# Regional anaesthesia and antithrombotic agents: recommendations of the European Society of Anaesthesiology

Wiebke Gogarten, Erik Vandermeulen, Hugo Van Aken, Sibylle Kozek, Juan V. Llau and Charles M. Samama

**Background and objectives** Performing neuraxial anaesthesia in patients receiving antithrombotic drugs is controversial due to the increased risk of spinal epidural haematoma. Strict adherence to the recommended time intervals between the administration of anticoagulants, neuraxial blockade and the removal of catheters is thought to improve patient safety and reduce the risk of haematoma. Appropriate guidelines have been prepared by a number of national societies of anaesthesiologists, but they do not have universal acceptance. The introduction of new anticoagulants together with recent reports of stent thrombosis in patients with perioperative cessation of antiplatelet drugs have considerably broadened the issue and made revision necessary. To overcome deficiencies in content and applicability, the European Society of Anaesthesiology has taken the initiative to provide current and comprehensive guidelines for the continent as a whole.
**Methods** Extensive review of the literature.
**Results and conclusions** In order to minimise bleeding complications during regional anaesthetic techniques, care should be taken to avoid traumatic puncture. If a bloody tap occurs when intraoperative anticoagulation is planned, postponing surgery should be considered. Alternatively, catheters can be placed the night before surgery. Regional anaesthesia in patients receiving full anticoagulation treatment continues to be contraindicated. Catheter manipulation and removal carry similar risks to insertion and the same criteria should apply. Appropriate neurological monitoring is essential during the postoperative recovery period and following catheter removal. The final decision to perform regional anaesthesia in patients receiving drugs that affect haemostasis has to be taken after careful assessment of individual risks and benefits.

***Eur J Anaesthesiol* 2010;27:999–1015**

**Published online 1 October 2010**

**Keywords: apixaban, aspirin, bleeding, cilostazol, clopidogrel, dabigatran, epidural, fondaparinux, haematoma, heparin, hirudin, idrabiotaparinux, low-molecular-weight heparin, prasugrel, regional anaesthesia, rivaroxaban, spinal, ticagrelor**

**Abbreviations: ACCP, American College of Chest Physicians; ACT, Activated Clotting Time; ADP, Adenosine Diphosphate; aPTT, Activated Partial Thromboplastin Time; ASRA, American Society of Regional Anesthesia; DVT, Deep Venous Thrombosis; ECT, Ecarin Clotting Time; ESA, European Society of Anaesthesiology; ESC, European Society of Cardiology; FDA, US Food and Drug Administration; HIT, Heparin-Induced Thrombocytopenia; INR, International Normalised Ratio; LMWH, Low-Molecular-Weight Heparin; NSAIDS, Non-Steroidal Anti-Inflammatory Drugs; PCC, Prothrombin Complex Concentrates; PF4, Platelet Factor 4; PDE, Phosphodiesterase; PT, Prothrombin Time; SSRI, selective serotonin uptake inhibitor; UFH, Unfractionated Heparin; VTE, Venous Thromboembolism**

The editors would like to thank Alain Borgeat (Switzerland), Elisabeth Gaertner (France, ESA Scientific subcommittee 8), Daniela Filipescu (Romania, ESA Scientific subcommittee 6), Klaus Görlinger (Germany, ESA Scientific subcommittee 6), Markus W. Hollmann (Netherlands, ESA Scientific subcommittee 8), Susan Mallett (UK, ESA Scientific subcommittee 6), and Andrew F. Smith (UK, Chair of the ESA Guidelines Committee) for their help in critically appraising the scientific content of this article. Potential conflicts of interest of the assessors are stated in the Acknowledgements section at the end of this paper.

## Background

The first national recommendations on neuraxial anaesthesia and antithrombotic drugs were published by the German Society for Anaesthesiology and Intensive Care in 1997[1] followed by the American Society of Regional Anesthesia (ASRA) in 1998,[2] and Belgian anaesthesiologists in 2000.[3] Since then new anticoagulant agents have been introduced and more information regarding the risk of neuraxial regional anaesthesia with concurrent anticoagulation is available. In addition, it has become clear that if antiplatelet drugs are withheld after coronary stent implantation, the risk of adverse perioperative cardiovascular events increases. Newer and more comprehensive recommendations are warranted.

The European Society of Anaesthesiology (ESA) working-party on Neuraxial Anaesthesia and Anticoagulants, composed of academic physicians experienced in this topic, has the aim of providing guidelines to assist European anaesthesiologists in their daily clinical practice. With regard to perioperative cardiac risk, the same working party has graded the level of recommendations and the level of evidence for the European Society of Cardiology (ESC)-ESA guidelines, using the definitions of the Committee for Practice Guidelines of the ESC (Table 1).[4]

From the Department of Anaesthesiology, Intensive Care and Pain Therapy, Harlaching Hospital, Municipal Hospitals of Munich, Munich, Germany (WG), Department of Anaesthesiology, University Hospitals, Katholieke Universiteit, Leuven, Leuven, Belgium (EV), Department of Anesthesiology and Intensive Care Medicine, University Hospital, Munster, Germany (WG, HVA), Department of Anaesthesiology, Intensive Care and Pain Management, Vienna, Medical University, Vienna, Austria (SK), Department of Anaesthesiology and Postsurgical Critical Care, Hospital Clinic Universiari, Valencia, Spain (JVL) and Department of Anaesthesiology and Intensive Care, Hotel-Dieu University Hospital, Paris (CMS), France

Correspondence to Wiebke Gogarten, MD, PhD, Department of Anaesthesiology, Intensive Care and Pain Therapy, Harlaching Hospital, Municipal Hospitals of Munich, Munich, Germany
Tel: +49 89 6210 2365; fax: +49 89 6210 3245;
e-mail: wiebke.gogarten@klinikum-muenchen.de



DOI:10.1097/EJA.0b013e32833f6f6f

**Table 1 Classes of recommendations and levels of evidence**

| Classes of recommendations | |
|---|---|
| Class I | Evidence and/or general agreement that a given treatment or procedure is beneficial |
| Class II | Conflicting evidence and/or divergence of opinion about the usefulness/efficacy of the treatment or procedure |
| Class IIa | Weight of evidence/opinion in favour of usefulness/efficacy |
| Class IIb | Usefulness/efficacy is less well established by evidence/opinion |
| Class III | Evidence or general agreement that the treatment or procedure is not useful or effective and in some cases may be harmful |
| Level of evidence | |
| Level A | Data derived from multiple randomised clinical trials or meta-analyses |
| Level B | Data derived from a single randomised clinical trial or large non-randomised studies |
| Level C | Consensus of opinion of the experts and/or small studies, retrospective studies, registries |

Due to the rarity of spinal epidural haematoma, recommendations regarding neuraxial regional anaesthetic procedures with concurrent thromboprophylaxis, are not based on prospective randomised studies, but rather on case reports and expert opinion. The latter is based mainly on knowledge of the pharmacokinetics of the individual agents concerned. A rule of thumb adopted by most national societies puts the time interval between cessation of medication and neuraxial blockade at two times the elimination half-life of the drug. This approach has recently been recommended by others.[5]

The decision for or against regional anaesthesia always requires a careful risk–benefit analysis, noting any history of bleeding, followed by a physical examination looking for signs of increased bleeding tendency, for example petechiae or haematoma[6] (Class I, level A). Laboratory tests, if indicated at all, should be appropriate to the individual (Class I, level A). Routine laboratory investigations do not always detect impaired coagulation. The perioperative cessation of anticoagulant drugs to improve the safety of neuraxial block needs to be critically evaluated. An alternative anaesthetic technique should be used if it is judged that the administration of the anticoagulant must not be interrupted (Class IIa, level C). Finally, the present guidelines are not intended to bypass clinical judgment. When the anaesthesiologist decides not to comply with these guidelines, the reasons should be noted in the patient's chart.

## Risk of spinal epidural haematoma

Spinal epidural haematoma often occur spontaneously, without any temporal relationship with neuraxial anaesthesia. The absolute risk of spinal bleeding during concurrent thromboprophylaxis is not known, and following neuraxial blockade, events are too rare to study in a randomised clinical trial. Relatively recent case series suggest that the risk of spinal epidural haemorrhage is possibly much higher than was previously thought.[7–13]

After enoxaparin 30 mg twice daily was introduced for thromboprophylaxis in the United States an alarming number of spinal epidural haematoma, some with permanent paraplegia, were reported,[7] triggering a warning from the US Food and Drug Administration (FDA). Collation of these cases in the USA allowed the risk of spinal epidural haematoma during concurrent administration of low-molecular-weight heparins (LMWHs) to be calculated at 1 : 40 800 for spinal anaesthesia, 1 : 6600 for single-shot epidural anaesthesia, and 1 : 3100 for epidural catheter anaesthesia.[7] What appears to be a relatively high incidence of bleeding was attributed to the twice daily administration of LMWH, and the lack of recommendations at that time regarding time intervals between neuraxial puncture or catheter removal and thromboprophylaxis. The response in the USA has been to introduce recommendations that are stricter than those in place in Europe, proposing avoidance of LMWH the entire time epidural catheters are in place. This does not adequately take into account the increased perioperative risk of venous thromboembolism (VTE).[14] In Europe, the widespread adoption of a single daily dose of enoxaparin 40 mg produced a lower incidence of complications. A retrospective analysis in Sweden found the risk was 1 : 156 000 after spinal anaesthesia and 1 : 18 000 after epidural anaesthesia, with bleeding occurring more rarely in obstetrics (1 : 200 000) than in female orthopaedic patients undergoing knee arthroplasty (1 : 3600).[8] Risk factors for spinal haematoma after neuraxial regional anaesthesia were identified as lack of guidelines, administration of antithrombotic agents, female sex, and difficult punctures. Subsequent reports from various countries indicate that spinal epidural haematoma after neuraxial blockade occurs in 1 : 2700 to 1 : 19 505 patients,[9–12] with one report indicating that haematoma may be more common after lumbar (1 : 1341) compared to thoracic epidural anaesthesia (0 : 10 199).[11]

The association of spinal haematoma with concurrent administration of antithrombotic drugs is not a new finding. Vandermeulen *et al.* reported as early as 1994[15] that 68% of patients with spinal epidural haematoma had received anticoagulants, and 20% had thrombocytopenia or drug-induced platelet dysfunction, something Wulf confirmed later in 1996.[16] Despite its frequent use, aspirin is rarely mentioned as a risk factor, but fibrinolytic agents and Bechterew disease are implicated. In an analysis of 79 haematoma cases, coagulation disorders were found in 72% of patients,[17] and other risk factors included bloody or traumatic punctures and anomalous

anatomy, for example spina bifida, and Bechterew's disease. The risk of haemorrhage is lowest in spinal anaesthesia, which employs fine needles, and highest in epidural catheter anaesthesia, which requires the largest needle gauges available. Nearly half of all cases of bleeding occur during the removal of an epidural catheter,[15] and this procedure must be regarded as critical as catheter insertion.

Spinal epidural haematoma are not restricted to LMWH, but can occur with any agent that interferes with haemostasis. The traditional coagulation screen is largely unaffected by antithrombotic agents and is not helpful in the assessment of bleeding risk. If recommended anticoagulant doses and time intervals between administration and blockade are observed, the neuraxial procedure should coincide with the lowest anticoagulant blood level. The smaller the amount prescribed, and the longer the delay between administration and blockade, the lower the risk of haemorrhage. Accordingly, recommended time intervals are based on the pharmacology of the individual agents concerned. Assessing risk becomes more difficult when antithrombotic agents are used in combination, for example LMWH and aspirin, necessitating greater caution.

In recent years, despite adhering to the recommendations, spinal epidural haematoma have still occurred. The patients concerned tended to be older and suffering from renal impairment, marking this as an important risk factor.[18,19] Most drugs used for thromboprophylaxis, with the exception of argatroban are eliminated by the renal route, and will accumulate in those with renal impairment, something that often goes undetected in everyday practice. The recommended time intervals therefore only apply to patients with normal renal function, and in those known to have reduced renal function, either dose adjustment or longer time intervals are required.

