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ORIGINAL ARTICLE

Role of Newer Oral Anticoagulants For Stroke Prevention In Patients With Atrial Fibrillation- Recent Update 2015

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ABSTRACT

For decades vitamin K antagonists (VKA) have been the mainstay of treatment and prophylaxis of thromboembolism, in particular in primary prevention of systemic embolism associated with atrial fibrillation. Despite their efficacy, the use of VKA is associated with several limitations, including a narrow therapeutic window and a wide variability in the anticoagulant effect due to several drug-food and drug-drug interactions of VKA. The several limitations of VKA have resulted in their underuse for prevention of thromboembolic complications in patients with atrial fibrillation. Recently, new classes of oral anticoagulants have emerged: factor Xa (FXa) inhibitors and direct thrombin inhibitors. These new anticoagulants have a more predictable effect and eliminate the need for routine monitoring. Even though recent clinical trials have demonstrated the safety and efficacy of the new compounds, several unanswered issues must be addressed before conclusions can be drawn towards their potential to replace VKA.

KEY WORDS : New Oral Anticoagulants(NOAC), Stroke prevention, Atrial Fibrillation(AF), Vitamin-K Antagonist (VKA).

Introduction

The discovery of vitamin K antagonists (VKA) was the first step towards oral anticoagulation, but VKA use has been associated with serious challenges from the perspectives of the physician and the patient. Because of their slow onset of action, VKA require an overlapping treatment with a rapidly acting parenteral anticoagulant in patients at high risk for thromboembolic events. Beside a narrow therapeutic index, VKA exhibit inter-individual response variations as well as several drug and food interactions, and therefore require frequent monitoring.

This is important because excessive anticoagulation increases the risk of bleedings and thrombotic events can occur if the level of anticoagulation is suboptimal. Hence, optimal VKA therapy requires continuous monitoring and high levels of patient compliance. These limitations contribute to the underuse of VKA for stroke prevention observed in patients with atrial fibrillation (AF), especially in developing countries where facilities for coagulation monitoring are lacking [1].

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In addition, community-based studies as well as results from recent Phase III trials indicate that the level of anticoagulation is frequently outside the therapeutic range, thereby placing patients on VKA therapy at a high risk for thromboembolic events or bleeding [2].

A new generation of oral anticoagulants with more predictable anticoagulant response has been shown to be effective for the prevention and treatment of venous thromboembolism and for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. The pharmacokinetic and pharmacodynamic profiles of the new agents differ in many ways from VKA.

Because these new oral agents have a rapid onset of action and can be given at fixed doses without the need for routine coagulation monitoring, they will most likely replace VKA in a majority of patients.

However, despite the imminent widespread use of new oral anticoagulants (NOAC), their use remains unfamiliar for most clinicians and requires careful phase IV surveillance.

Fig No. 1 Mechanism and site of action NOAC

Mechanisms of action and Pharmacological properties

VKA

Coumarins inhibit the g-carboxylation of glutamate residues in coagulation factors II, VII, IX, and X as well as in the anticoagulant proteins C and S, resulting in inactivation of the proteins. This carboxylation reaction leads to oxidation of vitamin K and results in the production of vitamin K 2,3-epoxide. Reduction of vitamin K epoxide via the vitamin K epoxide reductase (VKOR) reactivates Vitamin K. In addition to their inhibitory effect on g-carboxylation of glutamate residues, VKA inhibit the regeneration of Vitamin K by interfering with VKOR. Polymorphisms in the gene encoding VKOR have been linked to a reduced efficacy of VKA, in particular warfarin. Moreover, VKA are subject to cytochrome P450 metabolism.

Therefore, polymorphism of the CYP450 gene, in particular of the isoenzyme CYP2C9, as well as numerous drug interactions involving CYP450 often require a meticulous and cumbersome adaption of VKA dosages and frequent monitoring [3-4]. Warfarin is completely absorbed after oral administration, and peak concentrations occur within 4 hours. The drug is almost entirely metabolised and the excretion of unchanged warfarin is negligible [5]. A single, oral dose of warfarin is eliminated with first-order kinetics and the metabolites are recovered in urine (approximately 80%) and faeces (approximately 20%). The effective half-life of warfarin ranges from 20 to 60 hours, with a mean of about 40 hours and the duration of the anticoagulatory effects lasts 2 to 5 days [6–8].

