Anticoagulation for non-valvular atrial fibrillation: new anticoagulant agents

Non-valvüler atriyal fibrilasyonda antikoagülasyon: Yeni antikoagülan ilaçlar

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ABSTRACT

Atrial fibrillation (AF) is a common cardiac arrhythmia and it is associated with systemic thromboembolism. Until recently, vitamin K antagonists (VKA) such as warfarin were the only available oral anticoagulant therapy for prevention of stroke and systemic embolism in AF. Limitations of VKA therapy have prompted researchers to search for novel anticoagulant drugs, which do not necessitate coagulation monitoring due to their more predictable pharmacokinetic profile. Large-scale phase III trials have been completed for some of these drugs and 'U.S. Food and Drug Administration (FDA)' approved dabigatran and rivaroxaban for prevention of systemic embolism in non-valvular AF patients. In this review, we will first focus on pharmacodynamic and pharmacokinetic profiles of these medications and then try to overview clinical trial results. We will also try to mention the current controversies regarding the clinical application of these drugs. *(Anadolu Kardiyol Derg 2013; 13: 379-84)*

Key words: Atrial fibrillation, stroke, systemic embolism, anticoagulation, vitamin K antagonists, novel anticoagulant drugs

ÖZET

Atriyal fibrilasyon (AF) sistemik tromboembolizm ile ilişkili olan nispeten sık bir aritmidir. Yakın zamana kadar AF ile ilişkili sistemik embolizm ve inmenin engellenmesinde yalnızca varfarin gibi K vitamini antagonistleri kullanılmıştır. Buna karşın K vitamini antagonistlerinin kısıtlılıkları araştırmacıları farmakokinetik profilleri daha stabil olan ve koagülasyon monitorizasyonu gerektirmeyen yeni antikoagülan ilaçların geliştirilmesine teşvik etmiştir. Bu ilaçların bazılarının faz 3 klinik çalışmaları sonuçlanmış olup 'Amerikan İlaç ve Gıda Dairesi (FDA)' tarafından dabigatran ve rivaroksabanın non-valvüler AF hastalarında inme ve sistemik embolizm profilaksisinde kullanımı onaylanmıştır. Bu derleme yazıda öncelikle yeni antikoagülan ilaçların farmakodinamik ve farmakokinetik özellikleri üzerinde durulacak, daha sonra klinik çalışma sonuçları özetlenecektir. Ayrıca, günümüzde bu ilaçların klinik pratikte kullanımındaki çekinceli durumlara da değinilmeye çalışılacaktır. *(Anadolu Kardiyol Derg 2013; 13: 379-84)*

Anahtar kelimeler: Atriyal fibrilasyon, inme, sistemik embolizm, antikoagülasyon, K vitamini antagonistleri, yeni antikoagülan ilaçlar

Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia and it is associated with systemic thromboembolism (1, 2). Loss of atrial mechanical function and atrial dilatation predispose to thrombus formation and certain risk factors increase the risk. Antithrombotic therapy is the established method for both primary and secondary prevention of stroke or systemic embolization in patients with AF (3).

Until recently, vitamin K antagonists (VKA) such as warfarin were the only available oral anticoagulant therapy for stroke prevention in AF. In six clinical trials of patients with AF at high risk of stroke, adjusted dose warfarin therapy decreased the risk of stroke or systemic embolism by 62% compared with placebo (4). However, warfarin therapy is difficult to use in clinical practice. VKA therapy has a wide variation regarding its dose-response profile, and potentially interacts with diets and other medications (5). Inadequate

