Background: When giving anticoagulants and inhibitors of platelet aggregation either prophylactically or therapeutically, physicians face the challenge of protecting patients from thromboembolic events without inducing harmful bleeding. Especially in the perioperative period, the use of these drugs requires a carefully balanced evaluation of their risks and benefits. Moreover, the choice of drug is difficult, because many different substances have been approved for clinical use.

Method: We selectively searched for relevant publications that appeared from 2003 to February 2013, with particular consideration of the guidelines of the European Society of Cardiology, the Association of Scientific Medical Societies in Germany (AWMF), the American College of Cardiology, and the American Heart Association.

Results: Vitamin K antagonists (VKA), low molecular weight heparins, and fondaparinux are the established anticoagulants. The past few years have seen the introduction of orally administered selective inhibitors of the clotting factors IIa (dabigatran) and Xa (rivaroxaban, apixaban). The timing of perioperative interruption of anticoagulation is based on pharmacokinetic considerations rather than on evidence from clinical trials. Recent studies have shown that substituting short-acting anticoagulants for VKA before a procedure increases the risk of bleeding without lowering the risk of periprocedural thromboembolic events. The therapeutic spectrum of acetylsalicylic acid and clopidogrel has been broadened by the newer platelet aggregation inhibitors prasugrel and ticagrelor. Patients with drug eluting stents should be treated with dual platelet inhibition for 12 months because of the risk of in-stent thrombosis.

Conclusion: Anticoagulants and platelet aggregation inhibitors are commonly used drugs, but the evidence for their perioperative management is limited. The risks of thrombosis and of hemorrhage must be balanced against each other in the individual case. Anticoagulation need not be stopped for minor procedures.

SUMMARY

The perioperative management of treatment with anticoagulants and platelet aggregation inhibitors is mainly indicated for patients with cardiovascular diseases. In this review article, we will discuss the main drugs of these two types and their individual properties, with special consideration of their perioperative use. Special attention will be devoted to the newer anticoagulants and newer platelet aggregation inhibitors in order to facilitate the use of these drugs in routine clinical practice.

Methods

We selectively searched the Medline database for publications that appeared from 2003 to February 2011 dealing with the perioperative management of patients being treated with anticoagulants and/or platelet aggregation inhibitors, with special attention to prospective randomized trials and cohort studies with a control group. Special consideration was also given to the recommendations of the European Society of Cardiology, the Association of Scientific Medical Societies in Germany (AWMF), the American College of Cardiology, and the American Heart Association.

Anticoagulants

Vitamin K antagonists

Vitamin K antagonists (VKA) inhibit the production of vitamin K–dependent clotting factors in the liver. The two vitamin K antagonists that have been approved for use in Germany are phenprocoumone and warfarin. The main indication for VKA is the prevention of thromboembolic events in patients with atrial fibrillation, prosthetic heart valves (for three months, as a rule, after the implantation of a tissue [biological] valve or indefinitely after the implantation of a mechanical valve), deep vein thrombosis, and/or pulmonary embolism. The intensity of anticoagulation is reflected by the INR value (international normalized ratio), where 1.0 is the normal value and the typical target range for anticoagulation is 2–3. More intensive anticoagulation may be needed in some situations, e.g., after the implantation of a mechanical mitral valve replacement (INR 2.5–3.5) (1). Any type of surgery where the risk of bleeding is low, including all outpatient surgical and dental
The CHA2DS2-Vasc score is used to estimate the risk of thromboembolism in patients with atrial fibrillation. A score of 1 or higher implies that oral anticoagulation with a vitamin K antagonist or a new oral anticoagulant is indicated for life, regardless of the clinical pattern of atrial fibrillation (paroxysmal, persistent, or permanent). Women under age 65 with no further risk factors (other than being female) are an exception: if their formal CHA2DS2-Vasc score is 1, anticoagulation is not indicated, and acetylsalicylic acid is not indicated either (3).

