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REVIEW

Bleeding in patients using new anticoagulants or antiplatelet agents: risk factors and management

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ABSTRACT

The most important adverse effect of antithrombotic treatment is the occurrence of bleeding. In case of serious or even life-threatening bleeding in a patient who uses anticoagulant agents or when patient on anticoagulants needs to undergo an urgent invasive procedure, anticoagulant treatment can be reversed by various specific strategies. Heparin and heparin derivatives can be counteracted by protamine sulphate, whereas the anticoagulant effect of vitamin K antagonists may be neutralised by administration of vitamin K or prothrombin complex concentrates. The antihaemostatic effect of aspirin and other antiplatelet strategies can be corrected by the administration of platelet concentrate and/or desmopressin, if needed. Recently, a new generation of anticoagulants with a greater specificity towards activated coagulation factors has been introduced and most of these agents are currently being evaluated in clinical studies, showing promising results. The new-generation anticoagulants include specific inhibitors of factor IIa or factor Xa (including pentasaccharides) and antiplatelet agents belonging to the class of thienopyridine derivatives. A limitation of the new class of anti-IIa and anti-Xa agents may be the lack of an appropriate strategy to reverse the effect if a bleeding event occurs, although in some cases the administration of recombinant factor VIIa may be an option.

KEYWORDS

Anticoagulants, haemorrhage, heparin, pentasaccharides, vitamin K antagonists, aspirin, clopidogrel, prasugrel, cangrelor

INTRODUCTION

Anticoagulant agents are usually for prevention and treatment of a wide range of cardiovascular diseases. 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 thromboembolic complications, such as in patients with atrial fibrillation or prosthetic heart valves, after myocardial infarction, percutaneous coronary interventions, or ischaemic stroke, and in patients with venous thrombosis or pulmonary embolism.[1] The most important complication of treatment with anticoagulants is haemorrhage, which may be serious, may cause long-term debilitating disease, or may even be life-threatening.[2] In a very large series of 34,146 patients with acute ischaemic coronary syndromes, anticoagulant-associated bleeding was associated with a fivefold increased risk of death during the first 30 days and a 1.5-fold higher mortality between 30 days and six months.[3] Major bleeding was an independent predictor of mortality across all subgroups that were analysed. 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 ischaemic stroke by vitamin K antagonists.[4] Nevertheless, in many situations clinical studies show a favourable balance between efficacy and safety in favour 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 required to reverse the anticoagulant effect of the various agents. Depending on the clinical situation, i.e. the severity of the

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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 1*).[5] Generally, each (immediate) reversal of anticoagulant treatment also needs 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 an intracoronary stent has recently been inserted will markedly increase the risk of acute stent thrombosis with consequent downstream cardiac ischaemia 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 article, we will describe the various strategies to reverse the anticoagulant effect of the currently most widely used antithrombotic agents and the new generation of anticoagulants.

INCIDENCE AND RISK FACTORS FOR BLEEDING IN PATIENTS ON VKAS

Vitamin K antagonists (VKAs) (such as warfarin, coumadin, acenocoumarol or phenprocoumon) are often used for prevention and treatment of a wide range of cardiovascular diseases. The most important complication of treatment with these agents is haemorrhage, which may be life-threatening.[2] In well-controlled patients in clinical trials treatment with VKAs increases the risk of major bleeding by 0.5%/year and the risk of intracranial haemorrhage by about 0.2%/year.[6]

The most important risk factor for haemorrhage in users of VKAs is the intensity of the anticoagulant effect.[6] Studies indicate that with a target INR of >3.0 the incidence of major bleeding is twice as high as in studies with a target INR of 2.0 to 3.0.[7] 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 haemorrhage with a similar antithrombotic efficacy.[8] A retrospective analysis of outpatients using warfarin who presented with intracranial haemorrhage demonstrated that the risk of this complication doubled for each 1 unit increment of the INR.[9] Patient characteristics constitute another important determinant of the risk bleeding. Elderly patients have a twofold increased risk of bleeding[10] and the relative risk of intracranial haemorrhage (in particular at higher INRs) was 2.5 (95% CI 2.3 to 9.4) in patients >85 years compared with patients 70 to 74 years.[11] 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 VKAs and (possibly) a higher risk of bleeding.[6,12] Other genetic factors that may influence the requirement of VKAs are variants in the vitamin K epoxide reductase complex subunit 1 gene (*VKORC1*).[13] Comorbidity, such as renal or hepatic insufficiency, may also significantly increase the risk of bleeding. A case-control study in 1986 patients on VKAs showed that this comorbidity increased

Table 1.

