Vitamin K antagonists
Ready to be replaced?

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Summary
For the last decades, anticoagulation for stroke prevention in atrial fibrillation (AF) as well as for the prophylaxis and long-term treatment of venous thromboembolism has been entirely based on vitamin K antagonists (VKA). Although very effective under optimal conditions, long-term treatment with these drugs is flawed by the fact that the time in the therapeutic range frequently is suboptimal due to biological factors, drug interactions and compliance.

The direct thrombin inhibitor dabigatran, as well as the direct FXa inhibitors rivaroxaban and apixaban provide more consistent anticoagulation and have proven their efficacy and safety against VKAs in several large scale randomized clinical trials for stroke prevention in atrial fibrillation as well as for the treatment and prevention of venous thromboembolism. In view of these convincing data and other advantages such as the lack of mandatory monitoring and only few drug interactions, VKAs will most likely be replaced in a majority of patients for these indications.

Based on the most recent trial evidence, the current review discusses the role of VKA treatment and that of the novel anticoagulants.

Keywords
Apixaban, atrial fibrillation, dabigatran, oral anticoagulants, rivaroxaban, RE-LY, AVERROES, ARISTOTLE, ROCKET AF

Vitamin-K-Antagonisten – Können sie ersetzt werden?
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Ever since their introduction in the 1950ties, vitamin K antagonists (VKA) have been used for stroke prevention in atrial fibrillation (AF) as well as for the prophylaxis and long-term treatment of venous thromboembolism (VTE) (Fig. 1) (1–3). Although very effective under optimal conditions, long-term treatment with these drugs is hampered with several problems (4, 5): First of all, due to their narrow therapeutic window, life-long coagulation monitoring and careful drug dosing is required to achieve effective anticoagulation and to avoid bleeding (6, 7). Furthermore, drugs interfering with their protein binding and/or metabolism, in particular the frequently prescribed non-steroidal anti-inflammatory drugs (NSAIDS) are problematic.

To overcome these limitations, several novel agents have recently been developed with the goal of replacing VKAs (3). After decades of research, numerous studies have now surfaced for stroke prevention in atrial fibrillation as well as for the treatment and long-term prophylaxis of VTE, demonstrating superiority with respect to safety and/or efficacy with these novel drugs as compared to VKAs for a large proportion of patients.

These impressive study results hence raise the question whether VKA treatment should still be considered the treatment of choice in any of these conditions. Based on the most recent trial evidence (Tab. 1), the role of VKA treatment in the light of the dawn of the age of novel anticoagulants is discussed. It is based on and extends previous publications of the authors on this topic (3, 8).

Vitamin K antagonists and novel anticoagulants

Vitamin K is an essential co-factor for the synthesis of coagulation factors II, VII, IX
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and X, as well for the anticoagulatory proteins protein C and protein S.

Vitamin K antagonists such as phenprocoumon (Marcoumar®), acenocoumarol (Sintrom®) or warfarin (Coumadin®) prevent hepatic synthesis of these factors by inhibiting vitamin-K dependent γ-carboxylation (9).

The three molecules differ primarily regarding their half-lives, which range from 9 hours (acenocoumarol) to 30–40 hours (warfarin) and up to 120–160 hours (phenprocoumon). Treatment with VKAs is frequently cumbersome due to numerous drug-drug interactions, in particular inducers and inhibitors of hepatic P450 isoenzymes, which may unpredictably increase or decrease VKAs anticoagulant effects (10–12). Furthermore, various foods, especially vegetables, may significantly alter both pharmacokinetics and pharmacodynamics of these drugs (10).

- Direct thrombin (factor IIa) blockers selectively inhibit the activity of thrombin both in solution as well as in its fibrin-bound state, thus preventing both the conversion of fibrinogen to fibrin and, most importantly, the amplifying auto-feedback activation of FXa via its co-factors (Fig. 1, “thrombin burst”).
- In contrast, factor Xa inhibitors exert their anticoagulant effect by blocking the conversion of thrombin from prothrombin (3).

Both types of substances hence differ from VKAs in two regards: They
- selectively block only one factor of the coagulation cascade (as opposed to the VKA “scattershot”),
- block the active form directly (as opposed to inhibition of hepatic de-novo synthesis of the inactive form with VKA).

