**Review article**

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# NEW ORAL ANTICOAGULANT DRUGS IN ATRIAL FIBRILLATION AND ACUTE CORONARY SYNDROME

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After an acute coronary syndrome, patients remain at risk of recurrent ischemic events despite the use of antiplatelet therapy. In order to reduce the risk of recurrent ischemia in the treatment of patients with acute coronary syndromes, standard oral anticoagulants, such as vitamin K antagonists, have been introduced. These drugs have an important role in preventing stroke and systemic embolism in patients with atrial fibrillation. Vitamin K antagonists (e.g., warfarin) reduce the risk of recurrent cardiovascular events and stroke but increase the risk of bleeding. In addition, the traditional anticoagulants have other significant drawbacks. Therefore, modulation of the coagulation process represents an important target in the development of new oral anticoagulants today.

The new oral anticoagulants selectively target thrombin (dabigatran etexilate) or factor Xa (rivaroxaban, apixaban, edoxaban). Unlike traditional anticoagulants, these drugs have rapid onset of action and a relatively wide therapeutic range, do not require routine prothrombin time (PT) monitoring and have low potential for food and drug interaction.

Dabigatran etexilate and rivaroxaban have been already approved in many countries for the prevention of stroke and systemic embolism in patients with atrial fibrillation. The third phase of clinical studies in which rivaroxaban was investigated in patients with acute coronary syndrome has been successfully completed. *Acta Medica Medianae 2013;52(3):42-48.*

***Key words:*** *new oral anticoagulants, acute coronary syndrome, atrial fibrillation, thrombin, factor Xa*

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## Introduction

During the first year after an acute coronary syndrome, patients remain at high risk of recurrent ischemic events, despite the use of antiplatelet therapy consisting of aspirin and clopidogrel (1-3). In order to reduce recurrent ischemia in the treatment of high-risk patients with acute coronary syndrome, standard oral anticoagulants, such as vitamin K antagonists, have been introduced (2,3).

These drugs also have an important role in preventing stroke and systemic embolism in patients with atrial fibrillation. Atrial fibrillation is the most common arrhythmia in the elderly. Prevalence of atrial fibrillation increases with age. It is present in about 10% of the population older than 75 years. Clinical and epidemiological studies suggest that atrial fibrillation increases the risk of stroke (4,5).

Clinical studies have shown that the use of warfarin, a vitamin K antagonist, reduces the risk of myocardial infarction and stroke, but also increases the risk of bleeding when applied with aspirin or a combination of aspirin and clopidogrel (1).

In addition, it should be noted that despite its clinical efficacy, warfarin has other, well-known drawbacks, such as variable pharmacokinetics, slow onset and offset of action, a narrow therapeutic window, numerous food and drug interactions, as well as significant inter- and intra-individual variability in dose response (Table 1) (6,7). Thus, for example, warfarin doses in the same patient can range from 1 to 25 mg/day (8). Therefore, regular laboratory monitoring of prothrombin time (PT) and dose adjustments are required to maintain the International Normalized Ratio (INR) in the therapeutic range. However, even with monitoring, INR often remains outside the target range (9).

In the recent years, in attempts to overcome some of the limitations of standard anticoagulants, new oral anticoagulants have been developed. Dabigatran etexilate and rivaroxaban have been already approved in many countries for the prevention of stroke and systemic embolism in patients with atrial fibrillation. Rivaroxaban has successfully completed the phase III clinical trial in patients with acute coronary syndrome, while the phase III trial of apixaban was terminated prematurely because of safety reasons. It has not been decided yet whether the third phase of testing dabigatran in patients with acute coronary syndrome will be performed (1).

**Method**

In order to collect data on new anticoagulant drugs we used several sources of information. Most data have been collected by searching large databases MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed). In databases, during the period 2007-2012, the following articles are requested: review articles related to new oral anticoagulant drugs and clinical studies that were carried out, tests related to the effectiveness and side effects of new oral anticoagulants in patients with atrial fibrillation and acute coronary syndromes (original articles). Each found article has been reviewed and further analyzed.