	Time until restoration of haemostasis after cessation of therapeutic dose	Antidote	Remark
Heparin	3-4 hrs	Protamine sulphate 25-30 mg; immediate reversal	1 mg of protamin per 100 anti-Xa units given in the last 2-3 hrs
LMW heparin	12-24 hrs	(Partially) protamine sulphate 25-50 mg; immediate reversal	1 mg of protamine per 100 anti-Xa units given in the last 8 hrs
Pentasaccharides	Fondaparinux: 24-30 hrs Idraparinux: 5-15 days	Recombinant factor VIIa 90 µg/kg (?); immediate thrombin generation	Based on laboratory endpoints, no systematic experience in bleeding patients
Vitamin K antagonists	Acenocoumarol: 18-24 hr Warfarin: 60-80 hrs Phenprocoumon: 8-10 days	Vitamin K iv; reversal in 12-16 hrs Vitamin K orall;: reversal in 24 hrs PCCs: immediate reversal	Dose of vitamin K or PCCs depends on INR and bodyweight
Oral thrombin and factor Xa inhibitors	Dependent of compound, usually within 12 hrs	Recombinant factor Xa for Xa inhibitors, unsure for IIa inhibitors	Based on laboratory endpoints, no systematic experience in bleeding patients
Aspirin	5-10 days (time to produce unaffected platelets)	DDAVP (0.3-0.4 µg/kg) and/or platelet concentrate; reversal in 15-30 min	Cessation not always required, also dependent on clinical situation and indication
Clopidogrel Prasugrel	1-2 days	Platelet concentrate, possibly in combination with DDAVP (0.3-0.4 µg/kg); reversal in 15-30 min	Cessation not always desirable, also dependent on clinical situation and indication

LMW heparin = low-molecular-weight heparin; PCC = prothrombin complex concentrate; DDAVP = de-amino d-arginin vasopressin or desmopressin.

the risk of bleeding by about 2.5.[14] 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 six trials with a total of 3874 patients and ten trials with a total of 5938 patients, found a relative risk of major bleeding when VKAs were combined with aspirin of 2.4 (95% CI 1.2 to 4.8) and 2.5 (95% CI 1.7 to 3.7), respectively.[15,16] A population-based case-control study confirmed the high risk of upper gastrointestinal bleeding in patients using VKAs in combination with aspirin and/or clopidogrel.[17] Nonsteroidal anti-inflammatory agents (NSAIDs) are also associated with an enhanced risk of gastrointestinal bleeding. The combined use of VKAs and NSAIDs may result in an 11-fold higher risk of hospitalisation for gastrointestinal bleeding as compared with the general population.[18] This risk is not significantly lower when using selective inhibitors of COX-2.[19]

In case of major bleeding it may be required to reverse the anticoagulant effect of the various agents.[5] When interrupting the administration of VKAs important differences in the half-lives of the various agents (9 hours for acenocoumarol, 36-42 hours for warfarin, and 90 hours for phenprocoumon, respectively) need to be taken into account.[20] The most straightforward intervention to counteract the effect of VKAs is the administration of vitamin K.[21] 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 randomised controlled trial did not find any difference in bleeding or other complications in nonbleeding patients with INR values of 4.5 to 10 who were treated with vitamin K or placebo.[22] In patients with clinically significant bleeding, administration of vitamin K is crucial to reverse the anticoagulant effect of VKAs. Vitamin K can be given orally and intravenously, whereas the parenteral route has the advantage of a more rapid onset of the treatment.[23] After the administration of intravenous vitamin K, the INR will start to drop within two hours and will be completely normalised within 12 to 16 hours,[24] whereas after oral administration it will take up to 24 hours to normalise the INR.[21] 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.[23] 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.[25]