The direct thrombin inhibitor dabigatran (Pradaxa®) has a bioavailability of approximately 6%. It is absorbed as a prodrug (dabigatran etexilate), and is subsequently converted into its active form by circulating esterases (13, 14). Elimination is 80% renal; its half-life is 14–17 hours, and it is given twice daily (13).

Rivaroxaban (Xarelto®) is an oral FXa inhibitor that blocks FXa both in its prothrombin-bound as well as in its free state (15). It has a half-life of 7–11 hours and is dosed either once or twice daily. Rivaroxaban has a dual mode of elimination, with one-third of the drug eliminated unchanged by the kidneys and two-thirds being metabolized by the liver (16). As a result, rivaroxaban is contraindicated in patients with coagulopathy due to liver disease, and care should be taken – as with dabigatran – when using it in patients with impaired renal function.

The oral direct FXa inhibitor apixaban equally inhibits both free and prothrombin-bound FXa (17, 18). It is eliminated largely via the faecal route (about 70%) (19), which has proven beneficial in patients with impaired renal function (ARISTOTLE study).

### Novel anticoagulants

#### Atrial fibrillation (AF)

**Dabigatran in AF**

In the landmark trial RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy), 18 113 patients with AF and at least one additional risk factor for stroke received dabigatran 110mg bid, dabigatran 150mg bid, or an adjusted dose of warfarin to an INR of 2.0 to 3.0 in a partial PROBE design (Prospective Randomized Open Trial with Blinded Adjudication of Events) (20, 21). After a mean follow-up of two years, both doses of dabigatran were shown to be non-inferior to warfarin: the primary end-point, stroke or systemic embolism, occurred at 1.69%/year with warfarin, 1.53%/year with dabigatran 110 mg bid (relative risk [RR] 0.91; 95% CI 0.74–1.11), and 1.11%/year with dabigatran 150 mg bid (RR 0.66; 0.53–0.82, Fig. 2). Major bleeding rates were statistically similar among patients on dabigatran 150 mg bid (3.11%/year) and on warfarin (3.36%/year, p = 0.31); in contrast, bleeding was less frequent in patients on the low dose of dabigatran (2.71%/year, p = 0.003 vs. warfarin). Haemorrhagic strokes were less frequent with both dabigatran doses compared to warfarin, occurring at 0.12%/year (p < 0.001) and 0.10%/year (p < 0.001) in patients on 110 mg bid and 150 mg bid dabigatran, respectively, as compared to 0.38%/year in warfarin treated patients. Indeed, intracranial haemorrhage was universally less frequently observed with all novel anticoagulants studied for atrial fibrillation (dabigatran, rivaroxaban, apixaban) as compared to warfarin.

Similarly, life-threatening bleeding was less frequent with both doses of dabigatran (RR 0.68, p < 0.001 and RR 0.81, p = 0.04 with dabigatran 110 mg bid and 150 mg bid.
bid, respectively). In contrast, gastrointestinal bleeding was more frequent with dabigatran 150 mg bid (1.51%/year) as compared to warfarin (1.02%/year, p < 0.001), while it was similar to warfarin with dabigatran 110 mg bid. Finally, dabigatran 150 mg bid fell just short of reducing the most robust end point of all-cause mortality (3.6%/year vs. 4.1%/year with warfarin, p = 0.051). Again, either a trend (rivaroxaban, p = 0.07), a strong trend (dabigatran, p = 0.051) or even a statistically significant reduction (apixaban, p = 0.047) in all-cause mortality was observed with all three novel anticoagulants studied in atrial fibrillation compared to warfarin.

Surprisingly, an increase in the risk of myocardial infarction (with albeit overall small numbers of the event) was observed with both doses of dabigatran in the original analysis of the data (20). A recent re-analysis of patients’ ECGs, however, identified 28 silent myocardial infarctions (distributed over the three groups), which were not included in the original analysis. When included in the data set, the numerical increase in myocardial infarction was no longer significant (21). Although a possible slight increase in myocardial infarctions should nevertheless be kept in mind, the fact that apparently no signal of a substantial increase in myocardial infarction has surfaced after more than one year of utilization of dabigatran in the US is reassuring in this regard. Furthermore, neither APRAISE-2 nor ATLAS-ACS, two large trials testing these novel compounds in patients with acute coronary syndromes, noted an increase in myocardial infarction; rather, in the latter trial the event rate was significantly reduced if given on top of dual antiplatelet therapy.

