

Anticoagulant treatment: the end of the old agents?

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Summary

New oral anticoagulants used as single target inhibitors of coagulation enzymes have been developed and tested in extensive trial programmes. Results of most of these trials showed non-inferior and/or superior efficacy and safety compared to standard treatment with LMWH or VKA. These results led to registration of these agents for the prophylaxis or treatment of thrombosis, as well as stroke prophylaxis in atrial fibrillation. In addition to good efficacy and safety these agents are more convenient in their use and promise advantages in quality of life. Caution is needed, though, since drug-interactions, interferences with coagulation tests and risk of accumulation in case of renal failure should always be taken into consideration when planning a treatment. In the present current-opinion review these advantages and disadvantages are discussed and expressed options are analysed.

Key words: *new anticoagulants; thrombosis treatment; stroke prophylaxis; factor Xa inhibitors; factor IIa inhibitors; rivaroxaban; dabigatran; apixaban*

Abbreviations

APTT	activated partial thromboplastin time
AUC	area under the curve
CYP3A4	cytochrome P ₄₅₀ 3A4
EU	European Union
FIIa	activated coagulation factor II = thrombin
FXa	activated coagulation factor X
GI	gastrointestinal
HIT	heparin-induced thrombocytopenia
INR	international normalised ratio
LMWH	low molecular weight heparin
MI	myocardial infarction
PCC	prothrombin complex concentrate
p-gp	p-glycoprotein
PT	prothrombin time
rFVIIa	recombinant activated coagulation factor VII
TTR	time in therapeutic range
VKA	vitamin K antagonist
VTE	venous thromboembolism

Introduction

In early 2012, heparins and coumarin derivatives are still the most commonly used anticoagulants worldwide. Heparin, a naturally occurring glycosaminoglycan was first isolated in 1916 by Jay McLean at the Johns Hopkins Medical School, Baltimore, USA [1] but it did not enter clinical trials before 1935. Half a century later, low molecular weight heparins (LMWH) with a more predictable effect were introduced to the market.

The first coumarin derivative was crystallised 1940 by Karl Link and co-workers [2]. Fourteen years later coumadin (Warfarin[®]) was approved for the use as a medication and since then has become the most widely prescribed oral anticoagulant drug in North America. Later, other vitamin K antagonists (VKA) such as phenprocoumon or acenocoumarol that differ mainly in their half-life were developed and introduced for clinical use.

Despite their beneficial effects both coumarin derivatives and heparins have several disadvantages. The pharmacokinetics of coumarin derivatives are variable due to genetic polymorphisms, their therapeutic window is rather small, they interact with a multitude of other drugs, both latency until onset of effect and half-life are long, and the effect is furthermore dependent on nutritional vitamin K uptake. Heparins can provoke an immunologic reaction, called heparin-induced thrombocytopenia (HIT), which is potentially life-threatening [3] and if given over a long period, side effects such as osteoporosis and alopecia can occur. Furthermore, only a parenteral application of heparins is possible.

All these disadvantages urged the search for new anticoagulants with better pharmacokinetic characteristics and good safety profiles.

New anticoagulants

In recent years, two targets within the coagulation cascade have been found to lead to an effective antithrombotic effect when inhibited: activated factor X (FXa) and thrombin (FIIa).

Fondaparinux, which was approved in 2001, was the first selective FXa inhibitor. It is a synthetic pentasaccharide, which is given subcutaneously and mediates its effect indir-

ectly through antithrombin. Fondaparinux was a milestone in anticoagulation because it provided the proof of the concept of selective FXa-Inhibition, providing excellent results in all major studies [4, 5]. However, its parenteral route of administration, elimination half-life of 17h, renal clearance as well as dosing frequency and bleeding complications similar to LMWH practically limited its main advantage to cases with heparin-induced thrombocytopenia or allergic reactions to the other LMWH [6]. Officially fondaparinux is registered for use in postoperative thrombosis prophylaxis, treatment of acute thrombosis and pulmonary embolism, prophylaxis in internal medicine as well as in the treatment of acute coronary events.