If interrupting the VKA is needed, and if there is time to plan it, then a subtherapeutic INR is reached at some time from 4 to 7 days after the drug is stopped. Bridging is performed in the following ways, as indicated:

- with low molecular weight heparin (LMWH) by subcutaneous injection, in patients with atrial fibrillation or status post deep vein thrombosis/pulmonary embolism
- with unfractionated heparin (UFH) IV, in patients with mechanical heart valves—this can only be done on an inpatient basis; alternatively, subcutaneous LMWH (1).

The decision whether to perform bridging treatment depends on the risk of thromboembolic events; for example, in patients with atrial fibrillation, the decision can be made on the basis of the CHA2DS2-Vasc score. For low-risk patients, oral anticoagulation can be interrupted for as long as 7 days (Figure 1) (3, 6). For patients with artificial heart valves, the type and position of the valve and the presence of risk factors (atrial fibrillation in addition to valvular heart disease) determine the thromboembolic risk (7). For patients who have had a deep vein thrombosis and/or pulmonary embolism, the time since the event is the most important factor in risk assessment (8).

In cases where the effect of VKA must be antagonized, 1–2 mg of vitamin K should be given orally or intravenously. Normalization of the INR usually occurs within 12 hours of intravenous administration or 24 hours of oral administration (1). Higher doses, e.g., 5–20 mg, should be considered in cases of active bleeding or a very high INR (> 9) (9). The preferred agents for reversing oral anticoagulation in emergency situations are prothrombin complex concentrate (PCC) or, alternatively, fresh frozen plasma (FFP). Procedures with a high risk of bleeding can be performed as long as the INR is below 1.5 (1).

**Unfractionated heparin**

Unfractionated heparin (UFH) is a mucopolysaccharide derived from porcine intestinal mucosa. When it is given subcutaneously, its resorption and the resulting plasma concentration of heparin are hard to predict; thus, where subcutaneous administration is indicated, LMWH is usually given instead of UFH (8). When UFH is given intravenously (e.g., to patients with mechanical heart valves or in intensive-care medicine), the activated partial thromboplastin time (aPTT) must be checked at least twice daily. In case of hemorrhagic complications, or for planned reversal of the anticoagulant effect (as for patients on a heart-lung machine), protamine is given. One unit of protamine antagonizes one unit of UFH. The activated clotting time (ACT) can be measured at the bedside as a practical method of monitoring the effect of UFH. Apparatus of this type is available in every cardiac operating room and catheterization suite (10).

The main, life-threatening complication of UFH treatment is thrombocytopenia (HIT), which results from the formation of antibodies against platelet factor 4. Micro- and macroscopic thrombosis in all of the body’s organs leads to peripheral platelet consumption and, in turn, to a drop in the platelet count. Organ failure can be prevented only by the immediate discontinuation of UFH and the immediate administration of another anticoagulant (11). The approved drugs for this purpose in Germany are argatroban (only for intravenous use) and danaparoid (for either subcutaneous or intravenous use). Fondaparinux is not recommended in such situations, but it can be considered for use in patients who newly require anticoagulation and have had HIT because of UFH treatment in the past. The efficacy of anticoagulation in patients who have had HIT must be checked frequently by an experienced team; the efficacy of argatroban is guided by aPTT values. Intravenously administered argatroban raises the INR by about one point, making the later reinstatement of VKA treatment more difficult (11, 12).

**Low molecular weight heparins**

Low molecular weight heparins (LMWH) are drugs that are mainly used for thrombosis prophylaxis. Anti-Xa tests are generally not needed when patients are treated with LMWH. The dose must be adjusted in patients with renal failure to prevent accumulation of the drug. Especially in older patients, the creatinine
clearance must be calculated, for example by the MDRF formula (where MDRF stands for “Modification of Diet in Renal Disease”), to enable a decision whether dose adjustment is needed, as it generally is when the creatinine clearance is less than 30 mL/min. Protamine has no more than a limited ability to antagonize the effect of LMWH. For example, protamine reduces the effect of enoxaparin by only 50–70% (8).