In contrast to warfarin, phenprocoumon is eliminated as parent compound (approximately 40%) and hydroxylated metabolites (approximately 60%) [9]. As for warfarin, elimination follows first order kinetics and occurs via urine (65%) and faeces (35%) [9]. The longer elimination half-life of phenprocoumon (110 to 156 hours) is the result of both, enterohepatic recycling of conjugated phenprocoumon and a lower

clearance of CYP enzymes regulating the hydrolysation of phenprocoumon.

Dabigatran etexilate

Dabigatran is a specific thrombin inhibitor. It is a polarised membrane impermeable molecule in a strongly basic state, permanently charged at physiologic pH and therefore very hydrophilic [10]. This hydrophilic state results in a poor intestinal absorption following oral intake with a bioavailability of approximately 6.5%. The prodrug dabigatran etexilate requires ester cleavage to be transformed into its active form, resulting in a reduced number of drug-drug interactions as esterases have high catalytic capacity and low substrate specificity [11-12]. CYP enzymes are not involved in the proteolytic reaction converting dabigatran etexilate to dabigatran.

Peak plasma concentrations are reached within two hours of oral administration, and the half-life is approximately eight hours after a single dose, ranging from 12–17 hours after multiple doses[11]. The percentage of dabigatran bound to plasma proteins is approximately 35%, and the extent of protein binding does not depend on dabigatran plasma concentration. Renal excretion is the predominant elimination pathway of dabigatran; more than 80% of systemically available dabigatran is eliminated unchanged, and a small fraction undergoes biotransformation into glucuronide conjugates [13]. This is of high clinical relevance as alterations of renal function may lead to a prolonged elimination of dabigatran [13].

Rivaroxaban

Rivaroxaban inhibits FXa in a concentration-dependent manner, with rapid and reversible binding [14-15]. Rivaroxaban competitively inhibits free and clotbound FXa by >10,000-fold selectivity compared with other serine proteases such as thrombin and activated protein C [16]. The bioavailability of rivaroxaban is high (>80%) and the maximum concentration occurs 2–4 hours after oral intake [17]. It is extensively bound (~90%) to plasma proteins, and its maximum plasma concentration is dose dependent. The half-life is 5–9 hours and the kidneys excrete 66% of the orally in gested drug of which half constitutes inactive metabolites [18]. Other modes of excretion involve faecal elimination and hepatic metabolism via the isoenzymes CYP3A4 and CYP2J2 [19].

Apixaban

In vitro experiments for apixaban demonstrate that it is a potent and highly selective inhibitor of free FXa with additional minimal affinity for thrombin [20-21]. Apixaban is well absorbed from the intestinal tract and achieves a peak plasma concentration in approximately three hours. The effective half-life is 8–11 hours when given twice daily and 12–15 hours when given once daily. The elimination of apixaban involves multiple pathways. Hepatic metabolisation occurs via O-demethylation through the CYP3A4 system [22]. Apixaban has multiple routes of elimination. Of the administered apixaban dose approximately 25% is recovered as metabolites in faeces. Renal excretion of apixaban accounts for approximately 27% of total clearance. Additional contributions from biliary and direct intestinal excretion were observed in clinical and nonclinical studies [22].

Edoxaban

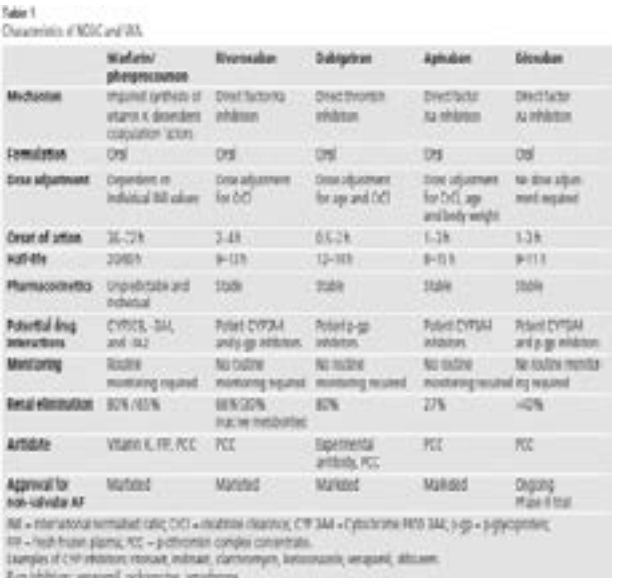
Edoxaban is an oral, direct, specific FXa inhibitor with an approximate 10,000-fold selectivity for Factor Xa over thrombin [23]. Edoxaban exhibits dose-dependently inhibited thrombus formation and Factor Xa activity in a venous stasis thrombosis model. It also exerted a significant anticoagulant