**New oral anticoagulants**

The new oral anticoagulants selectively target thrombin (dabigatran etexilate) or factor Xa (rivaroxaban, apixaban, edoxaban) (Table I, Figure 1) (10-12). Dabigatran etexilate and rivaroxaban have been approved in many countries for the prevention of venous thromboembolism after hip and knee arthroplasty, as well as for the prevention of stroke and systemic embolism in patients with atrial fibrillation, and so far only rivaroxaban is approved for the treatment of deep vein thrombosis (1,13-15). Unlike warfarin, new oral anticoagulants have a rapid onset of action and a relatively large therapeutic range, so that these drugs do not require laboratory control (16). In addition, the new oral anticoagulants act selectively on one specific coagulation factor, and rarely interact with food and drug (10).

It is well-known that thrombin plays a central role in the coagulation process as it not only converts fibrinogen to fibrin, but also amplifies its own generation by feedback activation of coagulation factors V, VIII, XI and XIII and activated platelet PAR-1 and PAR-4 receptors (PAR - protease activated receptors). Therefore, thrombin is an important target for new anticoagulants (10,11). Oral direct thrombin inhibitors cause direct inhibition of thrombin binding to the active site located on the surface of thrombin (11).

In addition to thrombin, factor Xa is also an attractive target for new anticoagulants. Factor Xa is positioned at the convergence of the extrinsic and intrinsic pathways of coagulation, and, when activated, one molecule of factor Xa can generate >1000 thrombin molecules (10,11). Oral factor Xa inhibitors are small molecules that can reversibly bind to the active site of factor Xa (10).

*Table 1.* Features of warfarin, dabigatran etexilate, rivaroxaban and apixaban.

| Drug | Warfarin | Dabigatran etexilate | Rivaroxaban | Apixaban |
|---|---|---|---|---|
| Target | Vitamin K epoxide reductase | Thrombin | Factor Xa | Factor Xa |
| Prodrug | No | Yes | No | No |
| Bioavailability | > 95% | 6-7% | 80-100% | ~66% |
| T(max) | 72-96h | 1-2h | 2-4h | 3h |
| Half-life | 40h | 9-13h | 7-11h | 8-15h |
| Routine coagulation monitoring | Yes | No | No | No |
| Dosing | Once daily (INR-adusted) | Fixed, once or twice daily | Fixed, once or twice daily | Fixed, twice daily |
| Elimination | No | 80% | 67% renal (half is inactive drug), 33% fecal | 25% renal, 75% fecal |
| Potential drug interactions | CYP2C9, 3A4 and 1A2 | Potent p-gp inhibitors | Potent CYP3A4 and p-gp inhibitors | Potent CYP3A4 inhibitors |

T(max) - peak plasma levels; h- hours; INR - international normalized ratio;
CYP - Cytochrome P; p-gp transporter - p-glycoprotein transporter.