The American College of Chest Physicians (ACCP) in its 2008 recommendations state that appropriate patient selection and caution is required when neuraxial blockade is performed in the presence of antithrombotic drugs. They advise that cautions applicable to neuraxial blockade should also be applied to deep peripheral nerve blocks, and if a bloody puncture occurs, thromboprophylaxis should be delayed.[20]

## Timing of thromboprophylaxis

In most European countries thromboprophylaxis begins preoperatively; the exception to this is neurosurgery, wherein it is started postoperatively. The reason for preoperative prescribing is the belief that thrombus formation occurs intraoperatively and that patients should be protected during this period. In order to reduce bleeding and to enable neuraxial blockade, LMWH are usually administered the night before as opposed to the morning of surgery. Scientific support for this approach is poor. A single study including 1472 hip replacements, in whom dalteparin given 2 h preoperatively was compared to dalteparin given 4 h postoperatively,[21] found no difference in the incidence of VTE, and patients in the preoperative group required significantly more transfusions. A meta-analysis of preoperative versus postoperative studies shows that LMWH given 12 h preoperatively does not reduce the risk of VTE compared to a postoperative regimen.[22] The most recent German guidelines on thromboprophylaxis, emanating from a number of different specialties, and also the ACCP, refer to preoperative administration only as an option, and not as a requirement.[20,23] As antithrombotic drugs increase the risk of spinal epidural haematoma after neuraxial blockade, a postoperative start may be advantageous, especially in patients also receiving aspirin (Class IIb, level B).

## Antithrombotic drugs

### Heparins

#### *Unfractionated heparins*

Thromboprophylaxis with low-dose heparin does not lead to an increased risk of bleeding after neuraxial blockade, provided that a time interval of 4–6 h is observed between heparin administration and puncture or catheter manipulation and withdrawal. Further administration of low-dose heparin should be delayed for at least 1 h after the block (Class IIb, level C). Coagulation studies are not required during prophylaxis with unfractionated heparin (UFH), except when treatment has lasted 5 days or more, when a platelet count is needed to exclude heparin-induced thrombocytopenia (HIT) (Class I, level B) (Tables 2 and 3).

Whereas doses of UFH used for venous thromboprophylaxis are relatively safe, an increased risk of bleeding does occur at therapeutic doses, when puncture and removal of a catheter are contraindicated (Class III, level C). If, after careful consideration, a neuraxial blockade or catheter removal is planned, intravenous heparin administration should be interrupted at least 4 h earlier and the activated partial thromboplastin time (aPTT) and/or anti-Xa activity should have normalised before the procedure (Class IIa, level C). UFHs have equal anti-IIa and anti-Xa activity, and some laboratories might find it simpler to use a single test for both UFH and LMWH.

#### *Neuraxial blockade and intraoperative heparinisation*

Intraoperative heparinisation does not necessarily represent a contraindication to neuraxial blockade. Rao and El-Etr[24] reported in 1981 that in patients undergoing vascular surgery, the risk of haemorrhage after epidural anaesthesia and subsequent heparinisation is not increased if heparin is delayed for 1 h after insertion and the activated clotting time (ACT) is maintained at twice the baseline value. This contrasts with a very high 2% incidence of paraplegia when patients taking aspirin

**Table 2 Recommended time intervals before and after neuraxial puncture or catheter removal[a]**

| | Time before puncture/catheter manipulation or removal | Time after puncture/catheter manipulation or removal | Laboratory tests |
|---|---|---|---|
| Unfractionated heparins (for prophylaxis, ≤15 000 IU per day) | 4-6 h | 1 h | Platelets during treatment for more than 5 days |
| Unfractionated heparins (for treatment) | i.v. 4–6 h<br>s.c. 8–12 h | 1 h<br>1 h | aPTT, ACT, platelets |
| Low-molecular-weight heparins (for prophylaxis[b]) | 12 h | 4 h | Platelets during treatment for more than 5 days |
| Low-molecular-weight heparins (for treatment) | 24 h | 4 h | Platelets during treatment for more than 5 days |
| Fondaparinux (for prophylaxis, 2.5 mg per day) | 36–42 h | 6–12 h | (anti-Xa, standardised for specific agent) |
| Rivaroxaban (for prophylaxis, 10 mg q.d.) | 22–26 h | 4–6 h | (PT, standardised for specific agent) |
| Apixaban (for prophylaxis, 2.5 mg b.i.d.) | 26–30 h | 4–6 h | ? |
| Dabigatran (for prophylaxis, 150–220 mg) | Contraindicated according to the manufacturer | 6 h | ? |
| Coumarins | INR ≤1.4 | After catheter removal | INR |
| Hirudins (lepirudin, desirudin) | 8–10 h | 2–4 h | aPTT, ECT |
| Argatroban[c] | 4 h | 2 h | aPTT, ECT, ACT |
| Acetylsalicylic acid | None | None | |
| Clopidogrel | 7 days | After catheter removal | |
| Ticlopidine | 10 days | After catheter removal | |
| Prasugrel | 7–10 days | 6 h after catheter removal | |
| Ticagrelor | 5 days | 6 h after catheter removal | |
| Cilostazol[c] | 42 h | 5 h after catheter removal | |
| NSAIDs | None | None | |

ACT, activated clotting time; aPTT, activated partial thromboplastin time; b.i.d., twice daily; ECT, ecarin clotting time; INR, international normalised ratio; IU, international unit; i.v., intravenously; NSAIDs, non-steroidal anti-inflammatory drugs; s.c., subcutaneously; q.d., daily. [a] All time intervals refer to patients with normal renal function. [b] Maximum prophylactic dosages for low-molecular-weight heparins are listed in Table 3. [c] Prolonged time interval in patients with hepatic insufficiency.

received intravenous heparin less than 1 h after diagnostic lumbar puncture.[25] The increased bleeding risk attached to the coadministration of aspirin and heparin was confirmed by a Canadian research group. They calculated that even if a 1 h time interval between the neuraxial block and subsequent intravenous heparinisation was observed, the risk of spinal epidural haematoma in those taking aspirin was increased to 1 : 8500 after epidural anaesthesia and 1 : 12 000 after spinal anaesthesia.[26] In the American Society of Anesthesiology closed claims analysis, spinal epidural haematoma occurred most frequently in vascular surgical patients, suggesting that this particular patient group is at increased risk.[27]

**Table 3 Dose recommendations for venous thromboembolism prophylaxis in high-risk patients**

| Generic | Max. prophylactic dose per day |
|---|---|
| Unfractionated heparin | Heparin (3 × 5000 IU or aPTT in normal reference range) |
| Certoparin | 1 × 3000 anti-Xa U s.c. |
| Dalteparin | 1 × 5000 anti-Xa U s.c. |
| Enoxaparin | 1 × 40 mg s.c. |
| Nadroparin | 2850 anti-Xa U (0.3 ml) or weight-adjusted, max. 5700 anti-Xa U s.c. (0.6 ml) |
| Reviparin | 1 × 1750 anti-Xa IU s.c. |
| Tinzaparin | 1 × 4500 anti-Xa U s.c. |
| Fondaparinux | 1 × 2.5 mg s.c. |
| Danaparoid | 2 × 750 IU s.c. |
| Desirudin | 2 × 15 mg s.c. |
| Rivaroxaban | 1 × 10 mg p.o. |
| Apixaban | 2 × 2.5 mg p.o. |
| Dabigatran | 1 × 220 mg (first dose 110 mg)<br>1 × 150 mg p.o. in the elderly patient >75 years (first dose 75 mg) |

aPTT, activated partial thromboplastin time; max., maximum; p.o., orally; s.c., subcutaneously.

Manipulation or removal of epidural catheters should be carried out at least 4 h after the end of heparin administration and with normal aPTT, ACT, and anti-Xa activity (Class IIa, level C).

If a bloody puncture occurs in patients in whom intraoperative heparinisation is planned, it is recommended that low-dose anticoagulation (5000 IU heparin) should be avoided for 1–2 h and that full intraoperative heparinisation should be avoided for 6–12 h, with the operation being postponed to the next day, if necessary (Class IIa, level C). Alternatively, to avoid delays, epidural catheter placement can be carried out the evening before surgery (Class IIb, level C).

### *Cardiac surgery*

Evidence for thoracic epidural analgesia in patients undergoing cardiac surgery is still equivocal with most studies showing an improvement in pulmonary function, improved analgesia and less arrhythmia, but no reduction in length of ICU stay, time to discharge, myocardial infarction or mortality.[28,29] The accepted benefits need to be carefully weighed against the potentially catastrophic outcome of high thoracic spinal epidural haematoma. Ho *et al.*[30] estimated the maximum probability of haematoma formation in patients undergoing cardiac surgery with full heparinisation to be 1 : 1500 with epidural techniques. If full anticoagulation during cardiopulmonary bypass is planned, some guidelines advocate performing the block the day before surgery, or following a traumatic puncture, that surgery is delayed.[14,31,32] In many cardiac surgical centres, aspirin and clopidogrel are administered in conjunction with therapeutic postoperative heparinisation,

increasing the risk associated with catheter removal. If patients are not directly extubated in the operating room, close neurological surveillance is often delayed. Undetected cord compression reduces the chance of early haematoma evacuation, and the hope of full neurological recovery.

Analgesia with a single dose of spinal opioid may decrease the risk of neuraxial bleeding compared to a catheter technique, but needs to be performed directly before surgery and not in advance. The absence of local anaesthetic infusion removes the ability to adjust the quality of analgesia and significantly limits the benefits.[29]

Because neuraxial blockade in cardiac surgery confers no major effect on morbidity and mortality and has significant risks, it is arguable whether spinal and epidural techniques are justified at all and perhaps should be abandoned in this particular patient group[33] (Class IIb, level C).

#### *Low-molecular-weight heparins*

LMWHs are used for both prophylaxis and treatment of VTE.[34] Coagulation variables ACT and aPTT can remain unaffected by LMWH and monitoring is unhelpful (Class I, level A). Instead, the anticoagulant effect of LMWH is easily assessed by measuring plasma anti-factor Xa activity (Class I, level A). The advantages of LMWH lie in their high bioavailability (approximately 100%) after subcutaneous administration and their longer half-life of 4–7 h, which together make once-daily administration feasible. For thromboprophylaxis, they are the treatment of choice, being superior to UFH in high-risk groups such as hip or knee replacement and trauma patients, but without increasing the risk of bleeding.[35] Although individual LMWH differ with regard to molecular weight and pharmacokinetics, and have been approved for different indications, their clinical efficacy is similar. Compared to UFH, there is a 10-fold reduction in the risk of HIT.[36] Nevertheless, they are contraindicated in HIT due to the 90% level of cross-reactivity.

After subcutaneous administration of LMWH, maximum efficacy levels are reached in approximately 3–4 h, and the terminal elimination half-life in patients with normal renal function is 4–6 h[37,38] (Class I, level A). In those with severe renal insufficiency, anti-Xa activity reaches a higher maximum level and the elimination half-life can increase by up to 16 h. In contrast to UFH, LMWH show a higher degree of fibrinolytic activity and less platelet interaction.[39] This is reflected in greater thrombus regression in the treatment of deep venous thrombosis (DVT).[40] To avoid bleeding complications, there should be a time interval of at least 12 h between subcutaneous administration of LMWH at prophylactic doses and neuraxial blockade or removal of an epidural catheter[15,41] (Class IIa, level C). Administration of LMWH the evening before surgery or the night before catheter removal therefore does not interfere with neuraxial blockade (Class IIa, level C).

If thromboprophylaxis with LMWH is prescribed in a twice-daily schedule (e.g. enoxaparin $2 \times 30$ mg per day), compared to a once daily regimen, the risk of epidural haematoma may be increased because the trough levels of anti-Xa activity are higher.[42] In this situation, one dose of LMWH should be omitted creating a 24 h time interval before catheter removal and the subsequent dose (Class IIb, level C).