In terms of side effects, dyspepsia was more commonly observed with dabigatran 110 mg bid (11.8%) and 150 mg bid (11.3%) as compared to warfarin (5.8%), as well as a higher rate of study drug discontinuation after two years (21%, 21% and 17% for dabigatran 110 mg, 150 mg and warfarin, respectively). Importantly, no elevation in liver enzymes was observed with either of the dabigatran doses as compared to warfarin in RE-LY as well as in other trials with dabigatran (20).

Results from subgroup analyses from RE-LY mainly pointed into the same direction as the main study, confirming its findings in the subgroup of patients with different CHADS2 scores (22), prior stroke (23) and in those undergoing cardioversion (24).

When comparing dabigatran with different average levels of INR control in the warfarin population, patients in centers with the poorest INR control appeared to profit most in terms of stroke prevention (although no statistically significant interaction was observed) (25). No difference in time to major bleeding or intracranial bleeding was seen between centers with good and bad INR control (25), hence indicating a favourable efficacy and safety profile of the drug across all strata of INR control.

Most regulatory agencies followed the doses tested in RE-LY and approved both the 150 mg bid as well as the 1 mg bid doses. The FDA, however, decided to drop the 110 mg bid dose and decided, to the surprise of many, to allow a reduced dosing regimen (dabigatran 75 mg bid) for patients with severe renal insufficiency (creatinine clearance 15–30 ml/min) in the absence of any outcome data. In fact, severe renal insufficiency was an exclusion criteria in Re-Ly, and the approval was based solely on pharmacokinetic data from other dabigatran trials to enable treatment of patients with severe renal insufficiency.

**Rivaroxaban in AF**

In the phase III, double-blind, double-dummy study ROCKET AF (Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonist for prevention of stroke and Embolism Trial in Atrial Fibrillation, ROCKET-AF), rivaroxaban 2.5 mg bid was compared to warfarin (target INR 2.0–3.0) in patients with non-valvular atrial fibrillation who are considered to be at high risk of stroke. Rivaroxaban was non-inferior to warfarin in preventing stroke and systemic embolism, with a slightly lower risk of major bleeding, but a higher risk of intracranial bleeding. The FDA approved rivaroxaban in the US for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation at high risk of stroke who are also considered to be at high risk of intracranial bleeding.

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**Tab. 1 Important phase III randomized controlled trials involving the substances discussed; modified from Steffel and Braunwald (3)**

<table>
<thead>
<tr>
<th>oral anticoagulants</th>
<th>atrial fibrillation</th>
<th>DVT prevention</th>
<th>treatment</th>
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<td>orthopaedic:</td>
<td>AMPLIFY**</td>
<td>APPRAISE-2*</td>
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<td>edoxaban (Daiichi Sankyo)</td>
<td>ENGANGE TIMI 48**</td>
<td>orthopaedic:</td>
<td>AMPLIFY-Ext**</td>
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<tr>
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<td>Re-LY* RelY-ABLE**</td>
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<td>RE-COVER II*</td>
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<td>rivaroxaban (Bayer)</td>
<td>ROCKET-AF*</td>
<td>orthopaedic:</td>
<td>RE-MEDY**</td>
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<td>medical: long term:</td>
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*met predefined endpoint; ** ongoing; did not meet predefined endpoint or was terminated early due to safety concerns (APRAISE-2)
Atrial Fibrillation), rivaroxaban 20 mg once daily (15 mg daily for patients with creatinine clearance 30–45 ml/min) was compared to INR-adjusted warfarin in 14264 patients (26). The results demonstrated non-inferiority of rivaroxaban as compared to warfarin (hazard ratio 0.79; 95% CI 0.66, 0.96; p < 0.001) with event rates of 1.71%/year and 2.16%/year, respectively. In the “on treatment” analysis, rivaroxaban was superior to warfarin (p = 0.013), while statistical superiority was not observed in the intention-to-treat analysis, with event rates of 2.12%/year and 2.42%/year with rivaroxaban and warfarin, respectively (HR 0.88; 95% CI 0.74–1.03, p = 0.117). Most likely, factors in the trial design (i.e., the long period during which events were included after drug discontinuation in the intention-to-treat analysis) resulted in a significant increase in event rates in both arms and, subsequently, regression to the mean of the main results, leading to non-superiority of rivaroxaban in this analysis.