The direct thrombin inhibitor ximelagatran that was first approved in 2003 was believed to be a breakthrough in oral anticoagulation. But the substance had to be withdrawn and further development was discontinued in 2006 due to a high incidence of hepatotoxicity [7]. Since then, several other oral anticoagulants have been developed and three of them have now found place in clinical practice: the direct FXa inhibitors rivaroxaban, apixaban, and the direct thrombin inhibitor dabigatran etexilate. Further FXa inhibitors are in development.

Pharmacokinetic characteristics of direct FXa-Inhibitors

Rivaroxaban and apixaban are highly selective and reversible inhibitors of FXa (table 1). After oral intake, peak levels are reached within 1–3 hours and all substances reveal similar half-life times of between 7–14 h. Pharmacokinetic and pharmacodynamic properties of these agents are shown in table 1 [8]. Because of their relatively high bioavailability and the predictable pharmacokinetic, a routine monitoring of the anticoagulatory effect is not necessary [9].

Pharmacokinetic characteristics of dabigatran etexilate

In contrast to the described oral FXa Inhibitors the reversible direct thrombin inhibitor dabigatran etexilate shows a rather low oral bioavailability of only 6%. As dabigatran itself shows no oral absorption its pro-drug dabigatran etexilate was developed for this purpose. Dabigatran etexilate is converted to dabigatran by microsomal carboxylesterases in the liver. Due to the low bioavailability high doses of dabigatran etexilate are needed to maintain an adequate anticoagulatory effect. Elimination half-life of dabigatran is 14–17 h and thus somewhat longer than

the half-life times of the direct FXa-inhibitors [8]. More than 80% of the substance is eliminated by the kidneys which has the implication that it can accumulate in case of renal insufficiency but it can also be removed by haemodialysis [10].

Clinical study programmes

All new anticoagulants underwent or are still undergoing extensive phase III study programmes. These programmes cover both acute and chronic indications. Dabigatran etexilate (RE-NOVATE [11], RE-NOVATE II [12], RE-MODEL [13]), rivaroxaban (RECORD-1, RECORD-2, RECORD-3 [14–16]) and apixaban (ADVANCE-2, ADVANCE-3 [17, 18]) showed all at least a non-inferiority compared to enoxaparin 40 mg once daily for the prevention of venous thromboembolism (VTE) after total knee or hip replacement. If compared to the North American approved enoxaparin-regimen for VTE-prophylaxis after knee replacement (30 mg twice daily) rivaroxaban was even superior (RECORD-4 [19]) in contrast to both dabigatran etexilate (RE-MOBILIZE [20]) and apixaban (ADVANCE-1 [21]) that failed to show non-inferiority with the dosages used. However, these results do not inherently conflict with those mentioned above. The results of the trials mentioned are listed in table 2.

At least non-inferiority was found for stroke prevention comparing the new substances to warfarine (dabigatran etexilate: RE-LY [22], rivaroxaban: ROCKET-AF [23]; apixaban: ARISTOTLE [24]). Dabigatran etexilate and rivaroxaban have also already completed the study programme for treatment of symptomatic VTE (dabigatran etexilate: RE-COVER [25], RE-SONATE; rivaroxaban: EINSTEIN-DVT [26], EINSTEIN-PE [27] and EINSTEIN-Extension [26]).

The results of all these studies were the basis for the registration of the new anticoagulants in Europe (EU) and Switzerland (CH) for VTE-prophylaxis after hip or knee replacement (dabigatran etexilate [EU only], rivaroxaban, apixaban), for treatment of deep vein thrombosis (rivaroxaban) and stroke prevention in atrial fibrillation (rivaroxaban, dabigatran etexilate). Furthermore, rivaroxaban and apixaban were studied in VTE-prevention in medically ill patients with conflicting results. All three agents were also studied for secondary prevention of acute coronary syndromes. Only rivaroxaban (ATLAS-2 [28]) showed additional benefit if added on top of all other treatment. Studies with dabigatran etexilate or apixaban for the same in-

Table 1: Comparison of pharmacokinetic and pharmacodynamic properties of three new oral anticoagulants.