Similarly, when therapeutic doses of LMWH are being administered once or twice daily, catheter placement or removal should also be delayed for at least 24 h after the last dose (Class IIa, level B). Whether a 24-h interval is acceptable in relation to the risk of VTE needs to be considered on an individual basis. When the risk of thrombosis is high, for instance, with mitral or double mechanical valve replacement, one should refrain from neuraxial blockade and continue the administration of LMWH (Class III, level B). Following spinal/epidural puncture, or after removal of a spinal/epidural catheter, the next dose of LMWH should be delayed for at least 4 h (Class IIa, level C).

### Anti-Xa agents

#### *Fondaparinux*

Fondaparinux is a synthetic indirect Xa inhibitor with potent anticoagulant activity. It can be monitored using anti-factor Xa activity. Platelet aggregation is not affected. Although antibodies against the platelet factor 4 (PF4)/ heparin complex* that is responsible for HIT, may form during its administration, in the absence of heparin they do not bind well to PF4. To date, there are only two reports of a possible association of HIT with fondaparinux.[43,44] Despite these reports, platelet count monitoring is not recommended and fondaparinux has been successfully used for the treatment of HIT.[45] The ACCP currently suggests fondaparinux as an alternative anticoagulant for thromboprophylaxis in patients with a history of HIT (grade 2C).[46] Individual studies and a meta-analysis have shown that it is superior to LMWH in prevention of asymptomatic VTE following hip or knee replacement surgery and hip fractures.[47] In contrast to the European practice of starting VTE prophylaxis preoperatively, fondaparinux is initiated at least 6–8 h after the end of the operation to avoid complications from surgical bleeding (Class I, level A). The recommended prophylactic dose is 2.5 mg. Higher doses will increase the rate of complications from haemorrhage without reducing the rate of VTE and are only approved for therapeutic anticoagulation. Due to its long half-life of 18 h, fondaparinux is administered once daily and may accumulate significantly in patients with impaired renal function (Class I, level A). Even in patients with normal renal function, a stable plateau is achieved only after 2–3 days.[48] The manufacturer recommends reducing

the dose of fondaparinux to 1.5 mg per day in patients with moderate renal insufficiency (creatinine clearance 20–50 ml $min^{-1}$) and it is contraindicated in patients with severe renal insufficiency (creatinine clearance below 20 ml $min^{-1}$).

**Platelet factor 4**
PF4 is a small procoagulant cytokine that is released from the α-granules in platelets during aggregation. It binds to heparin with high affinity, and the PF4/heparin complex is the source of the antigen in HIT. Autoantibodies to PF4 have been found in a thrombotic state similar to HIT, but without administration of heparin.

This agent has advantages in neuraxial regional anaesthesia, because coagulation is not affected at the time of initiation of the block. However, rising plasma levels during the initial days of treatment and accumulation in patients with renal insufficiency need to be taken into account during removal of an epidural catheter. The EXPERT study with a total of 5387 patients included 1428 undergoing regional anaesthesia procedures, and a single dose of fondaparinux was omitted the evening before catheter removal.[49] This provided a time interval of 36 h before catheter removal and 12 h between catheter removal and the next dose of fondaparinux. Omitting one dose of fondaparinux did not increase the risk of VTE but did contribute to the safety of neuraxial blockade. No cases of spinal epidural haematoma occurred, but its incidence is so low that this study, like most others, lacked sufficient power to make firm conclusions in this regard.

Neuraxial regional anaesthesia should not be performed when therapeutic doses of fondaparinux (5–10 mg per day) are employed due to the substantial risk of accumulation (Class III, level C).

#### *Idrabiotaparinux*

Like fondaparinux, idraparinux is a pentasaccharide but with a half-life of at least 135 h, and possibly up to 66 days.[50] It is administered just once weekly by subcutaneous injection. Its clearance is exclusively renal. Phase III studies following DVT, pulmonary embolism, and in atrial fibrillation patients have reported an excess of major bleeding compared to vitamin K antagonist treated patients.[51] Its very long half-life may lead to accumulation, especially in the elderly and in renal insufficiency. This and the problems with haemorrhage have halted the development of idraparinux, which has been replaced with a new form coupled to biotin. The half-life of idrabiotaparinux is also long, it is mainly excreted through the kidneys, but unlike fondaparinux and idraparinux, an antidote is available. In a phase I trial, the anti-Xa activity of biotinylated idraparinux was immediately reversed by an intravenous infusion of avidin, a protein from hen egg white with a high affinity to biotin that is well tolerated. Although the half-life of avidin is very short (2 min), in preliminary studies a rebound effect on anticoagulation was not seen during 5 days of observation. Nevertheless, a rebound effect may be expected with redistribution of idrabiotaparinux from tissue sites. The concept is of great interest and studies continue, but caution is necessary as, in theory, avidin carries the risk of an allergic reaction. Idrabiotaparinux has not been developed for perioperative thromboprophylaxis, and there are no data regarding neuraxial anaesthesia, which is contraindicated pending further studies (Class III, level C).

#### *Rivaroxaban (Xarelto)*

Rivaroxaban acts through inhibition of factor Xa and is currently approved for the prevention of VTE in hip and knee replacement surgery. Rivaroxaban is eliminated through the kidney (33% active drug) and the liver, making accumulation less likely than with anticoagulants exclusively eliminated through the kidney. Rivaroxaban prolongs the prothrombin time (PT) in a dose-dependent manner, but until further data are available monitoring with PT is not recommended. Similar to most other anticoagulant drugs, no specific antidote is available. The first 10 mg dose of rivaroxaban is administered 6–8 h after surgery. In comparison with enoxaparin ($1 \times 40$ mg), rivaroxaban was superior in the prevention asymptomatic and symptomatic VTE.[52] A subsequent study has also shown improved efficacy in the treatment of DVT compared to heparins and vitamin K antagonists.[53] Although initial studies with rivaroxaban showed no increased bleeding risk compared to enoxaparin, an analysis performed by the FDA did identify an increased risk for non-major clinical bleeding events.[54] The plasma half-life of rivaroxaban is 5–9 h and is not significantly prolonged in patients with moderate renal impairment, but according to the manufacturer it is prolonged to 11–13 h in the elderly. A time interval of 22–26 h between the last dose of rivaroxaban (10 mg) and catheter withdrawal is thus required (Class IIa, level C). After catheter withdrawal the next dose of rivaroxaban may be given after 4–6 h (Class IIb, level C). Available experience with neuraxial blockade is very limited. Extreme caution is therefore recommended when using rivaroxaban in the presence of neuraxial blockade (Class IIb, level C).

#### *Apixaban*

Apixaban is an oral, reversible, direct factor Xa inhibitor related to rivaroxaban. Its bioavailability ranges from 51 to 85%, and its inhibition constant Ki (0.08 nmol $l^{-1}$) is better than that of rivaroxaban. The half-life is between 10 and 15 h,[55] and elimination follows multiple pathways, with only 25% excreted renally and 75% by hepatic and biliary metabolism, and intestinal excretion. A phase III study comparing a 2.5 mg dose twice daily, to twice daily enoxaparin 30 mg in orthopaedic surgery,

has been completed. It has a similar efficacy but appears to cause less bleeding when started 12–24 h after surgery.[56] Apixaban has currently no formal approval for use. As with most new anticoagulants, no specific monitoring or antidote is available. Applying the same rules to apixaban as to other anticoagulants 2 (× half-life) would yield a time interval of 26–30 h between the last dose of apixaban (2.5 mg) and catheter withdrawal and suggests that at least one dose should be omitted (Class IIb, level C). After catheter withdrawal, the next dose of apixaban may be given 4–6 h later (Class IIb, level C). As with all new anticoagulant drugs, experience with neuraxial blockade is limited and most patients received only single-shot spinal anaesthesia. Extreme caution is therefore recommended when using neuraxial blockade in the presence of apixaban (Class IIb, level C).

**Inhibition constant Ki**
The inhibition constant Ki represents the concentration of inhibitor that is needed to reduce the maximal rate of reaction to half that of the uninhibited value. The lower the Ki, the lower the concentration of inhibitor needed, and the more potent the inhibition.

#### *Danaparoid (Orgaran)*

Danaparoid is a glycosaminoglycan mixture consisting of 84% heparin sulphate, 12% dermatan sulphate and 4% chondroitin sulphate. Its effect occurs mainly through antithrombin-mediated inhibition of factor Xa. Danaparoid is used for VTE prophylaxis and treatment in HIT type II, although cross-reactivity with heparin-induced antibodies can occur in 10% of patients. Efficacy and bleeding risks have been compared with LMWH,[57] but clinical experience is limited. As the terminal half-life of danaparoid may be markedly prolonged in patients with renal insufficiency, dose adjustments are necessary (Class IIa, level B). Cases of severe bleeding have been observed with danaparoid. There is no antidote, and it cannot be haemofiltered, but it can be removed using plasmapheresis. Coagulation monitoring is only possible using anti-Xa activity. Despite its very long half-life of 22 h, the agent is administered twice daily for thromboprophylaxis, so that genuine trough levels are probably not achieved. Recommendations for VTE prophylaxis state that danaparoid should first be administered 2 h preoperatively. Although neuraxial blocks were carried out in a very small number of patients 1 h after danaparoid administration, this approach is strongly discouraged as, after subcutaneous injection, significant plasma levels are obtained at this time.[58] Instead, preoperative danaparoid administration should be avoided when neuraxial anaesthesia is planned (Class I, level C). Due to its very long half-life and accumulation in patients with renal insufficiency, it is preferable to carry out single-shot spinal anaesthesia and avoid the use of catheters, if neuraxial blocks are performed at all (Class III, level C).

### Direct thrombin inhibitors

Other agents for both perioperative thromboprophylaxis and therapeutic anticoagulation include direct selective thrombin inhibitors. In contrast to heparins, they can also inactivate fibrin already bound to thrombin, thus inhibiting further thrombus growth. When bound to thrombin, proteolytic properties are inhibited without antithrombin or other cofactors being necessary. Thrombin inhibitors influence, to various extents, all functional haemostasis tests based on fibrin formation, particularly aPTT, which is usually used for laboratory controls. The ecarin clotting time (ECT) is more specific and should be used with therapeutic doses of thrombin inhibitors. The most important side effect of higher doses of direct thrombin inhibitors, particularly when used in combination with other antithrombotic agents or platelet aggregation inhibitors, is increased bleeding.[59] There is no specific antidote, but hirudins and argatroban can be eliminated by dialysis.

#### *Desirudin, lepirudin*

The recombinant hirudins, desirudin and lepirudin, are first generation direct thrombin inhibitors that are administered parenterally. They are indicated for thromboprophylaxis (desirudin) and VTE treatment (lepirudin) in patients with HIT type II.

In contrast to heparins, a prolonged aPTT appears to be required for effective thromboprophylaxis. Following a single intravenous or subcutaneous injection of desirudin, there is a fast rise in the aPTT, which is measurable within 30 min and reaches a maximum after 2 h.[60] The aPTT is still prolonged 8 h after subcutaneous administration of low-dose hirudin (prophylactic dose $2 \times 15$ mg per day).[61] The elimination half-life is 2–3 h and is markedly prolonged in patients with impaired renal function.

In general, it is advisable to wait at least 8–10 h, and longer if possible, between the administration of these agents and neuraxial puncture, and to avoid combinations with other antithrombotic agents (Class I, level C).

Hirudins accumulate in patients with renal insufficiency. For desirudin, prophylactic doses should be monitored with aPTT in patients with creatinine clearance levels between 30 and 90 ml $min^{-1}$, and in those with creatinine clearance levels below 30 ml $min^{-1}$, it is contraindicated. The doses of lepirudin once approved are no longer in use; bolus administration is now avoided and the initial treatment in patients with normal renal function is started at 0.1 mg $kg^{-1}$ $h^{-1}$. For lepirudin, a dose reduction of up to 85% is recommended in patients with severe renal insufficiency. Treatment should be monitored using aPTT or ECT. Following several days of lepirudin

administration antibody formation may develop in approximately 40% of patients, delaying elimination and leading to substantial and unpredictable prolongation of its activity.[62] Bleeding complications are therefore frequent.