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.[26] Therefore, prothrombin complex concentrates (PCCs), containing all vitamin K-dependent coagulation factors, are more useful. Although PCCs can indeed be given using fixed dose schemes, it has been shown that individualised dosing regimens based on INR at presentation and body weight are more effective.[27] A prospective study in patients using VKA and presenting with bleeding also found that PCCs resulted in at least satisfactory and sustained haemostasis in 98%.[28] In recent years the safety of PCCs, in particular regarding the transmission of blood-borne infectious diseases, has markedly improved owing to several techniques, such as pasteurisation, nanofiltration, and addition of solvent detergent. The risk of disseminated intravascular coagulation (DIC) due to traces of activated coagulation factors in PCCs comes from older literature and modern PCCs do not seem to be associated with eliciting DIC.[27]

HEPARIN AND LOW-MOLECULAR-WEIGHT (LMW) HEPARIN

Herparin and heparin derivatives act by binding to antithrombin and thereby about 1000-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 to 90 minutes and therefore the anticoagulant effect of therapeutic doses of heparin will be mostly eliminated at three to four hours after termination of continuous intravenous administration.[30] The anticoagulant effect of high-dose subcutaneous heparin, however, will take a longer time to abolish. If a more immediate neutralisation 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 neutralise approximately 100 units of heparin. Hence, the protamine dose in a patient on a stable therapeutic heparin dose of 1000 to 1250 U/h should be about 25 to 30 mg (sufficient to block the amount of heparin given in the last two to three hours). The maximum dose of protamine is 50 mg. Since the half-life of protamine is only about ten minutes, the reversal of therapeutic dose subcutaneous heparin requires a repeated infusion of protamine sulphate (e.g. repeated after one hour). The effect of protamine can be monitored by measuring the activated partial thromboplastin time (aPTT), which should normalise after its administration.

The reversal of LMW heparin is more complex, as protamine sulphate will only neutralise 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.[31,32] 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.[32-34] As the aPTT is not useful as a monitoring assay when using LMW heparin, it can not be used for the monitoring of the neutralising effect of protamine either. 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 eight hours (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 haemodynamic and respiratory problems.[35] Most adverse reactions can be prevented or minimised 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 antisemen 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 ischaemic stroke[36,37] were not confirmed in a recent randomised controlled study.[38]

There are some other strategies to reverse (mostly unfractionated) 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.[39-41]

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, they have 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 to 20 hours for fondaparinux and $5^1/_2$ 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.[42] 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 who are treated with therapeutic doses of this type of anticoagulation. So far, there is no antidote for the pentasaccharides that have been studied in controlled clinical studies.[43] The only agent that has been systematically evaluated to reverse the anticoagulant effect of pentasaccharides is recombinant factor VIIa (rVIIa). Two randomised placebo-controlled studies in healthy volunteers have tested the hypothesis that rVIIa may be useful as a suitable antidote for pentasaccharide anticoagulation.[44,45] In the first study, 16 subjects were treated with therapeutic doses of the pentasaccharide fondaparinux and after two hours (at the time of maximal anticoagulation) challenged with rVIIa or placebo. Injection of rVIIa (90 μg/kg) after fondaparinux normalised 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, normalised up to six hours after rVIIa injection. In the second study 12 subjects received a single subcutaneous dose of 7.5 mg idraparinux (which is threefold 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 three hours after idraparinux administration. The administration of rVIIa one week after treatment with idraparinux (when much lower, though still therapeutic, doses of the pentasaccharide were present) resulted in an nearly complete reversal of anticoagulation, reflected by normalisation 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.

NEW DIRECT FACTOR XA INHIBITORS

In recent years a large number of new antithrombotic agents have been developed and tested in clinical trials and many of these new agents will become available for clinical practice in the very near future.[46] The need for new anticoagulant agents is quite obvious. Firstly, the current agents are insufficiently effective. For example, 10 to 15% of patients undergoing major orthopaedic surgery develop venous thromboembolism, despite prophylaxis with low-molecular-weight (LMW) heparin.[47] Furthermore, the available anticoagulants are relatively unsafe, mostly due to the occurrence of bleeding as

discussed above. 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 classes of anticoagulants are directed at factor Xa. Prototypes of these agents are rivaroxaban and apixaban, which have shown promising results in initial experimental and clinical studies.[48,49] Rivaroxaban was evaluated in a series of trials in patients undergoing major orthopaedic surgery (RECORD studies), which showed a higher efficacy of the direct anti-Xa inhibitor compared with enoxaparin and similar bleeding rates.[50,51] Apixaban was also compared with enoxaparin in patients undergoing knee replacement surgery and was shown to be equally effective but had significantly less bleeding complications (2.9% in the apixaban group compared with 4.3% in the enoxaparin group).[52] In dose-ranging 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 *vs* 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 antiplatelet agents.[56] Taken together, compared with LMW heparin, direct factor Xa inhibitors result in a lower bleeding risk at doses achieving equivalent efficacy and a similar bleeding risk at doses achieving higher efficacy. This means that for some clinical situations these drugs may represent an important improvement; however, the risk of (major) bleeding is still present.

