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REVIEW

# Antiplatelet and Anticoagulant Drugs in Interventional Radiology

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**Abstract** In treating peripheral arterial disease, a profound knowledge of antiplatelet and anticoagulative drug therapy is helpful to assure a positive clinical outcome and to anticipate and avoid complications. Side effects and drug interactions may have fatal consequences for the patient, so interventionalists should be aware of these risks and able to control them. Aspirin remains the first-line agent for antiplatelet monotherapy, with clopidogrel added where dual antiplatelet therapy is required. In case of suspected antiplatelet drug resistance, the dose of clopidogrel may be doubled; prasugrel or ticagrelor may be used alternatively. Glycoprotein IIb/IIIa inhibitors (abciximab or eptifibatide) may help in cases of hypercoagulability or acute embolic complications. Desmopressin, tranexamic acid, or platelet infusions may be used to decrease antiplatelet drug effects in case of bleeding. Intraprocedurally, anticoagulant therapy treatment with unfractionated heparin (UFH) still is the means of choice, although low molecular-weight heparins (LMWH) are suitable, particularly for postinterventional treatment. Adaption of LMWH dose is often required in renal insufficiency, which is frequently found in elderly patients. Protamine sulphate is an effective antagonist for UFH; however, this effect is less for LMWH. Newer antithrombotic drugs, such as direct thrombin inhibitors or factor X inhibitors, have limited importance in periprocedural treatment, with the exception of treating patients with heparin-induced thrombocytopenia (HIT). Nevertheless, knowing pharmacologic properties of the newer drugs facilitate correct bridging of patients treated with such drugs. This article provides a comprehensive overview of antiplatelet and anticoagulant drugs for use before, during, and after interventional radiological procedures.

**Keywords** Anticoagulation · Antiplatelet therapy · Drugs · Interventional angiography

## Introduction

Interventional treatment of peripheral arterial disease (PAD) is intrinsically coupled with the administration of antiplatelet and antithrombotic drugs. Knowledge of pharmacologic properties, including side effects, interactions with other drugs, and specific considerations in treating elderly patients, are mandatory to optimize the outcome of interventional treatment.

In this article, properties and indications of antiplatelet and anticoagulant drugs, as well as combinations of drugs and possibilities of antagonist agents in case of bleeding, are described. In addition, newer antiplatelet and anticoagulant drugs are presented that are not used routinely in interventional angiography. Knowledge of the properties of these drugs is crucial in bridging patients to standard therapy.

## Platelet Antagonists

Angioplasty is associated with vascular injury, atheromatous plaque disruption, platelet activation, and, at times, distal embolisation. Foreign materials, such as wires, catheters, and stents, contribute to platelet activation.

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The InterSociety Consensus for the Management of Peripheral Arterial Disease (TASC II) guidelines recommend antiplatelet therapy to be started before surgery and continued as adjuvant pharmacotherapy after endovascular or surgical procedures [1]. Unless subsequently contraindicated, this should be continued indefinitely.

Aspirin (ASA) is the first-line antiplatelet agent, followed by ticlopidine, clopidogrel, and prasugrel as representatives of the first, second, and third generation of thienopyridines. Ticlopidine compared with clopidogrel has an inferior side effect profile and currently acts as an alternative drug in case of clopidogrel intolerance.

Prasugrel, a more recent thienopyridine, shows advantages compared with clopidogrel concerning its antithrombotic effects and individual response in percutaneous coronary angioplasty [2]. Other clinical trials comparing prasugrel versus clopidogrel demonstrated a clinical benefit only for a certain group of patients, with decreased adverse vascular events but mild or moderately increased bleeding rates [3, 4]. The possible advantages of prasugrel compared with clopidogrel include a faster onset of action, decreased interpatient variability, and more potent platelet inhibition. For patients with high on-clopidogrel platelet reactivity, prasugrel may be the most reasonable alternative drug [5].

Ticagrelor is a new nonthienopyridine antiplatelet drug with rapid onset of action and partial recovery of platelet aggregation within 12 h after discontinuation of treatment. In the Platelet Inhibition and Patient Outcomes (PLATO) study, the combination of ASA and ticagrelor significantly decreased the risk of death from cardiovascular causes versus clopidogrel plus ASA in patients with acute coronary syndrome [6]. However, compared with clopidogrel, ticagrelor was associated with significantly greater rates of dyspnoea.

Whereas ASA and thienopyridines are used in long-term administration for secondary prevention of adverse vascular events, the potent glycoprotein (GP) IIb/IIIa receptor antagonists, such as tirofiban, eptifibatide, or abciximab, are given only during the periprocedural period.

## ASA

Today it is routine practice to have patients on ASA before, during, and after the procedure [7]. This drug, considered the prototypic platelet antagonist, has been available for more than a century and currently represents a mainstay both in the prevention and treatment of vascular events, including stroke, myocardial infarction (MI), peripheral vascular occlusion, and sudden death. In the Antithrombotic Trialists' meta-analysis [8] ASA in high-risk patients decreased the combined outcome of any serious vascular event by approximately 25%, nonfatal MI by approximately 33%, nonfatal stroke by 25%, and vascular mortality by 16% with no apparent adverse effect on mortality attributable to other causes.

### *ASA Mechanism of Action*

ASA is a cyclooxegenase antagonist. It exerts its antiplatelet effect by irreversibly acetylating a key serine moiety (serine 530) of cyclooxygenase-1 (COX-1) and inactivating it, thus impairing prostaglandin metabolism and thromboxane $A_2$ synthesis [9–12]. Because ASA more selectively inhibits COX-1 activity (found predominantly in platelets) than COX-2 activity (expressed in tissues after an inflammatory stimulus), its ability to prevent platelet aggregation, compared with the drug's anti-inflammatory effects, is seen at relatively low doses.

