

Chapter 7

Management of Bleeding Complications

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Introduction

Anticoagulant agents are often used for prevention and treatment of a wide range of cardiovascular diseases, including acute coronary syndromes. The most frequently used anticoagulants are heparin or its derivatives, vitamin K antagonists (such as warfarin or coumadin) and antiplatelet agents, including aspirin and thienopyridine derivatives, such as clopidogrel or prasugrel. A myriad of clinical studies have demonstrated that these agents (alone or in combination) can prevent or treat acute or chronic thrombo-embolic complications, such as in patients with atrial fibrillation or prosthetic heart valves, after myocardial infarction, percutaneous coronary interventions, or ischemic stroke, and in patients with venous thrombosis or pulmonary embolism [1]. The most important complication of treatment with anticoagulants is hemorrhage, which may be serious, may cause

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long-term debilitating disease, or may even be life-threatening [2, 3]. In a very large series of 34,146 patients with acute ischemic coronary syndromes, anticoagulant-associated bleeding was associated with a 5-fold increased risk of death during the first 30 days and a 1.5-fold higher mortality between 30 days and 6 months [4]. Major bleeding was an independent predictor of mortality across all subgroups that were analyzed. In some clinical situations the incidence of serious bleeding complications may annihilate or even overwhelm the efficacy of antithrombotic agents, as has been shown in the secondary prevention of patients with ischemic stroke by vitamin K antagonists [5]. Nevertheless, in many situations clinical studies show a favorable balance between efficacy and safety in favor of anticoagulant treatment. However, if severe bleeding occurs or if a patient needs to undergo an urgent invasive procedure, such as emergency surgery, it may be necessary to reverse the anticoagulant effect of the various agents [6]. Depending on the clinical situation, i.e. the severity of the bleeding or the urgency and estimated risk of the invasive procedure, this reversal may take place in a few hours, but in some cases immediate reversal is necessary (Table 7.1) [7, 8]. Generally, each (immediate) reversal of anticoagulant treatment needs also to take into consideration the indication for the antithrombotic agents. For example, the interruption of combined aspirin and clopidogrel treatment in a patient in whom recently an intracoronary stent has been inserted will markedly increase the risk of acute stent thrombosis with consequent downstream cardiac ischemia or infarction. Likewise, in a patient with a prosthetic mitral valve and atrial fibrillation, interruption of vitamin K antagonists may increase the risk of valve thrombosis and cerebral or systemic embolism. Each of these specific clinical situations requires a careful and balanced assessment of the benefits and risks of reversing anticoagulants (and potential strategies to keep the period of reversal as short as possible). In this chapter, we will describe the various strategies to reverse the anticoagulant effect of currently most widely used antithrombotic agents and the new generation of anticoagulants.

TABLE 7.1 Reversal of anticoagulant effect of different agents

| | Time until restoration of hemostasis after cessation of therapeutic dose | Antidote | Remark |
|--|---|--|---|
| Heparin | 3–4 h | Protamine sulphate 25–30 mg; immediate reversal | 1 mg of protamine per 100 anti-Xa units given in the last 2–3 h |
| LMW heparin | 12–24 h | (Partially) protamine sulphate 25–50 mg; immediate reversal | 1 mg of protamine per 100 anti-Xa units given in the last 8 h |
| Pentasaccharides | Fondaparinux: 24–30 h Idraparinux: 5–15 days | Recombinant factor VIIa 90 ug/kg; immediate thrombin generation | Based on laboratory end-points, no systematic experience in bleeding patients |
| Vitamin K antagonists | Acenocoumarol: 18–24 h Warfarin: 60–80 h Phenprocoumon: 8–10 days | Vitamin K i.v: reversal in 12–16 h Vitamin K orally: reversal in 24 h PCC's; immediate reversal | Dose of vitamin K or PCC's depend of INR and bodyweight |
| Oral thrombin and factor Xa inhibitors | Dependent of compound, usually within 12 h | Prothrombin complex concentrates or recombinant factor Xa for Xa inhibitors, unsure for IIa inhibitors | Based on laboratory end-points, no systematic experience in bleeding patients |

(continued)