effect in a rat model of tissue factor-induced intravascular coagulation [23]. In a single-dose (60 mg) study in healthy subjects, the maximum plasma concentration of edoxaban was observed at 1.5 hours after administration, corresponding to the maximum inhibition of FXa activity, which returned to baseline levels by 12 hours. The half-life ranges from 5.8 to 10.7 hours, and the rate of plasma protein binding is 40%–59%. Urinary excretion of unchanged edoxaban was 36% and 45% of the dose administered (90 and 120 mg daily doses, respectively) [24].

Drug and food interactions

VKA

Warfarin is subject to drug interactions that



can be caused by changes in enzyme activity or altered plasma-protein binding capacities. Several antibiotics such as metronidazole, cephalosporins, and fluconazole are associated with the aforementioned interactions [3-4]. Other interactions arise from reduced clotting factor synthesis, as seen in hepatic diseases. VKA treatment also requires significant dietary restrictions because foods rich in vitamin K, such as spinach, alter therapeutic levels [6–9]. Hence, patients are instructed to watch their diet closely to maintain therapeutic levels of warfarin.

Dabigatran

Because neither dabigatran nor its prodrug is metabo- lised by cytochrome P450, it has a better profile regarding drug interactions in comparison with VKA. However, dabigatran is a substrate of efflux transporter P-glycoprotein (pgp) that is involved in the transport of many drugs [25]. Co-administration of potent permeability pgp inhibitors such as quinidine, ketoconazole, amiodarone, and verapamil can increase plasma concentrations of dabigatran by decreasing its reabsorption via permeability glycoprotein into the gastrointestinal tract [26]. Administration of rifampicin, a strong pgp inducer, for seven days before a single dose of dabigatran etexilate resulted in a significant reduction in the bioavailability of dabigatran compared with administration of dabigatran etexilate alone [27].

The time to peak circulating concentration of dabigatran is delayed by a high-fat, high-caloric diet, but no difference in the extent of absorption has been noted in comparison with a fasting state [28].

Co-administration with platelet inhibitors such as clopidogrel, ticlopidine, glycoprotein IIb/IIIa inhibitors, and non-steroidal anti-inflammatory drugs, such as aspirin, increases the risk of bleeding. Treatment with dabigatran from 50 to 150 mg twice daily for 6 months was associated with a dose-related two to four times increased risk of bleeding in post-myocardial infarction patients receiving dual antiplatelet treatment (DAT). The total number of patients experiencing ischaemic cardiovascular events during the study was low, with only minor differences between the different treatment groups [29].

Rivaroxaban

Rivaroxaban is metabolised by CYP3A4 and CYP2J2- dependent mechanisms. In addition rivaroxaban is a substrate for p-gp transporters. These properties subject it to a wide variety of drug interactions (ketoconazole, clarithromycin, verapamil, amiodarone, rifampicin). In patients receiving HIV-protease inhibitors and antimycotics rivaroxaban is contraindicated, as those drugs are strong inhibitors of both CYP3A4 and pgp.

In a study of rivaroxaban in healthy subjects aspirin increased the time to onset of FXa inhibition by approximately 2 hours when administered with rivaroxaban, but the level of inhibition remained unaffected. Compared with aspirin alone, combination of rivaroxaban and aspirin led to an increased bleeding time, although this was not considered clinically significant in this phase I study [30]. However, the anticoagulant effect of rivaroxaban, assessed by PT, was not influenced by clopidogrel and aspirin alone, or in combination in this preclinical study.

In patients with a recent acute coronary syndrome and under (DAT), rivaroxaban reduced the risk of the composite end point of death from cardiovascular causes, myocardial infarction, or stroke. Despite an increased risk of major bleeding and intracranial haemorrhage, combination of rivaroxaban and DAT did not enhance the risk of fatal bleeding [32].

