Old and new anticoagulants

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Summary
Vitamin-K-antagonists (VKA) and heparins have been complementary anticoagulants for prevention and treatment of thrombosis for almost 70 years. In contrast to heparins, VKA have not been modified pharmacologically, however treatment surveillance has improved by introducing INR and self-monitoring/management. Disclosure of the molecular basis of interaction with VKORC1, the target enzyme of VKA, has helped to better understand coumarin sensitivity and resistance. New oral anticoagulants have been approved and stimulated expectations in patients and physicians to get rid of the burdening frequent controls of VKA without loss of efficacy and safety. This review will summarize the development and profile of the new substances. Main difference compared to VKA is their direct mode of action against one clotting factor which is factor IIa in dabigatran and factor Xa in rivaroxaban and other xabanes" currently under intensive investigation. Half lifes of the new anticoagulants are much shorter than that of the mainly used coumarins (phenprocoumon, warfarin), making anticoagulation bridging unnecessary before surgery. Therapeutic width of direct thrombin inhibitors and factor Xa inhibitors is broader and they are given at fixed doses. Clinical studies in thromboprophylaxis, thromboembolism and atrial fibrillation indicate at least non-inferiority or even superior efficacy compared with enoxaparin and VKA at comparable safety outcomes. Limitations of the new substances may arise from gastrointestinal side effects, mode of metabolism and route of elimination. Specific antidots are not available for none of them. Undoubtedly, the new oral anticoagulants are very promising. But, although thousands of study patients already have been treated, there are questions to be answered such as treatment adherence in absence of monitoring, safety and efficacy in risk patients, dosage adjustment and interactions with other drugs, before conclusions can be drawn towards their potential to replace VKA.

Schlüsselwörter
Vitamin-K-Antagonisten, Heparine, direkte orale Thrombininhibitoren, Faktor-Xa-Inhibitoren, klinische Studien

Zusammenfassung
In 2010, an estimated number of one million patients (according to patient networks) were treated with oral anticoagulants in Germany due to

- atrial fibrillation,
- deep vein thrombosis,
- pulmonary embolism,
- heart valve prosthesis,
- few other indications.

Another estimated one million patients with atrial fibrillation is supposed to benefit from antithrombotic therapy. For many decades vitamin K antagonists (VKA) have been the only choice for long-term treatment (1, 2). After more than 30 years of research new substances such as direct thrombin inhibitors and direct factor Xa inhibitors have been designed and more and more of them are approved. The principle expectation of patients and physicians is focussed on long term treatment with these substances instead of VKA which hopefully would relief them from the burden of frequent INR-controls and fear of bleeding due to the narrow therapeutic window of VKA.

This short review will summarize the development and profile of the new oral anticoagulants and compare them with the old agents in terms of pharmacology, mechanism of action, efficacy and safety. An overview of the relevant clinical trials will be given together with a careful projection of what we might expect in future.

Old anticoagulants

Vitamin K antagonists and heparins are used complementary for antithrombotic treatment. Unfractionated heparins with their short half-life, quick onset and parenteral mode of administration are safe and well controllable in thromboprophylaxis and/or acute treatment of thrombosis. But need of frequent applications in the s.c. route (twice to three times daily) and requirement of monitoring of intravenous therapeutic doses due to considerable intra- and interindividual variability makes therapy unpredictable and inappropriate for long-term use. Heparins inhibit all serine proteases to various extents with predominant inhibition of thrombin (factor IIa) and factor Xa requiring antithrombin as cofactor.

Further development of unfractionated heparin (UFH) by shortening the glycosaminoglycan chain resulted in low-molecular-weight heparin (LMWH) with higher bioavailability and therefore better predictability of effect and without need of routine monitoring. Longer half-life of LMWH (2–4 hours after single s.c. injection) allow once daily injection for thromboprophylaxis or twice daily for treatment of thrombosis (3).