TABLE 7.I (continued)

| | Time until restoration of hemostasis after cessation of therapeutic dose | Antidote | Remark |
|-------------|---|---|---|
| Aspirin | 5–10 days (time to produce unaffected platelets) | DDAVP (0.3–0.4 ug/kg) and/or platelet concentrate; reversal in 15–30 min | Cessation not always required, also dependent on clinical situation and indication |
| Clopidogrel | 1–2 days | Platelet concentrate, possibly in combination with DDAVP (0.3–0.4 ug/kg); reversal in 15–30 min | Cessation not always desirable, also dependent on clinical situation and indication |
| Prasugrel | | | |

LMW heparin low molecular weight heparin, *PCC* prothrombin complex concentrate, *DDAVP* de-amino d-arginin vasopressin or desmo pressin

Incidence and Risk Factors for Bleeding in Patients on Anticoagulants

In well-controlled patients in clinical trials treatment with heparin or vitamin K antagonists (VKA's) increase the risk of major bleeding by 0.5 %/year and the risk of intracranial hemorrhage by about 0.2 %/year [9]. The most important risk factor for hemorrhage in users of anticoagulants is the intensity of the anticoagulant effect [9]. Studies indicate that with a target INR of >3.0 the incidence of major bleeding is twice as large as in studies with a target INR of 2.0–3.0 [10]. In a meta-analysis of studies in patients with prosthetic heart valves, a lower INR target range resulted in a lower frequency of major bleeding and intracranial hemorrhage with a similar anti-thrombotic efficacy [11]. A retrospective analysis of outpatients using warfarin who presented with intracranial hemorrhage demonstrated that the risk of this complication doubled for each 1 unit increment of the INR [12]. Patient characteristics constitute another important determinant of the bleeding risk. Elderly patients have a 2-fold increased risk of bleeding [13] and the relative risk of intracranial hemorrhage (in particular at higher intensities of anticoagulation) was 2.5 (95 % CI 2.3–9.4) in patients >85 years compared to patients 70–74 year old [14]. Recently, genetic factors have been identified that may affect the risk of bleeding. Common polymorphisms in the P450 CYP2C9 enzyme were found to be associated with slow metabolism of VKA's and (possibly) a higher risk of bleeding [9, 15]. Other genetic factors that may influence the requirement of VKA's are variants in the vitamin K epoxide reductase complex subunit 1 gene (*VKORC1*) [16]. Co-morbidity, such as renal or hepatic insufficiency, may also significantly increase the risk of bleeding. A case-control study in 1,986 patients on VKA's showed that this comorbidity increased the risk of bleeding by about 2.5 [17]. Another very important determinant of the risk of bleeding is the use of other medication, in particular agents affecting platelet function. Two meta-analyses, comprising 6 trials with a total of 3,874 patients and 10 trials with a total of

5,938 patients, found a relative risk of major bleeding when VKA's or heparin were combined with aspirin of 2.4 (95 % CI 1.2–4.8) and 2.5 (95 % CI 1.7–3.7), respectively [18, 19]. A population-based case-control study confirmed the high risk of upper gastro-intestinal bleeding in patients using VKA's in combination with aspirin and/or clopidogrel [20]. Non-steroidal anti-inflammatory agents (NSAIDs) are also associated with an enhanced risk of gastro-intestinal bleeding. The combined use of VKA's and NSAIDs may result in an 11-fold higher risk of hospitalization for gastro-intestinal bleeding as compared to the general population [21]. This risk is not significantly lower when using selective inhibitors of COX-2 [22].

Heparin and Low Molecular Weight (LMW) Heparin

Heparin and heparin derivatives act by binding to antithrombin and thereby about 1,000-fold potentiating the anticoagulant effect of this endogenous inhibitor towards thrombin and factor Xa (and some other coagulation factors). Heparin has a relatively short half life of about 60–90 min and therefore the anticoagulant effect of therapeutic doses of heparin will be mostly eliminated at 3–4 h after termination of continuous intravenous administration [23]. The anticoagulant effect of high dose subcutaneous heparin, however, will take a longer time to abolish. If a more immediate neutralization of heparin is required, intravenous protamine sulphate is the antidote of choice. Protamine, derived from fish sperm, binds to heparin to form a stable biologically inactive complex. Each mg of protamine will neutralize approximately 100 units of heparin. Hence, the protamine dose in a patient on a stable therapeutic heparin dose of 1,000–1,250 U/h should be about 25–30 mg (sufficient to block the amount of heparin given in the last 2–3 h). The maximum dose of protamine is 50 mg. Since the half-life of protamine is only about 10 min, the reversal of therapeutic dose subcutaneous heparin requires a repeated infusion of protamine sulphate

(e.g. repeated after 1 h). The effect of protamine can be monitored by measuring the activated partial thromboplastin time (aPTT), which should normalize after its administration.

