to be seen whether these results will translate into other surgical settings. The impact of the new agents will be influenced by the balance between efficacy and safety, improved convenience for patient and physician, and any potential cost-effectiveness benefits.

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ANESTHESIOLOGY REFLECTIONS

Grandfather Crawford Long, M.D.



To my friend and physician, Dr. Charles Scott Venable,  
from  
Maude Long, grand-daughter of Dr. Crawford W. Long—  
January 25, 1935

In Jefferson, Georgia, on March 30, 1842, Crawford W. Long, M.D. (1815–1878), etherized James M. Venable to remove a neck tumor. In the Wood Library-Museum, a photograph of an oil portrait honoring Long is mat-inscribed to another Venable: “To my friend and physician, Dr. Charles Scott Venable, from Maude Long, grand-daughter of Dr. Crawford W. Long—January 25, 1935.” As early as 1907, Dr. Venable had written about the safety of Crawford Long’s anesthetic in an article titled “The Use of Adrenalin during Ether Anesthesia.” (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at [www.anesthesiology.org](http://www.anesthesiology.org).)

George S. Bause, M.D., M.P.H., Honorary Curator, ASA’s Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. [UJYC@aol.com](mailto:UJYC@aol.com).

# The risk of spinal haematoma following neuraxial anaesthesia or lumbar puncture in thrombocytopenic individuals

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## Summary

Neuraxial anaesthesia is increasingly performed in thrombocytopenic patients at the time of delivery of pregnancy. There is a lack of data regarding the optimum platelet count at which spinal procedures can be safely performed. Reports are often confounded by the presence of other risk factors for spinal haematomata, such as anticoagulants, antiplatelet agents and other acquired or congenital coagulopathies/platelet function defects or rapidly falling platelet counts. In the absence of these additional risk factors, a platelet count of  $80 \times 10^9/l$  is a 'safe' count for placing an epidural or spinal anaesthetic and  $40 \times 10^9/l$  is a 'safe' count for lumbar puncture. It is likely that lower platelet counts may also be safe but there is insufficient published evidence to make recommendations for lower levels at this stage. For patients with platelet counts of  $50\text{--}80 \times 10^9/l$  requiring epidural or spinal anaesthesia and patients with a platelet count  $20\text{--}40 \times 10^9/l$  requiring a lumbar puncture, an individual decision based on assessment of risks and benefits should be made.

**Keywords:** thrombocytopenia, lumbar puncture, epidural anaesthesia, spinal anaesthesia, spinal haematoma.

Epidural and spinal anaesthesia are common techniques with advantages over general anaesthesia. Overall, they are felt to be safe techniques but a feared complication is the occurrence of spinal haematoma. Tryba (1993) estimated the risk of spinal haematoma following epidural anaesthesia at 1:150 000 and 1:220 000 after spinal anaesthesia. Vandermeulen *et al* (1994) reviewed 18 studies combining 200 000 patients who underwent epidural anaesthesia without any cases of spinal haematoma, whereas Stafford-Smith (1996), in a review including 13 case series involving >850 000 epidurals, identified three haematomas (0.0004%). Similarly, Ruppen *et al* (2006) found a risk of 1:168 000 of spinal haematoma in obstetric patients receiving epidural anaesthesia. The incidence of spinal

haematomata appears to be lower in obstetric patients than in older individuals: Moen *et al* (2004) found an incidence of 1:200 000 in obstetric patients but 1:3600 in elderly women undergoing total knee replacement. Vandermeulen *et al* (1994) also reviewed 61 case reports of spinal haematoma after epidural or spinal anaesthesia between 1906 and 1994, the majority of which (39 of 61) were described after 1980. Of these 61 cases, 41 (68%) had evidence of abnormal haemostasis. This was due to heparin in 30 cases and a variety of other causes in the remaining 11. Of these, only four had a reported thrombocytopenia of which one also received heparin and another was a chronic alcoholic. Fifteen were reported not to have any haemostatic abnormalities (although two had a spinal ependymoma and one spina bifida occulta with a vascular tumour) and in five no information on haemostasis was available. The review also suggested that the removal of epidural catheters poses an equal risk to insertion. The situation is similar for lumbar punctures (LPs) but there are no reliable estimates on the risk for spinal hematoma.

Therefore, in many of the reports of spinal haematomata following epidural or spinal anaesthesia, risk factors other than thrombocytopenia were present, being similar to reports of spontaneous spinal haematomata (Groen & Ponssen, 1990). After the introduction of low molecular weight heparin (LMWH) in the USA, nearly 60 spinal haematomata related to neuraxial anaesthesia were reported between 1993 and 1998 (Horlocker *et al*, 2003) whereas this complication was rare in European reports. The higher incidence was probably related to different dosing regimens of peri-operative LMWH in the USA. Introduction of guidelines reduced the frequency (Horlocker *et al*, 2003). The American Society for Regional Anaesthesia (ASRA), in its Second Consensus Conference on Neuraxial Anaesthesia and Anticoagulation, discusses in detail the relationship between the occurrence of spinal haematomas and haemostatic abnormalities, particularly those related to anticoagulant and antiplatelet agents (Horlocker *et al*, 2003). In common with other guidelines, however, they did not discuss the risk associated with thrombocytopenia. A degree of thrombocytopenia is a relatively common occurrence but what constitutes a safe platelet count for these techniques in relation to the occurrence of spinal haematomata is debated.