ASA's effect is transient in endothelial cells because ASA plasma half-life is short, and the constitutive enzyme regenerates rapidly. In platelets, which have no nuclei and cannot resynthesize mRNA, this effect is irreversible and lasts during the entire platelets' circulating life span.

### *ASA Pharmacology*

After oral ingestion, ASA is promptly absorbed, achieving peak serum levels within 15–20 min and platelet inhibition within 40–60 min. Despite the drug's rapid clearance, platelet inhibition persists for the platelet's life span ($7 \pm 2$ days). Because 10% of circulating platelets are replaced every 24 h, platelet activity returns toward normal ($\geq$50% activity) within 5–6 days of the last ASA dose [13, 14].

### ASA Adverse Effects

The adverse-effect profile of ASA is determined by dose, duration of administration, associated peptic ulcer disease, hemostatic abnormalities, and concomitant use of other antithrombotic agents. ASA is usually well tolerated when given in low doses ($\leq$325 mg daily) for brief periods of time (6–8 weeks) to patients at low risk for bleeding complications.

However, even short-term administration of low-dose ASA may be associated with mucosal abnormalities of the small-bowel mucosa as petechiae and erosions [15]. Enteric coating of ASA has not been shown to decrease the likelihood of adverse effects involving the gastrointestinal (GI) tract.

With long-term use, as in atherosclerotic disease, indigestion occurs often (>1/10) and vomiting or nausea occur less often (>1/100). Gastric bleeding, anemia, and allergic reactions occur occasionally (>1/1000). ASA hypersensitivity may be manifested as acute asthma, urticaria, angioedema, or as a systemic anaphylactoid reaction [16].

Desensitization can be performed safely in selected patients [17]. ASA should not be routinely used in children (Reye syndrome).

### *ASA Administration in Clinical Practice*

The positive effects of ASA are determined by the absolute risk of vascular events. Low-risk patients, i.e. healthy individuals without predisposing risk factors for vascular disease benefit modestly, although those at high risk (unstable angina, previous MI, stroke) benefit considerably [18]. A risk-based approach to ASA administration is recommended to circumvent adverse effects.

### *ASA Dosing*

Dosing data are largely based on cardiologic studies. In clinical practise, ASA is given per oral ingestion but can be also given intravenously. Low-dose ASA (75–162 mg [oral] daily) appears to be an effective antiplatelet regimen for long-term use [8], but in the acute setting an initial loading dose of 300–325 mg ASA should most likely be used. When ASA is administered with other antiplatelet agents or with anticoagulants, it is reasonable to use a daily dose of 75–162 mg (rather than 325 mg) to minimize bleeding complications. This strategy is supported by data analysis from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial [19], which showed that in acute coronary syndrome patients, adding clopidogrel to ASA is beneficial regardless of the ASA dose, with bleeding risks increasing at greater ASA doses, with or without clopidogrel, without a concomitant increase in efficacy.

### *ASA Antagonisation*

Because of irreversible inhibition of platelets, no specific antagonist is available. Platelet infusion may work but seldom is needed. The vasopressin antagonist desmopressin, primarily used in the treatment of diabetes insipidus, improves primary hemostasis and is a first-line therapy for moderate von Willebrand factor deficiency or hemophilia [20]. In addition, desmopressin improves congenital or acquired platelet dysfunction. In case of bleeding, 0.2–0.4 desmopressin μg/kg body weight are infused slowly for >30 min as recommended in the patient information leaflet.

### *ASA Response Variability and Failures (ASA Resistance)*

ASA is not universally effective. It still fails to prevent most (at least 75%) serious vascular events in patients with symptomatic atherothrombosis. ASA resistance has been used to describe several different phenomena [21]. One is the inability of ASA to protect patients from ischaemic vascular events, referred to as "clinical ASA resistance." This definition is nonspecific and could apply to any of the after-causes, such as inadequate intake, decreased bioavailability (poor compliance), concurrent intake of certain nonsteroidal anti-inflammatory drugs (e.g. ibuprofen [22, 23]), perhaps preventing the access of ASA to the COX-1 binding site. Moreover, alternative pathways of platelet activation, increased turnover of platelets, and genetic polymorphisms may be involved [13].

ASA resistance has also been used to describe an inability of ASA to produce an anticipated effect on one or more tests of platelet function [21, 24, 25], such as inhibiting biosynthesis of thromboxane, inhibiting platelet aggregation, and causing prolongation of bleeding time. This has been labelled "laboratory ASA resistance." Depending on different laboratory methods, resistance rates from 5 to 50% are found. A prospective study involving 700 patients suggested that poor clinical outcomes in ASA-treated patients are better correlated with platelet hyperreactivity to collagen, ADP, and shear stress rather than with residual COX-1 function [26]. However, the precise qualitative and quantitative abnormalities of platelet function, as well as their clinical relevance, that characterize biochemical ASA resistance have not been established. While awaiting the development of a reliable test and effective treatment for ASA resistance, the most efficient strategy for clinicians to prevent ASA failure is to make sure that the index event was atherothrombotic in origin, use an appropriate dose of ASA, call for a high level of compliance, and avoid combining ASA with competing drugs, such as ibuprofen.

## Clopidogrel

Clopidogrel, a thienopyridine derivate of the second generation, is more potent than the first-generation thienopyridine ticlopidine and more potent than the COX-1-inhibitor ASA [27, 28].