The reversal of LMW heparin is more complex, as protamine sulphate will only neutralize the anti-factor IIa activity and has no or only partial effect on the smaller heparin fragments causing the anti-factor Xa activity of the compound [24, 25]. The net effect of protamine reversal of LMW heparin is not completely clear. There are no clinical studies that have systematically studied this and small case series and experimental animal studies show contradictory results [25–27]. As the aPTT is not useful as a monitoring assay when using LMW heparin, it can also not be used for the monitoring of the neutralizing effect of protamine. Given the relatively long half-life of LMW heparin, the lack of an adequate strategy to reverse its anticoagulant action may sometimes cause a problem in clinical situations. A practical approach is to give 1 mg of protamine per 100 anti-factor Xa units of LMW heparin given in the last 8 h (whereas 1 mg of enoxaparin equals 100 anti-factor Xa units). If bleeding continues, a second dose of 0.5 mg per 100 anti-factor Xa units can be given.

The most important adverse effect of protamine is an allergic response, including hemodynamic and respiratory problems [28]. Most adverse reactions can be prevented or minimized by slowing the rate of administration of the drug or by pretreatment with steroids and antihistamines. Risk factors for an adverse reaction are sensitivity to fish (as may occur in traditional fishermen that are often exposed to fish proteins when cutting themselves), a history of vasectomy (which may demolish the blood-testis barrier with consequent formation of anti-semen antibodies) and a history of receiving protamine sulphate containing insulin. Initial reports that the use of protamine sulphate could lead to an increased risk of rebound thrombosis, in particular ischemic stroke [29, 30], were not confirmed in a recent randomized controlled study [31].

There are some other strategies to reverse (mostly unfractonated) heparin, such as platelet factor-4, heparanase, or

extracorporeal heparin-removal devices, but none of these approaches have been properly evaluated and they are not currently approved for clinical use [32–34].

Pentasaccharides

Pentasaccharides are recently developed synthetic compounds that effectively bind and potentiate antithrombin to block factor Xa. Since they lack the additional glycosaminoglycan saccharide residues to bind to thrombin, it has an effect on factor Xa exclusively. The prototype pentasaccharide (and the only one approved for clinical use so far) is fondaparinux. Another pentasaccharide that is currently under study is idraparinux. The main difference between these two agents is the elimination half-life, which is 15–20 h for fondaparinux and 5½ days for idraparinux. This means that idraparinux can be administered once weekly, which renders the subcutaneous route of administration less cumbersome. Pentasaccharides were shown to be effective in the prophylaxis and treatment of venous thromboembolism and are currently evaluated in other types of thrombosis [35]. The (very) long half-life of pentasaccharides necessitates the availability of a suitable antidote if major bleeding complicates the treatment, which may especially occur in patients that are treated with therapeutic doses of this type of anticoagulation. So far, there is no antidote for pentasaccharides that has been studied in controlled clinical studies [36]. The only agent that has been systematically evaluated to reverse the anticoagulant effect of pentasaccharides is recombinant factor VIIa (rVIIa). Two randomized placebo-controlled studies in healthy volunteers have tested the hypothesis that rVIIa may be useful as a suitable antidote for pentasaccharide anticoagulation [37, 38]. In the first study 16 subjects were treated with therapeutic doses of the pentasaccharide fondaparinux and after 2 h (at the time of maximal anticoagulation) challenged with rVIIa or placebo. Injection of rVIIa (90 µg/kg) after fondaparinux normalized the

prolonged aPTT and prothrombin time (PT) and reversed the decrease in prothrombin activation fragments 1+2 (F(1+2)), as observed with fondaparinux alone. Thrombin-generation time and endogenous thrombin potential, which were inhibited by fondaparinux, normalized up to 6 h after rVIIa injection. In the second study 12 subjects received a single s.c. dose of 7.5 mg idraparinux (which is 3 fold higher than the currently recommended dose). The inhibition of thrombin generation by idraparinux, as reflected by an increased thrombin generation time (TGT) and decreased level of prothrombin fragment 1+2 (F_{1+2}), was partially reversed by injection of rVIIa 3 h after idraparinux administration. The administration of rVIIa 1 week after treatment with idraparinux (when much lower, though still therapeutic, doses of the pentasaccharide were present) resulted in a nearly complete reversal of anticoagulation, reflected by normalization of thrombin generation time and other markers of thrombin generation. As mentioned, there are no controlled trials in patients who present with pentasaccharide-induced bleeding but there is some anecdotal experience suggesting that rVIIa may indeed be able to stop bleeding in patients anticoagulated with fondaparinux.