Although desirudin (Revasc) has been administered in a small number of patients immediately after neuraxial puncture without development of spinal epidural haematoma, this is not advised due to the agent's pharmacokinetics (Class IIa, level B). A delay of at least 2–4 h after neuraxial regional anaesthesia should be observed (Class IIa, level C). Time intervals of 8–10 h before puncture apply only in patients with normal renal function and without antibody formation, and it is therefore recommended that aPTT should be checked before puncture (Class IIa, level C). A case of spontaneous epidural haematoma during lepirudin treatment has been reported.[63] Due to side effects resulting from antibody formation, and anaphylactic reactions at re-exposure, in some countries both drugs have been replaced by fondaparinux for thromboprophylaxis and by argatroban for treatment of acute HIT.

#### *Argatroban (Argatra)*

Argatroban is a reversible direct thrombin inhibitor, which has been approved for the treatment of HIT type II. Argatroban is administered intravenously and is eliminated exclusively by the liver, making renal insufficiency an indication for its use. The recommended intravenous dose is 0.5–2.0 $\mu g\,kg^{-1}\,min^{-1}$ in patients with normal organ function, and the dose should be adjusted to maintain the aPTT between 1.5 and 3 times normal. Dose reduction is required in the critically ill and in those with heart failure or impaired hepatic function. When hepatic function is good, normalisation of the aPTT takes only 2–4 h after the end of argatroban infusion, due to the short half-life of 35–45 min.[64]

If neuraxial blockade is considered, a distinction needs to be made between patients with a history of HIT, who require only thromboprophylaxis, usually with low-dose danaparoid, or fondaparinux (off-label) subcutaneously, and those with acute HIT type II, in whom therapeutic anticoagulation is required. In the latter, there is a high risk of VTE if anticoagulation is interrupted. In practice this group frequently suffers from multiple organ failure that includes coagulation, and they may be ventilator dependent, making neuraxial blockade inadvisable (Class III, level C).

#### *Dabigatran (Pradaxa)*

Dabigatran is an oral reversible monovalent thrombin inhibitor that has recently been approved for VTE prophylaxis in patients undergoing hip or knee replacement.[55] The oral prodrug dabigatran etexilate is metabolised by plasma esterases into dabigatran. The first dose of dabigatran 110 mg is given 1–4 h postoperatively, followed by 220 mg on subsequent days. In patients with renal impairment, the respective dosing recommendations are 75 and 150 mg. Dabigatran prolongs the aPTT, and at doses recommended for thromboprophylaxis, this effect is significantly pronounced in renal failure[65] because elimination is through the kidneys with potential for accumulation. The efficacy of dabigatran (220 mg) in the prevention of VTE is comparable to enoxaparin ($1 \times 40$ mg) without increasing bleeding.[66] In the initial studies with dabigatran, neuraxial blockade was performed in approximately 70%, but all epidural catheters were removed at least 4–6 h before the first dose. There are no reports of dabigatran use and indwelling epidural catheters. The 12–17 h half-life of dabigatran in healthy patients would suggest a time interval of 34 h between the last dose of dabigatran and catheter manipulation or withdrawal, however, the manufacturer advises against the use of dabigatran in the presence of neuraxial blockade (Class III, level C). This warning may have medicolegal consequences if a spinal epidural haematoma occurs.

### Vitamin K antagonists (acenocoumarol, fluindione, phenprocoumon, warfarin)

Therapeutic anticoagulation with vitamin K antagonists remains an absolute contraindication to neuraxial blockade. As it can take several days after these drugs have been withdrawn before coagulation returns to normal, progress has to be checked using the international normalised ratio (INR). The process can be accelerated by administering vitamin K, prothrombin complex concentrates (PCC), or, if PCC is unavailable, fresh frozen plasma. This requires an appropriate indication and should follow an individual risk-benefit analysis. The use of coagulation factors purely to normalise coagulation before neuraxial anaesthesia, is inappropriate (Class III, level C).

In contrast to most European countries, in the United States postoperative use of vitamin K antagonists for thromboprophylaxis is widespread, but they are less effective than UFH or LMWH. Horlocker *et al.*[67] described 188 patients with epidural analgesia, who received postoperative low-dose thromboprophylaxis with warfarin. Epidural catheters were removed during warfarin therapy, without incident. The small number of patients included, and the early removal of epidural catheters before the onset of effective anticoagulation (INR <1.4), prevent any worthwhile comment on the safety or otherwise of this practice. Withdrawal of epidural catheters when vitamin K antagonists have already taken full effect is not recommended, and accordingly they should be administered only after the catheter has been removed (Class IIa, level B). Another analysis of 950 patients undergoing epidural analgesia, in whom vitamin K antagonists were started

preoperatively, similarly found no complications. However, no detailed information was provided regarding coagulation status.[68]

These two studies apart, there are several reports of spinal epidural haematoma following neuraxial regional anaesthesia with concurrent use of vitamin K antagonists.[17] In view of the high rate of bleeding complications in patients receiving therapeutic doses, this is not surprising. In the United States, as in Europe, therapeutic anticoagulation with oral vitamin K antagonists is regarded as a contraindication to neuraxial blockade. However, in contrast to Europe, despite the problems associated with catheter removal, perioperative thromboprophylaxis with warfarin is still an option in the United States.[14]

### Platelet aggregation inhibitors

#### *Acetylsalicylic acid (aspirin) and the risk of bleeding*

Even after a single dose, aspirin leads to irreversible inhibition of platelet function as a result of cyclo-oxygenase inhibition. Due to the lack of a nucleus, platelets are not able to synthesise new cyclo-oxygenase, so that the effect persists for the entire lifetime of the platelets, usually 7–10 days. However, healthy bone marrow will replace more than 30% of the irreversibly inhibited platelets within 3–4 days.[69,70] With a normal platelet count, this is usually sufficient to return haemostasis to normal. Bleeding effects of aspirin appear to be dose-dependent, with more adverse events observed in patients receiving more than 100 mg daily.[71] Analyses of medical patients have shown that the risk of spontaneous bleeding in those taking aspirin is doubled, although the risk remains generally very low. A total of 800 patients annually would need to be treated for one additional bleeding event to occur.[72] A slight increase in bleeding complications is also observed in surgical patients receiving aspirin, but transfusion is rarely required. In cardiac surgery, the risk of relevant bleeding is increased 1.4-fold, making aspirin less important than the duration of extracorporeal circulation or the presence of renal insufficiency.[73] In a meta-analysis of non-cardiac surgical procedures, 1.5-fold higher bleeding rates were reported in patients receiving aspirin. With the exception of intracranial procedures, prostatic resections and tonsillectomies, no severe cases of bleeding were observed.[74]

Only three studies consider the safety of neuraxial regional anaesthesia during aspirin administration.[75–77] Although the Collaborative Low-dose Aspirin Study in Pregnancy (CLASP) included a total of 9364 pregnant women, only 2783 of the women underwent epidural analgesia. Of the latter, 1422 had taken aspirin during their pregnancy, and only half had continued it up to delivery, leaving approximately 700 women for analysis. None of the women in this study experienced a problem related to aspirin. Pregnancy is associated with a general low-grade activation of coagulation, and aspirin was taken alone rather than in combination with other thromboprophylaxis. These two factors would have reduced the risk of epidural haematoma in this cohort.[8] Horlocker *et al.*[76] included a total of 924 orthopaedic patients in their study, 193 of whom had taken aspirin preoperatively. Intake of aspirin was defined as intake within the previous week, although the extent of platelet aggregation inhibition declines measurably 3 days after withdrawal.[70] The number of neuraxial blocks in patients receiving aspirin was small. Only 22 of 1000 patients received concurrent thromboprophylaxis with heparin, and no epidural haematomas were observed. In another study including 1035 patients with no accompanying thromboprophylaxis, again no epidural haematoma occurred in 158 patients who had taken aspirin within the previous week.[77]

Although the administration of aspirin alone does not appear to increase haematoma formation, a higher rate of complications has been observed in both surgical and medical patients when heparins were administered concurrently.[25,26] Because preoperative, versus postoperative, thromboprophylaxis is not proven to be beneficial,[21] a cautionary approach in the presence of aspirin would be to start VTE prophylaxis postoperatively (Class I, level B).

Non-steroidal anti-inflammatory drugs (NSAIDS) also inhibit cyclo-oxygenase and thus platelet aggregation in a reversible manner that is proportional to the half-life of the agent used. With the exception of tenoxicam and piroxicam, platelet function normalises within 12–24 h after withdrawal.[78] To avoid any negative effect of NSAIDS on platelet function and neuraxial block, it is sufficient to miss a dose the evening before a planned procedure or catheter removal. For selective COX-2 inhibitors, there is no evidence of any relevant effects on platelet aggregation capacity or an increased bleeding tendency.[79] The non-opioid analgesics paracetamol (acetaminophen) and metamizole (dipyrone) have not been linked to spinal epidural haematoma to date.

On the basis of the available data, NSAIDS, including aspirin, when given in isolation, do not increase the risk of spinal epidural haematoma and are not a contraindication to neuraxial block (Class IIb, level C). Spinal anaesthesia has better support than epidural (Class IIb, level C).

#### *Aspirin and the risk of adverse cardiovascular events*

In patients with a history of acute coronary syndrome, stroke, or peripheral arterial occlusive disease, aspirin reduces the risk of a recurrent cardiovascular event by around 30%, and mortality by approximately 15%.[80] Case series in recent years suggest that morbidity and mortality, particularly in patients with recently implanted coronary stents or unstable coronary syndromes, is markedly increased if aspirin is stopped before a surgical

procedure.[74,81,82] A rebound phenomenon has also been discussed.[83] The risk of late stent thrombosis is greatest in patients with drug-eluting stents. In summary, the preoperative withdrawal of aspirin is unnecessary in most cases and is associated with a high risk of acute thrombosis (Class IIa, level C). It is recommended that patients with acute coronary syndromes or stent implantation should continue to take aspirin on a lifelong basis.[84] Those with drug-eluting stents should only stop aspirin before a planned operation when there is a life-threatening bleeding risk such as in neurosurgical procedures (Class IIa, level C). It should be noted that concurrent intake of ibuprofen may lead to a reduction in the efficacy of aspirin[79] and that all NSAIDS increase the risk of adverse cardiovascular events. The ACCP does not currently recommend assessment of platelet function before invasive procedures because there is no apparent correlation with bleeding (Class II, level C).[85]

#### *Thienopyridines*

Ticlopidine (Ticlid) and clopidogrel (Iscover, Plavix) are platelet aggregation inhibitors belonging to the thienopyridines group. They act by antagonising adenosine diphosphate (ADP) at the platelets' purine receptors. ADP-induced aggregation is non-competitively and irreversibly inhibited, whereas arachidonic acid metabolism is unaffected. The two agents undergo hepatic conversion into active metabolites *in vivo*. Consequently, several days are required before full effect is reached, and the process is dose-dependent. The active metabolites are eliminated by the kidneys.[86] Finally, a reduction in ADP-dependent activation of the glycoprotein IIb/IIIa receptor takes place, causing a reduction in fibrinogen fixation and platelet cross-linking.

#### *Ticlopidine*

Maximum aggregation-inhibiting effect is achieved after 8–11 days on a ticlopidine 500 mg per day regimen. The elimination half-life is 24–32 h, but because platelet function inhibition is irreversible, the effect is still evident more than 72 h after its withdrawal.[87] With long-term administration, the elimination half-life increases to over 90 h, and following cessation, 10 days should be allowed before normalisation can be expected.[88] In contrast to clopidogrel, ticlopidine can lead to neutropenia in up to 1% of patients, limiting widespread use of the drug and making regular blood count checks necessary in the initial weeks.

Neuraxial regional anaesthesia should not be performed until 10 days have elapsed between the last ingestion and the procedure (Class IIa, level C).

