Do novel oral anticoagulants do better than standard therapy in the treatment of deep vein thrombosis?

M. Brodmann
Division of Angiology, Medical University Graz, Austria

Keywords
Deep vein thrombosis, DVT, vitamin K antagonist, VKA, novel oral anticoagulants, NOACs

Summary
The focus of DVT treatment is the prevention of recurrence and thrombus migration by treatment with anticoagulants. The aim is to improve outcomes by reducing clot burden and by preventing thrombus propagation, in order to prevent PE and the development of long-term complication. Actually, initial therapy is parenteral anticoagulation, mainly with low molecular weight heparin followed by a vitamin K antagonist (VKA) for triggered and idiopathic DVT. The long term treatment suggestion with a VKA is for sure the most challenging therapeutic scenario, showing all the disadvantages of VKA especially in the onset phase when therapeutic levels of VKA are difficult to achieve. The difference between VKAs and NOACs is the fact, that NOACs target a specific factor in the coagulation cascade. At time now two pathways have been chosen for treatment options, the direct inhibition of active sites of thrombin and factor Xa. Routine monitoring is not required and the drugs can be administered in fixed doses, which should increase patient adherence to long term treatment. At time now, four novel anticoagulants are called to be options for DVT treatment. Rivaroxaban, apixaban and edoxaban are direct FXa inhibitors, whereas dabigatran etexilate is a direct thrombin inhibitor.

Sind neue orale Antikoagulanzien zur Behandlung der tiefen Venenthrombose besser als die Standardtherapie?

Zusammenfassung
Der Fokus der TVT-Therapie ist die Prevention des Rezidivereignisses und die Migration der Thromben. Das Ziel ist es den Outcome durch die Reduktion der Thrombusmasse und der Verhinderung der Thrombenmigration zu verbessern. So sollen Akut- und Langzeitfolgen verhindert werden. Zum gegenwärtigen Zeitpunkt besteht die Initialtherapie aus parenteraler Antikoagulation, in der Regel niedermolekulares Heparin, gefolgt von oraler Antikoagulation mit einem Vitamin-K-Antagonisten (VKA) für TVT in Risikosituation und idiopathischer TVT. Die Langzeittherapie der TVT mit VKA ist sicherlich die größte therapeutische Herausforderung, da sie alle Nachteile der VKAs aufzeigt, vor allem zu Beginn der Therapie mit der Problematik die therapeutischen Zielwerte zu erreichen. Der Unterschied zwischen VKAs und NOACs (neuen oralen Antikoagulanzien) ist die Tatsache, dass NOACs einen spezifischen Angriffspunkt in der Gerinnungskaskade aufweisen. Zurzeit gibt es zwei Pfade, die zur Therapieoption gewählt wurden: die direkte Inhibition von Thrombin und Faktor Xa. Routinemonitoring ist nicht nötig und die Medikamente können in fixen Dosen verabreicht werden, was die Patienten-Compliance vor allem in der Langzeittherapie verstärken soll. Zurzeit gibt es vier neue Antikoagulanzien als Therapieoption der TVT: Rivaroxaban, apixaban sind Faktor-Xa-Inhibitoren, Dabigatran ist ein direkter Thrombininhibitor.

Deep vein thrombosis (DVT) is a major burden to every healthcare system due to its short and long term consequences. The most feared as possible deadly, short term consequence is the occurrence of pulmonary embolism (PE), which counts directly or indirectly for at least 100,000 deaths annually in the US (1). A long term costly consequence is the development of a post-thrombotic syndrome (PTS), which occurs in about 9% within two years (2) as severe PTS with leg ulcers, consecutive longtime infections at the site of the ulcers, hyperpigmentation and fragile skin of the lower legs. As DVT is a preventable entity a huge effort has been made in the last years for the improvement of thromboprophylaxis especially in orthopaedic, cancer and abdominal surgery, but also for the prevention of DVT in critically ill patients (3). Awareness has been created that DVT is an often seen complication in patients with acute stroke (4, 5). This has found its de-

