The influence of new antithrombotic drugs on regional anesthesia
Wiebke Gogarten

Purpose of review
Antithrombotic drugs are known to increase the risk of spinal epidural hematoma after neuraxial blockade. During the last few years, several new anticoagulants have been introduced, some of them more potent than the drugs currently available. More potency, however, may also indicate a higher risk of bleeding.

Recent findings
Case series from the last few years indicate that spinal epidural hematoma is more common than previously estimated, with a prevalence from 1:100,000 in obstetric patients to as high as 1:3600 in female orthopedic patients. In order to diminish this risk, most national societies have issued guidelines in which time intervals were established between administration of antithrombotic drugs and performance of neuraxial blockade.

Summary
Guidelines are perceived to be capable of reducing the incidence of spinal epidural hematoma with the inherent risk of permanent paraplegia. These guidelines, however, will only be a valuable aid for clinicians if they are constantly updated and newer antithrombotic drugs are included. Although the resurgence of peripheral nerve blocks may diminish patient hazards, deep nerve blocks such as lumbar sympathetic blockade are not devoid of serious complications and should probably be handled in the same way as neuraxial blockade.

Keywords
guidelines, introduction and risk evaluation, neuraxial blockade, peripheral nerve blocks, spinal epidural hematoma, thromboembolism prophylaxis

Introduction
Spinal epidural hematoma formation is a rare but devastating complication after neuraxial blockade and may lead to permanent paraplegia if hematoma evacuation is not performed within the first 6–12 h after symptom onset. Risk factors involved were first described by Vandermeulen et al. [1] and are delineated in Table 1. In this analysis, concomitant use of antithrombotic drugs or an acquired coagulopathy were of paramount importance. Since then, newer and more potent antithrombotic and antiplatelet drugs have been introduced, which may potentially further increase the risk.

Previous estimates of the risk of epidural hematoma with 1:150,000 after epidural anesthesia and 1:220,000 after spinal anesthesia may significantly underestimate the prevalence in light of recently published reports [2,3]. In the United States, a series of more than 50 patients with spinal hematoma occurred after the introduction of low molecular weight heparins (LMWHs), although LMWHs had been used for some years in Europe without a major rise in complications. Analyzing these patients, Schroeder et al. [2] estimated the risk of spinal epidural hematoma as one in 40,000 after spinal anesthesia and one in 3100 after epidural anesthesia and most of them occurred at the time of catheter removal in older orthopedic patients. Possible explanations were the lack of guidelines and the higher US dosing regimen (enoxaparine 30 mg twice daily). Subsequently, Moen et al. [3] published a case series from Sweden covering 1 260 000 spinal and 450 000 epidural anesthetics. The prevalence of spinal epidural hematoma varied from one in 100 000 after epidural labor analgesia to one in 3600 in female orthopedic patients. In addition to a lack of guidelines, other explanations for the high risk in orthopedic patients included frequent dual therapy with antiplatelet and antithrombotic drugs in combination with undetected renal impairment.

In order to minimize bleeding complications most countries have now developed guidelines for neuraxial blockade [4–8]. These guidelines are not evidence based but rely on the evaluation of case reports and pharmacokinetics of the drugs involved. Recommended time intervals do not differ much among countries and aid clinicians in estimating when trough levels of anticoagulants are reached (Table 2). Time intervals may be derived as early as pharmacokinetic studies are available and need not await the first case reports with newly introduced drugs.
Low molecular weight heparins
LMWHs have become the mainstay in thromboembolism prophylaxis in moderate and high-risk patients. Major advantages include an increased bioavailability, a more predictable anticoagulant effect, and reduced bleeding complications compared with unfractionated heparin.

Dosing strategies differ between Europe and the United States and may explain some of the discrepancies between different national guidelines. The European approach to start thromboembolism prophylaxis before surgery is based on theoretical concerns without substantiation by clinical trials. Metaanalyses comparing preoperative with postoperative LMWH prophylaxis did not show any benefit of enoxaparine given 12 h prior to surgery compared with initiating thromboembolism prophylaxis postoperatively [9]. This is not surprising considering that the anti-Xa activity after a single bolus of 40 mg enoxaparine has nearly returned to baseline after 12 h in patients with normal renal function [10].

Derived from this study it is recommended to initiate neuraxial blockade at least 10–12 h after the last dose of enoxaparine to ensure that trough levels are achieved [4,5,8]. If LMWHs are administered in higher therapeutic doses, a time interval of at least 24 h should elapse prior to neuraxial blockade.