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Additionally, different causes of thrombocytopenia may have different bleeding risks. In another review, Douglas (2001) recommended a minimum platelet count of  $75 \times 10^9/l$  for epidural anaesthesia but emphasized the importance of the clinical situation and bleeding history. In particular, in patients with idiopathic thrombocytopenic purpura (ITP) with generally good functioning platelets, a level of  $50 \times 10^9/l$  may be sufficient, whereas in patients with HELLP (*haemolysis, elevated liver enzymes, low platelet count*) syndrome and rapidly falling platelet counts a higher count may be preferable (Douglas, 2001). A more recent publication (Douglas & Ballem, 2008), suggested a minimum level of  $40 \times 10^9/l$  in patients with ITP in whom the risks of general anaesthesia are high. Similarly, Kam *et al* (2004) also suggested a minimum platelet count of  $50 \times 10^9/l$  for epidural anaesthesia in parturients with ITP and that the entire clinical situation should be taken into account if epidural anaesthesia is considered, including a rapidly falling platelet count. Gill and Kelton (2000) also suggested a minimum count of  $50 \times 10^9/l$  in ITP patients provided there are no suggestions of platelet dysfunction. Bombeli and Spahn (2004) quoted a minimum platelet count of  $50 \times 10^9/l$  but did not further elaborate on this.

We reviewed the current guidelines, case series and case reports on epidural and spinal anaesthesia as well as LPs in thrombocytopenic patients. Relevant papers were identified by Medline searches for thrombocytopenia, spinal h(a)ematoma, subdural h(a)ematoma, epidural, spinal anaesthesia, regional anaesthesia, neuraxial anaesthesia, LP, spinal puncture, contra indication and guidelines. Other papers were identified by cross checking the references in papers identified above. As there is a clear relationship between anticoagulant use and spinal haematoma for which detailed guidelines exist, we limited the searches to thrombocytopenia only in relation to spinal punctures. Finally, the use of laboratory tests, such as thrombelastography, thrombin generation and others to predict bleeding is the subject of further research and is not discussed in this paper.

### Case series in regional anaesthesia

We identified nine single centre case series discussing regional anaesthesia in thrombocytopenic patients; these are summarized in Table I (Beilin *et al*, 1997; Bernstein *et al*, 2008; Deruddre *et al*, 2007; Frenk *et al*, 2005; Rasmus *et al*, 1989; Rolbin *et al*, 1988; Sharma *et al*, 1999; Waldman *et al*, 1987; Webert *et al*, 2003). In all studies the procedures were performed at the reported platelet count given below. Some procedures may have been performed after a platelet transfusion, if necessary, to achieve the reported level, and is included in Table I, if reported. All of the studies but one (Sharma *et al*, 1999) were retrospective and all assessed the safety of regional anaesthesia in obstetric patients except Waldman *et al* (1987), who discussed multiple caudal epidural blocks in 19 patients with a platelet count  $<50 \times 10^9/l$  and

malignancies. The main aim of the one prospective study (Sharma *et al*, 1999), describing 27 parturients who had epidurals with platelet counts  $<100 \times 10^9/l$  out of a cohort of 306 patients (38 with platelets  $<100 \times 10^9/l$ ), was to evaluate thrombelastography (TEG). Patients with abnormal TEG parameters were excluded from epidural anaesthesia (Sharma *et al*, 1999). Two series specifically assessed the safety of regional anaesthesia in parturients with immune thrombocytopenia (ITP) only (Deruddre *et al*, 2007; Webert *et al*, 2003). Altogether these series described a total of 345 patients with a platelet count  $<100 \times 10^9/l$  receiving either epidural or spinal anaesthesia. There were no complications. Of these, 246 had a platelet count between 70 and  $100 \times 10^9/l$ , 24 had a platelet count between 50 and  $70 \times 10^9/l$  and 20 had platelet counts  $<50 \times 10^9/l$ . In the remainder of the patients the series do not specify how many patients were in each group. The lowest platelet count for an epidural during delivery was in the series by Rasmus *et al* (1989) who described 14 epidurals during delivery with platelet counts between 15 and  $99 \times 10^9/l$ . The largest series was by Frenk *et al* (2005) who described 177 patients with a platelet count  $<100 \times 10^9/l$ , of which 170 had regional anaesthesia (platelet count 50– $100 \times 10^9/l$ ). The upper limit of the 95% confidence interval (CI) for complications in this series was 1.8% (Frenk *et al*, 2005).

Overall, the studies included patients with a variety of conditions leading to thrombocytopenia, were retrospective and, although some excluded specific patient groups from having regional anaesthesia (abnormal TEG (Sharma *et al*, 1999), bleeding or rapidly falling platelet counts (Beilin *et al*, 1997), platelet count  $<50$  or  $70 \times 10^9/l$  (Bernstein *et al*, 2008; Frenk *et al*, 2005)), exclusion criteria were not always clear and it is therefore difficult to compare the studies or to make recommendations on the safety of specific platelet counts.