Review
position in the ACCP guidelines of the recent years. As a consequence the number of preventable DVT has been reduced. Nevertheless, a considerable number of DVT is of unknown cause, so called idiopathic. Large population studies indicate that patients with a first venous thromboembolic event are at an increased risk for recurrence and long-term complications (6, 7), such as chronic thromboembolic pulmonary hypertension (CTPEH). According to the primary cause of DVT, triggered or idiopathic, patients differ for the risk of recurrence after treatment cessation (8). Therefore, current treatment guidelines discriminate between both entities for treatment duration, with a clear tendency for long term treatment in idiopathic DVT patients. At time now initial therapy is parenteral anticoagulation, mainly with low molecular weight heparin followed by vitamin K antagonists (VKAs) for triggered and idiopathic DVT (9). The long term treatment suggestion with VKAs in idiopathic DVT is for sure the most challenging therapeutic scenario, showing up all advantages and disadvantages of VKAs.

Established anticoagulants

For decades, unfractionated heparin (UFH), followed by low molecular weight heparin (LMWH) and VKAs has been the cornerstone of DVT treatment.

UFH and LMWH are indirect anticoagulation inhibitors, with the limitations of parenteral application and frequent monitoring for UFH and the risk of heparin induced thrombocytopenia (10, 11). LMWH has replaced UFH widely (10), because of

• improved bioavailability,
• easier application, and therefore ambulatory potential,
• lower levels of binding to plasma proteins and
• no requirements for routine monitoring.

Studies in the early nineties have shown the efficacy of LMWH in the initial phase of DVT and PE treatment with lower bleeding rates compared to UFH and higher efficacy related to prevention of recurrent VTE (12).

VKAs used for longterm treatment have the advantage that at least three generations of medical doctors are used to their unpredictable pharmacokinetics and pharmacodynamics.

VKAs show a narrow therapeutic window, variety in patient dose response and multiple interactions with food and drugs. All these facts transfer a cheap bill into an expensive treatment, referring to the costly monitoring and occurrence of side effects, bleeding and thromboembolic complications as well. The treatment is time consuming as adjustment is necessary, which should be performed every 1–4 weeks (13).

Nevertheless, only 60% of the patients will spend most of their treatment time with an INR in therapeutic range (2.0–3.0) (14).

Especially in the first three months with the overlapping treatment of LMWH this is difficult to achieve, which counts for severe side effects. Bülter and colleagues showed that in a recent publication (15).

Besides the side effects this complicated therapeutic regime results in poor patient adherence and provokes patients to discontinue their therapy.

The aim of the development of novel anticoagulants was to create a simpler and safer, by means more efficient method of anticoagulation treatment.

Novel anticoagulants

The biggest difference between VKAs and novel anticoagulants (NOACs) is the fact, that NOACs target a specific factor in the coagulation cascade (Fig. 1). At time now two pathways have been chosen for treatment options, the direct inhibition of active sites of thrombin and factor Xa (16).

Routine monitoring is not required and the drugs can be administered in fixed doses, which should increase patient adherence to long term treatment.

At time now, four novel anticoagulants (NOACs) are called to be options for DVT treatment. Rivaroxaban, apixaban and edoxaban are direct FXa inhibitors, whereas dabigatan etexilate is a direct thrombin inhibitor (Tab. 1):

• Rivaroxaban has been approved by FDA and EMEA for the acute and long term treatment of DVT and PE,
• dabigatran has finished the clinical trials and published data for both indications,
• apixaban and edoxaban are finishing their clinical therapeutic VTE trials.

Fig. 1 Targets for novel anticoagulants in the coagulation pathway

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**Direct activated FXa inhibitors**

Activated factor X (FXa) is in interaction with activated factor V responsible for the conversion of prothrombin into thrombin. One molecule of FXa is capable of generating 1000 molecules of thrombin, this process is well-documented to be inhibited by direct FXa inhibitors. The final effect of decreased thrombin levels is the interruption of clot formation. Direct FXa inhibitors have a broad therapeutic window, low patient variability and nearly no drug or food interaction (17).