Long-term anticoagulation is still done by VKA, which are therapeutically used coumarins, acting indirectly by inhibition of carboxylation of the vitamin K dependent factors II, VII, IX and X and proteins C, S and Z, thereby abolishing their potential to be activated on phospholipid surfaces after calcium-dependent binding. Carboxylation does not take place because vitamin K is needed in this reaction and VKA inhibit regeneration of vitamin K by interfering with vitamin K epoxide reductase (VKOR).

The gene was discovered in 2004 and encodes several isoforms, collectively termed VKOR complex 1 (VKORC1) (4, 5). Since introduction of dicumarol in 1941 in the US and phenprocoumon (Marcumar®) in 1954 in Germany these compounds have not been altered pharmacologically. However, much has been done to improve treatment surveillance. Increasing knowledge of mechanism of VKA-action as well as insights into interaction with foods and other drugs rendered them more predictable. Introduction of INR and self-measurement/monitoring and more careful and individually tailored loading doses have further increased safety (6, 7). Recognition of VKORC1 as the target of VKA and subsequent disclosure of mutations and polymorphisms in VKORC1 as well as in CYP2C9 have contributed substantially to understand phenomena of coumarin sensitivity and resistance (8, 9).

Common characteristics of new anticoagulants

The new anticoagulants are synthetically produced small molecules that act against one clotting factor. In contrast to heparins and fondaparinux their effect is independent of antithrombin. They are binding selectively and with high affinity to the active site of the enzyme, thereby competitively inhibiting the turnover of the natural substrates. Reversible binding to the enzymes is thought to be important for lowering the bleeding risk. Whether factor IIa or factor Xa inhibitors are better remains to be investigated. Principle of factor Xa inhibition is reduction of thrombin burst in the propagation phase of coagulation, an approach with a straightforward effect. Inhibition of thrombin itself, which is the key enzyme in the coagulation cascade with many other functions such as platelet activation, interaction with fibrinolysis, inflammatory processes, and cell proliferation is less predictable as it may affect all properties of thrombin, however, this pleotropic effect may provide advantages, too (10).

Direct thrombin inhibitors

Direct thrombin inhibitors (DTI) selectively block the activity of the protease thrombin (soluble and fibrin-bound) resulting in inhibition of fibrin generation and thrombus formation. DTI were initially only available for parenteral use, later followed by orally applicable substances. Development was accompanied by severe draw backs, the most surprising was withdrawal of the first oral DTI ximelagatran (Exanta®) in 2006 due to suspected liver toxicity after it had been introduced on the markets in 2004 (11). Lepirudin (Refudlin®) and argatroban (Argatra®) have been implemented already some years ago as alternative anticoagulants in heparin-induced thrombocytopenia type II. Desirudin (Revasc®) is approved for thromboprophylaxis in hip and knee replacement surgery and bivalirudin (Angiox®) for percutaneous coronary interventions.

Danigatran (Pradaxa®)

Dabigatran is a nonpeptide small molecule acting as reversible inhibitor of thrombin. In contrast to factor Xa inhibitors dabigatran is a very polar, permanently charged hydrophilic molecule, which itself has no
bioavailability after oral administration. Hence, a double prodrug was generated, dabigatran etexilate (Pradaxa®), by masking the polar amidinium moiety as a carbamate ester and by turning the carboxylate into an ester group which allows bioavailability of 6.5%. After resorption of the prodrug, both polar groups of dabigatran are restored quickly in plasma and liver by esterase-mediated hydrolysis leading to rapid onset of action with peak plasma concentrations after 1 to 2 hours after ingestion. Terminal half-life is 14–17 hours. Galenism of the drug was constructed with tartaric acid allowing for solubility and resorption in an acidic milieu. This however accounts for gastrointestinal side effects, mainly dyspepsia, and leads to reduction of approximately 30% of bioavailability of dabigatran when combined with proton pump inhibitors. Dabigatran is not metabolized by cytochrome P450, reveals low interactions with other drugs and no interactions with foods. It is excreted renally, approximately 85% as active drug (12, 13).