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monitoring will lead to either ineffective protection or excessive anticoagulation associated with increased bleeding complications. In a cohort of patients with AF receiving warfarin who were ≥ 65 years of age, the rate of intracranial hemorrhage was 2.5% (6). In addition, 17% of first admissions for intracranial hemorrhage have been reported to be associated with anticoagulant therapy and 98% of these patients have been reported to be on warfarin treatment (7). VKA therapy also has a slow onset of action and bridging with heparin or low molecular weight heparin is necessary until anticoagulation level becomes adequate as assessed with INR value (5). An ideal anticoagulant should have a predictable dose response curve and kinetics. It should be administered in fixed doses (preferentially single daily dose) without the need for routine coagulation monitoring. It should also have minimal or no interaction with food and other drugs. Limitations of VKA therapy have prompted researchers to search for ideal anticoagulant and we now have an array of new anticoagulants that act by directly inhibiting thrombin or factor Xa (8, 9). These drugs have a more predictable pharmacokinetic profile than the VKA in addition to no need for coagulation monitoring. Although VKA's are still the only available oral anticoagulant agents for stroke and systemic embolism prevention in patients with valvular AF, new anticoagulant agents have shown promise as an alternative to VKA in patients with non-valvular AF.

In this review, we aimed to focus on new oral anticoagulant agents that have been tested in phase III randomized trials for prevention of stroke and systemic embolization in patients with non-valvular AF.

Oral direct thrombin inhibitors

Dabigatran

Dabigatran etexilate is available as an oral pro drug that is converted to dabigatran after absorption. It is a potent reversible direct thrombin inhibitor (8). It binds to clot-bound and free thrombin with high affinity and specificity (8). The bioavailability of dabigatran etexilate ranges from 3% to 7% and the absorption is facilitated by the presence of an acidic milieu (10). Commercially available formulation of dabigatran etexilate contains tartaric acid which allows a steady absorption of the drug despite fluctuations in enteric pH (10). Presence of tartaric acid in the formulation is also responsible for dyspepsia, which is a common side effect of this drug (11). Time to peak concentration occurs 1.5 to 3 hours after oral administration and food intake on absorption increases the time to peak concentration (10). Approximately 80% of the administered drug is excreted in the urine and the remaining amount undergoes conjugation and glucuronidation within the liver (11). The elimination half-life is 12 to 17 hours after multiple doses in healthy patients with normal renal function and half-life is prolonged in patients with renal dysfunction (10). The metabolism of dabigatran is independent of cytochrome p450 and there is less interaction with other medications compared with warfarin (11). Unlike ximelagatran there is no reported hepatotoxicity with this agent (12). These pharmacodynamic and pharmacokinetic properties of dabigatran allow predictable anticoagulant effect

with this agent and it is possible to be used with fixed doses without need for coagulation monitoring (10,11). Dabigatran etexilate, but not dabigatran, is a substrate for p-glycoprotein (P-gp) and co-administration of P-gp inducers (rifampicin or some antiepileptic drugs) or inhibitors (azole-antimycotics, immunosuppressants, human immunodeficiency virus protease inhibitors) may alter plasma concentrations of dabigatran (11, 13). Verapamil has also been reported to increase plasma concentration of dabigatran especially if immediate-release verapamil is given 1 hour before dabigatran (14). It is suggested that verapamil should be given 2 hours after dabigatran so that the interaction between these two drugs will be minimal (14). Dabigatran therapy was compared with warfarin in the phase III 'Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY)' trial which enrolled 18.113 patients with non-valvular atrial fibrillation (15). The mean age of the patients was 71 years. 63.6% of the study population was men and half of the patients received long-term oral anticoagulation with VKA. The mean CHADS$_2$ score was 2.1. Patients were assigned to two fixed doses of dabigatran (110 mg or 150 mg twice daily) in a blinded fashion or to adjusted-dose warfarin in an open label fashion. The median duration of the follow-up period was 2 years. Rates of stroke or systemic embolism were 1.69% per year in the warfarin group, as compared with 1.53% per year in the group that received 110 mg bid of dabigatran (p<0.001 for noninferiority) and 1.11% per year in the group that received 150 mg bid of dabigatran (p<0.001 for superiority). Rate of major bleeding was similar between dabigatran 150 mg bid and warfarin groups (3.11% vs 3.36% respectively, p=0.31) whereas dabigatran 110 mg bid was associated with significantly lower rates of major bleeding (2.71% vs 3.36% respectively, p=0.003). There were significantly lower rates of hemorrhagic stroke in both 110 mg bid and 150 mg bid dabigatran groups compared with warfarin. The mortality rates were similar. However, there was a nonsignificant increase in myocardial infarction with dabigatran compared with warfarin (16). Dyspepsia was significantly more common with dabigatran and there was no significant difference between dabigatran and warfarin groups regarding the rate of elevation of serum aspartate aminotransferase or alanine aminotransferase levels. Subgroup analysis of data from the RE-LY was performed in patients with prior transient ischemic attack (TIA) or stroke; patients undergoing cardioversion; patients with low, moderate and high CHADS$_2$ score and elderly patients (17-21). Similar results were obtained from subgroup analysis of patients with previous stroke or transient ischemic attack; 150 mg bid dabigatran was superior and 110 mg dabigatran bid was non-inferior compared with warfarin for prevention of stroke or systemic embolism (18). In the subgroup analysis of patients who had undergone cardioversion during the trial, there were no significant differences between both doses of dabigatran and warfarin groups regarding stroke and major bleeding rates (19). Patients with higher CHADS$_2$ scores were observed to have higher rates of stroke or systemic embolism, major bleeding or vascular and total mortality in each treatment group in RE-LY trial. However, effects of 110 mg bid dabigatran and 150 mg bid dabigatran were similar with general study population and