No difference in the rate of major and non-major clinically relevant bleeding (HR 1.03; 95% CI 0.96–1.11, p = 0.442) was observed between rivaroxaban and INR-adjusted warfarin. Although bleeding requiring transfusion as well as epistaxis were more common with rivaroxaban (HR 1.25, 95% CI 1.01–1.55), the most serious forms of haemorrhage, i.e. intracranial haemorrhage (HR 0.67; 95% CI 0.47–0.94, p = 0.019) and fatal bleeding (HR 0.50; 95% CI 0.31–0.79, p = 0.003) were less common than with warfarin. As indicated earlier, a trend towards a reduction in all-cause mortality (HR 0.85; 95% CI 0.70–1.02, p = 0.07) was equally observed with rivaroxaban in the on-treatment analysis.

There was no difference in other side effects, including acute myocardial infarction and serious adverse events. The main results of ROCKET AF were consistent across pre-specified subgroups including patients with renal insufficiency, different CHADS2 scores, prior warfarin use, center time in therapeutic range, and prior stroke (27). Rivaroxaban has recently been approved by the FDA as well as the EMEA for stroke prevention in atrial fibrillation based on the results of ROCKET AF.

Apixaban in AF

Apixaban has been studied in two phase III, double blind randomized trials for stroke prevention in atrial fibrillation. In the trial AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Strokes), patients with AF and at least one additional risk factor, who were either expected to be unsuitable for treatment with a VKA (60%) or who had used and discontinued a VKA (40%) were randomized to receive either apixaban (5 mg bid or, in selected patients, 2.5 mg bid) or acetylsalicylic acid (ASA) (81–324 mg/d) (28). Due to compelling evidence of efficacy, the data monitoring committee recommended early study termination at the first planned interim analysis. After a median follow-up of one year, stroke or systemic embolism was observed in 52 patients (1.6%/year) and 112 patients (3.6%/year) in the apixaban and ASA group, respectively (RR 0.46; 95% CI 0.33–0.64, p < 0.001). In hindsight, this was not entirely unexpected due to the established superiority of VKA vs. aspirin in protecting patients with AF from developing a thromboembolic stroke. Importantly, intracranial (0.4%/vs. 0.3%, p = 0.83), major (1.4%/year vs. 1.2%/year for apixaban and aspirin, respectively, p = 0.56), and fatal bleeding events (0.1% in both groups, p = 0.77) were similar between the two study arms. In contrast, minor bleeding was more common with apixaban (5.2%/year vs. 4.1%/year, p = 0.04).

In the trial ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation), INR-adjusted warfarin was chosen as the comparator for apixaban (5 mg bid or, in selected patients, 2.5 mg bid) in patients with AF (29). A 21% relative risk reduction (1.27%/year vs. 1.60%/year, p = 0.011) in the primary end-point (stroke or systemic embolism) was observed with apixaban, demonstrating not only non-inferiority but statistically significant superiority versus dose-adjusted warfarin. In the same direction, major bleeding (HR 0.69, p < 0.001), and intracranial bleeding (HR 0.42, p < 0.001) were less frequent with apixaban. Finally, as indicated earlier, a significant reduction in all-cause mortality was equally observed (HR 0.88, p = 0.047), hence underscoring the overall positive effect of the drug.

All exploratory subgroup analysis of ARISTOTLE demonstrated results pointing into the same direction as the main study with no significant interactions for age, gender, prior stroke, CHADS2-Scores, renal insufficiency and others regarding the primary efficacy endpoint. With respect to major bleeding complications, patients without diabetes experienced significantly less bleeding than those with diabetes (both compared to warfarin), a phenomenon which will require further study (bias of multiple testing?). Interestingly, patients with severe or moderate renal impairment had significantly less bleeding that those with only mild or no impairment (all compared to warfarin), which is likely due to the only small amount of the drug eliminated via the kidneys.

Treatment and long-term prevention of venous thromboembolic disorders

Dabigatran in VTE

Based on the results from the RE-NOVATE and REMODEL trials, dabigatran etexilate has been approved by the EMEA for the prevention of VTE events in patients undergoing elective total hip or knee replacement (30–33).