Vitamin K Antagonists

When interrupting the administration of VKA's important differences in the half-lives of the various agents (9 h for acenocoumarol, 36–42 h for warfarin, and 90 h for phenprocoumon, respectively) need to be taken into account [39]. The most straightforward intervention to counteract the effect of VKA's is the administration of vitamin K [40]. There is quite some debate on the use of vitamin K in patients with a too high INR but no signs of bleeding. However, a recent randomized controlled trial did not find any difference in bleeding or other complications in nonbleeding patients with INR values of 4.5 to 10 that were treated with vitamin K or placebo [41]. In patients with clinically significant bleeding

administration of vitamin K is crucial to reverse the anticoagulant effect of VKA's. Vitamin K can be given orally and intravenously, whereas the parenteral route has the advantage of a more rapid onset of the treatment [42]. After the administration of i.v. vitamin K, within 2 h the INR will start to drop and will be completely normalized within 12–16 h [43], whereas after oral administration it will take up to 24 h to normalize the INR [40]. Intramuscular injections of vitamin K should be avoided in patients who are anticoagulated and subcutaneous administration of vitamin K results in a less predictable bioavailability [42]. A potential concern with the use of parenteral vitamin K is the occurrence of anaphylactic reactions, although the incidence of this complication is very low, in particular with the more modern micelle preparations [44].

In case of very serious or even life-threatening bleeding, immediate correction of the INR is mandatory and can be achieved by the administration of vitamin K-dependent coagulation factors. Theoretically, these factors are present in fresh frozen plasma, however, the amount of plasma that is required to correct the INR is very large, carries the risk of fluid overload, and will probably take hours to administer [45]. Therefore, prothrombin complex concentrates (PCC's), containing all vitamin K-dependent coagulation factors, are more useful. Although PCC's can indeed be given using fixed dose schemes, it has been shown that individualized dosing regimens based on INR at presentation and body weight are more effective [46]. In a prospective study in patients using VKA and presenting with bleeding also found that PCC's resulted in at least satisfactory and sustained hemostasis in 98 % [47]. In recent years the safety of PCC's, in particular regarding the transmission of blood-borne infectious diseases, has markedly improved owing to several techniques, such as pasteurization, nanofiltration, and addition of solvent detergent. The risk of disseminated intravascular coagulation (DIC) due to traces of activated coagulation factors in PCC's comes from older literature and modern PCC's seem not to be associated with eliciting DIC [48].

New Direct Factor Xa Inhibitors

In recent years a large number of new antithrombotic agents has been developed and tested in clinical trials and many of these new agents will become available for clinical practice in the very near future [49]. The need for new anticoagulant agents is quite obvious; Firstly, the current agents are insufficiently effective. For example 10–15 % of patients undergoing major orthopedic surgery develop venous thromboembolism, despite prophylaxis with low molecular weight (LMW) heparin [50]. Furthermore, the available anticoagulants are relatively unsafe, mostly due to the occurrence of bleeding as discussed hereabove. Lastly, current anticoagulant agents are often cumbersome with regards to their clinical use, requiring repeated laboratory control and frequent dose adjustments. Increasing knowledge on the function of the haemostatic system *in vivo* has resulted in a new generation of anticoagulant agents.

Some of these new class of anticoagulants are directed at factor Xa. Prototypes of these agents are rivaroxaban and apixaban, which have shown promising results in clinical studies [51, 52]. In trials in patients with acute venous thromboembolism rivaroxaban and apixaban were as effective as LMW heparin but rivaroxaban was associated with a lower incidence of bleeding complications (2.2 % versus 8.8 %) [53, 54]. Rivaroxaban was also studied in patients with acute coronary syndromes and showed a dose-dependent efficacy but also increased rates of major bleeding at higher doses [55]. Similarly, apixaban showed a similar pattern and exhibited 2.5 fold increased bleeding rates, in particular in patients using simultaneous anti-platelet agents [56]. Taken together, compared to LMW heparin direct factor Xa inhibitors result at doses achieving equivalent efficacy a lower bleeding risk and at doses achieving higher efficacy a similar bleeding risk. This means that for some clinical situations these drugs may represent an important improvement, however, the risk of (major) bleeding is still present. Recently it was shown that the administration of prothrombin complex concentrate