### *Clopidogrel Mechanism of Action*

Clopidogrel is an adenosine diphosphate (ADP) receptor antagonist. It selectively inhibits the binding of ADP to its platelet receptor ($P2Y_{12}$) and the subsequent G-protein-linked mobilization of intracellular calcium and activation of the GP IIb/IIIa complex [29]. The specific receptor has been cloned and is abundantly present on the platelet surface [30]. Clopidogrel has no direct effect on cyclooxegenase, phosphodiesterase, or adenosine uptake.

*Clopidogrel Pharmacology*

Clopidogrel is rapidly absorbed after oral administration. It is extensively metabolized in the liver, with peak plasma levels of the predominantly circulating metabolite occurring approximately 60 min later. Administration with meals does not significantly modify the bioavailability of clopidogrel. Dose-dependent inhibition of platelet aggregation is noted 2 h after a single oral dose, with more significant inhibition achieved with loading doses (≥300 mg) by approximately 6 h. Repeated doses of 75 mg/d inhibit adenosine diphosphate-mediated aggregation, with the steady state being reached between days 3 and 7. At steady state, the average inhibition to ADP is between 40 and 60%. Platelet inhibition persists for the platelet's life span (7 ± 2 d), and platelet activity returns toward normal (≥50% activity) within 5–6 days of last clopidogrel dose. No restriction is necessary in patients with renal failure or moderate liver insufficiency [13, 31, 32].

*Clopidogrel Adverse Effects*

The adverse-effect profile of clopidogrel include in first-line use includes mild abdominal disorders, such as diarrhea and dyspepsia. Occasional allergic reactions, gastrointestinal ulcerations, leucopenia, and thrombocytopenia are seen. In the Clopidogrel versus ASA in Patients at Risk for Ischemic Events (CAPRIE) study [27], the rate of bleeding was similar for the ASA and clopidogrel groups: 9.3%. Major bleeding occurred in both groups at <2%. Agranulocytosis, aplastic anemia, and thrombotic thrombopenic purpura are rare. There are no known specific adverse interactions with other drugs.

*Clopidogrel Dosing*

Clopidogrel is given per oral ingestion, and 75 mg clopidogrel/d is the standard dose, which is commonly combined with a loading dose of 300 mg.

*Clopidogrel Response Variability and Failures (Clopidogrel Resistance)*

The data found in the literature are similar to those for ASA (see previous text). Depending on different methods, published laboratory resistance rates range from 5 to 50%. Studies have verified the importance of dose with regard to clopidogrel response variability [33] and correlations to clinical outcome [34, 35]. The influence of clopidogrel on antiplatelet action is decreased by other medications being metabolised in the liver by cytochrome P450 2C19 just as clopidogrel. In particular, omeprazole should not be given together with clopidogrel.

*Clopidogrel Antagonisation*

Similar to ASA, no specific antagonist is available because of the irreversible inhibition of platelet function. Platelet infusions or desmopressin [36] may help.

*Clopidogrel in Daily Practice*

In PAD, data of randomized studies are lacking regarding the indication of platelet antagonists in primary and secondary prevention. TASC II guidelines [1] have been adapted from data on secondary prevention from cardiology studies. Data from randomized studies, such as the CAPRIE study, although not powered to identify differences in specific subsets, showed a relative risk decrease of 23.8% for clopidogrel (3.71%) versus ASA (4.86%) regarding the annual event rate in patients with peripheral vascular disease in secondary prevention. Despite these results, ASA still is the mainstay in peri-interventional antiplatelet treatment in patients with PAD; the greater costs for clopidogrel administration versus ASA may be a motive.

*Dual Antiplatelet Therapy*

Clopidogrel exerts modest benefit when used alone in patients at risk for vascular events. In contrast, the combination of ASA and clopidogrel offers considerable proven benefit in patients with acute coronary syndromes and after coronary arterial stent placement [27, 37–39]. Regarding TASC II, European Society of Cardiology (ESC), and American Heart Association (AHA)/American College of Cardiology (ACC)/Society for Cardiovascular Angiography and Interventions (SCAI) recommendations [1, 40, 41] dual antiplatelet therapy is empirically used preprocedurally, periprocedurally, and postprocedurally in patients with PAD, especially for stenting of the carotid arteries (CAS) [42], the superficial femoral artery, and the tibial arteries using clopidogrel for some time (weeks to months) in combination with ASA. Clinical Practice in Interventional Radiology (Cardiovascular and Interventional Radiological Society of Europe [CIRSE] Task Force) recommends the use of ASA and clopidogrel for 3–6 months after CAS [43]. Attention must be given to these patients for increased bleeding rates from the puncture side, so closure devices may be considered at the end of the procedure. In contrast, care is mandatory if antiplatelet therapy must stop. Switching to heparin after CAS in the first weeks after stent implantation may lead to early stent thrombosis [44].

In PAD, long-term dual antiplatelet therapy is not general recommended. Benefit comes with increased risk of

bleeding in secondary prevention of PAD [45] and stroke [46]. Exceptions may be patients with drug-eluting stents corresponding to cardiological guidelines, but there is still a lack of comparing studies proving any benefit of long-term dual antiplatelet therapy in PAD.

## GP IIb/IIIa Receptor Antagonists

The platelet-receptor GP IIb/IIIa serves as the "final common pathway" for platelet aggregation. Inhibition of the GP IIb/IIIa receptor profoundly alters platelet hemostatic function and prevents thrombus growth. Currently there are three available intravenous inhibitors of the GP IIb/IIIa receptor: abciximab, eptifibatide, and tirofiban. They represent strong platelet antagonists with a narrow therapeutic window and bind rapidly to platelets in <1 min. Usually given in combination with ASA and UFH, the risk of major bleedings is approximately 2% in short-term administration [47].