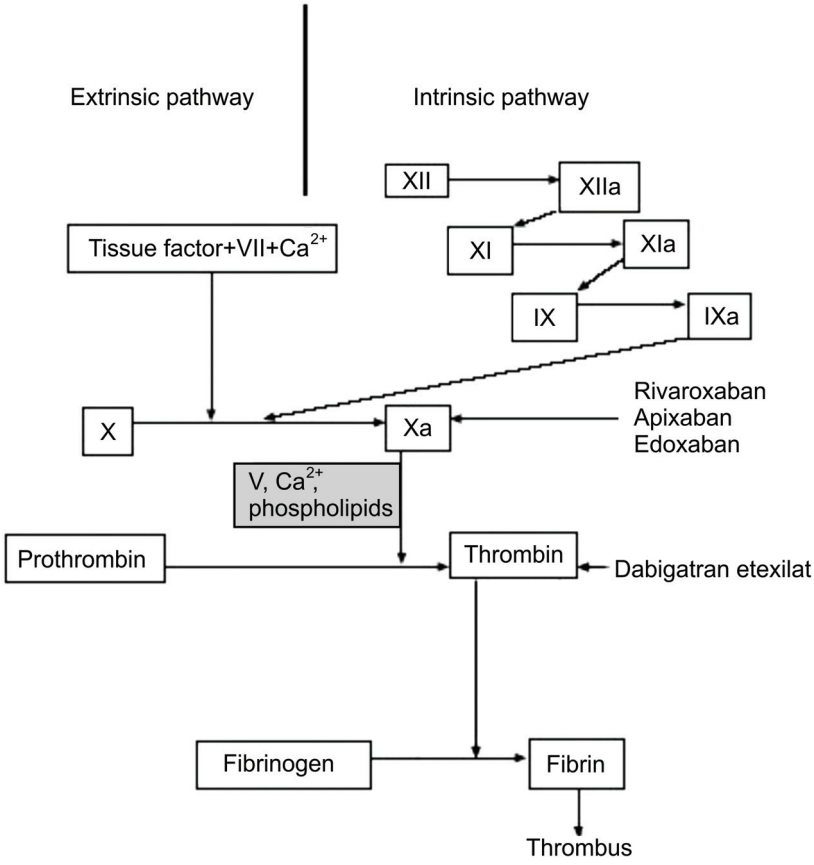


*Figure 1.* ***Ta****rgets of new oral anticoagulants: dabigatran etexilate, rivaroxaban, apixaban and edoxaban*

a) Oral direct thrombin inhibitors

Dabigatran etexilate

Dabigatran etexilate is a prodrug of dabigatran, a competitive direct thrombin inhibitor. After oral administration, dabigatran etexilate is rapidly and completely converted to its active form dabigatran by esterases (10,11). Oral bioavailability of dabigatran is low, 6-7%, as the dabigatran drug capsule contains tartaric acid which creates an acidic microenvironment that allows absorption of dabigatran, independent of gastric pH (11,17). It seems that the tartaric acid is responsible for the 6-12% incidence of dyspepsia observed in the dabigatran-treated patients (18). Peak plasma concentrations are achieved 1-2 hours after administration. Dabigatran has a half-life of 9-13 hours, which allows once- or twice-daily administration (10,11). Given that about 80% of drug is excreted unchanged by the kidney, and 20% in the bile after conjugation of active metabolites, the use of dabigatran is contraindicated in patients with severe renal insufficiency and in patients with severe hepatic insufficiency, although there is no evidence that dabigatran is associated with hepatotoxicity (18). Dabigatran has relatively few drug interactions because its metabolism is independent of cytochrome P450 (CYP) (11,18). However, dabigatran etexilate is a substrate for P-glycoprotein (P-gp) membrane transporter that is highly expressed in the small intestine, and kidney, and coadministration of potent P-gp inhibitors, such as amiodarone or verapamil, can increase its concentration in plasma. The use of rifampicin, a P-gp inducers, which reduces the anticoagulant effect of dabigatran should be avoided (8,10,11). There is no specific antidote to reverse the anticoagulant effect of dabigatran; hemodialysis is effective in removing about 60% of the dabigatran in the blood over 2-3 hours, and can be used to treat dabigatran toxicity (11).

Following successful phase III clinical studies ((RE-MODEL (n=2076) and RE-NOVATE (n=3494)) in patients undergoing total hip replacement or total knee replacement (conditions associated with a high rate of venous thromboembolism) dabigatran etexilate has been initially approved for this clinical indication in Europe, Canada and Australia in 2008 (13,14). Studies have shown that dabigatran, at doses of 220 or 150 mg once daily, effective and safe as enoxaparin was applied at a dose of 40 mg daily in the prevention of venous thrombosis after orthopedic surgery of the lower extremities (19,20).

Based on the results of the RE-LY trial, dabigatran etexilat has been approved in the U.S. in October 2010, and in Europe in April 2011, for the prevention of stroke and systemic embolism in patients with atrial fibrillation (15). This study compared dabigatran etexilate (110 and 150 mg

twice daily) with warfarin in 18.113 patients with atrial fibrillation. The primary efficacy outcomes were stroke or systemic embolism; the major safety endpoint was major bleeding. The stroke or systemic embolism rate was significantly lower with dabigatran etexilate at a dose of 150 mg twice daily ($p<0.001$) compared to warfarin, but not at a dose of 110 mg twice daily ($p=0.34$). The rate of major bleeding with the 150 mg dose was not different from that with warfarin ($p=0.31$), while it was significantly lower with 110 mg dose compared with warfarin ($p=0.003$) (21). In some countries, both doses of dabigatran etexilate are approved, while in the U.S. approved only the higher dose (22).

The U.S. Food and Drug Administration (FDA) continuously evaluates post-marketing reports of serious bleeding events in patients with atrial fibrillation taking dabigatran etexilate. In addition, FDA is working to determine whether the reports of bleeding in patients taking dabigatran etexilate are occurring more commonly than would be expected, based on observations in the RE-LY study (23).