**Rivaroxaban**

As a direct FXa Inhibitor rivaroxaban is able to inactivate free and also clot-associated FXa. It should be administered once daily, with a high bioavailability of 80% (18–20), is rapidly absorbed and reaches Cmax 2–4 hours after application. 90% of rivaroxaban are bound to plasma protein. Half life time is up to 12–13 hours in healthy elderly subjects. The main elimination pathway is the liver mainly with most CYP independent mechanisms, besides CYP 3A4 and 2C8. Only one third is eliminated via the kidney. Caution is demanded in patients with severe renal insufficiency (CLCr <30 ml/min) and in patients with impaired liver function.

Rivaroxaban was approved in Europe and many other countries for thrombosis prophylaxis based on the RECORD phase III clinical trial program for prevention of VTE in orthopedic surgical patients, which was partially placebo controlled. The whole trial program enrolled 12,500 patients suitable for thromboprophylaxis in orthopaedic surgery. In all trials rivaroxaban 10 mg daily demonstrated superiority over enoxaparin for VTE and all-cause mortality after elective orthopedic surgery with no increase in bleeding complications (21–24).

The EINSTEIN VTE Evaluation program was adjoined as a clinical trial program comparing rivaroxaban with VKA for the treatment of VTE. The revolutionary point behind that clinical trial was the fact that rivaroxaban was prompted as a therapeutic option right from the diagnosis of DVT and PE, without any initial treatment with LMWH. A treatment with 15 mg rivaroxaban twice daily given orally for three weeks were followed by 20 mg once daily versus weight adjusted enoxaparin followed by VKA for 3 to 12 months in patients with acute symptomatic DVT and in a separate study with acute symptomatic PE as the leading symptom (25, 26).

Einstein DVT was a multicenter, randomized, open-label, event driven, non-inferiority study which included 3400 patients with confirmed acute, symptomatic DVT without symptomatic PE. The results showed that rivaroxaban was non inferior to enoxaparin/VKA with respect to prevention of recurrent symptomatic VTE (2.1% versus 3.0%, p < 0.001). Combined major and non-major clinically relevant bleeding events were similar in both groups (25).

The EINSTEIN Extension study demonstrated that 20 mg once-daily rivaroxaban for 6 or 12 months was superior to placebo (1.3 vs. 7.1%, p < 0.001) in the secondary prevention of recurrent symptomatic VTE in patients with symptomatic DVT or PE who already been on treatment with either rivaroxaban or VKA for 6 or 12 months. The benefit of extended rivaroxaban treatment was independent from the previous treatment (VKA or rivaroxaban). Major bleeding complications were rare with 0.7% in the rivaroxaban group vs 0% in the placebo group, although the combined safety endpoint of major and non-major clinically relevant bleeding was much higher in the rivaroxaban group than in the placebo group (6% vs. 1.2%) which could be expected when anticoagulation treatment is compared to no anticoagulation therapy. No fatal bleeding occurred during extended treatment (25).

The EINSTEIN trials demonstrated that a single oral treatment option right from the beginning is at least as effective as standard therapy with LMWH followed by VKA, with no increase in bleeding for the primary event, as well as for an extended treatment option.

**Apixaban**

Apixaban is also an oral, direct inhibitor of Factor Xa, which shows a high bioavailability and reaches Cmax after 1–3 hours after administration. The half-life is 8–11 h when administered twice daily and 12–15 h when given once daily and about 87% is bound to plasma proteins (27). Concerning elimination most of apixaban is eliminated via the feces, other via CYP3A4 depending pathway in the liver, and one-fourth by renal clearance. Therefore it might be safe in patients with decreased renal function.