### Case series in lumbar punctures

For LPs, seven single centre retrospective series were identified and are summarized in Table II (Breuer *et al*, 1982; Feusner, 2004; Howard *et al*, 2000; Kitanovski *et al*, 2008; Ruell *et al*, 2007; van Veen *et al*, 2004; Vavricka *et al*, 2003). In all studies the procedures were performed at the reported platelet count given below. Some procedures may have been performed after a platelet transfusion, if necessary, to achieve the reported level; this is included in Table II, if reported. Five were in a paediatric population with acute leukaemia (Howard *et al*, 2000; Feusner, 2004; Kitanovski *et al*, 2008; Ruell *et al*, 2007; van Veen *et al*, 2004). Three of these series describe a total of 1918 LPs in patients with a platelet count  $<100 \times 10^9/l$  (Howard *et al*, 2000; Kitanovski *et al*, 2008; van Veen *et al*, 2004), the fourth describes 738 LPs in patients with platelet counts over  $30 \times 10^9/l$  and into the normal range without specifying the number of patients at different platelet counts (Ruell *et al*, 2007) and the final study described LPs in 163 patients with newly diagnosed Acute Lymphoblastic Leukaemia (ALL) with a median platelet count of  $87 \times 10^9/l$  ( $47$ – $239 \times 10^9/l$ ) without subdividing patients by

Table 1. Case series of regional anaesthesia in thrombocytopenic patients.

Reference and study design	Patient group	Platelet count and number of patients	Complications (%)	Comments on risk factors	Conclusion
(Rasmus <i>et al.</i> , 1989) Retrospective review of 2929 parturients with epidural anaesthesia (Beilin <i>et al.</i> , 1997)	Adult delivery	14 epidurals Platelet count $15\text{--}99 \times 10^9/l$	0	2 patients with severe pre-eclampsia, 1 with amnionitis and 1 with streptococcal sepsis	Regional anaesthesia at platelet counts $<100 \times 10^9/l$ may be safe but individual risk benefit assessment should be made
Retrospective review of: a) epidurals during delivery b) patients becoming thrombocytopenic after epidural	Adult delivery	a) 30 epidurals with platelet count $69\text{--}98 \times 10^9/l$ b) 22 epidurals with subsequent platelet count $58\text{--}99 \times 10^9/l$	0	Excluded patients with falling platelet counts and bleeding	Regional anaesthesia should not necessarily be withheld when the platelet count is $<100 \times 10^9/l$
(Rolbin <i>et al.</i> , 1988) Retrospective review 2204 healthy random selected parturients. 104 thrombocytopenic, 61 with epidural, 3 with platelet count $<100 \times 10^9/l$	Adult delivery	61 epidurals with a platelet count $<150 \times 10^9/l$ , 2 with a platelet count $50\text{--}74 \times 10^9/l$ and 1 with a count $75\text{--}99 \times 10^9/l$	0	Excluded patients with conditions associated with thrombocytopenia	Epidural anaesthesia is safe if the platelet count exceeds $100 \times 10^9/l$ in otherwise healthy women and the platelet counts are not falling and there are no associated coagulopathies or platelet dysfunction
(Sharma <i>et al.</i> , 1999) Prospective study of the use of TEG during labour: a) 52 healthy women b) 254 with pre-eclampsia, 38 with platelets $<100 \times 10^9/l$	Adult delivery	27 epidurals in patients with pre-eclampsia and platelet count $<100 \times 10^9/l$	0	Patients with abnormal TEG were excluded from epidural	TEG may be used to assess haemostasis in pre-eclamptic women
(Frenk <i>et al.</i> , 2005) Retrospective chart review of 177 patients with platelet count $<100 \times 10^9/l$	Adult delivery	153 regional anaesthesia with platelet count $70\text{--}100 \times 10^9/l$ 11 regional anaesthesia with platelet count $60\text{--}70 \times 10^9/l$ 6 regional anaesthesia with platelet count $50\text{--}60 \times 10^9/l$	0	Patients with a platelet count $>60 \times 10^9/l$ had predominantly epidural anaesthesia Upper limit of 95% CI for complications 1.8%	Need to evaluate the risk-benefit ratio on a case-by-case basis before administering regional anaesthesia to parturients
170 received regional anaesthesia Included patients with gestational thrombocytopenia, pre-eclampsia and ITP		Patients with a platelet count $>60 \times 10^9/l$ had predominantly epidural anaesthesia			
(Webert <i>et al.</i> , 2003) Retrospective review of 119 deliveries in patients with ITP, 42 with epidural	Adult delivery	8 epidurals with platelet count $>150 \times 10^9/l$ 8 epidurals with platelet count $101\text{--}150 \times 10^9/l$ 19 epidurals with platelet count $76\text{--}100 \times 10^9/l$ 6 epidurals with platelet count $50\text{--}75 \times 10^9/l$ 1 epidural with platelet count $<50 \times 10^9/l$	0	Not discussed	No specific comments related to regional anaesthesia

Table I. (Continued).