**Factor Xa inhibitors**

Factor Xa inhibitors can be “indirect” (e. g. fondaparinux, idraparinux, idrabiotaparinux) or “direct” (e. g. rivaroxaban, apixaban, edoxaban) depending on the requirement of antithrombin to exert their antithrombotic effect. They reduce thrombin burst during propagation of coagulation. Whereas fondaparinux was rapidly integrated into clinical use and the “xabanes” have started to follow, idraparinux as a derivate of fondaparinux with longer half-life (80 hours) was investigated for treatment of deep vein thrombosis and pulmonary embolism with a once weekly subcutaneous administration, however it revealed increased bleeding complications and is no longer followed (14).

**Fondaparinux (Arixtra®)**

Fondaparinux was the first substance of the factor Xa inhibiting group, synthetically generated, further condensating the low-molecular heparin structure to the essential pentasaccharid motif, responsible for binding to antithrombin. The fondaparinux-mediated conformational change of antithrombin results in reversible binding to factor Xa with 700-fold higher affinity compared to heparins. Its administration is once daily subcutaneously, half-life is 14–17 hours and it is excreted renally (15). Fondaparinux is approved since 2002, meanwhile with a broad spectrum of indications comparable to that of enoxaparin, including thromboprophylaxis, treatment of venous thrombosis, pulmonary embolism and unstable angina pectoris (16). However, like all heparins, it is dependent on the presence and functionality of antithrombin. Nevertheless, the favourable profile and convincing outcomes in clinical trials in comparison to low-molecular-weight heparins, mainly enoxaparin, has stimulated a lot of work on factor Xa as promising target for antithrombotic agents.

**Rivaroxaban (Xarelto®)**

Rivaroxaban is the first and most advanced representative of the direct oral factor Xa inhibitors with 10000-fold higher selectivity for factor Xa than for other serine proteases. It is an oxazolidininon derivate which is also used in some antibiotics. Inhibition of factor Xa is concentration-dependent and affects prothrombinase complex-bound as well as clot-associated factor Xa. Pharmacokinetic and pharmacodynamics have been shown to be predictable across 5 to 80 mg daily ingestion. Range of mean plasma concentration was 12 to 201 ng/ml after daily intake of 5 to 20 mg of rivaroxaban. Peak plasma concentrations are achieved after 2 to 4 hours. Bioavailability is 80–100% and terminal half-life of 7–11 hours is between that of LMWH and fondaparinux. Two third of the drug are metabolised, one third is excreted unchanged. Two third are eliminated renally, one third through faeces. Rivaroxaban is metabolised in the liver involving cytochrome P450 (CYP3A4, CYP2J2) (17, 18). Of the coagulation assays it affects prothrombin time more than aPTT and it can be monitored by anti-factor-Xa assays if desired (19).

**Apixaban**

Pharmacokinetics of apixaban have been studied in healthy human males after administration of a single 20 mg oral dose of radiolabeled [14C]apixaban (20) and in other species including rabbits (21). Bioavailability in humans is more than 50% and peak plasma concentrations are reached in 3 to 4 hours (22). Other properties are summarized in Table 1.

**Edoxaban (DU-176b)**

Pharmacokinetics and pharmacodynamics of edoxaban have been investigated in ani-

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**Table 1.** Pharmacological characteristics of the direct thrombin inhibitor dabigatran and the oral factor Xa inhibitors rivaroxaban, apixaban and edoxaban