Apixaban

Potent inhibitors of CYP3A4, such as ketoconazole, induce significant changes in pharmacokinetics of apixaban and should at least stopped 14 days prior to the use of apixaban. Moderate inhibitors of CYP3A4, such as selective serotonin reuptake inhibitors, diltiazem, and cimetidine, are to be used with caution. However, the effect of concomitant administration of apixaban and the statins, which are also metabolised by cytochrome P450 3A4, has not been reported [33].

In the APPRAISE-2 trial the addition of apixaban to a standard antiplatelet therapy in patients who were at high risk for recurrent ischaemic events following acute coronary syndrome significantly increased the risk for major bleeding events without reducing the incidence of recurrent ischaemic events.

The trial was discontinued based on the clinically important increase in bleeding among patients randomised to apixaban and the recommendations from data monitoring committee [34].

Edoxaban

Similar to dabigatran and rivaroxaban, edoxaban is also a substrate for the efflux transporter gp. Therefore in the ongoing ENGAGE AF–TIMI 48 trial reduction of the edoxaban dosage by 50% is required when concomitant use of strong pgp inhibitors, such as verapamil, is anticipated.

There are currently no data available on drug–drug interactions for edoxaban. Food intake had no clinically significant effects on the pharmacokinetics and pharmacodynamics of edoxaban [25].

Monitoring

VKA

Warfarin treatment requires close monitoring of its anticoagulant effect through assessment of the pro-thrombin time (PT). The accuracy of the prothrombin Time (PT) is subject to a strong variability.

The World Health Organisation has addressed this system variability problem by establishing international reference preparations of thromboplastin and proposed a statistical model for the calibration of thromboplastin to derive the International Sensitivity Index (ISI). The therapeutic range for oral anticoagulation is de fined in terms of International normalised ratios (INR).

INR is a ratio between patient's PT and the mean of normal PT range assigned to the thromboplastin reagent used. The current recommended INR range for prophylaxis and treatment is 2–3 for most thrombotic disorders. A higher range (2.5–3.5) is recommended for high-risk groups, including patients with prosthetic heart valves.

NOAC

One of the advantages of the new drugs is that routine monitoring of their anticoagulant effect is unnecessary because most patients taking a standard dose will have a therapeutic anticoagulant effect. NOAC have been designed on a one-size-fits-all basis. Therefore, the need for monitoring has been neither suggested nor addressed. However, this is of prime concern with regard to safety and in clinical situations such as emergency surgeries and therapeutic failure.

In particular changes in renal function may seriously affect the anticoagulatory effect of the NOAC and re- quire frequent clinical monitoring. Until now monitoring of VKA therapy provided an opportunity for clinicians to assess their patient for additional problems unrelated to monitoring during these visits. As the need to monitor the NOAC disappears, it can be postulated that patients may suffer other adverse events simply because they no longer attend frequent follow-up visits.

Dabigatran

The effects of dabigatran on blood coagulation tests correlate with plasma dabigatran concentrations. Dabigatran prolongs both the PT and the activated partial thromboplastin time (aPTT) in vitro and ex vivo [35]. However, the linear relationship with the plasma concentration is lost at high concentrations and neither PT nor aPTT are recommended to quantify dabigatran concentrations. A recent study showed that the HEMOCLOT direct thrombin inhibitor assay is accurate for the rapid assessment of dabigatran's anticoagulatory activity [35]. Ecarin clotting time (ECT) is an alternative assay recommended by the Italian Federation of Thrombosis Centers. ECT requires calibra tion with dabigatran standards to offers good linearity with adequate assay sensitivity.

Rivaroxaban

Rivaroxaban was not monitored with any clotting as- says in clinical trials, although it is known to affect aPTT, PT, and HEPTEST. PT prolongation due to rivaroxaban correlates with the drug's plasma concentration and its inhibition of FXa activity [36]. The readout for PT has to be done in seconds, because the INR is only calibrated and validated for VKA so far. However, accuracy and validation of monitoring rivaroxaban by PT have not been established. No effect of rivaroxaban on ECT has been demonstrated.