In the phase III RE-COVER trial, dabigatran etexilate 150 mg bid was compared to INR-adjusted warfarin for 6 months in the treatment of an acute VTE (34). Recurrent VTE occurred in 2.1% of patients on warfarin vs. 2.4% on dabigatran (p < 0.001 for non-inferiority, HR 1.10 for dabigatran (0.65–1.84). While major bleeding was similar in the two study groups (1.6% and 1.9% for dabigatran and warfarin, respectively), overall bleeding was more frequent under warfarin (21.9% vs. 16.1%, HR with dabigatran 0.71 (0.59–0.85), p < 0.001). A second VTE treatment study (RE-COVER II) has recently confirmed these findings (presented at the American Society of Hematology 2011 Annual Meeting). These results indicate that fixed dose dabigatran etexilate compares favourably with INR-ad-
justed warfarin for the treatment of acute VTEs. Furthermore, two trials are underway for long-term secondary prevention of VTE following successful treatment with warfarin for 3–6 months (REMEDY, NCT00329238) or 6–18 months (NCT00558259) after an acute symptomatic VTE event.

**Rivaroxaban in VTE**

Rivaroxaban has been approved for the prevention of VTE in adult patients undergoing elective hip or knee replacement due to the results of the study program RECORD (REgulation of Coagulation in major Orthopaedic surgery reducing the Risk of Deep vein thrombosis and pulmonary embolism) (35–39).

In the phase III EINSTEIN-DVT study, 3,449 patients with deep vein thrombosis were treated with either rivaroxaban or a vitamin K antagonist (40). The primary endpoint, first symptomatic VTE, was reached in 51 patients (3.0%) in the conventional treatment arm as compared to 36 patients (2.1%) on rivaroxaban (HR 0.68 [95% CI 0.44–1.04], p < 0.0001 for non-inferiority and p = 0.076 for superiority of rivaroxaban). Major bleeding or clinically relevant non-major bleeding were similar in both groups (HR 0.97, 0.76–1.22, p = 0.77). Both efficacy and safety outcomes were consistent across all subgroups. Death of any cause was observed in 38 (2.2%) and 49 (2.9%) of patients on rivaroxaban and on the conventional regimen, respectively (HR 0.67; 95% CI 0.44–1.02, p = 0.06), indicating almost statistical superiority of rivaroxaban. Taken together, these results demonstrate that rivaroxaban is at least as effective as the standard treatment regimen of enoxaparin/fondaparinux followed by VKA for the treatment of DVT, at a similar risk of relevant bleeding.

The EINSTEIN-Extension study was designed to assess the efficacy and safety of rivaroxaban for secondary long-term prevention of secondary VTE. Depending on the presumed etiology of the event, current guidelines recommend an initial treatment duration for acute VTE usually between 3–12 months; however, recurrent events after an initial round of treatment are not infrequently observed, and the optimal duration of treatment is therefore still debated (6). A total of 1,197 patients who, according to their treating physician’s decision had completed their designated duration of anticoagulation (6–12 months) for an acute episode of VTE, were included in the EINSTEIN-Extension study. Symptomatic recurrent VTE events were reduced by 82% with rivaroxaban as compared to placebo (HR 0.18, p < 0.0001) after a mean treatment duration of 190 days, at similar bleeding rates (40). These impressive results hence not only demonstrated efficacy and safety of rivaroxaban in this setting, but may also challenge current guidelines with respect to the optimal treatment duration of VTE in these patients.

**Practical considerations and uncertainties**

Three novel oral anticoagulants have hence proven their efficacy and safety against VKAs in stroke prevention atrial fibrillation as well as for the treatment and prevention of venous thromboembolism. In spite of the – understandable – enthusiasm associated with the use of these drugs, some uncertainties remain, and ringing in the funeral bells for VKAs may still be premature at this point in time.

**Lack of monitoring vs. possibility to assess the degree of anticoagulation**

One of the greatest advantages of these novel agents in long term treatment is the lack of necessity for routine INR monitoring. Indeed, data from the above discussed phase III trials have indicated that this approach appears to be safe and effective for the studied indications. In fact, routine monitoring of the anticoagulant effect is neither backed by study-derived target values nor possible due to fluctuating drug levels depending on drug intake.