Reference and study design	Patient group	Platelet count and number of patients	Complications (%)	Comments on risk factors	Conclusion
(Bernstein <i>et al</i> , 2008) Retrospective review of 10-369 births, 131 patients with platelet count $<150 \times 10^9/l$ , 65 had regional anaesthesia	Adult delivery	56 patients with platelet count $101-150 \times 10^9/l$ and regional anaesthesia 9 patients with platelet count $79-99 \times 10^9/l$ and regional anaesthesia	0	Patients with platelet count $<70 \times 10^9/l$ had platelet transfusion Only 20% of patients with a platelet count $<100 \times 10^9/l$ had regional anaesthesia vs. 50% overall Not discussed	Parturients with low platelet counts may be candidates for regional anaesthesia
(Derudder <i>et al</i> , 2007) Retrospective review of 10-203 births including 59 patients with ITP 32 with platelets $<100 \times 10^9/l$ (written in French) (Waldman <i>et al</i> , 1987)	Adult delivery	25 episodes of neuraxial anaesthesia and platelet count $88-99 \times 10^9/l$	0	Not discussed	Regional anaesthesia should not necessarily be withheld in ITP and platelet count $<100 \times 10^9/l$
	Adult, malignancy	19 caudal epidural blocks with platelet count $<50 \times 10^9/l$	0	Not discussed	Caudal epidural blocks in patients with significant thrombocytopenia are safe

TEG, thrombelastography; ITP, idiopathic thrombocytopenic purpura; 95% CI, 95% confidence interval.

platelet count (Feusner, 2004). Based on the studies where patients were grouped by platelet count, 39 LPs were performed at a count  $<10 \times 10^9/l$ , 204 at counts between 11 and  $20 \times 10^9/l$ , 817 with a count between 21 and  $50 \times 10^9/l$  and 858 with counts between 51 and  $100 \times 10^9/l$ . There were no bleeding complications in these studies. The majority of these patients were contributed by the series of Howard *et al* (2000) who described 5223 LPs in children with ALL, of which 941 had a platelet count  $<50 \times 10^9/l$ . The upper limits of the 95% CI for complications of the latter series were 1.75% for platelets  $<20 \times 10^9/l$  and 0.37% for platelets  $<50 \times 10^9/l$  (Howard *et al*, 2000).

The series in adult patients described a total of 131 LPs in patients with platelet counts  $<100 \times 10^9/l$  (Breuer *et al*, 1982; Vavricka *et al*, 2003). Vavricka *et al* (2003) described 118 procedures at platelet counts  $<100 \times 10^9/l$  and 75 with counts  $21-50 \times 10^9/l$ . There were no complications and the upper limit of 95% CI for complications was 10% for counts between 20 and  $30 \times 10^9/l$ , 8.81% for counts between 31 and  $50 \times 10^9/l$ , 8.22% for counts  $51-100 \times 10^9/l$  and 1.87% for counts  $>100 \times 10^9/l$  (Vavricka *et al*, 2003). The study by Breuer *et al*, (1982) described 20 LPs at counts below  $20 \times 10^9/l$ , 13 without platelet transfusion of which two were complicated by a spinal subarachnoid haematoma found on autopsy. There was no comment on other possible risk factors (Breuer *et al*, 1982). The latter study, as well as a study by Edelson *et al* (1974) (see below) describing eight spinal haematoma's is frequently quoted as a safe lower limit of  $20 \times 10^9/l$  (Breuer *et al*, 1982; Edelson *et al*, 1974).

Three studies commented on a relationship between platelet count and traumatic LP as defined by the number of red cells present per high power field or per microlitre of cerebrospinal fluid (CSF). The largest study was by Howard *et al* (2002), in a paediatric population, who retrospectively examined 5506 LPs in 965 patients with ALL for modifiable and non modifiable risk factors for traumatic tap (Howard *et al*, 2002). They reported increased 95% CIs for traumatic taps ( $>500$  red cells per high power field) at platelet counts  $<100 \times 10^9/l$ . Other risk factors for traumatic/bloody taps were operator experience, black race, age  $<1$  year, LPs within 2 weeks of each other (particularly if the previous tap was traumatic or bloody or was done at a platelet count  $<50 \times 10^9/l$ ). They also suggested that, although in routine LPs a count of  $>10 \times 10^9/l$  is sufficient for LP in children, platelet transfusions may be necessary at counts  $<100 \times 10^9/l$  in the presence of bacteraemia or circulating blasts to prevent meningitis or central nervous system (CNS) disease. In respect to the latter, there are two reports suggesting a relationship between traumatic LPs ( $>10$  red blood cells/ $\mu l$ ) in children with lymphoblasts in the CSF sample and an increased relapse rate (Burger *et al*, 2003; Gajjar *et al*, 2000).

Vavricka *et al* (2003) also reported a trend towards more traumatic taps at lower platelet counts in adults and recommended platelet transfusions if counts are  $<20 \times 10^9/l$ . (Ruell *et al* (2007) did not find a relationship between traumatic taps and platelet counts.

Table II. Case series of thrombocytopenic patients having lumbar punctures.