Unfractionated heparin and LMWHs accumulate in patients with renal insufficiency, thereby increasing the risk of bleeding complications [10]. Most current guidelines fall short of making clear recommendations, but a prolongation of the time interval or determination of the anti-Xa activity need to be considered. Whereas serum creatinine is too insensitive to detect moderate to severe kidney dysfunction, it may be easily evaluated by calculating the creatinine clearance according to the Cockcroft formula. LMWHs and fondaparinux are contraindicated in patients with severe renal impairment in Europe (creatinine clearance < 30 ml/min). The American Food and Drug Administration (FDA) recommends to half the dose of LMWHs in cases of severe renal impairment.

Fondaparinux
Fondaparinux is a novel synthetic anti-Xa inhibitor that has proved superior in the prevention of deep vein thrombosis in patients undergoing hip and knee arthroplasty compared with LMWHs [11]. The estimated risk reduction is approximately 50% with 2.5 mg of fondaparinux once daily. It is the first antithrombotic drug that has received approval for postoperative initiation of thromboembolism prophylaxis in Europe. Although initial studies included more than 7000 patients, they received predominantly single shot spinal anesthesia, eliminating any risk assessment of neuraxial blockade. In a subsequent study [12] in abdominal surgery, 506 patients

Table 1 Risk factors associated with spinal epidural hematoma formation

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<tr>
<td>Female gender</td>
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<td>Advanced age</td>
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<tr>
<td>Orthopedic patients</td>
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<tr>
<td>Ankylosing spondylitis</td>
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<td>Renal insufficiency</td>
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<td>Coagulopathy or use of antithrombotic drugs</td>
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<td>Multiple needle passes</td>
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<td>Catheter insertion and withdrawal</td>
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Table 2 Comparison of guidelines from different national societies

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<thead>
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<tbody>
<tr>
<td>UFH s.c.</td>
<td>Not contraindicated</td>
<td>4 h/1 h</td>
<td>4 h/1 h</td>
<td>Not indicated</td>
</tr>
<tr>
<td>UFH i.v.</td>
<td>2–4 h/1 h</td>
<td>4 h/1 h</td>
<td>4 h/1 h</td>
<td>Normal aPTT/1 h</td>
</tr>
<tr>
<td>LMWH (low dose)</td>
<td>12 h/2 h</td>
<td>24 h/2–4 h</td>
<td>12 h/4 h</td>
<td>24 h/4 h</td>
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<tr>
<td>LMWH (therapeutic dose)</td>
<td>Contraindicated</td>
<td>24 h/2–4 h</td>
<td>24 h/4 h</td>
<td>24 h/4 h</td>
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<tr>
<td>Fondaparinux</td>
<td>Not indicated</td>
<td>22/2–4 h*</td>
<td>24 h/2–4 h</td>
<td>36 h/4 h</td>
</tr>
<tr>
<td>Hirudins</td>
<td>Not indicated</td>
<td>8–10 h/2–4 h</td>
<td>10 h/4 h</td>
<td>8–10 h/2–4 h</td>
</tr>
<tr>
<td>Coumadins</td>
<td>INR &lt; 1.5</td>
<td>INR &lt; 1.4 restart after catheter withdrawal</td>
<td>INR &lt; 1.4</td>
<td>INR &lt; 1.4 restart after catheter withdrawal</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Not contraindicated</td>
<td>3 days*</td>
<td>2 days spinal, 3 days epidural</td>
<td>Not contraindicated</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>14 days</td>
<td>10 days</td>
<td>10 days</td>
<td>10 days</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>7 days</td>
<td>7 days</td>
<td>7 days</td>
<td>7 days</td>
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<tr>
<td>Tiroliban/epitifibatide</td>
<td>8 h</td>
<td>Contraindicated</td>
<td>8h/4 h</td>
<td>8h/4 h</td>
</tr>
<tr>
<td>Abciximab</td>
<td>48 h</td>
<td>Contraindicated</td>
<td>48 h/4 h</td>
<td>24–48 h</td>
</tr>
<tr>
<td>Thrombolytics</td>
<td>Fibrinogen level</td>
<td>Contraindicated</td>
<td>Not indicated</td>
<td>Contraindicated</td>
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</table>