#### *Clopidogrel (Iscover, Plavix)*

Following oral administration of clopidogrel 75 mg, the maximum platelet function-inhibiting effect is observed after 3–7 days, or after approximately 12–24 h following initial bolus administration of 300–600 mg. Recovery of platelet function occurs only 6–7 days after the end of clopidogrel administration,[89] so that neuraxial anaesthesia should only be performed at least 7 days after the last intake (Class IIa, level C).

#### *Thienopyridines and the risk of bleeding*

Clopidogrel treatment in patients undergoing cardiac surgery may cause severe surgical bleeding, with a 2.5-fold increase in the need for transfusion and a 5–10-fold increase in the risk of repeat surgery, as well as a prolonged course of intensive therapy.[90–92] Severe perioperative bleeding is clearly more frequent with clopidogrel than with aspirin. The incidence of severe bleeding is increased by simultaneous treatment with vitamin K antagonists, dextrans, or heparins.[86] The extent of bleeding complications in other surgical procedures without full intraoperative heparinisation has not been adequately investigated. Immediate improvement of haemostasis is only possible by administering platelets (Class IIa, level C).

As there have already been reports of spinal epidural haematoma following neuraxial blockade during clopidogrel administration,[18,19] current advice is against all such procedures unless the treatment has been interrupted for 7 (clopidogrel) to 10 days (ticlopidine).

#### *Thienopyridines and the risk of adverse cardiovascular events*

Compared to aspirin, clopidogrel and ticlopidine are better at preventing ischaemic cerebral infarction, myocardial infarction, and vascular deaths in general.[93] Patients with unstable coronary syndromes, previous percutaneous coronary interventions, and stent implantations, benefit from long-term dual platelet aggregation inhibition with aspirin and clopidogrel.[94] If this treatment combination is prematurely withdrawn following coronary intervention, the risk of acute stent thrombosis and myocardial infarction is substantially increased, with high mortality.[95] This also appears to be the case even when perioperative bridging is carried out using heparin, and the platelet aggregation inhibitors are only withdrawn very briefly.[96] Patients with a drug-eluting stent are at risk for a particularly long period, due to late and incomplete endothelialisation.[97] Consequently the American Heart Association currently recommends that drug-eluting stents are only used provided no surgery is planned within the following 12 months, and the patients show a high degree of compliance.[98] A cardiologist should be consulted before any interruption of platelet aggregation inhibition, and clopidogrel with aspirin should be administered during the perioperative period (Class I, level C). With bare metal stents, dual platelet aggregation inhibition should be administered for at least 4–6 weeks and with both types of stent, the administration of aspirin should be continued on a lifelong basis and perioperative interruption should be avoided.[98]

### *Prasugrel (Efient)*

This novel thienopyridine is a prodrug that requires conversion to an active metabolite (R-138727) before binding to the platelet $P2Y_{12}$ receptor to develop antiplatelet activity. The latter has a rapid onset, and is 10 times greater than that of clopidogrel.[99] Conversion to the active metabolite is fast and there is less variability in response between individuals. This is a particularly potent antiplatelet agent.

**$P2Y_{12}$**
During platelet activation, ADP is released from granules to bind with platelet receptor $P2Y_{12}$, promoting further activation. It provides an opportunity for pharmacological antagonism.

A large phase III study randomly assigned 13 608 patients with moderate-to-high-risk acute coronary syndromes scheduled for percutaneous coronary intervention, to receive prasugrel or clopidogrel for 6–15 months. Prasugrel therapy was associated with significantly reduced rates of ischaemic events, including stent thrombosis, but with an increased risk of major haemorrhage that was occasionally fatal.[100]

No data are available regarding the perioperative use of this agent (except for cardiac surgery).[100] The antiplatelet effect lasts for the platelet lifespan and pre-treatment levels of platelet function are achieved 7–10 days after discontinuation. In view of the higher incidence of bleeding compared to clopidogrel, neuraxial anaesthesia should be strongly discouraged during prasugrel treatment, unless a time interval of 7–10 days can be observed (Class III, level C).

### *Ticagrelor (Brilanta)*

In contrast to the thienopyridines, ticagrelor acts directly on the P2Y12 receptor rather than requiring cytochrome P450 biotransformation. Its metabolites are also active. Like prasugrel, ticagrelor provides much faster (<2 h), greater (approximately 70%), and more consistent P2Y12 inhibition than clopidogrel (30–40%).[99] It has a rapid onset of action with reversible binding and a shorter duration (48–72 h), leading to a twice daily oral administration. An initial effect on platelet aggregation is observed as early as 30 min after a loading dose. Following cessation, it took 4.5 days to achieve near normal platelet function.[101] The Platelet Inhibition and Patient Outcomes (PLATO) trial, with more than 18 000 acute coronary syndrome patients, compared treatment with clopidogrel and ticagrelor. Patients treated with the latter had significantly reduced rates of death from vascular causes, myocardial infarction, and stroke without an increase in the rate of overall major bleeding, but there was an increase in the rate of bleeding unrelated to a procedure.[102] A higher incidence of minor bleeding was also observed in a subsequent study.[101]

No data are available regarding the perioperative use of this agent. In theory, the shorter, reversible antiplatelet effect could facilitate perioperative manipulation. However, neuraxial anaesthesia should be discouraged during treatment with ticagrelor, unless at least 5 days have lapsed since the last dose (Class III, level C).

### *Cilostazol (Pletal)*

Cilostazol produces a selective inhibition of phosphodiesterase (PDE) IIIA, thereby increasing the intracellular level of cyclic adenosine monophosphate and causing a weak reversible inhibition of platelet aggregation.[103,104] As vascular smooth muscle contains PDE IIIA, cilostazol also produces direct arterial vasodilatation. Nevertheless the entire mechanism of action of cilostazol is not fully understood. It has been used for years in Japan for the treatment of chronic peripheral arterial disease, and has also been approved by the FDA for this indication. It was recently recommended by the ACCP for the treatment of moderate-to-severe disabling intermittent claudication in patients who do not respond to exercise therapy and are not candidates for revascularization.[105] Recent investigation found that adding cilostazol to a dual antiplatelet treatment with aspirin and clopidogrel was superior in the prevention of coronary artery restenosis and cardiac death after primary percutaneous coronary intervention with drug eluting stents, without increasing the incidence of bleeding.[106,107]

Cilostazol is used orally at a dose of 100 mg twice daily. After oral ingestion, maximum plasma levels are reached after 2.7–3.6 h. The compound is eliminated predominantly by hepatic metabolism and subsequent urinary excretion of the metabolites. The terminal elimination half-life of cilostazol and its active metabolites are around 21 h, and some of its metabolites inhibit platelet aggregation to a greater extent than the parent compound.[108] The total pharmacologic activity of cilostazol and its metabolites in mild hepatic or mild to moderate renal impairment was similar to that of healthy individuals. Because metabolites undergo renal excretion, cilostazol is contraindicated in patients with severe renal insufficiency (creatinine clearance $< 25\ \mathrm{ml\ min^{-1}}$) as it may accumulate. Moderate-to-severe hepatic impairment has not been studied yet, but the manufacturer considers it to be a contraindication due to the primary hepatic metabolism.

Neuraxial block or removal of catheter should only be performed at least 2 elimination half-lives after the last dose of cilostazol (42 h), though the manufacturer recommends 5 days. The next dose of cilostazol should only be administered at least 5 h after catheter withdrawal.[5,109] There has been one recent report of a haematoma following epidural catheter removal during treatment with cilostazol,[110] but in general any prospective data on the perioperative use of the drug are lacking and the effect on the incidence of bleeding is currently unknown. Clinical

studies suggest that the risk of bleeding with cilostazol may be much lower than with thienopyridines. Currently, the use of neuraxial techniques in the presence of cilostazol cannot be recommended.

#### *Selective serotonin reuptake inhibitors*

Selective serotonin reuptake inhibitors (SSRIs) are often used to treat depression as there is a consistent association with dysfunction of serotonergic neurotransmission. SSRIs also deplete serotonin in platelets by blocking reuptake and can produce a range of disorders through decreased platelet-binding affinity, blockade of platelet calcium mobilisation, and reduced platelet secretion.[111–113] A slight bleeding tendency may be evident during the perioperative period,[114–116] and one study found blood transfusion requirements to be higher in patients on SSRI.[117] However, another recent study failed to find increased perioperative bleeding in patients undergoing coronary artery bypass grafting.[118,119] Finally, the use of SSRI with other drugs that have an influence on coagulation, such as aspirin, thienopyridines, NSAIDS, vitamin K antagonists or even LMWH seems to increase the bleeding tendency.[120–122]

Although SSRIs are used widely, there are no reports of spinal haematoma following neuraxial block during their use. There are no recommendations concerning the preoperative withdrawal of these drugs and they are not currently considered a contraindication.

#### *Glycoprotein IIb/IIIa inhibitors*

Blocking the glycoprotein IIb/IIIa receptor, the final common pathway of platelet aggregation, represents the most potent form of platelet inhibition. It is reversible. After intravenous administration, abciximab inhibits over 80% of ADP-induced platelet aggregation and reduces thrombin generation. It also has additional antithrombotic properties that distinguish it from other agents in this group. It binds to platelets very quickly and its presence can still be observed 2 weeks after the last administration. No significant renal elimination takes place. If coronary artery bypass graft surgery has to be carried out after percutaneous coronary intervention, the administration of abciximab should be stopped as early as possible. Other glycoprotein IIb/IIIa antagonists such as eptifibatide and tirofiban should be stopped at least 4 h preoperatively.[123] If severe bleeding occurs, transfusion of platelet concentrates is required, although redistribution of abciximab among the freshly infused platelets can also partly inhibit these. With eptifibatide and tirofiban, it can be assumed that there is 50–80% platelet aggregation capacity 4 h after intravenous administration.[124]

The most frequent side effects are severe bleeding and thrombocytopenia,[125] which after abciximab occurs in 0.3–1.0%.[124] Thrombocytopenia is most likely to have an immunological cause and occurs within the first 24 h, so platelet count is required at this time.[123] In acute coronary intervention, glycoprotein IIb/IIIa inhibitors reduce the incidences of myocardial infarction and mortality. Abciximab is more effective than tirofiban or eptifibatide.[126] In contrast to the acute effects of intravenous glycoprotein IIb/IIIa inhibitors, long-term administration of oral preparations does not appear to reduce cardiovascular complications; instead, an increased tendency to bleed and an increased mortality rate were observed.[124]

As glycoprotein IIb/IIIa inhibitors are used only in acute coronary syndromes, in combination with anticoagulants and aspirin, and as cardiac surgery procedures are usually conducted as emergencies with continuing anticoagulation, neuraxial blockade is contraindicated (Class III, level C). If a catheter has to be removed after their administration, most guidelines recommend waiting at least 48 h after abciximab, and 8–10 h after tirofiban or eptifibatide.[127] At this time, a platelet count should always be obtained to exclude thrombocytopenia.

### Neuraxial anaesthesia and thrombolysis

Spinal epidural haematomas occasionally occur spontaneously in the presence of thrombolysis. If neuraxial regional anaesthesia or a neurosurgical procedure has taken place within the previous few weeks, the case for thrombolysis must be carefully considered.[128]

As the indication for thrombolysis is usually an emergency situation such as severe pulmonary embolism or myocardial infarction, recommendations cannot always be observed if the epidural catheter is already in place. Because epidural haematoma are more frequent after placement or removal of a catheter, it is safer to leave the catheter *in situ*, even during thrombolysis. In three reports of spinal epidural haematoma after thrombolytic therapy, the first administration of urokinase was intraoperative, shortly after neuraxial puncture.[129–131] Catheters should only be removed when the thrombolytic effect has worn off. Recommendations for other anticoagulants, such as heparins, apply and coagulation should be allowed to normalise. It must be borne in mind that the effect on coagulation may persist for much longer than the half-life of the individual thrombolytic agent.