	Apixaban	Rivaroxaban	Dabigatran
C_{max}	3–4 h	2–3 h	2 h
T_{1/2}	8–15 h	7–11 h	14–17 h
Elimination	27% renal 73% hepatic	33% renal active 33% renal inactive 33% hepatic	80% renal 20% hepatic
Dosis regimen	2×/d	1×/d	1×/d, 2×/d
Monitoring	No	No	No
Interactions	CYP3A4 P-gp	CYP3A4 P-gp	P-gp
Interferences	Yes	Yes	Yes
HIT-II	No	No	No

dication had to be prematurely stopped because of higher bleeding rates in the test arm.

Anti-IIa or anti-Xa?

The concept of single enzymes as target for anticoagulant activity is emerging as an efficient innovation in the development of new anticoagulants. Both FXa and FIIa are key-enzymes in the coagulation process. But, does inhibition of one perform better than the other? We cannot answer this question definitely yet. There are advantages and disadvantages for both options. Until now no head-to-head comparisons of the new substances have been performed and due to different study protocols and study populations the

study results of the different substances are hard to compare.

An issue, which has additionally been discussed in the literature and still remains open, is the possibility of thrombogenic effects (myocardial infarctions, MI) induced by the thrombin Inhibitor dabigatran [29, 30]. In certain studies and in a meta-analysis a higher rate of MIs has been described in comparison to the vitamin K antagonists. This does not seem to be a class effect but rather unmasks a missing protective action, which is present with the VKA. Theoretically through, thrombin inhibition might block or delay activation of protein C by reducing binding of thrombin to thrombomodulin on the endothelial cells, a necessary step in protein C activation. This in turn might function as a procoagulant phenomenon in certain cases, since activated

Table 2: List of the clinical studies (phase III) of dabigatran etexilate, rivaroxaban, and apixaban.