Apixaban

Apixaban shows a concentration-dependent effect in FXa-mediated assays and a dose-dependent mild prolongation in INR and aPTT is also seen [37]. Apixaban has no effect on human platelet aggregation [20]. Modest changes are seen in PT assays modified for more sensitivity to the effects of direct-acting FXa inhibitors; however, these assays are not approved for clinical monitoring of apixaban.

Edoxaban

Edoxaban induced a concentration-dependent prolongation of PT, aPTT and thrombin generation in pooled plasma from healthy subjects [38]. However, PT and aPTT prolongation were reagent dependent and correction of PT ratio using INR did not reduce variability in response.

Efficacy of NOAC versus VKA for stroke prevention in non-valvular atrial fibrillation

Atrial fibrillation confers a high risk of cardioembolic stroke and systemic embolism [39-40]. In patients with atrial fibrillation aspirin and VKA reduce the risk of ischaemic stroke by about 21% and 68% in comparison to no antithrombotic therapy, respectively [41]. However, warfarin is associated with a higher rate of intracranial bleeding with respect to aspirin and no treatment (0.3%, 0.2% and 0.1% per year, respectively) [42].

Thus, oral anticoagulant therapy with VKA was, until recently, only recommended for patients with atrial fibrillation at sufficiently high risk for stroke or systemic embolism [43]. In 2012, the ESC issued updated guidelines for the management of atrial fibrillation including new recommendations for prophylaxis of thromboembolism in patients with non-valvular atrial fibrillation [44].

Those recommendations are based on data from clinical trials demonstrating that the NOACs tested so far have all shown non-inferiority compared with VKAs, with better safety, limiting the number of major bleedings. Thus, the guideline now recommends their use in the majority of patients with non-valvular AF. Moreover, rather than trying to identify the high risk patients, the new guidelines recommend identifying the truly low-risk patients with atrial fibrillation (i.e. CHA2DS2-Vasc Score 0; or age <65 years and lone atrial fibrillation) who do not require any antithrombotic therapy. In deed, patients with AF who have a CHA2DS2-Vasc Score ≥1 are recommended to receive effective stroke prevention therapy, with either well controlled VKA therapy or one of the NOAC. The use of antiplatelet therapy should be limited to patients refusing preventive treatment with VKA or NOAC.

In view of recently published reviews, the following section will only provide a brief summary of the key findings of the published clinical trials on the use of NOAC for prevention of thromboembolism in patients with atrial fibrillation [45-46].

Dabigatran

The efficacy and safety of dabigatran for the prevention of stroke or systemic embolism in patients with atrial fibrillation was assessed in a prospective randomised non inferiority trial including 18,113 patients [47]. Dabigatran 150 mg twice daily was superior and dabigatran 110 mg twice daily was non inferior to warfarin for the prevention of stroke and systemic embolism. Dabigatran 150 mg reduced both, ischaemic and haemorrhagic stroke compared with warfarin. The incidence of major bleeding was similar between dabigatran 150 mg and warfarin while the treatment with dabigatran 110 mg resulted in fewer major bleedings than warfarin. An increase in gastro intestinal bleeding was observed with dabigatran with respect to warfarin. Overall, the 150 mg dose was more effective than warfarin with similar bleeding risk. The 110 mg dose was noninferior in efficacy with less bleeding. Both dosages definitely resulted in fewer intracranial bleeds.

Initially, a significantly higher rate of myocardial infarction was found in both dabigatran groups and raised the suspicion that myocardial infarction risk could be

higher in patients receiving dabigatran. However, it is important to keep in mind that this finding was only based on a secondary endpoint and that in a published revision of the data no more significant difference in myocardial infarction rates were observed.

Rivaroxaban

The randomised double-blind ROCKET AF trial compared rivaroxaban (20 mg daily) with warfarin in 14,266 high risk patients with atrial fibrillation [48]. Rivaroxaban was non inferior to warfarin for the prevention of stroke or systemic embolism in both the intention to treat and the on treatment analyses. Rivaroxaban achieved superiority when analysis was limited to the on treatment period but this benefit was lost in the follow up after study treatment discontinuation. Intracranial haemorrhage and fatal bleedings were less frequent in patients receiving rivaroxaban.