### Abciximab

The macromolecule abciximab is the Fab fragment of the chimeric human-murine monoclonal antibody c7E3.

#### *Abciximab Pharmacology*

After an intravenous bolus, free plasma concentrations of abciximab decrease rapidly with an initial half-life <10 min and a second-phase half-life of 30 min, representing rapid and irreversible binding to the platelet GP IIb/IIIa receptor. Abciximab remains in the circulation in the platelet-bound state for ≥10 days. In case of renal insufficiency, no decrease of dose is needed. Intravenous administration of abciximab in doses ranging from 0.15 to 0.3 mg/kg produces rapid dose-dependent inhibition of platelet aggregation in response to adenosine diphosphate. At the highest dose, 80% of platelet GP IIb/IIIa receptors are occupied within 2 h, and platelet aggregation is completely inhibited. Sustained inhibition is achieved with prolonged infusion (12–24 h), and low-level receptor blockade is present for ≤10 days after cessation of the infusion. Platelet aggregation returns to ≥50% of baseline within 24 h of drug cessation [13].

#### *Abciximab Antagonisation*

No specific antagonist is available. Platelet infusions and desmopressin may be helpful [48].

#### *Abciximab Adverse Effects*

Mild adverse effects, such as back pain, hypotension, and vomiting, are often seen. Thrombocytopenia is a rare but dangerous complication. The number of platelets must be determined before and every day throughout the duration of administration. When readministered, the rate of occurrence of thrombocytopenia is the same as for the primary exposure, but the severity appears to be greater [49].

### Eptifibatide

Eptifibatide is a nonimmunogenic cyclic heptapeptide with an active pharmacophore that is derived from the structure of barbourin, a platelet G IIb/IIIa inhibitor from the venom of the southeastern pigmy rattlesnake.

#### *Eptifibatide Pharmacology*

Eptifibatide is a selective and competitive antagonist of the GP IIb/IIIa receptor. The plasma half-life is 10–15 min, and clearance is predominantly renal (75%) and, to a lesser degree, hepatic (25%), so the dose must be decreased in cases of renal insufficiency. The antiplatelet effect has a rapid onset of action and is rapidly reversible, and 180 μg/kg as intravenous bolus, followed by infusion of 2 μg/kg/min, are recommended. Platelet function returns to >50% of baseline within 4 h of terminating the infusion.

#### *Eptifibatide Antagonisation*

There is no specific antagonist available. Desmopressin may be helpful [48]. Platelet infusions are ineffective until eptifibatide is eliminated from the blood as new platelets are inactivated.

#### *Eptifibatide Adverse Effects*

Thrombocytopenia in contrast to abciximab is a rare side effect of eptifibatide.

### Tirofiban

Tirofiban, a tyrosine derivative with a molecular weight of 495 kd, is a nonpeptide competitive inhibitor of the GP IIb/IIIa receptor. It mimics the geometric, stereotactic, and charge characteristics of the Arginine-Glycine-Aspartic acid (RGD) sequence of fibrinogen, consequently interfering with platelet aggregation.

#### *Tirofiban Pharmacology*

The pharmacology of tirofiban is similar to eptifibatide. As a competitive antagonist of the GP IIb/IIIa receptor, the plasma half-life is approximately two hours, and clearance is predominantly renal (75%) and, to a lesser degree,

hepatic (25%), so the dose must be decreased in cases of renal insufficiency. The antiplatelet effect is proportional to plasma concentration. The antiplatelet effect has a rapid onset of action and is rapidly reversible. Infusion of 0.4 μg/kg during >30 min, followed by infusion of 0.1 μg/kg over the next hours, is recommended. Platelet function returns to normal within 8 h of terminating the infusion.

*Tirofiban Antagonisation*

Correlating to eptifibatide, no specific antagonist is available. Desmopressin may be helpful [48]. Platelet infusions are ineffective until tirofiban is eliminated from the blood as new platelets are inactivated.

*Tirofiban Adverse Effects*

Thrombocytopenia is a rare side effect of tirofiban.

GP IIb/IIIa Receptor Antagonists in Daily Practise

Considerable experience with GP IIb/IIIa receptor antagonists underscores their benefit in high-risk patients undergoing PCI. Administration during and after PCI is associated with a 35–50% decrease in adverse clinical events after the procedure [50]. For PAD, no randomized trials exist. Studies and registries in acute PAD suggest that the addition of GP IIb/IIIa inhibitors in thrombolytic therapy offers efficacy benefits without a significant increase of bleeding risks [49, 51–53]. They are also recommended in severe complications, such as stroke, occurring during CAS [54]. Thus, in PAD, adjunct GP IIb/IIIa inhibitors should be restricted to selected patients with a greater risk of failure during thrombolysis or rethrombosis during time-consuming and technical complicated vascular interventions until data from larger prospective clinical trials are available.

## Thrombin-Directed Therapy

UFH

UFH is a heterogeneous mucopolysaccharide with a molecular weight of 5000–30,000 Da. Antithrombin, required for the interaction of UHF with thrombin and coagulation proteases, is bound by one third of the administered drug (only molecules containing the critical pentasaccharide sequence can bind antithrombin).

*Pharmacology*

UHF binds to a variety of plasma proteins, endothelial cells, and macrophages, explaining, to some extent, the wide variability in anticoagulant effects for a given dose. It is cleared from the circulation through both a rapid saturable mechanism and a slower first-order mechanism. As a result, there is a dose-dependent half-life ranging from 60 min after a dose of 100 U/kg to 180 min for a dose of 400 U/kg [55]. Corresponding to hepatic degradation and renal elimination, the anticoagulation effect of UFH is prolonged in patients with hepatic and renal insufficiency. Patients with active thrombosis may require greater UFH doses due to more rapid elimination or variations in the plasma concentrations of heparin-binding proteins. Antithrombin deficiency and increased factor VIII levels, which are common in pregnant patients, have also been linked to greater UFH dose requirements. The requirement of these greater UFH doses is called “heparin resistance.”