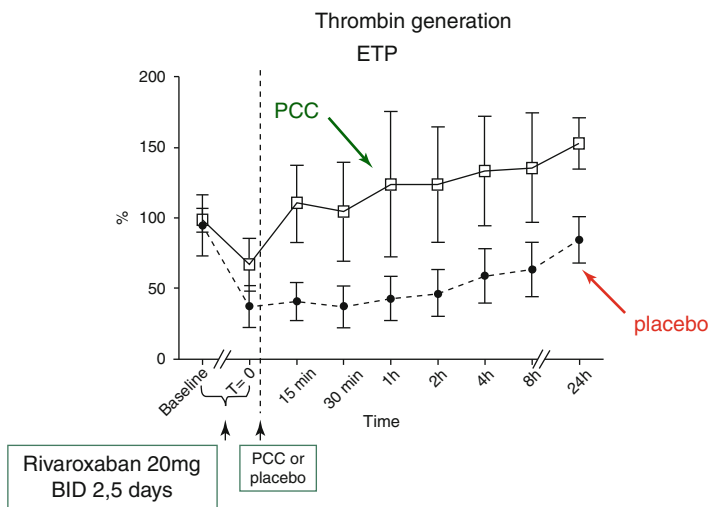


FIGURE 7.1 Restoration of rivaroxaban-induced impaired thrombin generation, measured by endogenous thrombin potential (ETP), by administration of prothrombin complex concentrates (squares) as compared to placebo (circles) in healthy volunteers. Mean \pm SD are reported, the difference between the two groups is statistically significant ($p < 0.001$ Repeated Measures ANOVA)

(PCC) resulted in a correction of the prolonged prothrombin time and restored depressed thrombin generation after rivaroxaban treatment in a controlled trial in healthy human subjects (Fig. 7.1) [57]. The effect of PCC's on reversal of the anticoagulant effect of oral factor Xa inhibitors was confirmed in a series of experiments in animals and human subjects [58–60]. The clinical efficacy in bleeding patients, however, needs to be established.

Direct Thrombin Inhibitors

Another important group of new anticoagulants is the class of direct thrombin inhibitors. Thrombin is the central enzyme in the coagulation process, not only mediating the conversion

of fibrinogen to fibrin, but also being the most important physiological activator of platelets and various other coagulation factors. Inhibition of thrombin can be achieved by administration of heparin, but in view of the limited capability of the heparin-antithrombin complex to inhibit surface-bound thrombin, new antithrombin-independent anticoagulants have been developed [61]. Prototype of these thrombin inhibitors is hirudin, originally derived from the saliva from leeches (*hirudo medicinalis*) and nowadays produced by recombinant technology. Melagatran is a synthetic thrombin inhibitor, which has predictable pharmacokinetic properties and can thus be used in a fixed dose [62]. Moreover, the pro-drug ximelagatran is relatively quickly absorbed after oral ingestion and results in a sufficient systemic availability, rendering this agent suitable for long-term use as oral anticoagulant. Despite clinical trials on prevention and treatment of venous thromboembolism and in patients with atrial fibrillation showing a promising efficacy of ximelagatran, the compound has been withdrawn by the manufacturer, due to the occurrence of enhanced liver enzymes in 6–7 % of patients. Recently, dabigatran, also a direct thrombin inhibitor with good and relatively stable bioavailability after oral ingestion, has been introduced and licensed for prevention of venous thromboembolism after orthopedic surgery. Indeed, clinical trials evaluating dabigatran against LMW heparin in patients undergoing major orthopedic surgery show similar or slightly better efficacy of the direct thrombin inhibitor and similar bleeding rates [63, 64]. The largest group of patients using long-term anticoagulants, however, are those with atrial fibrillation. In these patients dabigatran (150 mg twice daily) showed a significantly lower rate of thromboembolic complications compared to warfarin (relative risk 0.66; 95 % confidence interval 0.53–0.82) but also a slightly lower risk of major hemorrhage (3.11 %/year in the dabigatran group versus 3.36 %/year in the warfarin group) [65]. Based on these findings and if confirmed by other ongoing major trials, it may be quite likely that in the future oral anticoagulant treatment with vitamin K antagonists

is going to be replaced by treatment with directly acting anticoagulants, such as direct thrombin inhibitors. However, the risk of major bleeding is still relatively large and requires adequate management strategies.