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there was no significant difference in subgroups defined by CHADS$_2$ scores (20). In another subgroup analysis performed to evaluate the effect of age on dabigatran therapy, both doses of dabigatran were found to be associated with lower risk of intracranial and extracranial bleeding compared with warfarin in patients aged <75 years. In patients ≥75 years of age, intracranial bleeding risk was still lower however, extracranial bleeding risk was similar or higher with both doses of dabigatran compared with warfarin (21). Dabigatran therapy was also indirectly compared with dual-antiplatelet therapy (ASA plus clopidogrel) in patients with AF who cannot use warfarin (22). Both doses of dabigatran therapy were estimated to reduce the risk of all stroke significantly compared with dual-antiplatelet therapy without increasing the rates of intracranial or extracranial hemorrhage (22). The US Food and Drug Administration (FDA) has approved 150 mg bid dose for the prevention of stroke and systemic embolism in patients with non-valvular AF (9). Accordingly, dose should be reduced to 75 mg bid for patients with renal insufficiency. European Medicine Evaluation Agency (EMEA) approved both 150 mg bid and 110 mg bid and suggested 110 mg bid dosage for elderly patients, for patients who use verapamil and for patients with high bleeding risk such as those with moderate renal impairment (creatinine clearance 30-50 mL/min) (9,13). Dabigatran is not advised to be used in patients with severe renal insufficiency (creatinine clearance <30 mL/min) (9). Dabigatran (Pradaxa) has also been licensed by Turkish Ministry of Health for the prevention of stroke and systemic embolism in patients with non-valvular AF who have an indication for anticoagulation according to their CHA$_2$DS$_2$-VASc scores. There is no specific antidote to reverse the anticoagulant effects of dabigatran. Dabigatran etexilate has been advised to be discontinued at least 24 hours before invasive procedures and at least 48 hours before procedures associated with a high risk of bleeding (14). The management of bleeding complications in patients receiving dabigatran etexilate should be individualized. In most patients with normal renal function, discontinuation of the drug will be sufficient (14). Transfusion of erythrocytes or fresh frozen plasma may be required; however, fresh-frozen plasma does not reverse the anticoagulant effect of dabigatran. If these measures fail to control bleeding, the use of hemodialysis or administration of nonspecific pro-hemostatic agents such as activated prothrombin complex concentrate may be considered (23).