If complete interruption of anticoagulation with LMWH is needed perioperatively and the patient’s renal function is normal, the last dose of LMWH should be given two days before surgery and the drug should be restarted the day after the procedure. The dose may also need to be lowered after procedures with a high risk of bleeding. If the patient’s renal function is markedly impaired, the LMWH-free interval should be longer than 48 hours (8).

**Fondaparinux**

Fondaparinux inhibits activated clotting factor X selectively and indirectly (via antithrombin). It is approved for both the prophylaxis (1.5–2.5 mg/d) and the treatment (5–10 mg/d, depending on body weight) of deep vein thrombosis and/or pulmonary embolism, as well as in acute coronary syndrome (2.5 mg/d). Because of its long half-life (ca. 17 hours), a single subcutaneous injection per day suffices, but the risk of accumulation should be kept in mind as the drug is mainly renally eliminated. Fondaparinux is contraindicated for patients with a glomerular filtration rate (GFR) less than 30 mL/min (for therapeutic use) or less than 20 mL/min (for prophylactic use). For prophylactic use in patients whose GFR is between 20 and 50 mL/min, the dose must be lowered to 1.5 mg SC daily. These rules apply to the perioperative situation in particular. Depending on the patient’s renal function, fondaparinux should be discontinued 36 to 42 hours before any procedure that carries the risk of hemorrhage, or before spinal anesthesia (Table 1) (8).

**New oral anticoagulants**

The new oral anticoagulants (NOAC) dabigatran, rivaroxaban, and apixaban were initially approved only for the prevention of thromboembolism in patients undergoing elective hip or knee replacement surgery, but have since been used in higher doses for the treatment of deep vein thrombosis and pulmonary embolism (only rivaroxaban) and for stroke prevention in patients with atrial fibrillation (Table 2).

There has been only limited experience to date concerning the risk of perioperative bleeding when these substances are given therapeutically. The recommended intervals for perioperative discontinuation of treatment are based on pharmacokinetic considerations and have not been validated by clinical trials. There has also been limited experience with spinal anesthesia for surgery without interruption of therapeutic NOAC administration (with any of the three NOAC). This should be done only with utmost caution and after careful evaluation of the risks and benefits (Tables 1 and 2 and Box).

**Dabigatran**

The manufacturer states that dabigatran should be temporarily discontinued without bridging treatment two days before surgery in patients with normal renal function and a moderate to high risk of perioperative bleeding, two to three days before surgery in patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interval between last dose and puncture or catheter removal (hours)</th>
<th>Interval between puncture or catheter removal and next dose (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH (prophylactic)</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>UFH (therapeutic)</td>
<td>4–6</td>
<td>1</td>
</tr>
<tr>
<td>LMWH (prophylactic)</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>LMWH (therapeutic)</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>Danaparoid</td>
<td>if possible, no spinal anesthesia or single-shot technique</td>
<td></td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>36–42</td>
<td>6–12</td>
</tr>
<tr>
<td>Hirudins</td>
<td>8–10</td>
<td>2–4</td>
</tr>
<tr>
<td>Argatroban*</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Vitamin K antagonists</td>
<td>INR &lt;1.4</td>
<td>after catheter removal</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>not recommended, or single shot</td>
<td>6 (after single shot)</td>
</tr>
<tr>
<td>Rivaroxaban in a prophylactic dose</td>
<td>22–26</td>
<td>4–6</td>
</tr>
<tr>
<td>Apixaban</td>
<td>26–30</td>
<td>4–6</td>
</tr>
</tbody>
</table>
with moderately impaired renal function (creatinine clearance 50–80 mL/min), and four days before surgery in patients with severely impaired renal function. Dabigatran can be removed by hemodialysis in an emergency (dabigatran product information).

Rivaroxaban
The manufacturer of rivaroxaban recommends temporarily discontinuing the drug 24 hours before invasive procedures in general, and 36 to 48 hours before surgery with a high bleeding risk or any surgery involving the central nervous system (13).