At time now results from the ADVANCE program are available, which lead to the approval for VTE prevention after orthopedic surgery in Europe, although ADVANCE-1 did not meet non-inferiority for prevention of VTE in knee replacement. The main reason might be the higher US specific dosage regime with

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**Tab. 1  Pharmacokinetics profile of NOACs**

<table>
<thead>
<tr>
<th>property</th>
<th>dabigatran</th>
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<th>edoxaban</th>
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<td>20</td>
<td>34</td>
<td>75</td>
<td>65</td>
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od: once daily; bid: twice daily
Concerning treatment of VTE the AMPLIFY program is not finished yet. In this study patients with symptomatic DVT and PE were treated with apixaban 10 mg BID for one week followed by 5 mg BID for six months compared to enoxaparin 1mg/kg BID followed by warfarin (INR 2–3) for 6 months. The primary endpoint in this study is VTE occurrence or death during study treatment (32). Already published is the Amplify Extension study where apixaban 2.5 or 5 mg BID was compared to placebo BID in the extended treatment for DVT or PE. The data showed that with both dosages of apixaban (2.5 mg and 5 mg BID) the rate of recurrent venous thromboembolism and death from venous thromboembolism could be reduced compared to placebo (1.7% for both dosages vs. 8.8% in the placebo group; p < 0.001 for both dosages apixaban) without increasing the rate of major bleeding. The rates of clinically relevant nonmajor bleeding were 2.3% in the placebo group, 3.0% in the 2.5-mg apixaban group, and 4.2% in the 5-mg apixaban group (33).

For DVT treatment the dose-finding Botticelli trial with 520 patients with symptomatic lower extremity DVT (proximal or distal) showed in different dosages (5 mg BID, 10 mg BID or 20 mg once daily) similar efficacy compared to LMWH followed by VKA with events of 4.7% vs 4.2% in accordance with a similar bleeding rate, including also the high dosage group of apixaban (7.3 vs 7.9%) (34).

**Edoxaban**

Edoxaban is the third orally active direct FXa inhibitor under investigation for DVT treatment. It has a bioavailability of >50% and reaches a peak plasma level within 1.5 hours in healthy people. Elimination is once again achieved by multiple pathways and in 35% by the urinary pathway. Its elimination half-life is 9–11 hours, and needs a dosage adjustment if concomitantly used with potent P-gp inhibitors like verapamil and quinidine (35).

Edoxaban is not yet approved for VTE prophylaxis or VTE treatment, besides Japan, where edoxaban has the approval for VTE prophylaxis. Japanese trials showed results which might count the drug as an alternative for VTE prophylaxis in orthopedic surgery in different dosages varying from 5, 15, 30, 60 or 90 mg once daily. Bleeding complications were low and similar across the groups. Efficacy was dose-responsive, and in the dosage of 30 mg once daily superior to LMWH (36–38).

At time now Edoxaban is evaluated by the HOKUSA VTE study for treatment of VTE. This phase III clinical trial is evaluating 60 mg edoxaban/LMWH once daily compared to LMWH/VKA in patients with symptomatic DVT and PE. The trial has finished patient inclusion. The primary outcome is symptomatic recurrent VTE for 12 months from time to randomization (39).

**Direct thrombin inhibitors**

Direct thrombin inhibitors (DTIs) neutralize thrombin by directly binding to its active catalytic site and therefore blocking all interactions. Thrombin is the central player in clot generation, converts soluble fibrinogen to fibrin and activates factors V, VIII and XI. It also stimulates platelets and stabilizes the clot by activating factor XIII (40). The most widely known DTI is the now orally available dabigatran etexilate.

**Dabigatran etexilate**

Dabigatran is an oral, specific binding and reversible thrombin inhibitor. It acts as a prodrug, which is transformed into its active metabolite by CYP enzymes. Dabigatran reaches maximal plasma concentration within two hours of administration or within four hours when given with food. The plasma protein binding rate is about 35%. As elimination is mainly renal (80%) the dosage needs to be adjusted when creatinin clearance drops <50 ml/min (41). At time now there is no antidote to reverse dabigatran related effects.