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (Pradaxa®)</th>
<th>Rivaroxaban (Xarelto®)</th>
<th>Apixaban</th>
<th>Edoxaban (DU-176b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>molecular mass [g/mol]</td>
<td>628/472*</td>
<td>436</td>
<td>460</td>
<td>548</td>
</tr>
<tr>
<td>protein binding [%]</td>
<td>34–35</td>
<td>92–95</td>
<td>ca. 87</td>
<td>?</td>
</tr>
<tr>
<td>bioavailability [%]</td>
<td>6.5 30%</td>
<td>80–100 no</td>
<td>&gt; 50 no</td>
<td>45–50 unlikely</td>
</tr>
<tr>
<td>T(max) [h]</td>
<td>1–2</td>
<td>2–4</td>
<td>3–4</td>
<td>1–2</td>
</tr>
<tr>
<td>terminal half-life [h]</td>
<td>14–17</td>
<td>7–11</td>
<td>10–14</td>
<td>9–11</td>
</tr>
<tr>
<td>metabolism CYP450 dependent</td>
<td>ca. 20% no</td>
<td>ca. 66% (liver)</td>
<td>? CYP3A4</td>
<td>?</td>
</tr>
<tr>
<td>excretion urine (active)</td>
<td>ca. 85%</td>
<td>ca. 66% (ca. 33% active)</td>
<td>ca. 25% (ca. 22% active)</td>
<td>ca. 35% (ca. 24% active)</td>
</tr>
<tr>
<td>faeces (active)</td>
<td>ca. 6%</td>
<td>ca. 33%</td>
<td>ca. 56%</td>
<td>ca. 62%</td>
</tr>
</tbody>
</table>

*prodrug/drug
Clinical trials

Clinical trials are listed for the most advanced new oral anticoagulants with various indications (Tab. 2) and results are presented briefly. Additionally, further programs are under way concerning other indications including medically ill patients, paediatric cases, haemodialysis, elective percutaneous interventions.

Thromboprophylaxis in hip and knee arthroplasty

Dabigatran

Dabigatran was compared with enoxaparin in three phase III trials (RE-NOVATE, RE-MODEL, RE-MOBILIZE) including more than 8000 patients (25, 26, 27). Patients were randomly assigned to receive 220 mg or 150 mg dabigatran once daily, starting 1 to 4 hours with a half-dose after surgery, or enoxaparin (40 mg once daily or 30 mg bid), beginning the evening before surgery. A pooled analysis with 6200 evaluable patients revealed comparable efficacy and bleeding outcomes. The composite outcomes of major VTE (proximal deep vein thrombosis and/or pulmonary embolism) and VTE-related mortality occurred in 3.3% of the enoxaparin group versus 3.0% of the dabigatran 220 mg and 3.8% of the dabigatran 150 mg group (proof of non-inferiority). Major bleeding occurred in 1.4% of the enoxaparin group versus 1.4% in the 220 mg and 1.1% in the 150 mg dabigatran group (28).

Direct factor Xa inhibitors

Rivaroxaban was investigated in knee and hip arthroplasty in the RECORD 1–4 program (29–32). Patients were randomly assigned to 10 mg rivaroxaban once daily beginning 6–8 hours after surgery or enoxaparin (40 mg once daily or 30 mg bid), starting the evening before surgery in the 40 mg studies or beginning 12–24 hours after surgery in 2 x 30 mg study (RECORD 4). A pooled analysis of the four studies (12 729 patients) revealed better efficacy of rivaroxaban, but higher, though not statistically significant, different, bleeding rates. Composite endpoint of symptomatic VTE and all-cause mortality in the day 12 ± 2 active treatment pool occurred in 29/6183 patients receiving rivaroxaban (0.5%) versus 60/6200 patients receiving enoxaparin (1.0%; p = 0.001). Major bleeding was observed in 21 (0.3%) versus 13 (0.2%) patients, p = 0.23, major plus non-major clinically relevant bleeding in 176 (2.8%) versus 152 (2.5%) and any bleeding in 409 (6.6%) versus 384 (6.2%) patients, p = 0.38, respectively (33).

Huisman and co-workers compared Enoxaparin versus dabigatran and rivaroxaban by pooling 6 phase III trials (18 405 participants) and came to the conclusion that enoxaparin and dabigatran show similar rates of efficacy and bleeding, whereas enoxaparin was less effective than rivaroxaban but had a lower risk of bleeding (34).