### Alternative medicine

Up to 50% of patients take alternative medicines preoperatively, but they are rarely declared.[132] The most commonly used agents include echinacea, Ginkgo biloba, garlic, ginseng, ephedra, aloe, and dwarf palm. Ginkgo, garlic, and ginseng in particular have been linked to thrombocytopenia, platelet aggregation inhibition, interactions with vitamin K antagonists and the development of spinal epidural haematoma. The assessment of alternative medicines is made more difficult by the fact that their manufacture goes unregulated, except in Germany. Preparations often contain other active substances, including NSAIDS and aspirin, which may explain the interactions described in some studies.[133] The side

effects of alternative medicines commonly include heavy metal intoxication, hepatic failure, and allergic reactions, whereas bleeding complications are rarely reported.[134] Despite the widespread use of these substances, there is just one report of an epidural haematoma associated with intake of garlic,[135] making them an unlikely bleeding risk. Garlic and ginkgo have subsequently been shown to be clear of risk.[136,137] Warnings against neuraxial puncture in the presence of alternative medicines and recommendations to withdraw these substances preoperatively are at present unjustified (Class IIa, level C). This is in agreement with current recommendations of the ASRA.[14]

### Peripheral nerve blocks

The complications of peripheral nerve blocks are less serious than central neuraxial blockade, and do not include spinal epidural haematoma. Existing guidelines for neuraxial blockade do not routinely apply. Nevertheless, wound haematoma has the potential to make a significant contribution to morbidity and mortality and there are several reports of extensive retroperitoneal haematoma following lumbar plexus block during enoxaparin or clopidogrel administration. In one of these, the lumbar plexus catheter was removed 1.5 h after the last dose of enoxaparin.[138,139] Although most cases resolved without permanent neurologic damage, there was prolonged hospital stay due to significant discomfort, the need for transfusion of packed cells, the development of reversible sensory and motor deficits, acute renal failure, and even death from haemorrhage.[137–139] The German Society of Anaesthesiology and Intensive Care have considered it appropriate to issue guidelines on thromboprophylaxis and peripheral nerve blocks,[140] whereas the Austrian Society explicitly differentiates between neuraxial, deep peripheral and superficial nerve blocks.[141] The latter blocks such as axillary plexus block, femoral nerve block or distal sciatic nerve block may be performed in the presence of aspirin or anticoagulants. However, whenever possible, time intervals between LMWH administration and catheter insertion or withdrawal that apply to neuraxial blocks should be followed (Class IIa, level C). This is especially important for catheter withdrawal, as there is no reason to remove any catheter around the time of maximum anticoagulant activity. Because of the morbidity associated with retroperitoneal haematoma, lumbar plexus and paravertebral block merit the same recommendations that apply to neuraxial blockade (Class IIa, level C). The Austrian Society recommends that VTE prophylaxis and platelet aggregation inhibitors, including aspirin, are withheld before deep peripheral nerve blocks such as interscalene nerve, supraclavicular and infraclavicular nerve, and lumbar sympathetic blocks, where access is difficult and arterial trauma is a risk.[141]

### Avoidance of complications/patient monitoring

Neuraxial regional anaesthesia has to be carefully and appropriately explained to the patient, and requires an anaesthetist with experience in the technique. After the block, the patient should be monitored at least until the effect of regional anaesthesia is in decline, as indicated by a reduction in sensory blockade by two segments or a return of motor function. Particular attention should be given to persistent sensory or motor deficits, radicular back pain, sensitivity to pressure at the site of the puncture, and bladder dysfunction (Class I, level B). When there is a clinical suspicion of neuraxial haematoma, immediate steps must be taken to confirm the diagnosis, with adoption of any measures likely to limit the extent (Class I, level C).

When continuous or patient-controlled analgesia techniques are used, regular visits by the acute pain service are necessary and a high degree of vigilance is required from all attendants, and the patient as well (Class IIa, level C). Postoperative epidural analgesia should be with a low concentration local anaesthetic to achieve a purely sensory block, so that development of impaired motor function can serve as a sign of cord compression. In this respect, thoracic epidural analgesia has an advantage due to motor-sparing of the lower extremities.

When there is suspicion of cord compression, the diagnostic method of choice is magnetic resonance imaging, as this allows precise localisation of the haematoma and maps its extent. When it is unavailable, as an alternative, computed tomography or myelography should be requested immediately. A strategy aimed at getting the scan that is most readily available will reduce transfer time and lead to earlier surgery. The only effective treatment for cord compression is a laminectomy, and the sooner this is done, the better the result (Class I, level B). Less than 6–12 h should pass between the appearance of symptoms and surgical decompression.[142] Ideally, the appropriate algorithms, agreed in advance with neurosurgical and radiological colleagues, should already be in place.

## Conclusion

Performing central neuraxial procedures immediately before, during, and after anticoagulant drugs is controversial. Those with reduced coagulation have a higher risk for spinal haematoma, and although the general risk is low, it can have dramatic neurological consequences. Despite this, neuraxial blockade is safe if the recommendations described are observed, an atraumatic technique is used, and an individual risk–benefit analysis is carried out, even in patients who are to receive antithrombotic agents perioperatively. Aspirin alone does not increase the risk of spinal epidural haematoma after neuraxial regional anaesthesia, but when used in combination with other anticoagulants for thromboprophylaxis, the overall risk still remains unclear. Withdrawal of platelet function inhibitors such as aspirin or clopidogrel after coronary artery interventions carried out less than 12 months previously increases

the risk of adverse cardiovascular events. This should be taken into account during the individual risk–benefit analysis.

Both UFH and LMWH increase the risk of spinal epidural haematoma if administered at high doses or when puncture or removal of an epidural catheter occurs too soon before or after a dose. During anticoagulation with heparins or vitamin K antagonists at therapeutic doses, puncture and the removal of an epidural catheter continue to be contraindicated.

The lack of reports of spinal epidural haematoma with newer antithrombotic drugs, hirudins, fondaparinux, dabigatran, rivaroxaban, or apixaban, is insufficient reason to conclude that these agents may be relatively safer, as the numbers of patients studied are often too small. In routine clinical practice the recommendations for timing of blockade, supported by carefully planned prospective studies, for example with fondaparinux, must be observed.

ASRA has just published the third edition of its guidelines.[143] In the near future, a close collaboration is planned between the ESA working party and the ASRA working group is expected in a near future with a view to producing joint ASRA-ESA Guidelines.

## Acknowledgements

The authors are grateful to all of their colleagues who, by taking part in discussions and providing their individual expertise during the development of these recommendations, have helped reflect the current state of knowledge as comprehensively as possible while constantly remaining in touch with current practice.

The authors reported the following potential conflicts of interest: Wiebke Gogarten speakers honorarium from Boehringer-Ingelheim, Bayer, GlaxoSmithKline, adivsory board member Bayer, Boehringer-Ingelheim; Eric Vandermeulen advisory board member Boehringer-Ingelheim; Hugo Van Aken none; Sybille Kozek speakers honorarium AstraZeneca, Baxter CSL Behring, GlaxoSmithKline, Mitsubishi Pharma, NovoNordisk, Juan Llau speakers honorarium Sanofi-Aventis, GlaxoSmithKline, advisory board Bayer, Boehringer-Ingelheim, Charles M. Samama speaker honorarium Bayer, Biotest, CSL Behring, Boehringer-Ingelheim, advisory board Sanofi-Aventis, Bayer, GlaxoSmithKline, Pfizer, BMS, grants from Bayer, Sanofi, GlaxoSmithKlein, Pfizer, Schering, and Novo Nordisk for participating at scientific meetings.

The document assessors reported the following potential conflicts of interest in relation to this article: Alain Borgeat, none; Elisabeth Gaertner was an investigator of studies sponsored by Bayer, Boehringer and BMS; Daniela Filipescu received grants from Bayer, Sanofi, GlaxoSmithKlein, Pfizer, Schering, and Novo Nordisk for participating at scientific meetings; Klaus Görlinger, none; Markus Hollmann, none; Susan Mallett received speakers honorarium from CSL Behring; Andrew Smith, none.

## References

1 Gogarten W, Van Aken H, Wulf H, *et al.* Regional anaesthesia and thromboembolism prophylaxis/anticoagulation. *Anaesth Intensivmed* 1997; **38**:623–628.
2 Horlocker TT, Wedel DJ. Anticoagulation and neuraxial block: historical perspective, anesthetic implications, and risk management. *Reg Anesth Pain Med* 1998; **23**:129–134.
3 Anonymous. Belgian Guidelines concerning drug induced alterations of coagulation and central neuraxial anesthesia. *Acta Anaesth Belg* 2000; **51**:101–104.
4 Poldermans D, Bax JJ, Boersma E, *et al.*, (ESC) TFfPCRAaPCMiNcSoESoC, (ESA) ESoA. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: the Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *Eur J Anaesthesiol* 2010; **27**:92–137.
5 Rosencher N, Bonnet M-P, Sessler DI. Selected new antithrombotic agents and neuraxial anaesthesia for major orthopaedic surgery: management strategies. *Anaesthesia* 2007; **62**:1154–1160.
6 Pfanner G, Koscielny J, Pernerstorfer T, *et al.*, Austrian Society for Anaesthesia RaIC. Preoperative evaluation of the bleeding history. Recommendations of the working group on perioperative coagulation of the Austrian Society for Anaesthesia, Resuscitation and Intensive Care. *Anaesthesist* 2007; **56**:604–611.
7 Schroeder DR. Statistics: detecting a rare adverse drug reaction using spontaneous reports. *Reg Anesth Pain Med* 1998; **23**:183–189.
8 Moen V, Dahlgren N, Irestedt L. Severe neurological complications after central neuraxial blockades in Sweden 1990–1999. *Anesthesiology* 2004; **101**:950–959.
9 Cameron CM, Scott DA, McDonald WM, Davies MJ. A review of neuraxial epidural morbidity: experience of more than 8000 cases at a single teaching hospital. *Anesthesiology* 2007; **106**:997–1002.
10 Christie IW, McCabe S. Major complications of epidural analgesia after surgery: results of a six-year survey. *Anaesthesia* 2007; **62**:335–341.
11 Pöpping DM, Zahn PK, Van Aken HK, *et al.* Effectiveness and safety of postoperative pain management: a survey of 18 925 consecutive patients between 1998 and 2006 (2nd revision): a database analysis of prospectively raised data. *Br J Anaesth* 2008; **101**:832–840.
12 Cook T, Counsell D, Wildsmith J, Project OBOTRCOATNA. Major complications of central neuraxial block: report on the Third National Audit Project of the Royal College of Anaesthetists. *Br J Anaesth* 2009; **102**:179–190.
13 Tyagi A, Bhattacharya A. Central neuraxial blocks and anticoagulation: a review of current trends. *Eur J Anaesthesiol* 2002; **19**:317–329.
14 Horlocker TT, Wedel DJ, Benzon H, *et al.* Regional anesthesia in the anticoagulated patient: defining the risks (the second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). *Reg Anesth Pain Med* 2003; **28**:172–197.
15 Vandermeulen EP, Van Aken H, Vermylen J. Anticoagulants and spinal-epidural anesthesia. *Anesth Analg* 1994; **79**:1165–1177.
16 Wulf H. Epidural anaesthesia and spinal haematoma. *Can J Anaesth* 1996; **43**:1260–1271.
17 Vandermeulen E. Is anticoagulation and central neural blockade a safe combination? *Curr Opin Anaesthesiol* 1999; **12**:539–543.
18 Litz RJ, Gottschlich B, Stehr SN. Spinal epidural hematoma after spinal anesthesia in a patient treated with clopidogrel and enoxaparin. *Anesthesiology* 2004; **101**:1467–1470.
19 Tam NLK, Pac-Soo C, Pretorius PM. Epidural haematoma after a combined spinal-epidural anaesthetic in a patient treated with clopidogrel and dalteparin. *Br J Anaesth* 2006; **96**:262–265.
20 Geerts W, Bergqvist D, Pineo G, *et al.* Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133**:381S.
21 Hull R, Pineo G, MacIsaac S. Low-molecular-weight heparin prophylaxis: preoperative versus postoperative initiation in patients undergoing elective hip surgery. *Thromb Res* 2000; **101**:V155–V162.
22 Strebel N, Prins M, Agnelli G, Büller HR. Preoperative or postoperative start of prophylaxis for venous thromboembolism with low-molecular-weight heparin in elective hip surgery? *Arch Intern Med* 2002; **162**:1451–1456.
23 Association of the Scientific Medical Societies in Germany. German Recommendations on Venous Thromboembolism Prophylaxis 2009: http://leitlinien.net (accessed 7 September 2010).
24 Rao TL, El-Etr AA. Anticoagulation following placement of epidural and subarachnoid catheters: an evaluation of neurologic sequelae. *Anesthesiology* 1981; **55**:618–620.
25 Ruff RL, Dougherty JH. Complications of lumbar puncture followed by anticoagulation. *Stroke* 1981; **12**:879–881.
26 Stafford-Smith M. Impaired haemostasis and regional anaesthesia. *Can J Anaesth* 1996; **43**:R129–R141.