Reference and study design	Patient group	Platelet count: number of LPs	Complications (%)	Comments on risk factors	Conclusion
(van Veen <i>et al</i> , 2004) Retrospective study of 72 LPs in 72 ALL patients	Paediatric	<10 × 10 <sup>9</sup> /l: 9 11–20 × 10 <sup>9</sup> /l: 22 21–50 × 10 <sup>9</sup> /l: 41	0	30 (23%) >10 red cells/ $\mu$ l CSF	No support for prophylactic platelet transfusions May be useful if platelet count <10 × 10 <sup>9</sup> /l
(Ruell <i>et al</i> , 2007) Retrospective study of 738 LPs in 54 ALL patients	Paediatric	Platelet count ranged from 30 to >91 × 10 <sup>9</sup> /l No numbers given for each group Suggests they used a cut off for platelet transfusion of 29 × 10 <sup>9</sup> /l	0	65 (9%) >10 red cells/ $\mu$ l CSF. 30 (4%) >500 red cells/ $\mu$ l CSF	Platelet count of >30 × 10 <sup>9</sup> /l safe No relationship between traumatic tap and platelet count
(Howard <i>et al</i> , 2000) Retrospective study of 5223 LPs in ALL patients, 941 with platelet count <50 × 10 <sup>9</sup> /l	Paediatric	<10 × 10 <sup>9</sup> /l: 29 11–20 × 10 <sup>9</sup> /l: 170 21–50 × 10 <sup>9</sup> /l: 742 51–100 × 10 <sup>9</sup> /l: 858	0	Traumatic (>500 red cells/high powered field) = 10.8% ( <i>n</i> = 548)	95% CI platelet count <20 × 10 <sup>9</sup> /l = 0–1.75% 95% CI platelet count <50 × 10 <sup>9</sup> /l = 0–0.37% Prophylactic platelet transfusion is not necessary when platelet counts >10 × 10 <sup>9</sup> /l No conclusions can be drawn for below this level
(Kitanovski <i>et al</i> , 2008) Retrospective study in 51 patients (61 LPs) with ALL, AML or NHL (written in Slovenian)	Paediatric	<10 × 10 <sup>9</sup> /l: 5 of 6 had platelet transfusion 11–20 × 10 <sup>9</sup> /l: 7 of 19 had platelet transfusion 21–49 × 10 <sup>9</sup> /l: 2 of 36 had platelet transfusion	0	NA	NA
(Feusner, 2004) Retrospective report of 163 patients with newly diagnosed ALL (Vavricka <i>et al</i> , 2003) Retrospective review in 66 AML/ALL patients having 195 LPs	Paediatric  Adult	Median platelet count 87 × 10 <sup>9</sup> /l (47–239 × 10 <sup>9</sup> /l) No numbers given for each group 20–30 × 10 <sup>9</sup> /l: 35 31–50 × 10 <sup>9</sup> /l: 40 51–100 × 10 <sup>9</sup> /l: 43 >101 × 10 <sup>9</sup> /l: 77 Patients with platelet counts <20 × 10 <sup>9</sup> /l had a platelet transfusion	0  0	11 traumatic LPs  >500 red cells per high powered field in: 6: platelet count 20–30 × 10 <sup>9</sup> /l 4: platelet count 31–50 × 10 <sup>9</sup> /l 3: platelet count 51–100 × 10 <sup>9</sup> /l	No good supporting data for a safe minimum platelet count  Trend towards more traumatic taps at low platelet counts Minimum safe platelet count 20 × 10 <sup>9</sup> /l 95% CI 20–30 × 10 <sup>9</sup> /l: 0–10% 95% CI 31–50 × 10 <sup>9</sup> /l: 0–8.81% 95% CI 51–100 × 10 <sup>9</sup> /l: 0–8.22 95% CI >101 × 10 <sup>9</sup> /l: 0–1.87

Table II. (Continued).

Reference and study design	Patient group	Platelet count: number of LPs	Complications (%)	Comments on risk factors	Conclusion
(Breuer <i>et al</i> , 1982) Retrospective study of 20 cancer patients with a platelet count $<20 \times 10^9/l$	Adult	13 of 20 patients had LP without platelet transfusion	2 of 13 found to have spinal subarachnoid haematoma at post mortem	Not discussed	Suggest a minimum platelet count of $20 \times 10^9/l$ for LP

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; NHL, non-Hodgkin lymphoma; CSF, cerebrospinal fluid; 95% CI, 95% confidence interval.