Trial	Indication	Treatment	Results
RE-NOVATE	VTE-prophylaxis after hip replacement	Dabigatran 150 mg/d for 28–35 days vs dabigatran 220 mg/d for 28–35 days vs enoxaparin 40 mg/d for 28–35 days	Primary outcome (VTE): both dabigatran doses non-inferior to enoxaparin for efficacy ($p < 0.001$); major bleeding rates: no differences for both dabigatran doses compared to enoxaparin ($p = 0.44$ for 220 mg, $p = 0.60$ for 150 mg)
RE-NOVATE II	VTE-prophylaxis after hip replacement	Dabigatran 220 mg/d for 28–35 days vs enoxaparin 40 mg/d for 28–35 days	Primary outcome (VTE): dabigatran non-inferior to enoxaparin for efficacy ($p < 0.001$); major bleeding rates: no difference ($p = 0.40$)
RE-MODEL	VTE-prophylaxis after knee replacement	Dabigatran 150 mg/d for 6–10 days vs dabigatran 220 mg/d for 6–10 days vs enoxaparin 40 mg/d for 6–10 days	Primary outcome (VTE): both dabigatran doses non-inferior to enoxaparin for efficacy; major bleeding rates: no differences for both dabigatran doses compared to enoxaparin
RE-MOBILIZE	VTE-prophylaxis after knee replacement	Dabigatran 150 mg/d for 12–15 days vs dabigatran 220 mg/d for 12–15 days vs enoxaparin 2×30 mg/d for 12–15 days	Primary outcome (VTE): both dabigatran doses inferior to enoxaparin for VTE rates (dabigatran 220 mg: 31% ($p = 0.02$ vs enoxaparin, dabigatran 110 mg 34% ($p < 0.001$ vs enoxaparin), enoxaparin 25%); bleeding rates: no significant differences
RE-LY	stroke prophylaxis in atrial fibrillation	Dabigatran 2×110 mg/d vs dabigatran 2×150 mg/d vs warfarine (INR 2–3)	Primary outcome (stroke, systemic embolism): dabigatran 2×110 mg non-inferior to warfarine ($p < 0.001$), dabigatran 2×150 mg superior to warfarine ($p < 0.001$); major bleeding: dabigatran 2×110 mg superior to warfarine ($p = 0.003$), dabigatran 2×150 mg non-inferior to warfarine ($p = 0.31$)
RE-COVER	Treatment of acute VTE	Dabigatran 2×150 mg/d vs warfarine (INR 2–3), both for 6 months and both after an initial parenteral anticoagulation	Primary outcome (recurrent VTE): dabigatran non-inferior to warfarine ($p < 0.001$); bleeding rates: no significant difference
RECORD 1	VTE-prophylaxis after hip replacement	Rivaroxaban 10 mg/d for 35 days vs enoxaparin 40 mg/d for 35 days	Primary outcome (VTE): rivaroxaban superior to enoxaparin ($p < 0.001$); major bleeding: no significant difference
RECORD 2	VTE-prophylaxis after hip replacement	Rivaroxaban 10 mg/d for 31–39 days vs enoxaparin 40 mg/d for 10–14 days	Primary outcome (VTE): rivaroxaban superior to enoxaparin ($p < 0.001$); bleeding rates: no significant difference ($p = 0.25$)
RECORD 3	VTE-prophylaxis after knee replacement	Rivaroxaban 10 mg/d for 10–14 days vs enoxaparin 40 mg/d for 10–14 days	Primary outcome (VTE): rivaroxaban superior to enoxaparin ($p < 0.001$); major bleeding: no significant difference
RECORD 4	VTE-prophylaxis after knee replacement	Rivaroxaban 10 mg/d for 10–14 days vs enoxaparin 2×30 mg/d for 10–14 days	Primary outcome (VTE): rivaroxaban superior to enoxaparin ($p = 0.0118$); major bleeding: no significant difference ($p = 0.1096$)
ROCKET-AF	Stroke prophylaxis in atrial fibrillation	Rivaroxaban 20 mg/d vs warfarine (INR 2–3)	Primary outcome (stroke, systemic embolism): rivaroxaban non-inferior to warfarine ($p < 0.001$); bleeding rates: overall no significant difference ($p = 0.44$) but less intracranial haemorrhage with rivaroxaban ($p = 0.02$)
EINSTEIN-DVT	Treatment of acute VTE	Rivaroxaban (2×15 mg for 3 weeks followed by 20 mg/d) for 3, 6 or 12 months vs enoxaparin followed by a VKA for 3, 6 or 12 months	Primary outcome (recurrent VTE): rivaroxaban non-inferior to enoxaparin/VKA ($p < 0.001$); bleeding rates: no significant difference
EINSTEIN-PE	Treatment of symptomatic pulmonary embolism	Rivaroxaban (2×15 mg for 3 weeks followed by 20 mg/d) for 3, 6 or 12 months vs enoxaparin followed by a VKA for 3, 6 or 12 months	Primary outcome (recurrent VTE): rivaroxaban non-inferior to enoxaparin/VKE ($p = 0.003$); major bleeding: significant less in the rivaroxaban group ($p = 0.003$)
EINSTEIN-Extension	Extended treatment after VTE	Rivaroxaban 20 mg/d vs placebo for an additional 6 or 12 months in the EINSTEIN-DVT-population	Primary outcome (recurrent VTE): rivaroxaban superior to placebo ($p < 0.001$); major bleeding: no significant difference ($p = 0.11$)
ADVANCE 1	VTE-prophylaxis after knee replacement	Apixaban 2×2.5 mg/d for 10–14 days vs enoxaparin 2×30 mg/d for 10–14 day	Primary outcome (VTE): apixaban did not meet the criterias for non-inferiority to enoxaparin ($p = 0.06$); bleeding rates: significant less in the apixaban group ($p = 0.03$)
ADVANCE 2	VTE-prophylaxis after knee replacement	Apixaban 2×2.5 mg/d for 10–14 days vs enoxaparin 40 mg/d for 10–14 day	Primary outcome (VTE): apixaban non-inferior to enoxaparin ($p < 0.001$); major bleeding: no significant difference ($p = 0.09$)
ADVANCE 3	VTE-prophylaxis after hip replacement	Apixaban 2×2.5 mg/d for 35 days vs enoxaparin 40 mg/d for 35 day	Primary outcome (VTE): apixaban superior to enoxaparin ($p < 0.001$); bleeding rates: no difference
ARISTOTLE	Stroke prophylaxis in atrial fibrillation	Apixaban 2×5 mg/d vs warfarine (INR 2–3)	Primary outcome (stroke, systemic embolism): apixaban superior to warfarine ($p = 0.01$); bleeding rates: significant less major bleedings ($p < 0.001$) and haemorrhagic strokes ($p < 0.001$)

protein C is considered a natural anticoagulant protecting the patient from unnecessary thrombotic events.