*Indicated time intervals refer to the time before neuraxial blockade or catheter withdrawal and after neuraxial blockade or catheter withdrawal. s.c., subcutaneous; i.v., intravenous; aPTT, activated partial thromboplastin time; LMWH, low molecular weight heparin; INR, international normalized ratio.
*Time intervals refer to epidural anesthesia, not to spinal anesthesia.
*Only prophylactic doses with catheter in place, and first dose after withdrawal prophylactic.
*Normal renal function.
*Creatinine clearance less than 50 ml/min.
*In combination with thromboembolism prophylaxis.
with an indwelling epidural catheter were treated with fondaparinux without neurologic sequelae. Timing of catheter removal occurred 22 h after the last dose and at least 2 h before the next dose. Given the paucity of data, the long half life of 18 h, and the known accumulation in patients with renal impairment, the EXPERT study (evaluation of arixtra for the prevention of venous thromboembolism in daily practice) was designed with a specific emphasis on timing of catheter removal (F. Singelyn, C.C.P.M. Verheyen, P. Felicissimo, et al., submitted). Patients received extended prophylaxis with fondaparinux after major orthopedic surgery and 1626 of the patients had indwelling epidural catheters or deep peripheral nerve blocks. Fondaparinux was omitted the day before planned catheter removal, allowing a time interval of 36–42 h without an increased risk of thrombosis. These time intervals have been adopted by the Austrian, Belgian and German Societies [4,7,8].

There has so far been a single case report [13] on spinal epidural hematoma in a patient receiving 6 mg fondaparinux as part of a dose-finding study with multiple traumatic attempts at performing the block. It may thus be advisable to postpone thromboembolism prophylaxis if multiple needle passes or a bloody tap are encountered.

**Acetylsalicylic acid**

In patients at risk, platelet inhibition with aspirin is associated with a reduced cardiovascular mortality by 15% and reduced nonfatal cardiovascular events by 30% [14]. Complete irreversible inhibition of platelet thromboxane A2 formation has been observed with doses as low as 100 mg, whereas inhibition of cyclooxygenase-2 to induce analgesic and antiinflammatory effects requires much higher doses and shorter dosing intervals.

The safety of neuraxial blockade in the presence of antiplatelet drugs such as nonsteroidal antiinflammatory drugs (NSAIDS) or aspirin is based on three large trials with more than 9000 and 1000 patients, respectively [15–17]. Although the collaborative low-dose aspirin study in pregnancy (CLASP study) involved 9364 parturients, only 2783 received epidural anesthesia; of these, 1422 took aspirin, but only half of them continued aspirin until delivery, leaving approximately 700 patients for safety analysis. Likewise, in the study by Horlocker et al. [16] involving 924 patients, only 193 patients were treated with aspirin. In this study, aspirin intake was defined as aspirin ingestion within the past week before surgery. As it is known that the effect of aspirin diminishes after 3 days [18], the percentage of patients with inhibition of platelet aggregation at the time of neuraxial blockade was very low. In a subsequent study [17] with 1035 patients receiving epidural steroid injections, no increased bleeding was reported in a subgroup of 158 patients on aspirin within the last week.

Although these studies appear to support the safety of neuraxial blockade, the number of patients is too low to derive definite conclusions and none was performed in the presence of thromboembolism prophylaxis.

Based on these studies most guidelines consider neuraxial blockade is not contraindicated in the presence of aspirin or NSAIDS if given without concomitant thromboembolism prophylaxis [4–6]. Interpretation of these guidelines differs according to local policies. As thromboembolism prophylaxis is started preoperatively in Europe, antiplatelet therapy is often withheld to avoid dual therapy. In the United States the emphasis has been the opposite, with neuraxial blockade performed in the presence of antiplatelet therapy and initiation of LMWHs only after catheter withdrawal.

What is the evidence of an increased risk of bleeding in the presence of antiplatelet therapy? In patients with myocardial infarction receiving heparin plus aspirin, a twofold increase in major bleeding was observed [19] and aspirin has been identified as an independent risk factor of increased bleeding in patients undergoing coronary artery bypass graft (CABG) or urologic surgery, and tonsillectomies [20,21*], although the effect is usually moderate. In the EXPERT study, antiplatelet therapy increased the risk of major bleeding fivefold. In cases of neuraxial blockade, Ruff and Dougherty [22] described a 2% incidence of spinal epidural hematoma with subsequent paraplegia if a combination of aspirin and heparin was administered within 1 h after lumbar puncture. Stafford-Smith [23] calculated the risk of spinal epidural hematoma after epidural anesthesia as 1:150 000 in the presence of aspirin, 1:62 000 in the presence of unfractionated heparin, and 1:8500 in the presence of combined aspirin and heparin therapy.

By contrast, aspirin withdrawal prior to surgery may be hazardous in patients with coronary artery disease or a previous stroke and should be carefully evaluated. If dual therapy is to be avoided at the time of neuraxial blockade in patients on aspirin, initiation of thromboembolism prophylaxis may be postponed until after surgery and time intervals before catheter removal should be prolonged. This approach would comply with most guidelines.