Oral factor Xa inhibitors

Rivaroxaban

Rivaroxaban is an oral direct factor Xa inhibitor with a competitive and reversible binding effect to factor Xa. Rivaroxaban has an oral bioavailability of 60-80 % (17). Its half-life is reported to be between 5-9 h in young people and between 11-13 h in the elderly (13). Time to peak plasma concentration is approximately 3 hours after administration (13). Food results in delayed but increased absorption; therefore, therapeutic dosages of rivaroxaban are recommended to be taken with meals (13). Two-thirds of

the drug undergoes metabolic degradation in the liver and one-third is eliminated renally as unchanged (9). Rivaroxaban is metabolized by the liver through oxidative and hydrolytic pathways catalyzed by cytochrome P450 (CYP) enzymes and is a substrate for transport P-gp (13). Therefore, rivaroxaban may interact with drugs that interact with CYP3A4 and P-gp. Rivaroxaban has been reported to bind both to free factor Xa and to factor Xa in prothrombinase complex without the need of antithrombin as a cofactor (24). There is no need for routine coagulation monitoring with rivaroxaban; however, this drug has been reported to prolong activated partial thromboplastin time (aPTT) and prothrombin time (PT) (24). Similar to dabigatran there is no specific antidote to reverse the effects of rivaroxaban (8). It is not possible to remove rivaroxaban with dialysis because it is highly bound to plasma proteins (8). In the case of overdose or bleeding, rivaroxaban therapy should be stopped and supportive care should be considered. In the case of overdose, activated charcoal may also be used in order to reduce absorption of rivaroxaban (8). "The Rivaroxaban once daily direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET-AF)" was a phase III, double-blind and double-dummy designed study to assess the efficacy and safety of rivaroxaban compared with adjusted-dose warfarin in patients with non-valvular AF (25). A total of 14.264 patients with nonvalvular AF who were at increased risk for stroke were assigned to either rivaroxaban (at a daily dose of 20 mg) or dose-adjusted warfarin. Patients with renal insufficiency (estimated creatinine clearance 30-49 mL/min) received 15 mg of rivaroxaban daily. Patients with a history of prior stroke, TIA or systemic embolism, or with two or more of the following risk factors were included into trial: clinical heart failure and/or left ventricular ejection fraction ≤35%, hypertension, age ≥75 years, or diabetes mellitus. Mean CHADS$_2$ score of patients was 3.5 and 55% of patients had a history of previous stroke, systemic embolism, or TIA. Rivaroxaban was found to be noninferior but not superior to warfarin for the primary end point of stroke or systemic embolism. Rivaroxaban therapy was associated with significantly lower rates of intracranial hemorrhage and fatal bleeding; however, there were significantly more patients with major bleeding from a gastrointestinal site in the rivaroxaban group. There were also more patients with hemoglobin fall of ≥2 g/dL and those who needed transfusion in the rivaroxaban group (25). Based on these observations, rivaroxaban was approved by FDA for the prevention of stroke and systemic embolism in patients with nonvalvular AF at a dose of 20 mg od (15 mg od if creatinine clearance is 15-50 mL/min) (13). It is recommended to be taken with evening meals (13). Rivaroxaban (Xarelto) has also been licensed by Turkish Ministry of Health for the prevention of stroke and systemic embolism in patients with non-valvular AF who have an indication for anticoagulation.

Apixaban

Apixaban is also an oral, direct and reversible factor Xa inhibitor with an oral bioavailability of 50% (17). Its absorption