Safety profile of the new anticoagulants

Bleeding complications

In analogy to the LMWH lower bleeding rates were expected with the new oral anticoagulants. Actually bleeding complications in the large scale randomised studies turned out to be a matter of dosing. Indeed in postoperative thrombosis prophylaxis apixaban had numerically lower bleeding events, rivaroxaban and dabigatran numerically slightly higher events but in all cases statistically non-significant. In the thrombosis and atrial fibrillation trials although there was no difference if all bleeding events were taken together, critical and fatal bleeds were statistically less with the new anticoagulants. A consistent finding was the significant reduction of intracranial bleeds by 30%–60% with all three new agents. Apixaban could also reduce all-cause mortality in the thrombosis studies. Dabigatran and rivaroxaban tended to cause more gastrointestinal bleeds than VKA. About 72% of these patients had unrecognised, pre-existing GI-lesions predisposing to bleeding (ulceration, polyps, tumour).

A matter of debate in all studies with VKA was the issue of the time in therapeutic range (TTR) which functions as a performance index of a successful adjustment of the VKA intensity. At first glance it seemed to be unacceptably low ranging from 57%–64% in all studies. Subsequent comparisons with real life conditions showed that such a level was quite common and realistic [31]. Quintile analysis of the various TTR levels (high versus low) for dabigatran and rivaroxaban revealed no disadvantages of the new anticoagulants against VKA.

Combination of the new anticoagulants with LMWH, aspirin or clopidogrel caused more bleeding events but comparable to the combination of the same agents with VKA. Such combinations should be used with caution. Normally double antiplatelet treatment and use of the new anticoagulants should be avoided.

Reversibility, antidotes

New anticoagulants are small molecules without a known direct antidote. Manufacturers are working on the development of specific (e.g., monoclonal antibodies) or unspecific neutralising substances but no functional inhibitor is available yet. Reversibility of the action of the new anticoagulants is depending on the elimination half-life of the agent. In case of normal renal function just waiting for some hours reduces the concentration of the medicament considerably, thus allowing a spontaneous haemostatic effect. In cases of acute bleeding, where time is crucial, additional measures can be considered (table 3). Experience from the other indirect or direct FXa-Inhibitors shows that administration of haemostatic cocktails, such as tranexamic acid, PCC, recombinant factor VIIa (rFVIIa) might achieve a haemostatic effect. The use of haemostatic measures must be decided on a personalised basis according to the bleeding problem present. Combinations of PCC and rFVIIa are normally not

indicated, due to their considerable thrombogenic potential. PCC might be preferred in cases of bleeding after rivaroxaban, as an ex vivo study implicated [32]. In this study on healthy subjects, ex vivo prolongation of global coagulation tests was considerably shortened after administration of PCC intravenously. This was not found after dabigatran use. Whether this effect can be translated into a clinical advantage in case of bleeding remains to be seen. Dabigatran can additionally be removed by haemodialysis. If time allows it, gastric lavage and adsorption with active coal might also help.

Drug-interactions

All three new agents (rivaroxaban, apixaban, dabigatran) do not affect metabolising drug-enzymes but are affected themselves by CYP3A4 and p-glycoprotein (p-gp). Inducers or inhibitors of these enzymes cause a decrease or increase of the drug concentration in blood, respectively (table 4). Parallel use of common medications, such as certain antiviral agents, antiarrhythmics, antibiotics or even St. John's Wort, can considerably affect concentration of the new anticoagulants, as seen by the area under the curve (AUC) [33].