For each of the direct thrombin inhibitors no established antidote is available in case of serious bleeding complicating the anticoagulant treatment. Again, the half-life of most of the agents is relatively short, hence in case of less serious bleeding interruption of treatment will be sufficient to reverse the anticoagulant effect. However, if immediate reversal is required, it is not clear which would be the best strategy. In a controlled clinical study in healthy subjects the melagatran-induced effects on aPTT, thrombin generation and platelet activation were not affected by the administration of rVIIa [66]. Also, in human subjects challenged with dabigatran there was no reversal of the anticoagulation by administration of prothrombin complex concentrates [57]. An experimental study of intracerebral hematoma in dabigatran-treated rats, however, demonstrated that relatively high doses of prothrombin complex concentrates were able to reduce hematoma volume [67].

Aspirin

Aspirin is effective in the secondary prevention of atherothrombotic disease, in particular coronary artery disease, cerebrovascular thromboembolism and peripheral arterial disease [68]. As a consequence, aspirin is one of the most widely used agents in the Western world. Aspirin increases the risk of bleeding, in particular gastro-intestinal bleeding, and has been associated with a small but consistent increase in intracerebral hemorrhage. In addition, it has been shown that the use of aspirin is associated with increased perioperative blood loss in major procedures, although this does not necessarily translate into clinically relevant endpoints, such as the requirement for transfusion or re-operation [69]. Over

the last years the approach to the patient who uses aspirin and who presents with bleeding or needs to undergo an invasive procedure has changed considerably. In fact, in current clinical practice bleeding can almost always be managed with local hemostatic procedures or conservative strategies without interrupting aspirin and also most invasive procedures do not require the cessation of aspirin when adequate attention is given to local hemostasis. In contrast, interruption of aspirin has been associated with an increased risk of thromboembolic complications, potentially due to a rebound hypercoagulability. Obviously, in special clinical circumstances, such as intracranial bleeding or the need to undergo a neurosurgical or ophthalmic procedure, the anti-hemostatic effect of aspirin needs to be reversed immediately. The most rigorous measure to achieve that is the administration of platelet concentrate after cessation of aspirin. Another approach is the administration of de-amino d-arginin vasopressin (DDAVP, desmopressin). DDAVP is a vasopressin analogue that despite minor molecular differences has retained its antidiuretic properties but has much less vaso-active effects [70]. DDAVP induces release of the contents of the endothelial cell associated Weibel Palade bodies, including von Willebrand factor. Hence, the administration of DDAVP results in a marked increase in the plasma concentration of von Willebrand factor (and associated coagulation factor VIII) and (also by yet unexplained additional mechanisms) a remarkable augmentation of primary hemostasis as a consequence. DDAVP is effective in patients with mild hemophilia A or von Willebrand's disease and in patients with qualitative platelet defects, such as in uremia or liver cirrhosis. DDAVP seems also capable of correcting the aspirin-induced platelet dysfunction, although large clinical studies employing relevant outcome parameters are missing [71]. The combined effect of platelet concentrate and subsequent administration of DDAVP has also been advocated to correct the aspirin effect on platelets. The standard dose of DDAVP is 0.3–0.4 µg/kg in 100 ml saline over 30 min and its effect is immediate.