## Case reports in regional anaesthesia

Limited to case reports reporting on either epidural or single episodes of spinal anaesthesia without any form of anticoagulation, we identified 21 such reports (12 epidurals, nine spinal anaesthesia) at platelet counts  $<100 \times 10^9/l$  at the time of puncture or catheter removal (Bailey *et al*, 1999; Moen *et al*, 2004; Nguyen *et al*, 2006; Morisaki *et al*, 1995; Gustafsson *et al*, 1988; Chang *et al*, 2003; Ezri *et al*, 2002; Harnett *et al*, 2000; Hew-Wing *et al*, 1989; Kuczkowski & Benumof, 2002; Landau *et al*, 2003; Moeller-Bertram *et al*, 2004; Nafiu *et al*, 2004; Ozgen *et al*, 2004; Raft *et al*, 2005; Sibai *et al*, 1986; Steer, 1993; Tamakawa & Ogawa, 1998; Wulf *et al*, 1988; Yuen *et al*, 1999). Sixteen were for analgesia during delivery (Bailey *et al*, 1999; Nguyen *et al*, 2006; Moen *et al*, 2004; Chang *et al*, 2003; Ezri *et al*, 2002; Harnett *et al*, 2000; Hew-Wing *et al*, 1989; Kuczkowski & Benumof, 2002; Landau *et al*, 2003; Moeller-Bertram *et al*, 2004; Nafiu *et al*, 2004; Raft *et al*, 2005; Steer, 1993; Yuen *et al*, 1999; Sibai *et al*, 1986). Five of these 16 were complicated by a spinal haematoma (three patients with HELLP syndrome, one patient with pre-eclampsia and one patient with coagulopathy following resuscitation for haemorrhagic shock) (Yuen *et al*, 1999; Moen *et al*, 2004; Nguyen *et al*, 2006; Sibai *et al*, 1986) and one by an intracranial subdural haematoma in a patient with HELLP syndrome (Ezri *et al*, 2002). All six had additional risk factors for bleeding: in three cases there was a rapidly falling platelet count (from 99 to  $21 \times 10^9/l$ , 71 to  $46 \times 10^9/l$  and from within normal limits to  $16 \times 10^9/l$  respectively) and more than one attempt to insert the catheter (Ezri *et al*, 2002; Yuen *et al*, 1999), in two an otherwise unspecified coagulopathy associated with HELLP syndrome was described (Moen *et al*, 2004) whereas the last case had a platelet count of  $93 \times 10^9/l$  but a bleeding time of 15 min without further information on coagulation parameters available (Sibai *et al*, 1986). The last case was part of a cohort of 112 thrombocytopenic patients with HELLP syndrome, of whom 16 had epidural anaesthesia with a platelet count of  $83 \pm 8 \times 10^9/l$  (Sibai *et al*, 1986). The other 10 case studies did not report complications with platelet counts ranging from 2 to  $90 \times 10^9/l$  (eight had platelet counts between 63 and  $85 \times 10^9/l$ , one with platelets of  $26 \times 10^9/l$ , one with a count of  $2 \times 10^9/l$ ). Underlying diagnoses included gestational thrombocytopenia in one patient (Landau *et al*, 2003), ITP in five patients (Bailey *et al*, 1999; Chang *et al*, 2003; Hew-Wing *et al*, 1989; Moeller-Bertram *et al*, 2004; Steer, 1993), eclampsia in two patients (one with chronic disseminated intravascular coagulation; DIC) (Kuczkowski & Benumof, 2002; Nafiu *et al*, 2004), one with cryptogenic liver cirrhosis (Harnett *et al*, 2000) and one patient with familial thrombocytopenia (Raft *et al*, 2005). Two patients in this group had a prolonged prothrombin time (Harnett *et al*, 2000; Kuczkowski & Benumof, 2002).

The case reports of regional anaesthesia outside obstetric practice all reported the occurrence of spinal haematoma (Gustafsson *et al*, 1988; Morisaki *et al*, 1995; Ozgen *et al*, 2004; Tamakawa & Ogawa, 1998; Wulf *et al*, 1988). All had potential

risk factors in addition to thrombocytopenia. Rapidly falling platelet counts and prolongation of the prothrombin time were reported by three (Gustafsson *et al*, 1988; Morisaki *et al*, 1995; Ozgen *et al*, 2004), two of which also had liver disease (Gustafsson *et al*, 1988; Morisaki *et al*, 1995). A further paper described a patient with liver cirrhosis and platelet count  $<100 \times 10^9/l$  without further information (Tamakawa & Ogawa, 1998) and the last study described a patient with acute myeloid leukaemia, prior allogeneic bone marrow transplant and aspergillus pneumonia who was found to have an epidural haematoma on autopsy after having had an epidural catheter placed for pain relief and a platelet count between 10 and  $48 \times 10^9/l$  (Wulf *et al*, 1988). The minimum platelet count (if reported) in this group was  $10 \times 10^9/l$ . No clear conclusions can be drawn but the reports describing complications are in keeping with suggestions that the safety of epidural anaesthesia in thrombocytopenic patients not only depends on the absolute platelet count, but also on the underlying reason for the thrombocytopenia, how rapidly the platelet count is falling and the presence of a coagulopathy (Douglas & Ballem, 2008; Gill & Kelton, 2000; Kam *et al*, 2004).

### Case reports of LP

After excluding reports of LP in the presence of anticoagulants, 11 reports were found that described 18 LPs in thrombocytopenic patients (platelet count  $1-63 \times 10^9/l$ ), complicated by spinal haematomas (Scott *et al*, 1989; Ayerbe *et al*, 2005; Edelson *et al*, 1974; Lee *et al*, 2007; Mapstone *et al*, 1983; Pai *et al*, 2002; Wirtz *et al*, 2000; Wolcott *et al*, 1970; Blade *et al*, 1983; Dunn *et al*, 1979; Masdeu *et al*, 1979). An additional three patients without thrombocytopenia that had spinal haematomas were also described in these reports (Lee *et al*, 2007; Masdeu *et al*, 1979). Eight of the 18 patients were asymptomatic and found on autopsy (Dunn *et al*, 1979; Edelson *et al*, 1974; Masdeu *et al*, 1979). In all but one case, potential risk factors other than thrombocytopenia were present including CNS disease, rapidly falling platelet counts, DIC or multiple attempts/traumatic LP. The patient without other risk factors had ALL and a platelet count of  $26 \times 10^9/l$  (Ayerbe *et al*, 2005). A further patient with a platelet count of  $63 \times 10^9/l$  had relapsed ALL after a recent bone marrow transplant (Scott *et al*, 1989). Recent bone marrow transplantation and intrathecal chemotherapy have been associated with an increased risk of intracranial haematomas (Colosimo *et al*, 2000).