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has been reported to be independent of food administration (26). It has a half-life of 9–14 h in healthy subjects and it reaches its peak plasma concentration 3 hours after oral administration (17). Similar to rivaroxaban, much of the drug is metabolized in the liver with a cytochrome P450-dependent way and apixaban is also a substrate for transport P-gp (8). Much of the drug is removed from the body with intestinal excretion via the feces and approximately 25% of the drug is eliminated via the kidneys (27). Apixaban is highly bound to plasma proteins and it has a low distributing volume (13). Similar to rivaroxaban, apixaban binds both to free factor Xa and to factor Xa in prothrombinase complex (17). Multiple elimination pathways of apixaban may give this agent an advantage for the application in patients with renal or hepatic dysfunction (13). Two phase III studies have evaluated apixaban for the prevention of stroke and systemic embolism in AF patients. "The Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES)" study compared apixaban with ASA for the prevention of stroke or systemic embolism in a population of AF patients who are not on VKA prophylaxis (28). In a double-blinded design, 5599 patients were randomly assigned to receive apixaban (at a dose of 5 mg twice daily) or aspirin (81 to 324 mg per day) and mean follow up period was 1.1 years. The study was terminated early due to clear observed benefit in favor of apixaban with significantly lower rates of primary outcome events compared with ASA (1.6% vs 3.7% per year, respectively, p <0.001). Mortality rate was also lower for apixaban; however difference was not statistically significant (3.5% vs 4.4% per year, respectively, p=0.07). There was no significant difference between apixaban and ASA groups regarding major bleeding (1.4% vs 1.2% per year, respectively, p=0.57). The risk of a first hospitalization for cardiovascular causes was reduced with apixaban as compared with aspirin (12.6% vs. 15.9% per year, p<0.001) (28). "Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE)" study compared apixaban (at a dose of 5 mg bid) with dose adjusted warfarin in 18.201 patients with AF and at least one additional risk factor for stroke (29). The ARISTOTLE was a double-blind, non-inferiority trial and the primary outcome was ischemic or hemorrhagic stroke or systemic embolism. Secondary objectives were: testing for superiority with respect to the primary outcome and to define the rates of major bleeding and death from any cause. The mean $CHADS_2$ score for patients in the ARISTOTLE trial was 2.1, with less than 20% of patients having a prior stroke, transient ischemic attack or systemic embolism. The median duration of follow-up was 1.8 years. Apixaban therapy was found to be superior to warfarin for prevention of primary outcome (1.27% vs 1.60% per year, respectively, p <0.001 for noninferiority; p=0.01 for superiority). Apixaban therapy was associated with significantly lower rates of major bleeding and death from any cause (2.13% vs 3.09% per year, p <0.001 and 3.52% vs 3.94% per year, p=0.047). There were also fewer myocardial infarction and gastrointestinal bleeding events in patients

assigned to apixaban therapy but the differences were not statistically significant (p= 0.37 for each). Apixaban has not yet been approved by FDA for prevention of stroke or systemic embolization in AF.

Controversial issues regarding clinical application of novel anticoagulant agents

New oral anticoagulant agents seem to be relatively safe and simplify anticoagulation for the prevention of stroke and systemic embolism in patients with non-valvular AF. Their predictable pharmacodynamic profiles allow fixed dose regimens with no need for routine monitoring. Hence, they make life much easier for patients and physicians. It is worth mentioning of some differences and controversial issues regarding those novel anticoagulant drugs (dabigatran, rivaroxaban, apixaban). Three large-scale phase III trials (RE-LY, ROCKET AF, and ARISTOTLE) compared these new anticoagulant agents with warfarin for prevention of stroke and systemic embolism (15, 25, 28). There are certain methodological and drug specific differences among the trials. A double -blind and double- dummy design were used in ROCKET AF and ARISTOTLE trials whereas RE-LY was designed as a randomized trial only to different dabigatran doses in a blinded fashion or to warfarin in an open label fashion. All these trials ended up with noninferiority of the study drugs compared with warfarin for prevention of stroke and systemic embolism. They also demonstrated favorable bleeding profiles compared with warfarin. Apixaban significantly decreased mortality in ARISTOTLE trial. However, anticoagulation levels achieved with warfarin were suboptimal in these trials. Mean percentage of study population with international normalized ratio (INR) in the therapeutic range was 64% in RELY, 55% in ROCKET AF and 62.2% in ARISTOTLE trials (15, 25, 28). This might have resulted in an overestimation of the beneficial effects of the study drugs, such as dabigatran, apixaban and rivaroxaban. To decide whether one drug is superior over the other is not possible at this stage because there is a lack of data comparing three drugs directly head to head in one randomized trial. Hence, each drug has its own pros and cons as well as side effect profiles. Even though it has a short half-life, once-daily regimen of rivaroxaban may be advantageous for patient compliance. This, however, also has raised the question whether full anticoagulation coverage and therapeutic INR values throughout the whole day may not be necessarily considered as a prerequisite for stroke prevention. Although not frequent, new anticoagulant agents may also interact with other drugs by interfering through the same metabolic pathways (17). For example, dabigatran interferes with amiodarone, verapamil and quinidine, which belong to the group of P-glycoprotein inhibitors. Therefore, dose reductions of dabigatran may be necessary in patients who take those certain drugs. Plasma level of rivaroxaban increases with inhibitors of CYP3A4 or P-glycoprotein (e.g. ketoconazole, erythromycine, clarithromycine, rintonavir), whereas plasma level decreases with inducers of CYP3A4 (e.g. rifampicin) (17). There are still limited data regarding the effects