Apixaban
Apixaban should be stopped at least 48 hours before planned surgery or invasive procedures with a moderate to high risk of bleeding. If the risk of bleeding is low, apixaban can be stopped 24 hours beforehand (apixaban product information).

Antagonism of new oral anticoagulants
Laboratory values are harder to interpret under NOAC treatment, as these drugs affect the values of traditional coagulation tests (INR, aPTT) without necessarily altering clotting function in corresponding ways. Many clinical laboratories now use specific tests to monitor treatment with rivaroxaban (Anti-Xa assay) and dabigatran (modified thrombin time, e.g., Hemoctlot™ thrombin inhibitor assay).

The available initial reports on antagonism of the NOAC are derived from animal experiments and tests on human volunteers. In humans, the administration of prothrombin complex concentrate (PCC) normalizes the rivaroxaban-induced elevation of the INR. PCC was not found to normalize the aPTT after dabigatran administration (14), although animal experiments have shown that PCC can lessen the size and lethality of a dabigatran-induced cerebral hemorrhage (15).

As patients taking VKA or NOAC often cannot supply any information in an emergency and PCC is widely available in emergency and intensive-care medicine, it would seem appropriate to give 30–50 IU/kg body weight of PCC to antagonize anticoagulation in patients who sustain severe hemorrhagic complications while taking any kind of oral anticoagulant. Antagonism with recombinant factor VIIa can also be considered (16). All patients taking NOAC, like those taking VKA, should be given an anticoagulation card and should carry it on their person at all times.

Platelet aggregation inhibitors

Acetylsalicylic acid
Acetylsalicylic acid (ASA) irreversibly inactivates cyclooxygenase 1 (COX-1), thereby lessening the formation of thromboxane A2 and inhibiting platelet aggregation. The effect sets in within ten minutes and persists for the entire lifetime of platelets, i.e., about

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications (dosages)</strong></td>
<td>Thrombosis prophylaxis (110 mg qd perioperatively, 220 mg qd from postoperative day 1)</td>
<td>Thrombosis prophylaxis (10 mg qd)</td>
<td>Thrombosis prophylaxis (2.5 mg bid)</td>
</tr>
<tr>
<td></td>
<td>Secondary prophylaxis in patients with atrial fibrillation (150 mg bid; 110 mg bid for patients over age 80 or with renal impairment, and for patients simultaneously taking amiodarone or verapamil)</td>
<td>Secondary prophylaxis in patients with atrial fibrillation (20 mg qd; 15 mg qd for patients with creatinine clearance between 30 and 50 mL/min)</td>
<td>Secondary prophylaxis in patients with atrial fibrillation (5 mg bid for therapeutic anticoagulation in patients with atrial fibrillation; reduce to 2.5 mg bid in patients with serum creatinine concentration &gt;1.5 g/dL (133 μmol), over age 80, or weighing less than 60 kg)</td>
</tr>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Factor Ila (thrombin) inhibitor</td>
<td>Factor Xa inhibitor</td>
<td>Factor Xa inhibitor</td>
</tr>
<tr>
<td><strong>Half-life (hours)</strong></td>
<td>12–17</td>
<td>9–13</td>
<td>9–14</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>80% renal</td>
<td>66% renal</td>
<td>25% renal</td>
</tr>
<tr>
<td><strong>Main contraindications</strong></td>
<td>GFR &lt;30 mL/min</td>
<td>GFR &lt;15 mL/min; severe hepatic dysfunction</td>
<td>GFR &lt;15 mL/min; severe hepatic dysfunction</td>
</tr>
</tbody>
</table>

GFR, glomerular filtration rate
eight days. The common dose for long-term treatment is 100 mg daily.

**P2Y₁₂ inhibitors**

This group of drugs includes the irreversible thienopyridines clopidogrel and prasugrel as well as ticlopidine, which is now only rarely used (17).