**ADP antagonists**

Clopidogrel and ticlopidine are thienopyridines that specifically block the platelet P2Y12 ADP receptor irreversibly. Although the inhibition of ADP-induced platelet aggregation is selective, diverse platelet aggregation pathways such as activation by collagen or thrombin are additionally inhibited [24]. While aspirin is usually maintained for life after percutaneous coronary interventions, clopidogrel is given for 3–12 months depending on the type of stent implanted [25]. This dual antiplatelet...
therapy significantly reduces the incidence of recurrent cardiovascular events such as myocardial infarction, stroke and death, but also causes an increased bleeding risk. Clopidogrel has replaced ticlopidine in most indications due to a lower incidence of thrombocytopenia and aplastic anemia.

In patients undergoing cardiac surgery, an increased use of transfusions and a five to 10-fold increase in reexploration rates have been reported, underscoring the potential of clopidogrel to induce severe coagulation defects [26,27]. A higher bleeding tendency has also been described in other types of surgery and several cases of spinal epidural hematomas after neuraxial blockade have been reported [28].

In the perioperative period the risk of severe bleeding needs to be weighed against the risk of acute stent thrombosis with subsequent myocardial infarction. Mortality may be excessively high if clopidogrel is withdrawn within the first 6 weeks after stent implantation and elective surgery should not be performed during this period [29]. Recovery of normal platelet function is observed 6–7 days after clopidogrel cessation [30] and a time interval of 7 days after clopidogrel ingestion and 10–14 days after ticlopidine ingestion is advised by most guidelines [4,5].

**Glycoprotein IIb/IIIa antagonists**

Glycoprotein IIb/IIIa antagonists are administered to patients at high risk of immediate coronary artery occlusion undergoing percutaneous coronary artery interventions. Frequently applied drugs include abciximab, which strongly binds to platelet membrane glycoprotein IIb/IIIa receptors and inhibits platelet aggregation for more than 12 h. If abciximab is administered within 12 h of CABG, chest tube drainage and transfusion requirements are significantly increased [31]. The effects of tirofiban and eptifibatide on platelet aggregation are of much shorter duration, with platelet function normalizing 2–4 h after the end of infusion.

The addition of these drugs to aspirin and heparin reduces cardiovascular events by 20 per 1000 patients treated, but also increases the risk of major bleeding episodes by as much as 50% [32,33]. Although reduced blood loss was reported in patients undergoing CABG surgery with tirofiban, this refers to the short half-life of tirofiban and to the particular situation of cardiopulmonary bypass [34], when inhibition of platelet function may lead to improved platelet preservation while on cardiopulmonary bypass and thus improved platelet function postoperatively and may not be transferred to other procedures. As these drugs are generally given in combination with aspirin, clopidogrel, and heparin in a patient population that presents for emergency CABG surgery only, recommendations on time intervals are futile. If there is time to postpone surgery, time intervals will not be derived from the pharmacology of the glycoprotein IIb/IIIa antagonists alone, but also from concurrent drugs administered (clopidogrel, LMWHs) as well as from the planned procedure (full heparinization on cardiopulmonary bypass). Most guidelines strongly advise against neuraxial blockade in the presence of a multitude of antithrombotic and antiplatelet agents.

**Herbal medicine**

Although herbal medicines are not a new class of drugs the frequency and underreporting of their intake have raised major concerns about their safety in patients undergoing surgery. Some of the more commonly used herbal remedies such as gingko, garlic and ginseng have been shown to interact with platelet aggregation in vitro or to interact with the anticoagulant effect of coumadines [35]. Reports vary from isolated thrombocytopenia, inhibition of platelet aggregation, and prolonged postoperative bleeding to a case of spontaneous epidural hematoma [36–38].

Compared with the few data available on the efficacy of herbal medicine, there are even fewer studies evaluating their side effects. In a recent randomized controlled study [39] on the anticoagulant effects of ganoderma lucidum the authors reported no significant drug interaction in healthy volunteers. A multitude of different ingredients and frequent contamination with heavy metals or conventional drugs such as NSAIDs, however, make their evaluation in randomized controlled trials nearly impossible [38].

Most case reports have arisen from untoward events in the presence of herbal medicine intake; however, given the high frequency of herbal medicine use, this may not necessarily reflect a causal relationship. In one of the largest case series [40] on side effects of herbal remedies, there were four cases of thrombocytopenia associated with gingko biloba ingestion out of 8985 cases reported and none was involved in a fatal outcome, indicating that bleeding may be a rare event. In a case series [41] of pediatric patients no critical incident of severe bleeding was reported, with heavy metal poisoning leading by far the list of side effects.