For VTE prophylaxis dabigatran was approved already in 2008 in Europe for patients with elective hip and knee surgery (42–44). In 2010 the substance was approved by the FDA for prevention of stroke and systemic emboli in patients with nonvalvular atrial fibrillation (45).

Dabigatran has filed for approval for the treatment of VTE, as the VTE clinical trial program (REVOLUTION) has been finished.

Prophylaxis trials for elective hip or knee surgery have showed for 3 out of 4 trials noninferiority of dabigatran versus LMWH in the prevention of VTE. One trial, the REMOBILIZE trial, where dabigatran was compared to 30 mg enoxaparin twice daily, proved dabigatran to be inferior to enoxaparin. Nevertheless the compound data of the prophylaxis trials showed a proven efficacy of dabigatran for prevention of VTE in elective orthopedic surgery with a similar bleeding risk (46).

For the treatment of VTE four trials have been performed, with the RECOVER trial as the most important and first finished. This trial compares dabigatran in the treatment of acute DVT and PE (47). Dabigatran 150 mg twice daily was compared with dose-adjusted warfarin (INR 2-3) after initial treatment of parenteral anticoagulation over 5–10 days. The initial overlapping treatment with LMWH is in contrast to the apixaban and rivaroxaban trials, where the oral drug is given right from the beginning. Dabigatran was noninferior to warfarin (2.4% vs 2.1%, p < 0.001) in preventing recurrent VTE. Concerning bleeding, for major bleedings there was no difference, but for any bleeding dabigatran showed a significant reduction with 29% (p = 0.0002) compared to warfarin. REMEDY and RESONATE have been evaluating the effect of dabigatran for the extended use of anticoagulation in VTE patients (up to 36 months). In REMEDY dabigatran 150 mg BID proved to be as effective as warfarin in the prevention of VTE events (1.8 vs 1.3%, p = 0.003) in an up to 36 months treatment period. However, there was a significant increase of coronary events in the dabigatran group (0.9% vs 0.2%, p = 0.02) (48).

In the RESONATE trial (up to 18 months treatment), the occurrence rate of VTE after six months of treatment was 0.4% for dabigatran versus 5.6% for placebo. The major bleeding events were similar (48).

Recover II has been finished in May 2011, but data have not been published peer-reviewed so far.
Real world and conclusions

Only one drug (rivaroxaban) has been approved so far by the FDA and EMA for the treatment of VTE. This drug has gained treatment indication for DVT and PE acute, longerterm and extended treatment. Registries and prospective cohort studies will show the role for these drugs in real world scenarios, where patients will not be selected by in and exclusion criteria.

A main advantage of the new drugs will be better patient adherence and better cost effectiveness relating to lower short and longtime VTE complications, in adherence to lower costs for not necessary routine monitoring. Also the necessity of assistance for application of parenteral agents will subside, which by means could enable an earlier and easier ambulant treatment of VTE patients. Not to speak of quality of life.

There are some draw backs so far, as the fact that no direct antidote exist. Furthermore, substances are eliminated over the renal pathway and have proven to create high bleeding rates in AF patients. A recent phase I study has shown that thrombin complex concentrate completely resolved coagulation parameters after the use of rivaroxaban, but not with dabigatran (49). For apixaban and rivaroxaban a newly developed recombinant factor Xa might prove an effective antidote (50). Dabigatran is partially dialyzable (51). Nevertheless, it might be of some concern that missing a dose of the new oral AC drugs – compared to vitamin K and particularly phenprocoumon – would mean no anticoagulation effects for a certain time period for the patient.

Another challenging matter will be the perioperative, periprocedural bridging modality, as every drug has its own profile and in relationship to that its own “bridging” schedule. As known so far it is unlikely that any overlap of parenteral LMWH or UFH is beneficial in such situations.

It is for sure that with the development of NOACs not only AF but also VTE enters a new treatment era.

Conflict of interest

The author declares that she has received speaking honoraria from Bayer, Boehringer, Daichy Sankydo and from Pfizer.

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