Thienopyridine Derivatives

Clopidogrel, prasugrel and ticagrelor belong to the class of thienopyridine derivatives, which act by blocking the adenosine diphosphate (ADP) receptor on the platelet. Clinical studies have shown that clopidogrel is as good as aspirin in the secondary prevention of atherothrombotic events [72]. Importantly, the combination of aspirin and clopidogrel is vastly superior over aspirin alone in patients who have received intracoronary stents or in other patients with high risk coronary artery disease. There is ample evidence that dual platelet inhibition of aspirin plus clopidogrel has a significantly higher efficacy than aspirin alone in patients with acute coronary syndromes who have undergone coronary interventions for at least a year (and possibly longer) after the event. However, the increased efficacy of the combined use of aspirin and clopidogrel is also associated with a significantly higher bleeding risk [73]. Prasugrel is another thienopyridine derivative that after rapid and almost complete absorption after oral ingestion irreversibly binds to the ADP receptor. Prasugrel has a stronger anti-platelet effect than clopidogrel because of more effective metabolism and less dependence of cytochrome P450 enzymes that may be subject to genetic polymorphisms [74]. Prasugrel was shown to be more effective than clopidogrel in preventing ischemic events in patients with ST elevation myocardial infarction undergoing primary percutaneous coronary interventions (with or without stent) [75]. Rates of major bleeding were similar between clopidogrel and prasugrel, however, the rate of serious bleeding in patients requiring emergency coronary artery bypass grafting (CABG) was higher in the prasugrel group. In patients with acute coronary syndromes prasugrel was also more effective than clopidogrel in preventing cardiovascular death, myocardial infarction and stroke, however, major bleeding rates were higher in the prasugrel group (2.4 % versus 1.8 %) [76]. Of note, this disadvantage of prasugrel did not outweigh the efficacy benefit, and the net clinical benefit (defined as the efficacy gain minus the increased

risk of major bleeding) was preserved in favour of prasugrel. Ticagrelor is a cyclopentyltriazolopyrimidine that differs from thienopyridines (ticlopidin, clopidogrel, prasugrel), as ticagrelor is not a prodrug requiring active biotransformation by cytochromes in the liver and thus is characterized by a more rapid, more effective and more consistent platelet inhibition than ticlopidin or clopidogrel [77]. The Platelet Inhibition and Patient Outcomes (PLATO) trial determined whether ticagrelor was superior to clopidogrel for the prevention of vascular events and death in a broad population of patients presenting with an acute coronary syndrome [78]. Treatment with ticagrelor as compared with clopidogrel significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke. The ticagrelor and clopidogrel groups did not differ significantly with regard to the rates of major bleeding as defined in the trial or according to the Thrombolysis in Myocardial Infarction (TIMI) criteria. The two treatment groups did not differ significantly in the rates of CABG-related major bleeding or bleeding requiring transfusion of red cells. However, in the ticagrelor group, there was a higher rate of non-CABG-related major bleeding according to the study criteria and the TIMI criteria. With ticagrelor as compared with clopidogrel, there were more episodes of intracranial bleeding, including fatal intracranial bleeding. However, there were fewer episodes of other types of fatal bleeding in the ticagrelor group. Recently, a fourth thienopyridine derivative has been introduced: cangrelor. The advantage of this compound over the other members of this group is the faster onset of action, which may be critical in acute coronary syndromes. However, two major clinical trials comparing cangrelor with clopidogrel in patients undergoing percutaneous coronary interventions did not show a higher efficacy of cangrelor but did demonstrate a significantly higher risk of bleeding [79, 80]. Taken together, dual platelet inhibition, in particular with clopidogrel or even more outspoken with prasugrel, is highly effective in high risk patients with coronary artery disease but the bleeding risk with dual platelet inhibition is something to take into account and

strategies to reverse the antiplatelet effect may be warranted in case of serious bleeding.

The decision whether or not to interrupt or even reverse antithrombotic treatment with dual platelet inhibition in case of serious bleeding or the need to perform an invasive procedure will depend on the specific clinical situation but also on the indication for the antithrombotic treatment (see above). Especially in patients with recent implantation of an intracoronary stent (in the last 6–12 weeks), cardiologists will often not or only reluctantly agree with cessation of treatment [81]. In this period re-endothelization of the stent has not yet occurred and the patient is very vulnerable to acute thrombotic occlusion of the stent. In patients with drug-eluting stents this period may be even longer. If, however, the decision is made to stop and even reverse the treatment with aspirin and clopidogrel, administration of platelet concentrate is probably the best way to correct the hemostatic defect [82]. In addition, DDAVP was shown to correct the defect in platelet aggregation caused by clopidogrel, so this may be another option [83].

Conclusion

Conventional anticoagulant treatment can be reversed by specific interventions when the clinical situation requires immediate correction of hemostasis. For the new generation of anticoagulants, no specific antidotes are available, although some interventions are promising but need further evaluation. Antiplatelet therapy with aspirin, alone or in combination with thienopyridine derivatives, such as clopidogrel and prasugrel, can be reversed but this is often not required and sometimes not desirable in view of the indication for this treatment.

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