Apixaban

Patients with atrial fibrillation and at least one additional risk factor for stroke who were unsuitable for treatment with VKA were included in the AVER- ROES study and randomly assigned to apixaban 5 mg twice a day or aspirin 81–324 mg/day [49]. The trial was stopped before completion because of a clear benefit in favour of apixaban. The risk reduction observed with apixaban is mainly accounted for by a reduction in the rate of ischaemic stroke. In addition, a trend to ward a reduction in all cause mortality was observed in the apixaban group while a non significant increase in bleeding was observed with apixaban over aspirin.

In the Aristotle trial patients with atrial fibrillation were randomly assigned to apixaban 5 mg twice daily or warfarin in a double blind fashion [50]. The primary efficacy outcome of the study was stroke or systemic embolism. Apixaban reduced the incidence of stroke or systemic embolism with respect to warfarin. This result was mainly accounted for by a significant reduction in haemorrhagic stroke. In addition, apixaban significantly reduced the overall death rate. The incidence of major bleeding was lower in the apixaban group.

Edoxaban

1146 patients were randomised to receive four blinded doses of edoxaban (30 mg once daily, 60 mg once daily, 30 mg twice daily, and 60 mg twice daily) or warfarin (open label) in a large phase II trial (ENGAGE). The twice daily regimens were discontinued earlier be cause they were associated with increased bleeding compared with warfarin while the rate of bleeding was similar among once daily regimens of edoxaban and warfarin. Both the once daily doses (30 and 60 mg) were carried forward for evaluation in the phase III double blind non inferiority ENGAGE AF-TIMI 48 trial. In this ongoing study, 21,105 subjects with atrial fibrillation and CHADS2 score ≥2 are randomly assigned to edoxaban (30 or 60 mg once daily) or warfarin.

The median duration of followup will be 24 months. The primary endpoint is the incidence of stroke or systemic embolic events and the composite of stroke, systemic embolic event, or all cause mortality are secondary endpoints. Major bleeding and hepatic function are the major safety endpoints. Results are expected to be published in 2013.

Indirect comparison of NOAC for stroke prevention in non valvular atrial fibrillation : A head to head direct comparison of drugs is the standard method for comparing different treatments. A head to head comparison of the NOAC would require a large number of patients, thus be expensive and there fore unlikely to be performed. Another alternative to assess the relative effect of different treatment interventions would be to perform indirect comparisons, using a common comparator.

Recently published network meta analyses have indirectly compared the three large NOAC studies based on analytical techniques [51–53]. However, it is important to note that confounding factors such as different study design, differences in inclusion and exclusion criteria, numbers of risk factors according the CHADS2 score at entry, or varying time in therapeutic range (TTR), may result in residual confounding and persisting heterogeneity.

Overall, there was a significantly lower risk of stroke and systemic embolism for dabigatran 150 mg compared with rivaroxaban, as well as haemorrhagic stroke. No significant differences were observed for apixaban versus dabigatran (both doses) or rivaroxaban and between rivaroxaban and dabigatran 110 mg BID in preventing stroke and systemic embolism. Similar rates of ischaemic stroke were observed between all the NOAC.

In general, major bleeding was significantly lower with apixaban compared with dabigatran 150 mg and rivaroxaban, but not significantly different from dabigatran 110 mg. There were no statistical differences between apixaban and dabigatran 110 mg BID in safety endpoints. Dabigatran 110 mg was afflicted with lower major or clinically relevant bleeding compared with rivaroxaban and dabigatran 150 mg.

In all four metaanalyses dabigatran 110 mg was associated with significant lower intracranial bleeding rates compared with rivaroxaban. Finally in three of the studies, the use of rivaroxaban was associated with lower rates of myocardial infarction than the use of dabigatran (both doses), whereas no differences were observed between rivaroxaban and apixaban.

In summary the recently published meta analyses highlight consistently the substantial net clinical benefit of the NOAC compared to VKA for patients with non valvular AF.

Discussion

The new oral anticoagulants will shape the future of anticoagulation. Their acceptance among physicians and patients is expected to rise as they become more versed with the indications, side effect profiles and drug and food interactions. The concerns regarding lack of monitoring and reversal agents will need to be addressed if the acceptance of these medication is to be increased. As the current clinical trials with the new oral anticoagulants do not compare these drugs with all the indications for VKA use, VKA therapy likely will continue for some time to come.

Should every patient switch from VKA to NOAC?