27 Lee LA, Posner KL, Domino KB, *et al.* Injuries associated with regional anesthesia in the 1980s and 1990s: a closed claims analysis. *Anesthesiology* 2004; **101**:143–152.
28 Liu SS, Block BM, Wu CL. Effects of perioperative central neuraxial analgesia on outcome after coronary artery bypass surgery: a meta-analysis. *Anesthesiology* 2004; **101**:153–161.
29 Roediger L, Larbuisson R, Lamy M. New approaches and old controversies to postoperative pain control following cardiac surgery. *Eur J Anaesthesiol* 2006; **23**:539–550.
30 Ho AM, Chung DC, Joynt GM. Neuraxial blockade and hematoma in cardiac surgery: estimating the risk of a rare adverse event that has not (yet) occurred. *Chest* 2000; **117**:551–555.
31 Chaney MA. Intrathecal and epidural anesthesia and analgesia for cardiac surgery. *Anesth Analg* 1997; **84**:1211–1221.
32 Gogarten W, Van Aken H, Büttner J, *et al.* Regional anaesthesia and thromboembolism prophylaxis/anticoagulation. Revised recommendations of the German Society of Anaesthesiology and Intensive Care Medicine. *Anaesth Intensivmed* 2007; **48**:S109–S124.
33 Chaney MA. Cardiac surgery and intrathecal/epidural techniques: at the crossroads? *Can J Anaesth* 2005; **52**:783–788.
34 Samama CM, Albaladejo P, Benhamou D, *et al.*, (SFAR) CfGPSotFSfAaIC. Venous thromboembolism prevention in surgery and obstetrics: clinical practice guidelines. *Eur J Anaesthesiol* 2006; **23**:95–116.
35 Geerts WH, Jay RM, Code KI, *et al.* A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. *N Engl J Med* 1996; **335**:701–707.
36 Warkentin TE, Levine MN, Hirsh J, *et al.* Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995; **332**:1330–1335.
37 Weitz JI. Low-molecular-weight heparins. *N Engl J Med* 1997; **337**:688–698.
38 Sanderink G-JCM, Guimart CG, Ozoux M-L, *et al.* Pharmacokinetics and pharmacodynamics of the prophylactic dose of enoxaparin once daily over 4 days in patients with renal impairment. *Thromb Res* 2002; **105**:225–231.
39 Bacher P, Welzel D, Iqbal O, *et al.* The thrombolytic potency of LMW-heparin compared to urokinase in a rabbit jugular vein clot lysis model. *Thromb Res* 1992; **66**:151–158.
40 Harenberg J, Huisman MV, Tolle AR, *et al.* Reduction in thrombus extension and clinical end points in patients after initial treatment for deep vein thrombosis with the fixed-dose body weight-independent low molecular weight heparin certoparin. *Semin Thromb Hemost* 2001; **27**:513–518.
41 Bergqvist D, Lindblad B, Mätzsch T. Risk of combining low molecular weight heparin for thromboprophylaxis and epidural or spinal anesthesia. *Semin Thromb Hemost* 1993; **19 (Suppl 1)**:147–151.
42 Douketis JD, Kinnon K, Crowther MA. Anticoagulant effect at the time of epidural catheter removal in patients receiving twice-daily or once-daily low-molecular-weight heparin and continuous epidural analgesia after orthopedic surgery. *Thromb Haemost* 2002; **88**:37–40.
43 Warkentin TE, Maurer BT, Aster RH. Heparin-induced thrombocytopenia associated with fondaparinux. *N Engl J Med* 2007; **356**:2653–2655.
44 Rota E, Bazzan M, Fantino G. Fondaparinux-related thrombocytopenia in a previous low-molecular-weight heparin (LMWH)-induced heparin-induced thrombocytopenia (HIT). *Thromb Haemost* 2008; **99**:779–781.
45 Lobo B, Finch C, Howard A, Minhas S. Fondaparinux for the treatment of patients with acute heparin-induced thrombocytopenia. *Thromb Haemost* 2008; **99**:208–214.
46 Warkentin TE, Greinacher A, Koster A, Lincoff AM, Physicians ACoC. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133**:S340–S380.
47 Turpie AGG, Bauer KA, Eriksson BI, Lassen MR. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. *Arch Intern Med* 2002; **162**:1833–1840.
48 Boneu B, Necciari J, Cariou R, *et al.* Pharmacokinetics and tolerance of the natural pentasaccharide (SR90107/Org31540) with high affinity to antithrombin III in man. *Thromb Haemost* 1995; **74**:1468–1473.
49 Singelyn FJ, Verheyen CCPM, Piovella F, *et al.* The safety and efficacy of extended thromboprophylaxis with fondaparinux after major orthopedic surgery of the lower limb with or without a neuraxial or deep peripheral nerve catheter: the EXPERT Study. *Anesth Analg* 2007; **105**:1540–1547.
50 Veyrat-Follet C, Vivier N, Trellu M, *et al.* The pharmacokinetics of idraparinux, a long-acting indirect factor Xa inhibitor: population pharmacokinetic analysis from Phase III clinical trials. *J Thromb Haemost* 2009; **7**:559–565.
51 Harenberg J, Vukojevic Y, Mikus G, *et al.* Long elimination half-life of idraparinux may explain major bleeding and recurrent events of patients from the van Gogh trials. *J Thromb Haemost* 2008; **6**:890–892.
52 Eriksson BI, Borris LC, Friedman RJ, *et al.* Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008; **358**:2765–2775.
53 Buller H, Lensing A, Prins M, *et al.* A dose-ranging study evaluating once-daily oral administration of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis. The EINSTEIN-DVT Dose-Ranging Study. *Blood* 2008; **112**:2242–2247.
54 Xu Q. Xarelto (Rivaroxaban). Cardiovascular and Renal Drugs Advisory Committee Meeting; 19 March 2009. *FDA Cardiovascular and Renal Drugs* 2009.
55 Weitz JI, Hirsh J, Samama MM, Physicians ACoC. New antithrombotic drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133**:234S–256S.
56 Lassen MR, Raskob GE, Gallus A, *et al.* Apixaban or enoxaparin for thromboprophylaxis after knee replacement. *N Engl J Med* 2009; **361**:594–604.
57 Group TS. Thromboprophylaxis in hip fracture surgery: a pilot study comparing danaparoid, enoxaparin and dalteparin. The TIFDED Study Group. *Haemostasis* 1999; **29**:310–317.
58 Danhof M, de Boer A, Magnani HN, Stiekema JC. Pharmacokinetic considerations on Orgaran (Org 10172) therapy. *Haemostasis* 1992; **22**:73–84.
59 Schrör K. Antiplatelet drugs. A comparative review. *Drugs* 1995; **50**:7–28.
60 Verstraete M, Nurmohamed M, Kienast J, *et al.* Biologic effects of recombinant hirudin (CGP 39393) in human volunteers. European Hirudin in Thrombosis Group. *J Am Coll Cardiol* 1993; **22**:1080–1088.
61 Eriksson BI, Ekman S, Kalebo P, *et al.* Prevention of deep-vein thrombosis after total hip replacement: direct thrombin inhibition with recombinant hirudin, CGP 39393. *Lancet* 1996; **347**:635–639.
62 Eichler P, Friesen HJ, Lubenow N, *et al.* Antihirudin antibodies in patients with heparin-induced thrombocytopenia treated with lepirudin: incidence, effects on aPTT, and clinical relevance. *Blood* 2000; **96**:2373–2378.
63 Poidevin P, Salomé V, Riegel B, *et al.* Recombinant hirudin in neurosurgery. *Ann Fr Anesth Reanim* 2001; **20**:570–572.
64 Yeh RW, Jang I-K. Argatroban: update. *Am Heart J* 2006; **151**:1131–1138.
65 Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. *Clin Pharmacokinetics* 2008; **47**:285–295.
66 Eriksson B, Dahl O, Rosencher N, *et al.*, Group ftR-MS. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* 2007; **5**:2178–2185.
67 Horlocker TT, Wedel DJ, Schlichting JL. Postoperative epidural analgesia and oral anticoagulant therapy. *Anesth Analg* 1994; **79**:89–93.
68 Odoom JA, Sih IL. Epidural analgesia and anticoagulant therapy. Experience with one thousand cases of continuous epidurals. *Anaesthesia* 1983; **38**:254–259.
69 FitzGerald G, Oates J, Hawiger J, *et al.* Endogenous biosynthesis of prostacyclin and thromboxane and platelet function during chronic administration of aspirin in man. *J Clin Invest* 1983; **71**:676–688.
70 Gibbs NM, Weightman WM, Thackray NM, *et al.* The effects of recent aspirin ingestion on platelet function in cardiac surgical patients. *J Cardiothorac Vasc Anesth* 2001; **15**:55–59.
71 Serebruany VL, Steinhubl SR, Berger PB, *et al.* Analysis of risk of bleeding complications after different doses of aspirin in 192 036 patients enrolled in 31 randomized controlled trials. *Am J Cardiol* 2005; **95**:1218–1222.
72 McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. *Am J Med* 2006; **119**:624–638.
73 Ferraris VA, Ferraris SP, Joseph O, *et al.* Aspirin and postoperative bleeding after coronary artery bypass grafting. *Ann Surg* 2002; **235**:820–827.
74 Burger W, Chemnitius J-M, Kneissl GD, Rücker G. Low-dose aspirin for secondary cardiovascular prevention: cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation: review and meta-analysis. *J Intern Med* 2005; **257**:399–414.
75 CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group. *Lancet* 1994; **343**:619–629.

76 Horlocker TT, Wedel DJ, Schroeder DR, *et al.* Preoperative antiplatelet therapy does not increase the risk of spinal hematoma associated with regional anesthesia. *Anesth Analg* 1995; **80**:303–309.

77 Horlocker TT, Bajwa ZH, Ashraf Z, *et al.* Risk assessment of hemorrhagic complications associated with nonsteroidal antiinflammatory medications in ambulatory pain clinic patients undergoing epidural steroid injection. *Anesth Analg* 2002; **95**:1691–1697.

78 Cronberg S, Wallmark E, Söderberg I. Effect on platelet aggregation of oral administration of 10 non-steroidal analgesics to humans. *Scand J Haematol* 1984; **33**:155–159.

79 Catella-Lawson F, Reilly MP, Kapoor SC, *et al.* Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001; **345**:1809–1817.

80 Patrono C, Baigent C, Hirsh J, Roth G, Physicians ACoC. Antiplatelet drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133**:199S–233S.

81 Ferrari E, Benhamou M, Cerboni P, Marcel B. Coronary syndromes following aspirin withdrawal: a special risk for late stent thrombosis. *J Am Coll Cardiol* 2005; **45**:456–459.

82 Collet J, Montalescot G, Blanchet B, *et al.* Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes. *Circulation* 2004; **110**:2361–2367.

83 Herren T, Stricker H, Haeberli A, *et al.* Fibrin formation and degradation in patients with arteriosclerotic disease. *Circulation* 1994; **90**:2679–2686.