Interferences with coagulation assays

Efficient binding of the new anticoagulants to their target molecules in free as well as in complexed form, causes an interference with coagulation tests which use clot formation as an endpoint and therefore depend on FXa or FIIa generation in the test system. It has been clearly shown that prothrombin time (PT/INR) and activated partial thromboplastin time (APTT) can be falsely prolonged by 10%–20% [34, 35]. Even functional one-stage assays for coagulation factors can be affected, rendering false reductions of factor concentrations by 10%–20%. This effect is prominent during peak-time of the new anticoagulants 2–6 h after intake and diminishes 12h after intake, according to observations on healthy subjects. It might be expected that in real-life use of the new anticoagulants with variable influence of other pharmacokinetic parameters these effects will be more prominent. This might change the attitude especially of primary care givers, who should include in their differential diagnosis the option of the interference by a new anticoagulant in the background, whenever they find an unexpectedly increased PT/INR. The problem here is that the relationship between drug concentration and PT/INR prolongation is not linear at all and depends considerably on the properties of the PT-reagent used in the test-system. The only way to quantify the new anticoagulants, is to use one of the known validated reference methods (equivalent to the anti-FXa-activity for the LMWH for FXa-inhibitors and a modified clotting assay for the thrombin-inhibitor). This is a particular problem for acute patients in stroke-units, where indication for therapeutic thrombolysis depends (among others) on an INR-value of <1.5. Extending the laboratory investigation to the specific measurement of the anticoagulant activity might inevitably mean unnecessary loss of time, which is very important for keeping up with the allowed therapeutic window in these patients.

The end of the old agents?

Which patients should be treated with new anticoagulants?

Postoperative thrombotic prophylaxis after major orthopaedic surgery, treatment of deep vein thrombosis and prevention of recurrent venous thromboembolism as well as stroke prophylaxis in atrial fibrillation are the first indications for which the new anticoagulants have been registered. Dabigatran and rivaroxaban are available in the EU for all three indications, apixaban only for the postoperative prophylaxis. Excellent detailed guidelines on the use of anticoagulants have been recently published [36, 37].

Should the new agents replace totally the established old ones? The answer is rather no in those cases with a good level of control or in patients with renal failure or gastrointestinal disease. Also patients with mechanical heart valve prosthesis should remain on VKA because the new anticoagulants have not been yet tested for this indication. However, for patients with an unexplained poor VKA control or a poor level of control due to unavoidable drug-drug interactions the new substances are an alternative treatment (given there are no contra-indications).

VKA-naïve patients instead are good candidates for treatment with the new substances. It is important, though, that patients can participate in the decision-making of their therapy after being briefed on the advantages and disadvantages of the alternatives.

Considering orthopaedic surgery there are only few contra-indications such as severe renal or hepatic failure for the use of the new agents. If logistics of the department permit it and if the nature of the operation does not require a follow-up intervention then all patients could be given one of the new agents. FXa inhibitors have similar pharmacokinetics as LMWH, a fact which makes bridging or switching from one to another very easy, just change from the injection to the tablet the next day.

Patients with venous thrombosis are now treated for at least three months and if the event was unprovoked longer anticoagulation should be considered. These patients can be given the new oral anticoagulants considering of course

possible limitations because of renal or hepatic function or drug interactions (tables 4–6). Application is easy, there is no monitoring, there is no need for dose adjustment. The concept of single-agent treatment from the very beginning and once daily dosing (which has been tested in the EINSTEIN trials for rivaroxaban [26, 27]) might prove very convenient for the patients. It should be noted that a 24 h abstinence from medication is required as minimum medication-free time before an invasive procedure or a surgical operation.

Patients already on long-term anticoagulation with VKA can theoretically also be switched to the new agents. There are some caveats here, which are worth mentioning. Patients themselves might wish the change. If adjustment of VKA is very stable and this treatment has become part of the patient's life, there is no need to change to another agent. Usually these patients have additional medications or medical problems, which need frequent attention and/or consultation. Dropping the regular visits to the physician for adjustment of the VKA might cause problems with the adherence of the patients to the new anticoagulants. There will be no way to see if they take their medication or not.

New indications for stroke prophylaxis in atrial fibrillation could on the other hand be treated with new oral anticoagulants from the very beginning. Treatment is simple, dosing is given once or twice a day and there is no monitoring. These patients should be part of an observation scheme by visiting their physician at least a couple of times per year. These consultations could reveal unexpected problems, help avoid drug-interactions, keep sure that renal function has not deteriorated, and contribute to keeping adherence to the medication at high levels.