### Guidelines

A total of 17 national and international guidelines from blood transfusion and anaesthetic societies were examined for guidance (American National Red Cross 2007; American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies 2006; American Society of Anesthesiologists Task Force on Obstetric Anaesthesia 2007; British Committee for Standards in Haematology

(BCSH 2003a,b); Gibson *et al*, 2004; Gogarten *et al*, 2007; Horlocker *et al*, 2003; Kwaliteitsinstituut voor de Gezondheidszorg CBO 2004; Layton *et al*, 2006; Llau *et al*, 2001; National Health and Medical Research Council Australia 2002; Royal College of Obstetricians and Gynaecologists 2008; Samama *et al*, 2002; Schiffer *et al*, 2001; Vandermeulen *et al*, 2005; Working party on obstetric anaesthesia of the Belgian society for regional anaesthesia 2002). Of these, only four gave a specific recommendation for epidural anaesthesia (American National Red Cross 2007; BCSH 2003a,b; Samama *et al*, 2002). The American National Red Cross (2007), the French Society of Anesthesiology (Samama *et al*, 2002) and the BCSH in guidelines for the management of ITP (BCSH 2003a) suggested a minimum platelet count of  $80 \times 10^9/l$  whereas the BCSH in guidelines for platelet transfusions (BCSH 2003b) suggested a minimum platelet count of  $50 \times 10^9/l$ . Additionally, the Australian and New Zealand College of Anaesthetists (2008), in a special interest paper, suggested a safe platelet count of  $>100 \times 10^9/l$  and proposed that a count of  $>80 \times 10^9/l$  is safe when there are no risk factors and the platelet count is not falling. The American Society of Anesthesiologists Task Force on Obstetric Anaesthesia and the Belgian Association for Regional Anaesthesia suggested laboratory tests (including platelet count) in patients at risk of haemorrhagic complications but did not specify a safe platelet count (Working party on obstetric anaesthesia of the Belgian society for regional anaesthesia 2002; American Society of Anesthesiologists Task Force on Obstetric Anaesthesia 2007).

Four guidelines gave suggestions for platelet counts in relation to LPs (American National Red Cross 2007; BCSH 2003b; Gibson *et al*, 2004; Kwaliteitsinstituut voor de Gezondheidszorg CBO 2004). The BCSH suggested a minimum platelet count of  $50 \times 10^9/l$  in the guidelines for platelet transfusions, the American National Red Cross and the Dutch blood transfusion guidelines suggested a minimum count of  $40 \times 10^9/l$  (American National Red Cross 2007; Kwaliteitsinstituut voor de Gezondheidszorg CBO 2004) and the BCSH transfusion guidelines for neonates and older children suggested a platelet count of  $20-40 \times 10^9/l$  (Gibson *et al*, 2004). The American Society of Clinical Oncology emphasized the paucity of data in this field and therefore refrained from an evidence-based recommendation (Schiffer *et al*, 2001).

### Current practice in neuraxial anaesthesia

Given the uncertainty of safe levels of platelet counts for spinal puncture, it is not surprising that current practice in relation to giving neuraxial anaesthesia in thrombocytopenic patients is highly variable.

Stamer *et al* (2007) mailed questionnaires to 918 German departments of anaesthesiology. Three hundred and ninety-seven replied, representing 41.9% of deliveries in Germany. More than half of the respondents never performed spinal or

epidural anaesthesia when the platelet count fell below  $65 \times 10^9/l$ . For a platelet count of  $79 \times 10^9/l$ , epidural anaesthesia was thought to be contraindicated by 37% and spinal anaesthesia by 22.2% ( $P = 0.001$ ). There was a greater reluctance to use regional blockade in departments with <500 deliveries/year than in departments with >1000 deliveries/year. Preeclampsia (severity not specified) was considered an absolute contraindication for regional block by 15% and placenta praevia by 30% of respondents. The authors emphasized the need for guidelines (Stamer *et al*, 2007).

Beilin *et al* (1996) mailed questionnaires to 153 directors of obstetric anaesthesia in academic centres and 153 private anaesthesiologists. These authors found that 60% of American anaesthetists performed a block at platelet counts between 80 and  $100 \times 10^9/l$  without further investigations in otherwise healthy women during delivery and 16% carried out the procedure at platelet counts between 50 and  $79 \times 10^9/l$ .