84 Fleisher LA, Beckman JA, Brown KA, *et al.* ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: Executive Summary. *Circulation* 2007; **116**:1971–1996.

85 Douketis JD, Berger PB, Dunn AS, *et al.*, Physicians ACoC. The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133**:299S–339S.

86 Sharis PJ, Cannon CP, Loscalzo J. The antiplatelet effects of ticlopidine and clopidogrel. *Ann Intern Med* 1998; **129**:394–405.

87 Weber AA, Schrör K. Pharmacology of ticlopidine and clopidogrel in comparison with acetylsalicylic acid. *Internist (Berl)* 1997; **38**:1115–1120.

88 Buur T, Larsson R, Berglund U, *et al.* Pharmacokinetics and effect of ticlopidine on platelet aggregation in subjects with normal and impaired renal function. *J Clin Pharmacol* 1997; **37**:108–115.

89 Denninger MH, Necciari J, Serre-Lacroix E, Sissmann J. Clopidogrel antiplatelet activity is independent of age and presence of atherosclerosis. *Semin Thromb Hemost* 1999; **25 (Suppl 2)**:41–45.

90 Englberger L, Faeh B, Berdat PA, *et al.* Impact of clopidogrel in coronary artery bypass grafting. *Eur J Cardiothorac Surg* 2004; **26**:96–101.

91 Kapetanakis EI, Medlam DA, Petro KR, *et al.* Effect of clopidogrel premedication in off-pump cardiac surgery: are we forfeiting the benefits of reduced hemorrhagic sequelae? *Circulation* 2006; **113**:1667–1674.

92 Purkayastha S, Athanasiou T, Malinovski V, *et al.* Does clopidogrel affect outcome after coronary artery bypass grafting? A meta-analysis. *Heart* 2006; **92**:531–532.

93 Committee CS. A randomised, blinded, trial of Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996; **348**:1329–1339.

94 Mehta SR, Yusuf S, Peters RJ, *et al.*, Investigators CiUatpREtC. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001; **358**:527–533.

95 Wilson SH, Fasseas P, Orford JL, *et al.* Clinical outcome of patients undergoing non-cardiac surgery in the two months following coronary stenting. *J Am Coll Cardiol* 2003; **42**:234–240.

96 Vicenzi MN, Meislitzer T, Heitzinger B, *et al.* Coronary artery stenting and non-cardiac surgery: a prospective outcome study. *Br J Anaesth* 2006; **96**:686–693.

97 Joner M, Finn A, Farb A, *et al.* Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* 2006; 48:193–202.

98 Grines CL, Bonow RO, Casey DE, *et al.* Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents. *Circulation* 2007; **115**:813–818.

99 Angiolillo DJ, Bhatt DL, Gurbel PA, Jennings LK. Advances in antiplatelet therapy: agents in clinical development. *Am J Cardiol* 2009; **103**:40A–51A.

100 Wiviott SD, Braunwald E, McCabe CH, *et al.* Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; **357**:2001–2015.

101 Gurbel PA, Bliden KP, Butler K, *et al.* Randomized Double-Blind Assessment of the ONSET and OFFSET of the Antiplatelet Effects of Ticagrelor Versus Clopidogrel in Patients With Stable Coronary Artery Disease. Randomized Double-Blind Assessment of the ONSET and OFFSET of the Antiplatelet Effects of Ticagrelor Versus Clopidogrel in Patients With Stable Cornonary Disease: the ONSET/OFFSET Study. *Circulation* 2009; **120**:2577–2585.

102 Wallentin L, Becker RC, Budaj A, *et al.* Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; **361**:1045–1057.

103 Schror K. The pharmacology of cilostazol. *Diabetes Obes Metab* 2002; **4 (Suppl 2)**:S14–S19.

104 Woo SK, Kang WK, Kwon KI. Pharmacokinetic and pharmacodynamic modeling of the antiplatelet and cardiovascular effects of cilostazol in healthy humans. *Clin Pharmacol Ther* 2002; **71**:246–252.

105 Sobel M, Verhaeghe R. Antithrombotic therapy for peripheral artery occlusive disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133**:815S–843S.

106 Lee SW, Chun KJ, Park SW, *et al.* Comparison of Triple Antiplatelet Therapy and Dual Antiplatelet Therapy in Patients at High Risk of Restenosis After Drug-Eluting Stent Implantation (from the DECLARE-DIABETES and -LONG Trials). *Am J Cardiol* 2010; **105**:168–173.

107 Chen K-Y, Rha S-W, Li Y-J, *et al.*, Investigators KAMIR. Triple versus dual antiplatelet therapy in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Circulation* 2009; **119**:3207–3214.

108 Woo SK, Kang WK, Kwon K-I. Pharmacokinetic and pharmacodynamic modeling of the antiplatelet and cardiovascular effects of cilostazol in healthy humans. *Clin Pharmacol Ther* 2002; **71**:246–252.

109 Llau JV, Ferrandis R. New anticoagulants and regional anesthesia. *Curr Opin Anaesth* 2009; **22**:661–666.

110 Kaneda T, Urimoto G, Suzuki T. Spinal epidural hematoma following epidural catheter removal during antiplatelet therapy with cilostazol. *J Anesth* 2008; **22**:290–293.

111 Butler J, Leonard BE. The platelet serotonergic system in depression and following sertraline treatment. *Int Clin Psychopharmacol* 1988; **3**:343–347.

112 Helmeste DM, Tang SW, Reist C, Vu R. Serotonin uptake inhibitors modulate intracellular Ca2+ mobilization in platelets. *Eur J Pharmacol* 1995; **288**:373–377.

113 Markovitz JH, Shuster JL, Chitwood WS, *et al.* Platelet activation in depression and effects of sertraline treatment: an open-label study. *Am J Psychiatry* 1006-; **157**:8.

114 Norred CL, Finlayson CA. Hemorrhage after the preoperative use of complementary and alternative medicines. *AANA J* 2000; **68**:217–220.

115 Sewnath ME, van Hillegersberg R, Koopman MM, *et al.* Increased perioperative blood loss during treatment with paroxetine. *Ned Tijdschr Geneeskd* 2002; **146**:1800–1802.

116 Turner MS, May DB, Arthur RR, Xiong GL. Clinical impact of selective serotonin reuptake inhibitors therapy with bleeding risks. *J Intern Med* 2007; **261**:205–213.

117 Movig KL, Janssen MW, de Waal Malefijt J, *et al.* Relationship of serotonergic antidepressants and need for blood transfusion in orthopedic surgical patients. *Arch Intern Med* 2003; **163**:2354–2358.

118 Andreasen JJ, Riis A, Hjortdal VE, *et al.* Effect of selective serotonin reuptake inhibitors on requirement for allogeneic red blood cell transfusion following coronary artery bypass surgery. *Am J Cardiovasc Drugs* 2006; **6**:243–250.

119 Kim DH, Daskalakis C, Whellan DJ, *et al.* Safety of selective serotonin reuptake inhibitor in adults undergoing coronary artery bypass grafting. *Am J Cardiol* 2009; **103**:1391–1395.

120 Schalekamp T, Klungel OH, Souverein PC, de Boer A. Increased bleeding risk with concurrent use of selective serotonin reuptake inhibitors and coumarins. *Arch Intern Med* 2008; **168**:180–185.

121 Wallerstedt SM, Gleerup H, Sundstrom A, *et al.* Risk of clinically relevant bleeding in warfarin-treated patients: influence of SSRI treatment. *Pharmacoepidemiol Drug Saf* 2009; **18**:412–416.

122 Mansour A, Pearce M, Johnson B, *et al.* Which patients taking SSRIs are at greatest risk of bleeding? *J Fam Pract* 2006; **55**:206–208.

123 Bhatt DL, Topol EJ. Current role of platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes. *JAMA* 2000; **284**:1549–1558.

124 Coller BS. Anti-GPIIb/IIIa drugs: current strategies and future directions. *Thromb Haemost* 2001; **86**:427–443.

125 Harrington RA, Armstrong PW, Graffagnino C, *et al.* Dose-finding, safety, and tolerability study of an oral platelet glycoprotein IIb/IIIa inhibitor, lotrafiban, in patients with coronary or cerebral atherosclerotic disease. *Circulation* 2000; **102**:728–735.

126 Brown DL, Fann CS, Chang CJ. Meta-analysis of effectiveness and safety of abciximab versus eptifibatide or tirofiban in percutaneous coronary intervention. *Am J Cardiol* 2001; **87**:537–541.
127 Gogarten W. The influence of new antithrombotic drugs on regional anesthesia. *Curr Opin Anaesthesiol* 2006; **19**:545–550.
128 Smith RE, Bodin CJ, Kogutt MS. Recent epidural anesthesia: a relative contraindication to thrombolysis. *AJR Am J Roentgenol* 1997; **169**:445–446.
129 Dickman CA, Shedd SA, Spetzler RF, *et al.* Spinal epidural hematoma associated with epidural anesthesia: complications of systemic heparinization in patients receiving peripheral vascular thrombolytic therapy. *Anesthesiology* 1990; **72**:947–950.
130 Onishchuk JL, Carlsson C. Epidural hematoma associated with epidural anesthesia: complications of anticoagulant therapy. *Anesthesiology* 1992; **77**:1221–1223.
131 Rabito SF, Ahmed S, Feinstein L, Winnie AP. Intrathecal bleeding after the intraoperative use of heparin and urokinase during continuous spinal anesthesia. *Anesth Analg* 1996; **82**:409–411.
132 Wang S-M, Caldwell-Andrews AA, Kain ZN. The use of complementary and alternative medicines by surgical patients: a follow-up survey study. *Anesth Analg* 2003; **97**:1010–1015.
133 Fugh-Berman A. Herb-drug interactions. *Lancet* 2000; **355**:134–138.
134 Farah MH, Edwards R, Lindquist M, *et al.* International monitoring of adverse health effects associated with herbal medicines. *Pharmacoepidemiol Drug Saf* 2000; **9**:105–112.
135 Rose KD, Croissant PD, Parliament CF, Levin MB. Spontaneous spinal epidural hematoma with associated platelet dysfunction from excessive garlic ingestion: a case report. *Neurosurgery* 1990; **26**:880–882.
136 Köhler S, Funk P, Kieser M. Influence of a 7-day treatment with Ginkgo biloba special extract EGb 761 on bleeding time and coagulation: a randomized, placebo-controlled, double-blind study in healthy volunteers. *Blood Coagul Fibrinolysis* 2004; **15**:303–309.
137 Weller RS, Gerancher JC, Crews JC, Wade KL. Extensive retroperitoneal hematoma without neurologic deficit in two patients who underwent lumbar plexus block and were later anticoagulated. *Anesthesiology* 2003; **98**:581–585.
138 Aveline C, Bonnet F. Delayed retroperitoneal haematoma after failed lumbar plexus block. *Br J Anaesth* 2004; **93**:589–591.
139 Maier C, Gleim M, Weiss T, *et al.* Severe bleeding following lumbar sympathetic blockade in two patients under medication with irreversible platelet aggregation inhibitors. *Anesthesiology* 2002; **97**:740–743.
140 Büttner J, Bürkle H, Gogarten W, Wulf H. Thromboembolism prophylaxis and peripheral nerve blocks for regional anaesthesia. Guideline of the German Society of Anaesthesiology and Intensive Care Medicine. *Anaesth Intensivmed* 2005; **46**:319–322.
141 Kozek-Langenecker SA, Fries D, Gütl M, *et al.* Locoregional anesthesia and coagulation inhibitors. Recommendations of the Task Force on Perioperative Coagulation of the Austrian Society for Anesthesiology and Intensive Care Medicine. *Anaesthesist* 2005; **54**:476–484.
142 Lawton MT, Porter RW, Heiserman JE, *et al.* Surgical management of spinal epidural hematoma: relationship between surgical timing and neurological outcome. *J Neurosurg* 1995; **83**:1–7.
143 Horlocker TT, Wedel DJ, Rowlingson JC, *et al.* Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med* 2010; **35**:64–101.