*UHF Dosing*

In PCI, UFH doses of 60–100 IU/kg and a target (ACT) between 250 and 300 s are advocated on the basis of retrospective analyses [56]. According to these recommendations, during peripheral angioplasty, 2500–5000 IU of UFH are given in the beginning of the procedure, followed by a further bolus or continuous heparin infusion depending on the duration of the procedure. Intravenous administration of UFH is generally started with a bolus. This bolus should also be given in continuous application if an increase of activated thromboplastin time (aPTT) is desired. The steady state is reached much faster by bolus injection rather than merely increasing the continuous UFH dosing. In this case, aPTT should not be controlled for <2 h after bolus administration regarding the half-life of UFH. Time to wait before removal of the sheath can be calculated by the half-life of UFH or determined by measurement of aPTT or activated clotting time (ACT), with the latter being recommended for <200 s. In angioplasty, subcutaneous application of UFH is not advised. Intraarterial application is off label, but thus far there have been no reports relating to adverse effects.

*UHF Additive Effects*

ASA, clopidogrel, GPIIb/IIIa inhibitors, fibrinolytic drugs, warfarin, phenprocoumon, nonsteroidal antiphlogistic drugs (e.g. indometacin) increase the effect of UHF.

*UHF Adverse Effects*

Bleeding and heparin-induced thrombocytopenia (HIT type II) are the most feared complications of UHF administration.

- HIT type I (occurs often): Thrombocytopenia (100,000–150,000/μl) at the beginning of heparin administration

without antibodies and thrombosis. Heparinisation does not have to be stopped.

- HIT type II (rarely occurs): Thrombocytopenia with decrease of platelets <100,000/μl or rapid decrease to ≥50% regarding the cell number before administration of heparin. Arterial and venous thrombosis or embolic events occur often. HIT type II has an incidence of 1–3% and occurs 5–14 days after beginning UFH therapy. In case of former sensitisation, HIT type II may occur within ≤24 h in patients who have had previous exposure to heparin, particularly if the exposure has occurred within the previous 3 months. Rarely, the onset of thrombocytopenia and/or thrombosis may be delayed, occurring after several weeks of exposure. The diagnosis should also be suspected in patients who develop skin necrosis, particularly at subcutaneous injection sites.

Patients receiving heparin should be monitored for the development of HIT type II. Because HIT type II can occur with any form of heparin administration, including use of heparin-coated indwelling vascular catheters and stent-grafts, all patients exposed to heparin are potentially at risk.

Recovery of the platelet count into the reference range within several days of heparin cessation supports a diagnosis of HIT type II. A comprehensive laboratory evaluation should be considered to differentiate HIT type II from other causes of thrombocytopenia, including nonimmune heparin-induced thrombocytopenia (HIT type I).

In suspected cases of HIT type II, heparin must be stopped at once. Although low molecular-weight heparin (LMWH) was initially thought to be an effective treatment option, clinical studies have shown a high rate of laboratory-based cross-reactivity with existing antibodies. Anticoagulation is preferably accomplished with second-line alternatives argatroban, hirudin, danaparoid sodium, or fondaparinux.

Warfarin administration should be avoided in patients with HIT of either type because of its prothrombotic potential (rapid decrease in protein C levels). If warfarin or phenprocoumon are required for long-term treatment of thromboembolism, an alternative anticoagulant should be administered for several days before starting treatment.

### *UHF Antidote*

Antagonisation of UFH is performed with slow injection of protamine; 10 mg protamine (=1 ml) binds 1000 U UFH. Protamine overdosing should be avoided because non-heparin bonded protamine has an anticoagulative effect.

## LMWH

LMWH is prepared by depolymerisation of porcine UFH. A variety of processes are used, yielding distinctive products whose molecular weights range from 4000 to 6500 Da. Like UHF, approximately one third of LMWH polysaccharide chains contain the pentasaccharide-binding site for antithrombin. The LMWH–antithrombin complex has relatively weak antithrombin activity but retains the ability to inactivate factor Xa. The ratio of anti-Xa activity to anti-IIa (antithrombin) activity varies from 2:1 to 4:1. Similar to UFH, LNWH is not able to inhibit thrombin bound to fibrin. When LMWH is administered subcutaneously in either fixed or weight-adjusted doses, >90% of the dose is absorbed. In contrast to UFH, LMWH has minimal binding to cells or plasma proteins, resulting in persistence of free drug in the circulation and a longer half-life of activity. Although the half-life of UFH averages approximately 90 min, the half-life of LMWH averages approximately 90–260 min in patients with normal renal function. In elderly patients, creatinine is not a consistent parameter for renal function: The glomerular filtration rate may show a ≤50% decrease in patients with still-normal creatinine levels.

Thus, LMWH with particularly low molecular weight (e.g. enoxaparin sodium) are strongly retained, but decrease of renal function and half-life may be more than doubled. In such a case, LMWH administration should be stopped 24 h before interventional therapy in PVD to avoid additive effects with UFH and platelet antagonists.

### *LMWH Laboratory Control*

The effect of LMWH is measured by determination of the factor Xa activity. aPTT can only be used for activity measurement in UFH.

### *LMWH Antidote*

Factor VIIa products represents a treatment option in patients with life-threatening hemorrhage.