Dependent on the severity of the clinical situation and in view of the half-life of the direct Xa inhibitors, cessation of medication may be sufficient to reverse the anticoagulant effect in case of bleeding. However, if immediate reversal of anticoagulation is required, there is no evidence of any antidotes against the anticoagulant effect of any of these orally available factor Xa inhibitors so far. Based on the experience with rVIIa in the reversal of the anticoagulant effect of fondaparinux, one can postulate that rVIIa may be an effective antidote for these agents; however, direct proof has not been demonstrated.

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.[57] The 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.[58] 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 an oral anticoagulant. Despite clinical trials on prevention and treatment of venous thromboembolism and in patients with atrial fibrillation showing a promising efficacy of (xi) melagatran, the compound has been withdrawn by the manufacturer due to the occurrence of enhanced liver enzymes in 6 to 7% of patients. Recently, dabigatran, also a direct thrombin inhibitor with good and relatively stable bioavailability after oral ingestion, was introduced and licensed for prevention of venous thromboembolism after orthopaedic surgery. Indeed, clinical trials evaluating dabigatran against LMW heparin in patients undergoing major orthopaedic surgery show similar or slightly better efficacy of the direct thrombin inhibitor and similar bleeding rates.[59,60] 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 with warfarin (relative risk 0.66; 95% CI 0.53 to 0.82) but also a slightly lower risk of major haemorrhage (3.11% per year in the dabigatran group *vs* 3.36% per year in the warfarin group).[61] 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.

No established antidote is available in case of serious bleeding complicating the anticoagulant treatment for any of the direct thrombin inhibitors. Again, the half life of most of the agents is relatively short, hence with 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.[62] Based on

these results it seems that rVIIa is not effective in reversing direct thrombin inhibition. Since, however, rVIIa was able to correct the melagatran-induced prolongation of the prothrombin time and increased thrombin precursor protein concentrations, it might be that higher doses of rVIIa will have some effect in this situation, but this needs to be studied in future experiments.

ASPIRIN

Aspirin is effective in the secondary prevention of atherothrombotic disease, in particular coronary artery disease, cerebrovascular thromboembolism and peripheral arterial disease.[63] As a consequence, aspirin is one of the most widely used agents in the Western world. Aspirin increases the risk of bleeding, in particular gastrointestinal bleeding, and has been associated with a small but consistent increase in intracerebral haemorrhage. 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 reoperation.[64] 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 haemostatic 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 haemostasis. 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 antihaemostatic 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 vasoactive effects.[65] 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 haemostasis as a consequence. DDAVP is effective in patients with mild haemophilia A or von Willebrand's disease and in patients with qualitative platelet defects, such as in uraemia or liver cirrhosis. DDAVP also seems capable of correcting the aspirin-induced platelet dysfunction, although large clinical studies employing relevant outcome parameters are missing.[66] 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 to 0.4 μg/kg in 100 ml saline over 30 minutes and its effect is immediate.

THIENOPYRIDINE DERIVATIVES

Clopidogrel and prasugrel 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.[67] 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.[68] 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 antiplatelet effect than clopidogrel because of more effective metabolism and less dependence on cytochrome P450 enzymes that may be subject to genetic polymorphisms.[69] Prasugrel was shown to be more effective than clopidogrel in preventing ischaemic events in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary interventions (with or without stent).[70] 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 *vs* 1.8%).[71] 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. Recently, a third 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.[72,73] 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 the 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 to 12 weeks), cardiologists will often not or only reluctantly agree to cessation of treatment.[74] In this period re-endothelialisation 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 haemostatic defect.[75] In addition, DDAVP was shown to correct the defect in platelet aggregation caused by clopidogrel, so this may be another option.[76]

CONCLUSION

Conventional anticoagulant treatment can be reversed by specific interventions when the clinical situation requires immediate correction of haemostasis. 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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