Apixaban was assessed in knee replacement surgery in the ADVANCE-2 study with 3057 patients randomly allocated to oral apixaban 2.5 mg twice daily starting 12 to 24 hours after wound closure or enoxaparin 40 mg once daily starting 12 hours before surgery. In the recently published analysis, 1973 patients were selectable for primary outcome (composite of asymptomatic and symptomatic DVT, non-fatal PE and all-cause mortality) which occurred in 147/976 (15%) patients receiving apixaban versus 243/997 (24%) patients receiving rivaroxaban (35).
enoxaparin (p < 0.0001). Major or clinically relevant bleeding was observed in 53 (4%) of 1501 patients receiving apixaban and 72 (5%) of 1508 patients treated with enoxaparin. The investigators conclude from the study that apixaban 2.5 mg twice daily, starting on the morning after surgery, offers a more effective alternative to enoxaparin without increased bleeding (35). In a meta-analysis of patients with total knee arthroplasty it is concluded, that apixaban is non-inferior to enoxaparin when used for the same duration, but with considerable advantage regarding safety profile (36). In the phase III ADOPT study apixaban (2.5 mg bid) is investigated for prevention of thrombosis-related events in patients with acute medical illness during and after hospitalisation in comparison to enoxaparin and placebo (37).

**Direct factor Xa inhibitors**

**Rivaroxaban** is currently investigated in the EINSTEIN-DVT and EINSTEIN-PE program at a dosage of 15 mg twice daily for proof of non-inferiority compared to standard treatment with LMWH/VKA. In the EINSTEIN-extension-study, patients of the DVT- and PE-program will be further followed after 6 or 12 months of treatment in a placebo controlled arm receiving 20 mg once daily rivaroxaban (42).

**Apixaban** was investigated in a dose-finding phase II study (BOTTICELLI-DVT) at dosages of 5 mg twice-daily, 10 mg twice-daily or 20 mg once-daily compared to LMWH followed by VKA (43).

**Edoxaban** is currently under investigation in the phase III HOKUSAI-VTE study comparing LMWH/edoxaban tosylate (DU-176b) with LMWH/warfarin. Edoxaban is given once daily 60 mg (44).

**Acute coronary syndrome**

Dose-finding studies in patients with acute coronary syndrome (ACS) have not shown uniform risk reduction. In case of equal or superior efficacy by trend they tended to have increased bleeding risks in combination with single or dual anti-platelet therapy. RE-DEEM (45) evaluated 4 doses of dabigatran twice daily and placebo in addition to dual antiplatelet therapy. In the placebo controlled ATLAS-TIMI 51 study rivaroxaban is assessed with 2.5 mg and 5 mg twice daily additionally to aspirin alone or aspirin and clopidogrel (46). The APRAISE-2 study is a placebo-controlled study, too, investigating apixaban 5 mg twice daily against placebo additionally to standard care for ACS (47).

**Atrial fibrillation**

Atrial fibrillation (AF) is the predominant indication for long-term anticoagulation. Though it is no causal therapy, antithrombotic treatment represents basic care for stroke prevention. Greatest expectations with the new substances are focussed on long-term anticoagulation with hope that they finally may replace VKA. According to AF-guidelines, indication for anticoagulation in atrial fibrillation follows the CHADS2 score or the more recently proposed CHA2DS2-VASc score usually recommended when ≥2 points are given. Among the new anticoagulants **dabigatran** is so far the most intensively studied substance in atrial fibrillation. In the RE-LY study 18113 patients had received dabigatran 110 mg or 150 mg twice daily in comparison to adjusted-dose warfarin (INR 2.0–3.0). Mean CHADS2 score was 2.1. Primary outcome was stroke or systemic embolism and was observed after a median follow up period of 2 years in 1.69% of patients treated with warfarin compared to 1.53% in the group that received 110 mg dabigatran (p<0.001 for non-inferiority), and 1.11% in the 150 mg dabigatran group (p < 0.001 for superiority). Major bleeding complications were not significantly different in warfarin compared to higher dose of dabigatran (3.11 vs 3.36% per year) but were significantly lower in the patients that received 110 mg dabigatran (2.71%, p = 0.003). The rate of haemorrhagic stroke per year was lower with both dabigatran doses (110 mg bid 0.12%; 150 mg bid 0.10%) as compared to warfarin (0.38%; p < 0.001). However, gastrointestinal bleeds were 50% higher (p < 0.001) in the 150 mg dabigatran group compared to warfarin and this was related to patients >75 years and with reduced renal function. Gastrointestinal side effects, mainly dyspepsia, were more than twice as frequently as with dabigatran (11.8% and 11.3%) compared to warfarin (5.8%) and accounted for 21% of discontinuation of the study drug in the dabigatran group compared to 17% in warfarin (48).