### *LMWH Indications*

LMWH is not used routinely during interventional procedures because of its subcutaneous application, the difficulty to determine anticoagulation activity, the slow elimination in respect to UFH, and the absence of an easily available antidote.

### *Summary*

UFH is used routinely in PAD and angioplasty. The main adverse effect is HIT type II, with an incidence of 1–3%. Determination of platelet counts before starting heparin administration is mandatory. Knowledge of the half-lives of UFH and LMWH in patients with decreased renal

function, predominantly in elderly patients, is essential to avoid unwanted additive effects.

## Indirect Thrombin Inhibitors: Fondaparinux

### *Fondaparinux Pharmacology*

Fondaparinux, a synthetic polysaccharide, contains the same pentasaccharide sequence found on UFH or LMWH [57]. Fondaparinux lacks the sugar domain necessary to complex with PF4, making the likelihood of inducing HIT type II extremely low [58]. Data from clinical trials encompassing >7500 patients who received fondaparinux did not show cases of HIT type II [59]. After subcutaneous injection, the maximum peak plasma concentration is reached after 2 h, so the first injection may be given intravenously in urgent cases. Renal elimination without metabolism dominates, and elimination half-life is approximately 20 h for healthy persons and 72 h in cases of severe renal insufficiency. Interactions with other drugs, resulting in decreased antithrombotic effect, are not known.

### *Fondaparinux Indication*

Fondaparinux is approved for the treatment of the prophylaxis of deep venous thrombosis, MI, and pulmonary embolism. In PAD, it may be used for patients with a history of HIT type II.

### *Fondaparinux Dosing*

Fondaparinux, 1.5 mg to 10 mg daily subcutaneously, is given depending on indication, body weight, and renal function. It should not be used in cases of severe renal insufficiency with glomerular filtration rate <30 ml/h.

### *Fondaparinux Laboratory Control*

Low binding to plasma proteins circumvents the necessity for laboratory control.

### *Fondaparinux Antidote*

No reversal antidote is approved for fondaparinux, and excessive dosing may lead to hemorrhage. Fresh frozen plasma and cryoprecipitate can be used to control bleeding.

### *Fondaparinux Adverse Reactions*

Adverse reactions include bleeding, thrombocytopenia (seldom), and vomiting.

### *Fondaparinux in Daily Practise*

Fondaparinux is an alternative drug to LMWH. In angiography and PAD, this drug is used rarely because of its pharmacological properties, i.e. subcutaneous application and long half-life. It is more likely that patients receiving fondaparinux because of previous HIT type II are occasionally sent to angiography; accordingly the interventionalist should know this drug and how to switch to alternatives if needed.

## Direct Thrombin Inhibitors: Argatroban

Argatroban is an intravenous applicable anticoagulant approved for use in patients with or at risk for HIT type II, who are undergoing an interventional procedures. HIT type II should be confirmed, for example, by heparin induced platelet activation assay (HIPAA test); regardless, commencement of therapy should not be delayed by these tests.

### *Argatroban Pharmacology*

Argatroban, a synthetic L-arginine derivate, acts as a reversible direct thrombin inhibitor that blocks both clot-bound thrombin and free thrombin effectively [60]. In addition, it inhibits coagulation factors V, VIII and XIII and the activation of thrombocytes as well as the activation of factor C by thrombin. Steady state is reached within 1–3 h and is maintained until the end of infusion. Metabolisation occurs in the liver, and the antithrombotic effect of the metabolites is weak. The apparent half-life is approximately 1 h, and elimination occurs two thirds in faeces and one third in urine. Clearance in patients with liver disease is approximately one fourth that of healthy subjects, and argatroban is contraindicated in patients with severe liver insufficiency.

### *Argatroban Dosing*

The initial intravenous dose for HIT of either type is 2 μg/kg/min, and the recommended maximum dose 10 μg/kg/min.

### *Argatroban Laboratory Control*

Measuring of antithrombotic activity is performed by activated thromboplastin time (aPTT). The target is 1.5- to 3-fold extension of the normal value of aPTT. The first control should be performed 2 h after start of infusion.

*Argatroban Antidote*

No specific antidote is known.

*Argatroban Adverse Reactions*

Adverse reactions include bleeding, anemia (frequently), coagulopathy (seldom), and dyspepsia.

*Argatroban in Daily Practise*

Argatroban is a valuable drug that is helpful in patients with HIT of either type. Other indications have not been established.

New Oral Anticoagulative Drugs: Dabigatran Etexilate

Dabigatran etexilate, an oral applicable direct thrombin inhibitor, is approved for the prophylaxis of deep venous thrombosis after knee joint replacement.

*Dabigatran Etexilate Pharmacology*

Dabigatran etexilate is a pharmacologically inactive prodrug that is resorbed quickly after oral ingestion and hydrolysed in plasma and liver. Maximum plasma concentration is reached 0.5–2 h after ingestion in healthy subjects but considerably later in patients after surgery (approximately 6 h). Approximately 10% of the drug is metabolised, but the main fraction is renally eliminated unchanged. The half-life is approximately 14 h in healthy subjects and approximately 14–17 h in patients after surgery, which is in between the half-lives of LMWH and fondaparinux.

*Dabigatran Etexilate Dosing*

Dabigatran etexilate, 220 mg in two capsules of 110 mg, is recommended. In case of moderate renal insufficiency, 110 mg daily (at the most) should be given. In severe cases of renal insufficiency, the drug is contraindicated.

*Dabigatran Etexilate Antidote*

No specific antidote is known.

*Dabigatran Etexilate Adverse Reactions*

Adverse reactions include bleeding (in studies this is more likely than with enoxaparin), anemia, thrombocytopenia, and moderate GI disturbance.