Current prospective trials with NOAC did not address the unmet need for anticoagulation in special populations such as pregnant patients, children, and patients with mechanical heart valves, severe pulmonary hypertension or cancer. The phase 2 trial, Realign, investigated the safety and efficacy of dabigatran etexilate (150 mg, 220 mg or 300 mg b.i.d.) in patients undergoing cardiac valve replacement.

In the first phase patients were randomised to dabigatran etexilate or dose adjusted warfarin during their initial hospital stay, while the second phase of the trial randomised patients three months after surgical valve replacement. Following advice of the Data Safety Monitoring Board, the trial was partly halted due to interim reports suggesting an imbalance of thromboembolic events in the first phase, which may be related to unexpected low dabigatran plasma levels. Hence, these results indicate that the off label use of NOAC based on the extrapolation of results from one indication to another should be considered with great caution.

VKA will also remain the first choice for patients who cannot afford the NOAC, and

those with poor compliance, because the risk of thromboembolic events is likely to increase substantially with poor adherence to shorter acting oral anticoagulants. VKA might remain the anticoagulants of choice for patients who may require quick reversal of the anticoagulant effect under certain clinical circumstances and who might be at greater risk of gastrointestinal bleeding with dabigatran and rivaroxaban than with VKA.

Patients already on long term anticoagulation with VKA may be switched to the new agents. However, subgroup analyses of the recently published trials found, that superior efficacy of the new drugs is offset when compared to VKA in patients with well-adjusted INR values. Hence, if adjustment of VKA is very stable and this treatment has been well integrated into the patient's life, there is probably no need to change to NOAC. Since these patients usually have additional comorbidities, dropping the regular visits for VKA monitoring might cause problems with the adherence of the patients to the new therapy and might deteriorate the outpatient care. For patients with an unexplained poor VKA control or a poor level of control due to unavoidable VKA-drug interactions there is no doubt, that NOAC will represent a valuable alternative treatment.

VKA patients instead are good candidates for treatment with the NOAC. Treatment is simple, effective, safe and monitoring is not required. Nevertheless, these patients should undergo regular follow up visits to maintain adherence to the medication at high levels, help to prevent drug interactions, and monitor renal function. It is important, though, that patients are involved in the decision making of their therapy after weighing up the advantages and disadvantages of the different anticoagulatory strategies.

Which NOAC to choose?

All published trials have demonstrated the net clinical benefit of NOAC compared with VKA in prevention of stroke and systemic embolism in patients suffering from non valvular atrial fibrillation. As mentioned before recent meta analyses have attempted to provide indirect comparisons of the NOAC regarding safety and efficacy.

However, it is important to point out that decision making can only rely on randomised, prospective head to head comparisons between the NOAC, which are currently lacking. There is some evidence to suggest that FXa inhibitors in contrast to thrombin inhibitors incompletely block thrombin generation. The residual active thrombin can potentially maintain haemostasis by binding to thrombomodulin on endothelial cells and thereby activate the protein C system, augmenting the antithrombotic potential [54]. In vitro assay analysis suggests that FXa is progressively inhibited over a much wider concentration range than thrombin and thereby may have a wider therapeutic window than a thrombin inhibitor [55]. Moreover, in animal models, dabigatran was proven to have additional anti inflammatory and antiatherosclerotic effects [56].

Reversal

If severe bleeding complications occur the first steps to take are cessation of the anticoagulant, mechanical compression, and administration of fluids to assist diuresis [55-56]. Activated charcoal may constitute an option in the case of a recent overdose.

Laboratory coagulation tests, renal function, and complete blood count should be measured to later help to establish the cause and extent of the bleeding.

The anticoagulatory effects of warfarin can be effectively reversed with prothrombin complex concentrates (PCC) or fresh frozen plasma in conjunction with vitamin K [58]. PCC consist of concentrates which contain either the coagulation factors FII, FVII, FIX, and FX (four-factor PCC) or FII, FIX, and FX (three factor PCC). In contrast there are currently no specific antidotes available to immediately reverse the effect of NOAC in the acute setting. Haemodialysis may remove circulating dabigatran that is not protein bound, but it remains unclear whether this procedure effectively antagonises the anticoagulatory effect of dabigatran. Dialysis is not effective for rivaroxaban and apixaban because these drugs are mainly protein bound. An experimental study in a murine model showed that PCC and fresh frozen plasma may prevent the expansion of intracerebral haemorrhages [59]. Intravenous administration of four factor PCC, immediately and completely normalised the PT in healthy controls taking rivaroxaban, but not the a PTT in controls taking dabigatran [60].