Clopidogrel is a prodrug with low bioavailability. When a dose of it is taken orally and resorbed, about 85% of the amount ingested is rapidly converted to inactive metabolites through the catabolic activity of esterases, and only the remainder reaches the liver, where it is biologically activated. The bioactivation of clopidogrel can be blocked by proton pump inhibitors such as omeprazole. At the usual dose of 75 mg per day, the therapeutic efficacy of clopidogrel sets in within a few days; this interval can be shortened to a few hours by the administration of a loading dose (300–600 mg) (18).

Prasugrel was approved in Europe in 2009. This substance, given at a loading dose of 60 mg followed by a maintenance dose of 10 mg daily, has been found to lower the incidence of ischemic events significantly for patients undergoing percutaneous coronary interventions in comparison to clopidogrel, though with a higher rate of hemorrhage (19-21). In contrast, a trial in patients undergoing conservative treatment of acute coronary syndrome (ACS) showed no advantage of prasugrel over clopidogrel (22).

Ticagrelor is a new, reversible P2Y₁₂ inhibitor that is not a thienopyrine, but belongs rather to the group of the cyclopentyl-triazolo-pyrimidines. In the approval trial, ticagrelor prevented ischemic coronary endpoints more effectively than clopidogrel but led to a higher rate of major bleeding not related to coronary-artery bypass grafting (23). Because of its short half-life, ticagrelor is taken in a dose of 90 mg bid (loading dose, 180 mg). Its main active metabolite has a longer half-life, and its biological efficacy can therefore last up to five days (24). Furthermore, hemorrhagic complications of ticagrelor are harder to treat with platelet concentrates, because, unlike the thienopyridines, ticagrelor is apparently released when platelets are consumed and can then bind again to transfused platelets (25).

**Perioperative management of monotherapy with a platelet aggregation inhibitor**

ASA elevates the risk of a hemorrhagic complication during surgery by 50% but does not increase operative mortality (26). Therefore, in its current guidelines, the European Society of Cardiology (ESC) recommends in general that ASA for secondary prevention should not be discontinued perioperatively (27). Nonetheless, for intracranial, intraspinal, and intraocular procedures, even small hemorrhages can cause significant morbidity, so that temporarily discontinuing ASA would seem to be necessary. ASA should be stopped seven days before surgery to be sure that no anti-aggregatory effect persists (26).

ASA that is taken for primary prevention can be interrupted for surgery (28, 29). According to the current recommendations of the German Society of Anaesthesiology and Intensive Care Medicine (DGAI,

### BOX

**Risk factors for hemorrhage during treatment with anticoagulants (from Ref. 22)**

- **Morbidity**
  - renal impairment (creatinine clearance <50 mL/min)
  - thrombocytopenia or platelet dysfunction
  - acute gastrointestinal ulcers, gastritis, gastro-esophageal reflux disease
  - bacterial endocarditis

- **Concurrent medication**
  - inhibitors of platelet function (acetylsalicylic acid [ASA], P2Y₁₂ inhibitors, other drugs)
  - non-steroidal anti-inflammatory drugs (NSAID)
  - selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI)

- **Medical history**
  - age >80
  - recent intracranial hemorrhage
  - recent major trauma
  - recent intracranial, intraspinal, or intraocular surgery

### FIGURE 2

The perioperative management of platelet inhibition depends on the magnitude of the risks of thrombosis and hemorrhage. These risks are in inverse relation. The triangles indicate the extent of the risk. The blue arrows represent continued administration of platelet aggregation inhibitors, while the red circles with a diagonal line through them represent interruption of their administration. The greater the risk of thromboembolism, the more necessary it is to continue giving the drugs. Dual inhibition of platelet aggregation can be interrupted for procedures with a high risk of bleeding and a low risk of thrombosis (modified from e12).
Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin, the daily intake of 100 mg ASA alone (without simultaneous thrombosis prophylaxis) is not a contraindication for neuraxial blocks (30).

Management of dual inhibition of platelet aggregation

The simultaneous intake of ASA and a P2Y₁₂ inhibitor—usually by patients who have received a coronary stent—can cause major problems in the perioperative period (Figure 2).