*Dabigatran Etexilate Drug Interactions*

There is a strong interaction with amiodarone and verapamil, which makes dose decrease necessary. Combination with chinidine is strictly forbidden. Pantoprazole weakens the effect of dabigatran.

Rivaroxaban

This orally given direct factor-Xa inhibitor is also approved for the prophylaxis of deep venous thrombosis after knee joint replacement. Data show no influence on thrombocyte count.

*Rivaroxaban Pharmacology*

Rivaroxaban, an oxazolidinone, is resorbed quickly in the intestine. Maximum plasma concentration is reached after 2–4 h. Metabolism occurs to approximately two thirds of the drug, and elimination of the metabolites is in equal parts renally and faecally. One third of the drug is eliminated unchanged by the kidneys. The half-life is 7–11 h after oral ingestion. No dose adaption is necessary in elderly patients or in patients with low or high body weight.

*Rivaroxaban Dosing*

Rivaroxaban, 10 mg daily, is recommended. Ingestion seems to be independent of nutrition. In case of mild to moderate renal insufficiency, no dose adaption is necessary. However, cautious dosing seems to be needed in cases of severe renal insufficiency. The drug is contraindicated in case of liver disease combined with coagulopathy.

*Rivaroxaban Antidote*

No specific antidote is known.

*Rivaroxaban Adverse Reactions*

Adverse reactions include bleeding (in studies this occurs less likely than with enoxaparin), thrombocytosis, dyspepsia, pruritus, edema, and worsening of renal function. Because of lactose is one of the ingredient, it should not be used in patients with lactose intolerance.

*Rivaroxaban Drug Interaction*

Potential interaction occurs with strong inhibitors or accelerators of CYP3A4, e.g. azol antimycotics, or human immunodeficiency virus–protease–inhibitor drugs.

*Dabigatran and Rivaroxaban in Daily Practise*

As of now, these drugs are not used in interventional angiography. Nevertheless, interventionalists may be confronted with patients who are taking these drugs, so they should be informed about these newer medications pertaining to their pharmacological properties.

## Discussion

In interventional treatment of PAD, ASA is still the basic drug and first choice in antiplatelet therapy. This may astonish, but there are good reasons: It is low priced; the relation between clinical benefit and adverse reactions is acceptable; and in case of urgent surgery, surgeons can operate without interruption of medication. The possibility of a suboptimal antiplatelet medication leading to early arterial occlusion after percutaneous transluminal angioplasty (PTA) must be traded against the likelihood of possible adverse short- and long-term events caused by more potent drugs, such as clopidogrel, prasugrel, or ticagrelor. In angioplasty of peripheral arteries, early occlusions are rather rare and seldom perilous because perfusion is partially maintained by collaterals. Vessel occlusion after PTA is primarily caused by neointimal hyperplasia, which cannot be suppressed by platelet inhibition. Therefore, cardiologic studies only hint at the use of antiplatelet medication in PTA and are not a reliable basis of treatment, especially when using bare metal und drug-eluting stents, considering the different behaviour of peripheral and coronary arteries to endothelial lesions and blood flow.

Given the lack of evidence, the use of antiplatelet medication in PAD is based mainly on empiricism. The frequency and importance of adverse outcomes caused by postinterventional artery occlusion, as well as the adverse effects for the patient and costs for the community, influence the use of different medications. Differences in vessel diameter, blood-flow velocity, and peripheral resistance influence the occurrence of early stent thrombosis. Therefore, dual platelet inhibition for several weeks is common in bare-metal stenting of the carotid, femoral, and tibial arteries but not in stenting of the aorta, iliac, renal, or visceral arteries. The Sirolimus-eluting versus bare nitinol stent for obstructive superficial femoral artery disease (SIROCCO) and SILVER PTX studies [61, 62] compared the patency rates of bare metal stents versus drug-eluting stents in superficial femoral arteries. In contrast to the recommendations regarding coronary artery stenting, those 2 studies did not find evidence for long-term dual platelet inhibition.

Accepting dual antiplatelet therapy as a justified medication for specific indications, it remains unclear, how long it should be maintained. Are 4 weeks adequate, or are 8 or 12 weeks better? The result is influenced more by the hopes to decrease the effect of drug resistance and by concerns about costs and adverse effects than by data.

There is a basic problem in antiplatelet therapy. Patient specific properties, such as drug resistance and high platelet reactivity, make optimizing of individually tailored medication difficult. A standardized, reliable, and low-priced determination of laboratory resistance and high platelet reactivity could help to adapt medication on individual needs, avoid overdosing and adverse effects, and increase patient compliance.

Prasugrel is a good alternative to clopidogrel in cases of drug resistance, and ticagrelor is an alternative to prasugrel for patients with cerebral infarction in history and a body weight $<60$ kg. Moreover, ticagrelor has an advantage compared with ASA, clopidogrel, and prasugrel in that it binds reversible to platelets and therefore partial platelet activity returns after 12 h, making coagulation better controllable and allowing restoration of coagulation in case of bleeding. Dyspnoea as adverse reaction occurs in $\leq 14\%$ of cases, i.e. 2-fold compared with clopidogrel.

Intraprocedurally given potent platelet inhibitors, such as GP IIb/IIIa inhibitors, are helpful, when platelet aggregation is the dominant factor, resulting in early vessel occlusion, further rethrombosis, or thrombus formation along catheters during lysis. They help to avoid perithrombal platelet clotting in case of embolisation or vessel occlusion caused by slow flow. This is particularly useful in angioplasty of the supra-aortic arteries, such as carotid stenting combined with intracranial embolism. In such cases, drugs with reversible binding to platelets, such as eptifibatide, may be easier to handle than irreversible antagonists, such as abciximab. Dosing is equivalent to coronary interventions with weight-adapted bolus followed by intravenous infusion. Direct intra-arterial application is off-label use, but it may cause a stronger effect. It should be kept in mind that these drugs do not directly aid in lysis of older thrombus because older thrombus mostly consists of fibrin. Nevertheless, they help to avoid perithrombal appositional thrombosis, which hampers the effect of thrombolytic agents, such as urokinase or tissue plasminogen activator, on fibrin clots.