Findings from another study of healthy volunteers given either rivaroxaban or dabigatran showed that activated four component PCC corrected rivaroxaban induced impaired thrombin generation in a dose dependent fashion and had a less pronounced effect on reduced thrombin generation after administration of dabigatran [61]. However, research is still needed to test the effect of PCC administration on bleeding cessation in patients taking the new anticoagulants. In an animal study PCC and recombinant activated factor VII (rFVIIa) both did not fully reverse bleeding induced by rivaroxaban overdose, despite correction of several laboratory coagulation parameters [62].

Currently, research efforts focus on the development of specific reversal agents targeting the active sites of the NOAC. Recently, a monoclonal antibody was shown to potently and specifically inhibit the anticoagulatory effect of dabigatran both in vitro and in vivo [63].

Anticoagulation in patients with renal failure

NEWER INSIGHTS

Patients with renal impairment pose a problem for of anticoagulant treatments due to their increased risk for both thromboembolic and bleeding events. In a recent analysis of the Danish national registries including more than 130,000 patients with non valvular atrial fibrillation, the authors demonstrated that the risk for stroke as well as bleeding was significantly higher in patients with renal disease than in those without it [64].

In patients with any renal disease, warfarin significantly reduced the risk for stroke but also significantly increased bleeding risk, whereas aspirin significantly increased bleeding risk without any significant reduction in stroke risk [64].

Given the predominant renal excretion of some of the new oral anticoagulant agents, only patients with a creatinine clearance of at least 30 ml/min have been included in the trials, and patients with moderate renal dysfunction were assigned a reduced dose of rivaroxaban (15 mg/day) and apixaban (2,5 mg/day) [48, 50].

Up to 80% of circulating unchanged dabigatran is excreted via the kidneys [65]. Thus, impaired renal function significantly increases dabigatran plasma levels and drug half-life [65-66]. A recently published sub-analysis of the Aristotle study showed that apixaban was more efficient than warfarin

at preventing the primary outcome, stroke or systemic embolism regard less of renal function [67].

Moreover, apixaban was also associated with fewer major bleeding events across all ranges of glomerular filtration rates (GFR), with the relative risk reduction in major bleeding being greater in patients with a GFR <50 ml/minute. Importantly, sensitivity analyses confirmed that the reduction in bleeding in patients with impaired renal function was not simply due to the use of the lower apixaban dose. Based on these findings treatment with dose adjusted apixaban appears to particlularly appealing in patients with impaired renal function.

A subgroup analysis of the ROCKET-AF trial per formed in patients with moderate renal impairment confirmed the results of the overall trial, demonstrating that dose adjusted rivaroxaban had a similar effect than VKA on the reduction of thromboembolism while causing fewer fatal bleedings [68].

Since the proportion of patients who received adjusted dose regimens in the trials was small, data about the safety and efficacy of the NOAC in patients with severe and moderate renal dysfunction remain limited and further investigations, in particular in patients with severe renal failure or end stage renal disease, are required. In the meantime, it appears prudent to closely monitor renal function after initiation of treatment.

Conclusion

With the NOAC entering the stage; anticoagulation is experiencing a shift of paradigm. Although VKA are effective drugs, they do have limitations, and from a practical point of view, challenge patients as well as clinicians.

As the shift approaches, it is important to note that VKA are cheap, highly effective and well established. Warfarin and phenprocoumon have been used in clinical practice for more than 50 years. The implementation of the INR and point of care INR devices, enabling patients to monitor their INR level more frequently have rendered oral anticoagulation with VKA a safe and efficient therapy.

Patients on a stable dose of VKA for a long time are not expected to switch to a NOAC. Instead, NOAC are likely to offer the greatest benefit to patients who are orally anticoagulated but only achieve low TTR values and those who are eligible for anticoagulation with VKA but refuse to take it for some reason.

Furthermore, whether these novel agents will be safe and effective in special populations remains to be evaluated. Finally, it is difficult to predict how clinicians will handle agents that lack evidence based reversal strategy and a standardised monitoring technique.

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