Nevertheless, application of these novel agents for long-term care of patients with intercurrent diseases, multiple comorbidities and polypharmacy, will require large observational studies. As with VKA, both under- and overtreatment may lead to serious consequences. In particular transient changes in renal function may represent a serious problem with these agents. Furthermore, urgent assessment of the anticoagulant status in case of emergency surgery or after trauma may certainly be desirable. With VKAs, decades of research and experience are available, which have resulted in the definition of the target range of INR 2.0–3.0. However, standard coagulation parameters, including prothrombin time, Quick, and INR are unsuitable for these novel agents (if not counter-productive due to potentially misleading results), which is why recent efforts have focussed on the establishment of appropriate other measures to assess their anticoagulant effect. For dabigatran, measurement of thrombin time has turned out to be the best suited anticoagulant test (13, 41), which may be referenced against external standards for comparable absolute values (Hemoclot® Thrombin Inhibitor Assay, Hyphen BioMed, Neuville-sur-Oise, France). In contrast, assessment of FXa activity using specialized chromogenic assays has been shown to be most appropriate for direct FXa inhibitors (42–44), which have equally made commercially available specifically tailored to the novel FXa inhibitors (e.g., Biophen, Hyphen BioMed, Neuilly-sur Oise, Frankreich; Modified STA-Rothrom, Diagnostica Stago, Asnieres, Frankreich; Technochrome Anti-Xa Test Technoclone). Only long-term experience in the application of these assays, however, will show their practicability and usefulness in the real-world clinical setting.

**Lack of specific antidote – a difference to VKA?**

At present, none of the novel anticoagulants discussed has a specific antidote, with which an immediate reversal of anticoagulation can be achieved. Nevertheless, the results of the aforementioned large scale clinical trials have demonstrated that major and / or intracranial bleedings do not occur more frequently in patients treated with these substances as compared to VKA, despite the lack of a specific, rapid acting antidote. One of the reasons for this may be the significantly quicker return of normal co-
agulation status after cessation of the drug as compared to VKAs due to their much shorter half-life. Indeed, in patients with normal liver and kidney function, this time span may be comparable to the time to full effect of vitamin K application in VKA treated patients. This furthermore shows that a specific, quick acting antidote for the acute reversal of VKA-induced anticoagulation is equally not available, and application of non-specific antagonists such as fresh frozen plasma (FFP) or coagulation factors (PPSB) is required. While in theory, these agents should also work for the novel anticoagulants, their efficacy may be less (or the required doses higher) than with VKA due to presence of the active thrombin/FXa inhibiting agent in the circulation. The clinical usefulness and safety of application of FFP and/or coagulation factors for reverting the novel anticoagulants’ effects hence remains to be proven. In addition, antidotes for the acute and specific reversal of the novel anticoagulants are in the process of being developed. Indeed, both a potent, selective monoclonal antibody for the reversal of dabigatran (van Ryn et al., American College of Cardiology Meeting 2011) as well as a recombinant, universal FXa antidote (r-Antidote, PRT064445) have so far been successfully tested in vitro and in vivo (Lu et al., European Society of Cardiology Meeting 2011).

**Renal insufficiency**

Patients with renal insufficiency pose a problem with any anticoagulant treatment. Indeed, both the impaired renal function per se as well as frequent co-morbidities in these patients puts them at high risk for embolic as well as bleeding events. Indeed, over 300 fatal bleeding complications were reported worldwide under dabigatran since its introduction in November 2010, which apparently occurred mainly in patients with renal insufficiency or worsening renal function. As a result, regular monitoring of renal function is strongly recommended in any patient on dabigatran. However, although vigilance is required with respect to bleeding complications, especially fatal ones, these numbers have to be put into context of both the overall number of patients treated as well as the number of bleeds expected under the alternative (i.e., VKA). Extrapolated from Re-LY, 230 and 330 fatal bleeds would have been expected to occur in 100 000 patient-years of treatment with dabigatran 150 mg bid and warfarin, respectively. As such, after over 400 000 patient years of “real-world” application of dabigatran, an even larger number of fatal bleedings would have been expected and, accordingly, even more under VKA treatment.

Hence, although notoriously difficult to manage, patients with renal insufficiency would likely be better candidates for apixaban, which is >70% excreted via the intestines. In fact, in ARISTOTLE, patients with moderate renal failure had fewer bleedings than those with mild or no impairment (both compared to warfarin). Although VKA therapy is tempting in these patients due to the possibility to monitor the anticoagulant status, the increased bleeding risk of patients with renal insufficiency under VKA treatment has to be kept in mind – independent of monitoring capabilities.