In case of bleeding, no direct antidote is available to suppress the effect of all antiplatelet drugs mentioned previously. However, desmopressin is a possible drug by which to improve platelet aggregation, and it should be available in the angiography suite. Platelet infusions are preferable, but their preparation and delivery is time consuming.

UFH as unfractionated heparin product is yet the first choice during angioplasty of peripheral and coronary arteries. The handicap of lesser controllability and

antagonisation exceed the advantage of LMWH with regard to more specific effect, simple dosing, and fewer complications, such as HIT type II.

Conversely, LMWH is the better periprocedural drug, but medication should be stopped 24 h before angioplasty to avoid accumulation in elderly patients with renal insufficiency. This should be remembered especially in interventional biopsy or abscess drainage, when the needle passes regions with ample blood supply, e.g. muscles or abdominal organs.

LMWH plays an important role in long-term treatment of cancer-associated thrombosis. Vitamin K antagonists are relatively ineffective in patients with malignancy, with a recurrence rate that is twice as high as LMWH [63].

Deactivation of UFH is easily performed with protamine in case of bleeding. Using LMWH antagonisation is only partly possible. Calculation of the adequate dose and determination of time management of repeated necessary protamine infusions is difficult.

In case of HIT type II, every kind of heparin administration must be stopped. However, how should we recognize this adverse reaction? A dramatic decrease in platelet number is a good indicator, but clotting may start before the platelet decrease becomes obvious. Therefore, heparin should be stopped in any case of unexpected clotting, even if there are many other reasons causing thrombus formation, such as high protein binding, ATIII deficiency, or other inherited disorders of coagulation, which may be undiscovered because of subclinical expression or multifactorial origin.

Argatroban is a convenient alternative drug in cases of suspected or proven HIT type II and should be available in the angiography suite. In severe thrombotic situations without bleeding complications, additional short-term administration of a potent platelet inhibitor may be useful.

In patients with suspected history of HIT type II, an indirect thrombin inhibitor, such as fondaparinux, is a good alternative to LWMH as periprocedural medication. It is given subcutaneously, and low binding to plasma proteins circumvents the necessity for laboratory control. The long half-life of fondaparinux and the retention in cases of renal insufficiency should be considered.

Vitamin K antagonists are the first choice for long-term anticoagulation. However, they have profound disadvantages: slow initiation of adequate effect, initial increased coagulability, long half-life and slow loss of effect, narrow therapeutic window, high binding to plasma proteins, and interaction with food requiring frequent laboratory controls and adaptation of dose. After research of 30 years new oral anticoagulants, such as dabigatran and rivaroxaban, are available with the potential to replace vitamin K antagonists at some point.

In contrast to vitamin K antagonists, dabigatran and rivaroxaban show full anticoagulant effect after just a few hours. Effect decrease takes place within 1 day. Effect correlates with plasma level and is not influenced by genetic factors. Interactions with other drugs are known but are less frequent than with vitamin K antagonists. The therapeutic window is much broader and renders controls unnecessary. Dabigatran is eliminated renally and is therefore contraindicated in cases of severe renal insufficiency, whereas rivaroxaban is eliminated by multiple pathways, so dosing is independent of renal function.

In clinical practice, the prescription alone does not guarantee therapeutic security because blood levels of dabigatran and rivaroxaban quickly reach subtherapeutic levels in patients with poor compliance. Therefore, the development of laboratory tests is required; until then, these new drugs are far from being the ideal long-term anticoagulant.

## Summary

Although the armamentarium of drugs to influence coagulation in peripheral arterial intervention has grown in the last years, the basic drugs are still the same. ASA continues to be the standard in antiplatelet therapy and should be used routinely before, during, and after intervention if no drug related contraindications are present. Clopidogrel is a helpful antiplatelet drug when used as an alternative or additional drug. The efficiency of both is influenced significantly by drug resistance, which may be overcome by using the newer thienopyridine, prasugrel. Although there is still a lack of an international standard, laboratory testing of antiplatelet drug resistance has become more important and easily available and is recommended in certain patients, e.g. those with early stent thrombosis.

Glycoprotein IIb/IIIa inhibitors are not applied routinely but may be a helpful support drug in, e.g. CAS complicated by embolism or in cases of peripheral lysis with slow flow and rethrombosis during intervention. UFH still dominates intervention because of its short half-life, hepatic and renal elimination, and the possibility to be neutralized by protamine. LMWHs are preferred for anticoagulation up to 24 h before and after intervention because of easier and safer handling, greater efficacy, and lesser rates of HIT of both types.

Argatroban and fondaparinux are alternative drugs in case of HIT of both types. Dabigatran etexilate, an orally given direct thrombin inhibitor, and rivaroxaban, a direct factor-Xa inhibitor, are not used during interventional procedures because of their pharmacologic properties, but the interventionalist may be confronted with patients who are taking these drugs and should be familiar with their properties to be able to correctly change the anticoagulant regime before and after intervention.

## Conclusion

In conclusion, it appears advisable for the interventionalist to regularly update his or her knowledge on drugs in the interventional environment, especially regarding drug interactions and altered metabolisms, for an increasingly ageing patient collective.

**Conflict of interest** The authors have no conflict of interest.

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