How should a patient switch to the new anticoagulants?

If the treatment is new, patients should start taking the new oral agents as indicated by the manufacturer. Possibility of drug-interactions, interferences and influence of renal function should be taken into consideration in advance.

If patients have to switch from LMWH to the new oral anticoagulants then they just change the next administration from the injection to the tablet at the indicated dosing.

Table 3: Treatment of bleeding in case of overdosing or intoxication.

	Dabigatran	Apixaban	Rivaroxaban
Specific antidote	No	No	No
Ceiling effect	No ceiling effect up to 600 mg (linear increase)	–	Ceiling effect above 60 mg
Overdose, no bleeding	Watchful waiting Gastric lavage, if <8 h following ingestion	Watchful waiting Gastric lavage, if <8 h following ingestion	Watchful waiting Gastric lavage, if <8 h following ingestion
Overdose, with bleeding	Consider haemostatic cocktail plus haemodialysis	Consider haemostatic cocktail	Consider haemostatic cocktail

Table 4: Drug interactions of new anticoagulants.

Rivaroxaban, apixaban
<i>CYP3A4- and P-gp-Inhibitors: increase AUC</i>
Azoles (AUC 1.8×), ritonavir (AUC 2.5×), clarithromycine (AUC 1.6×)
<i>CYP3A4- und P-gp-Inducers: decrease AUC 1.5×</i>
Rifampicin, phenytoin, phenobarbital, carbamazepine, St. John's Wort
Dabigatran
<i>P-gp-Inhibitors: increase AUC</i>
Amiodarone, verapamil, quinidine, ketoconazole, clarithromycine

If patients have to switch from VKA to the new anticoagulants, then the known principles of bridging should be used, as we know them from the LMWH. VKA should be stopped and INR monitored closely during the following days. As soon as the INR falls below 2.0 the first dose of a new oral anticoagulant should be given.

Caution is needed with patients having gastrointestinal lesions (ulcerations, polyps, tumours), since they have been shown to bleed more frequently at these sites, probably because of a direct local effect of the medication taken orally. Caution is also needed for the elderly patients, since they might have unpredictable deteriorated renal function which can cause accumulation of the drugs. It has been shown that the AUC in these patients is increased by 30% with apixaban, by 60% with rivaroxaban and even more with dabigatran.

Considering mechanical heart valves, there are no data in humans on the efficacy and safety of the new oral anticoagulants yet. Therefore they should be not used in such patients.

All new anticoagulants are contraindicated during pregnancy and lactation.

Conclusion

New oral anticoagulants used as single target inhibitors of coagulation enzymes have been developed and tested in extensive trial programmes. Results of most of these trials showed non-inferior and/or superior efficacy and safety compared to standard treatment with LMWH or VKA. These results led to registration of these agents for the prophylaxis or treatment of thrombosis and/or stroke prophylaxis in atrial fibrillation. In addition to good efficacy and safety of these agents are more convenient in their use and promise advantages in quality of life. First observations in real life post-launch registries with these agents confirm the initial study results and promise on-going success. It remains to be seen how they will perform on a long-term basis in comparison to the good old VKA, which we are familiar with for at least 50 years now.

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Table 5: Dosing of new anticoagulants in patients with renal insufficiency.

Creatinine clearance	Dabigatran (2×150 mg/d)	Apixaban (2×2.5 mg/d)	Rivaroxaban (1×20 mg/d)
30–49 ml/min	Dosis reduction to 2×110 mg/d	No dosis reduction	Dosis reduction to 1×15 mg/d
15–29 ml/min	EU: not indicated USA: 2×75 mg/d	Use with caution	Use with caution (AUC 1.6×)
<15 ml/min	Not indicated	Not indicated	Not indicated

Table 6: Dosing of new anticoagulants in patients with liver failure.

Liver failure	Dabigatran (2×150 mg/d)	Apixaban (2×2.5 mg/d)	Rivaroxaban (1×20 mg/d)
Mild Child A/B ALT/AST >2× Bilirubin >1×	Contra-indicated	Use with caution	Use with caution
Severe with or without coagulopathy	Contra-indicated	Contra-indicated	Contra-indicated

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