**Dabigatran**

Dabigatran has already shown non-inferiority in treatment of DVT and PE compared to warfarin. In the RE-COVER study 2564 patients with DVT (~70%), PE (~20%) or both (~10%) were randomly assigned after initial treatment with therapeutic LMWH, UFH or fondaparinux for 9 days to receive 150 mg dabigatran twice daily or warfarin (INR 2.0–3.0) and followed for 6 months. Primary endpoints (recurrence of thromboembolism and/or death) were observed in 30/1274 (2.4%) patients treated with dabigatran versus 27/1265 (2.1%) under warfarin. Major bleeding episodes occurred in 1.6% versus 1.9% in dabigatran and warfarin, respectively. However, discontinuation of the study drug due to adverse events, among these diarrhoea and dyspepsia (significant), was more frequent in dabigatran (9.0%) than in warfarin (6.8%, p = 0.05), (39). RE-MEDY (40) will look at long term (18 months) secondary prophylaxis after symptomatic VTE in comparison to warfarin in patients with successful initial treatment for 3 to 6 months. RE-SONATE (41) is a placebo-controlled trial in patients with recurrent VTE who have completed 6 to 18 months of treatment.

**Treatment of deep vein thrombosis and pulmonary embolism**

Several study programs have been initiated and are awaiting completion, analysis/interpretation and publication (Tab.1). The comparators are therapeutic doses of UFH/LMWH/fondaparinux and VKA.
More than 14,000 patients have been randomised in the ROCKET AF study to 20 mg once daily rivaroxaban or dose-adjusted warfarin (INR 2.0–3.0). Follow up is planned until 405 primary outcomes are observed (49). In the ARISTOTLE study 18,206 patients with AF have been randomised to apixaban 5 mg twice daily with warfarin as comparator. At least 448 primary efficacy outcomes will be awaited (50). The AVER-ROES trial investigates apixaban 5 mg twice daily compared to acetylsalicylic acid (81–324 mg) in AF patients with at least one risk factor for stroke and who have failed or are unsuitable for VKA therapy (51).

Conclusions, perspectives

After decades of constant and nearly unchanged options for antithrombotic treatment new competitive and innovative substances are rushing on the markets backed with very promising results of historically large clinical trials. Most data at present are available for the direct thrombin inhibitor dabigatran and the factor Xa inhibitor rivaroxaban, being caught up by other factor Xa inhibitors as apixaban and edoxaban. Although already thousands of patients have been treated under study conditions, the new substances have to be further followed carefully and intensively in post-approval studies when a broad spectrum of patients will be treated in order to clarify open questions such as:

- treatment adherence in absence of monitoring,
- safety aspects in patients with renal/hepatic impairment and multi morbidity,
- side effects (e. g. gastrointestinal) and drug interactions,
- monitoring of risk patients,
- interpretation of coagulation tests (e. g. before surgery).

Answering these questions will be one prerequisite before conclusions can be drawn towards the potential of the new substances to replace vitamin K antagonists. If they in deed turn out to be superior and/or safer than VKA in routine use with no need of drug monitoring at regular intervals would implicate a great step in the direction of substantially improved medical care.

References

35. Lassen MR, Raskob GE, Gallus A et al. ADVANCE II investigators: Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (AD-
27 U. Harbrecht: Old and new anticoagulants

37. Website: http://clinicaltrials.gov/ct2/NCT00457002
38. Website: http://clinicaltrials.gov/ct2/NCT01181102
   NCT00439777; NCT00439725
49. ROCKET-AF Study Investigators: Rivaroxaban once daily, oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in atrial Fibrillation: rationale and design of the ROCKET AF study. Am Heart J 2010; 159: 340–347.