In summary, there is little evidence to indicate that herbal medicine increases the risk of bleeding complications and should be stopped in advance before surgery.

**Cardiac surgery**

Results of thoracic epidural analgesia in patients undergoing cardiac surgery are still equivocal, with most studies showing an improvement in pulmonary function, improved analgesia and fewer arrhythmias, but no
reduction in length of intensive care unit stay, time to discharge, myocardial infarction or mortality [42,43]. These potential benefits need to be carefully weighed against the potential catastrophic outcome of high thoracic spinal epidural hematoma [44**]. Ho et al. [45] estimated the maximum probability of spinal epidural hematoma formation in patients undergoing cardiac surgery with full heparinization to be 1:1500 with epidural techniques. If full anticoagulation on cardiopulmonary bypass is planned, guidelines advocate performing the block the day before surgery or to delay surgery in cases of a traumatic puncture [4,5]. In many cardiac surgical centers aspirin is continued in conjunction with postoperative therapeutic heparinization, increasing the risk for catheter removal. Close neurologic surveillance in these patients is often delayed if patients are not directly extubated in the operating room, reducing the chance to perform early hematoma evacuation and thus the likelihood of full neurologic recovery.

Single-dose spinal opioid analgesia may decrease the risk of bleeding complications, but needs to be performed directly before surgery and not in advance. The lack of continuously administered local anesthetics limits the advantages to modestly improved analgesia [42].

In view of the limited benefits of neuraxial blockade in cardiac surgery with no major effect on morbidity and mortality and considering the significant risks, it is disputable whether spinal and epidural techniques are justified at all or should be abandoned in this specific patient population [44**].

Peripheral nerve blocks

Peripheral nerve blocks cause less serious complications and are devoid of the risk of spinal epidural hematoma; existing guidelines for neuraxial blockade, therefore, have not been routinely applied. Nevertheless, wound hematomas may also significantly contribute to morbidity and mortality and several case reports on extensive retroperitoneal hematoma with lumbar plexus block under enoxaparine or clopidogrel have been published. In one of these cases [46], the lumbar plexus catheter was removed 1.5 h after enoxaparine administration. Although most cases dissolved without permanent neurologic damage, bleeding complications caused significant patient discomfort, made transfusion of packed cells necessary, led to reversible sensory and motor deficits, and acute renal failure, prolonged the length of hospital stay and caused death from hemorrhage [46–48]. The German Society of Anesthesiology and Intensive Care recently issued guidelines on thromboembolism prophylaxis and peripheral nerve blocks [49]. Performance of superficial peripheral nerve blocks such as axillary plexus block, femoral nerve block or distal sciatic nerve block are not considered a contraindication in the presence of aspirin or anticoagulants; whenever possible, however, time intervals established for neuraxial blockade between LMWH administration and catheter insertion or withdrawal should be followed. The latter especially applies for catheter withdrawal as there is no reason to remove any catheter at the time of maximum anticoagulant activity. Due to the severe consequences of retroperitoneal hematoma, patients receiving a lumbar plexus block should be treated like patients receiving a neuraxial blockade. Similarly, the Austrian Society advises stopping thromboembolism prophylaxis and platelet aggregation inhibitors, including aspirin, in cases of deep peripheral nerve blocks with difficult access to arterial vessels, such as interscalene nerve blocks, supra and infracavicular nerve blocks, and lumbar sympathetic blockade [8].

Conclusion

The risk of spinal epidural hematoma is probably much higher than previously thought, with recent case series estimating the prevalence as high as 1:20000 after epidural anesthesia, with an even higher prevalence in orthopedic patients. Bleeding occurs more frequently in patients on a multitude of antithrombotic and antiplatelet drugs and may be especially high in patients with impaired renal function. A careful risk–benefit analysis weighing the potential for bleeding against the risk of infarction and thromboembolism in the case of discontinuation of antiplatelet and antithrombotic therapy is therefore required. Other measures taken to reduce this risk include the establishment of guidelines for neuraxial blockade and an increased use of peripheral nerve blocks. For the latter, guidelines are now being developed with special attention paid to deep peripheral blocks and lumbar sympathetic block, as bleeding after deep blocks may significantly increase morbidity and mortality.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 583).


Regional anaesthesia


45 This invaluable editorial on the risks and benefits of neuraxial blockade should be read by anyone performing neuraxial blockade in cardiac surgery.

46 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; 17:551–555.