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of these drugs in populations who have not been adequately represented in the above mentioned trials (e.g. elderly patients, patients with renal insufficiency, or patients with liver impairment) (17). These agents are generally recommended to be cautiously used in patients with mild -to -moderate renal impairment and contraindicated in patients with severe renal insufficiency. There may be wide variations regarding the pharmacological and metabolic effects of new anticoagulants and there is currently no specific test for monitoring these drugs. Although some special coagulation tests may be applied to estimate the extent of thrombin or factor Xa inhibition, lack of standardized monitoring tests is still an important limitation for therapy with new anticoagulants especially in acute situations where measuring the anticoagulant effect is desirable (30). Monitoring the level of anticoagulation may also be necessary when there is a need for additional antithrombotic therapy such as after percutaneous coronary intervention where dual antiplatelet therapy should be additionally used. Another problematic issue related to new anticoagulant agents is the lack of any specific antidote to reverse the action of these drugs, especially in case of severe bleeding. Although not firmly established and supported by clinical data, activated prothrombin complex concentrate containing coagulation factors II, VII, IX, and X is suggested to reverse the effects of thrombin or factor Xa inhibitors (23). Recombinant factor VIIa is also another option to reverse the effects of factor Xa inhibitors, however its high cost and unproved efficacy to reduce bleeding are main drawbacks related with this agent (23). Research is ongoing for developing standardized tests and novel antidotes for the new anticoagulant agents.

Cost effectiveness of new anticoagulants is also an important issue. The cost of dabigatran and rivaroxaban therapy of one-month duration is approximately 25 times higher than that of warfarin in Turkey. Although the price of warfarin is relatively inexpensive, the costs of laboratory monitoring and potential complications are worth of mentioning. As such, clinical application, risks and benefits of new anticoagulants should be individually balanced. Cost effectiveness of new agents will be dependent on cost of individual drug, ability to achieve desired levels of anticoagulation with warfarin, individual patient risk for clotting and bleeding (more cost effective for higher risk patients) and performance of these drugs over warfarin.

It should also borne in mind that long-term follow up data of new anticoagulants are not yet available. Results of long-term follow up trials are needed to clarify the long term safety and efficacy of these drugs.

Conclusion

There is ongoing research with the aim of developing ideal anticoagulants for the prevention of thromboembolic events in patients with atrial fibrillation. Large-scale phase III trials are completed for dabigatran, which is an oral direct thrombin inhibitor and for rivaroxaban and apixaban which are oral factor Xa inhibitors. All these trials ended up with non-inferiority of these new anticoagulant drugs compared with warfarin for prevention of stroke and systemic embolism. They also showed a favorable bleeding profile compared with warfarin. Dabigatran and rivaroxaban have been approved by FDA for the prevention of stroke and systemic embolization in patients with non-valvular AF. However, there are still some controversies regarding application of these drugs in daily clinical practice. It seems that further research is necessary to resolve these controversies and clarify the clinical indications for each of these novel anticoagulants.

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