According to the current recommendations, patients with a coronary stent must take ASA for life and a P2Y₁₂ inhibitor either for at least six weeks (bare metal stents [BMS]) or for at least twelve months (drug eluting stents [DES]) (31). Dual inhibition of platelet aggregation is also recommended for twelve months in patients who have had an acute coronary syndrome.

About 5% of patients in whom coronary stents are implanted have non-cardiac surgery of some kind in the first year thereafter (32). Thus, in Germany, about 12,500 operations are performed each year on patients with coronary stents that have been in place for less than one year (33).

During this period, stent thrombosis is a worrisome risk. Stent thrombosis is a sudden thrombotic occlusion of a coronary stent leading to myocardial infarction, which is fatal in up to 75% of cases (34, 35).

The risk of stent thrombosis depends on a number of risk factors, including the type of stent and the time since implantation (ca. 2% in the first 30 days). The main risk factor for stent thrombosis is the premature discontinuation of dual inhibition of platelet aggregation, which raises the risk as much as ninety-fold (hazard ratio 89.9) (34, 36).

In patients who receive dual inhibition of platelet aggregation as recommended and do not undergo any surgery, the frequency of early stent thrombosis (in the first 30 days) is 0.7%, and the frequency of late stent thrombosis (up to one year) is 0.4% (37). Patients whose dual inhibition of platelet aggregation is temporarily interrupted so that surgery can be performed have a cumulative incidence of stent thrombosis of 4–5% (38–40).

The timing of surgery under dual inhibition of platelet aggregation

Elective surgery should be postponed until dual inhibition of platelet aggregation has been given for the entire recommended duration of treatment and then replaced with monotherapy (usually with ASA) (27, e1). This implies that elective procedures should be performed no sooner than three months after BMS implantation or twelve months after DES implantation (Figures 3a and b) (27). The later an operation is performed after stent implantation, the lower the cardiac risk (e2, e3).

When surgery must be performed as an emergency, the anti-aggregatory medication cannot be changed and the main emphasis lies rather on the management of any hemorrhagic complications that may arise.
concentrates generally need to be given, possibly in combination with desmopressin (DDAVP) and/or antifibrinolytic drugs (e4). Whatever type of stent is present, emergency surgery is associated with a higher rate of major cardiac complications (a 1.7-fold increase for urgent surgery and a 3.2-fold increase for emergency surgery) (e2, e9).

**Preoperative issue: Should dual inhibition of platelet aggregation be interrupted before surgery, or continued?**

If an operation cannot be postponed and must be performed during the critical period, it is recommended that dual inhibition of platelet aggregation be continued perioperatively (27, e1, e6). If this is unacceptable from the surgical point of view, thienopyridines should be stopped seven days before surgery (30); ticagrelor, according to current recommendations, five days before surgery (29, e7).

In view of the high risks of both hemorrhage and thromboembolism, the effective interruption of the inhibition of platelet aggregation should be restricted to a minimal period of a few hours around the time of the surgical procedure. Preoperative bridging with short-acting drugs cannot be performed on a routine basis. In some cases, bridging with GPIIb/IIIa inhibitors, under continuous monitoring, can be considered in centers that have experience with this treatment (e9, e10).

**Postoperative issue: When should the dual inhibition of platelet aggregation be restarted?**

If the dual inhibition of platelet aggregation has been interrupted for surgery, P2Y12 inhibitors must be restarted as soon as possible after the operation. In general, the preoperative dose is given again, but the administration of a loading dose can be considered in order to regain the full effect of the drug more rapidly (e11).

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Dr. Schilling has received lecture honoraria from Sanofi-Aventis and Bayer.

Prof. Zwilliger states that he has no conflict of interest.

**REFERENCES**


REVIEW ARTICLE

The Perioperative Management of Treatment with Anticoagulants and Platelet Aggregation Inhibitors

Axel Schlitt, Csilla Jámbor, Michael Spannagl, Wiebke Gogarten, Tom Schilling, Bernhard Zwissler

eREFERENCES