**Is the age of vitamin-K antagonists over?**

The impressive study results of novel anticoagulants in AF and VTE prevention intuitively raise the question whether VKA treatment should still be considered the therapy of choice in any of these conditions, and if not all patients (newly diagnosed on VKA) would need to be started on or switched to one of these new drugs. When compared to VKAs, these substances possess a number of desired features, including ease of use, lack of routine monitoring and less food- and drug interactions, all of which are particularly attractive in the long-term use in VTE and stroke prevention. As a result, a substantial increase in the number of patients on adequate anticoagulation may be hoped for, as many of them are not properly treated today due to the inconvenience and drawbacks of VKA therapy (45). Universally applying these drugs to all patients without weighing the risks and benefits, however, is not advisable, as some circumstances may still favour treatment with a VKA. Furthermore, in certain health systems, the low costs of VKA may outweigh the benefits of the new agents.

For example, data from Re-LY indicate that patients least likely to derive an incremental benefit from being switched from a VKA to dabigatran (in relative terms) are those who are well controlled on warfarin with INR values consistently in the target range. Although even these patients would benefit from a reduced probability for intracranial bleeding, it will be difficult to persuade the patient, caregiver and particularly the insurer to change a patient who has been faring very well on a VKA to any of the novel substances. Maybe over time, with the availability of additional real-world evidence, also these patients will be candidates for a change; until then, there is probably little to gain for them (but potentially to lose). This may be particularly true for patients on INR self-monitoring or management, who usually have a high percentage of their INR values in the target range.

Most patients, however, do not belong into this category and are in fact not well controlled under VKA treatment, and are hence very good candidates for the novel anticoagulants. An exemption may be the patient with poor compliance, who will definitely be problematic to manage both with the novel drugs as with VKAs. For optimal management, it will be indispensable to include these patients in the decision process regarding the differential therapeutic options, to actively engage them in their treatment, and to make them assume responsibility for compliance with their therapy. If in doubt, VKA treatment may nevertheless be the better of two suboptimal options in these patients to at least be able to monitor malcompliance and educate the patient about it, while no such feedback can be given with the newer agents.

Patients with atrial fibrillation and an acute coronary syndrome are notoriously difficult to manage, as most of them require dual antiplatelet therapy (for the ACS) as well as full anticoagulation (for the AF). Recent European guidelines on atrial fibrillation have established a scheme from which the duration of triple anticoagulation can be derived (7). Novel anticoagulants intuitively appear to be a good option in this situation given their reduced propensity for bleeding as compared to VKA –...
which should turn out positive in patients treated simultaneously with two antipla- telet agents. Results from the APPRAISE-2 study, however, have demonstrated that this may not necessarily be the case (46). In fact, the study had to be terminated early due to an increase bleeding risk in patients treated with ASA, clopidogrel and apixaban (in the dose used for stroke prevention in AF) as compared to ASA, clopidogrel and placebo. In contrast, the ATLAS TIMI 51 study found a reduction in mortality in pa-
tients treated with rivaroxaban (2 × 2.5 mg) on top of dual antiplatelet therapy as com-
pared to placebo (47). Although encourag-
ing, this latter treatment regimen may not be considered “true” triple anticoagulation as the dose chosen for rivaroxaban was sig-
ificantly lower than the one studied in ROCKET-AF for stroke prevention in AF (1 × 20 mg). Hence, until further data be-
come available, VKA treatment appears to the therapy of choice in these patients, using meticulous INR monitoring to walk the thin line between efficacy and safety.

Finally, it has to be kept in mind that VKAs have been around for several de-
ades, resulting among others in substantial experience in the treatment of "special population" patients such as pregnant women. Also, patients with highly pro-
-thrombotic conditions such as valvular atrial fibrillation or a mechanical mitral valve, which have equally all been included in the aforementioned studies on novel anticoagulants, certainly remain candidates for VKA therapy until further evidence emerges.

**Conclusion**

In view of the convincing data from recent large scale phase III trials, VKAs will most likely be replaced by several novel anti-
coagulants for a majority of patients for
- stroke prevention in AF
- VTE prophylaxis and treatment.

However, there may be situations in which treatment with VKA still has its place, and proclaiming the death of vitamin K antago-
nists is certainly premature. As with every type of new therapy, the undifferentiated utilisation of any of these novel substances

in virtually all patients is neither justified nor advisable, particularly not in special

situations as discussed. Until more evidence and experience is available from eli-
gible patients for such therapy (who, any-
how, represent the majority of patients in absolute terms), these special circum-
stances mostly call for VKA treatment.

The most important aspect, however, is to install some form of anticoagulation at all in these patients, because one of the most prevalent problems is the underutilization of anticoagulant therapy in patients who clearly qualify for it – with a significant negative impact on morbidity and mortality.

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