Spinal cord injury associated with anaesthesia was a leading cause for claims of nerve damage in the 1990s (Cheney *et al*, 1999). Cheney *et al* (1999) identified 73 claims related to spinal cord injury, 50 of which were related to regional anaesthesia (35 lumbar epidurals, nine subarachnoid blocks and four thoracic epidural blocks) with epidural haematoma being the most common reason for injury (16 cases). Major factors associated with spinal cord injury were blocks for chronic pain management (14 claims) and systemic anticoagulation in the presence of neuraxial block (13 claims). They also reported that delays in diagnosis of spinal haematoma were often due to attributing the postoperative weakness or numbness to persisting local anaesthetic effects rather than spinal cord ischaemia. Delays in the recognition of and response to neurological compromise was also emphasized in a recent document of the Victorian Consultative Council on Anaesthetic Mortality and Morbidity (Hughes, 2005).

## Discussion

Although spinal haematomas after spinal puncture are rare, the consequences can be devastating and they are the most common reason for claims resulting from nerve damage in this setting. An extensive review only identified 613 case reports over a 170-year time span (Kreppel *et al*, 2003). In this report no definite triggering factor could be identified in nearly half of cases (43.6%) but 16.9% of patients were receiving anticoagulant therapy. Spinal/epidural anaesthesia or LP in combination with a haemorrhagic diathesis (mainly anticoagulant therapy) was the fifth common cause (6.0%) whereas spinal/epidural anaesthesia or LP without a haemorrhagic diathesis was a triggering factor in 4.2%. There was no specific mention of thrombocytopenia (Kreppel *et al*, 2003). Although it is logical that thrombocytopenia will be a risk factor for occurrence of spinal haematomata, the threshold at which this occurs may be fluid and dependent on the co-existence of other risk factors and it is therefore not surprising that no clear

guidelines on the safety of these procedures in the presence of thrombocytopenia exist and that clinical practice varies substantially between centres. Previously, platelet counts  $>100 \times 10^9/l$  were suggested prior to epidural anaesthesia, primarily based on personal opinion (Bromage, 1993). On current practice, the majority of anaesthetists however would not view a platelet count of  $80\text{--}100 \times 10^9/l$  as a contraindication. The same threshold is also reflected in the available guidelines and through the retrospective case series that describe a total of 246 patients having an epidural without complications. Whether regional anaesthesia is safe at counts between 50 and  $80 \times 10^9/l$  is even more difficult to answer. There are studies suggesting that this is indeed safe, particularly in patients with ITP. However, in patients with a rapidly falling platelet count, conditions associated with platelet dysfunction or coagulopathies, as well as in patients where a difficult or traumatic puncture is more likely (such as ankylosing spondylitis), more caution is required. This is also reflected in the case reports where all haematomas in obstetric patients occurred with other risk factors present. An obvious coagulopathy was present in one of the three case reports outside the setting of obstetric practice whereas in the other two the clinical setting makes a coagulopathy a likely possibility (liver cirrhosis and neutropenic sepsis with aspergillus pneumonia) but no coagulation parameters are available.

For LPs there is equal uncertainty regarding a safe threshold of platelet count. In total there were 817 LP's described in children with a platelet count between 21 and  $50 \times 10^9/l$  and 243 LP's in children with a platelet count of  $<20 \times 10^9/l$ . The vast majority, however, was contributed by the study of Howard *et al* (2000) and even though their safety record is excellent, with upper limits of 95% CIs of 1.75% and 0.35% for platelet counts  $<20 \times 10^9/l$  and  $50 \times 10^9/l$  respectively, it is difficult to give evidence-based recommendations on (predominantly) a single centre retrospective study. Even less evidence is available for adults. The case reports all reported the occurrence of spinal haematomas. This occurred in 11 LPs with a platelet count  $<20 \times 10^9/l$ , six LPs with a count between 20 and  $50 \times 10^9/l$  and in four with a platelet count  $>50 \times 10^9/l$  (including in two with a normal platelet count). All but one however had other potential risk factors for bleeding. Therefore it may well be safe to perform LPs at platelet counts  $<20\text{--}50 \times 10^9/l$  (recommended as a minimum platelet count in different guidelines) but, similar to the discussion on neuraxial anaesthesia, this is probably strongly influenced by the presence of other risk factors.

## Conclusion

In view of the above we conclude that  $80 \times 10^9/l$  is a safe count for placing/removing an epidural or spinal anaesthetic and  $40 \times 10^9/l$  is a safe count for LP. This, however, is provided that:

- 1 The platelet count is stable.
- 2 There is no other acquired or congenital coagulopathy.

- 3 The platelet function is normal and the patient is not on an antiplatelet drug.
- 4 The patient is not on an anticoagulant. If the patient is on a low molecular weight heparin, 12 h should have elapsed from the last dose of a prophylactic dose or 24 h after a therapeutic dose before an epidural or spinal anaesthetic is placed (Horlocker *et al*, 2003).

It is possible that lower platelet counts may also be safe but there is insufficient published evidence to make recommendations for lower levels at this stage. For patients with platelet counts of  $50\text{--}80 \times 10^9/l$  requiring epidural or spinal anaesthesia and patients with a platelet count  $20\text{--}40 \times 10^9/l$  requiring a LP, an individual decision based on risks and benefits should be made.

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