Dabigatran etexilate (50-150 mg twice daily) was also studied in the second phase of the RE-DEEM studies that involved 1861 patients (on dual antiplatelet treatment consists of aspirin and clopidogrel) after acute coronary syndrome. The primary outcome was the composite of major or clinically relevant minor bleeding; secondary outcomes were indicators of efficacy such as reduction in D-dimer levels. Compared with placebo, D-dimer concentrations were reduced in all dabigatran dose groups ($p<0.001$), indicating a possible, significant potential of dabigatran in reducing cardiovascular events when applied in combination with dual antiplatelet therapy. However, the results showed that dabigatran etexilate, compared with placebo, a dose-dependently increases the risk of bleeding (7.8% vs. 2.2%, $p<0.001$), so it is not known whether the third phase of the study for this indication will be conducted (24).

b) Oral factor Xa inhibitors

Rivaroxaban

Rivaroxaban is a direct, specific factor Xa inhibitor that does not require a cofactor. It is rapidly absorbed after ingestion and the maximal plasma concentrations achieved within 2-4 hours (12). Rivaroxaban has a half-life of 7-11 hours (10,11). Rivaroxaban is a substrat for P-gp and CYP3A4, and concomitant administration of potent inhibitors of both P-gp and CYP3A4, such as ketoconazole or HIV protease inhibitors (eg, ritonavir) are contraindicated because they increase plasma drug levels. Because of its pharmacokinetic and pharmacodynamic properties, rivaroxaban can be given at fixed doses to adult patients with no requirement for routine coagulation monitoring (12).

Based on the results of the phase III ROCKET-AF trial (n=14264), rivaroxaban was approved in the Europe and U.S. in 2011 for the prevention of stroke and systemic embolism in patients with atrial fibrillation (1). The results of ROCKET-AF trial showed that rivaroxaban was noninferior to warfarin for the prevention of stroke and systemic embolism in patients with atrial fibrillation ($p<0.001$ for noninferiority). In addition, it was shown that there was no significant difference in the risk of major and clinically relevant nonmajor bleeding, between two study groups ($p=0.44$), although there was a significant reduction in intracranial ($p=0.02$) and fatal bleeding ($p=0.003$) in the rivaroxaban group (25).

Rivaroxaban has been approved in Europe and Canada for the prevention of venous thromboembolism after hip and knee arthroplasty. This was based on the results of phase III RECORD program (n>12700) which included four RECORD trials (12).

In addition, rivaroxaban has also been approved in Europe only (2011), for the treatment of deep venous thrombosis based on EINSTEIN program of trials (EINSTEIN-Acute DVT (n=3449) and EINSTEIN-Extension trial (n=1197)) (2).

In all four RECORD trials, rivaroxaban was superior to enoxaparin in preventing venous thromboembolism, with a similar risk of major bleeding (12,26-29). The approved dose of rivaroxaban is 10 mg daily, starting 6-8 hours post-operatively (8). However, pooled analysis of four trials indicated a small increase in bleeding, an issue of particular concern to orthopedic surgeons that carries a potential need for reoperations (30).

The results of phase III EINSTEIN-Acute DVT study showed that rivaroxaban alone (15 mg twice daily for 3 weeks, followed by 20 mg once daily for 3,6 or 12 months) was noninferior for the prevention of recurrent venous thrombosis versus standard care (enoxaparin plus vitamin K antagonist) ($p<0.001$ for noninferiority). In addition, rivaroxaban did not significantly increase the risk of major or clinically relevant nonmajor bleeding ($p=0.77$). The EINSTEIN-Extension study included patients with confirmed, symptomatic deep vein thrombosis or pulmonary thromboembolism, who had been treated for 6-12 months with a rivaroxaban or a vitamin K antagonist. This study showed that rivaroxaban (20 mg once daily for an additional 6 or 12 months) were significantly more effective in the prevention of recurrent venous thrombosis compared with placebo ($p<0.001$). However, the results showed that rivaroxaban, compared with placebo, increases the risk of major or clinically relevant bleeding ($p<0.001$) (31).

It is also important to note that in early 2012 a supplement of New Drug Application (NDA) was submitted to the U.S. FDA for the rivaroxaban in combination with standard anti-

platelet therapy to reduce the risk of (thrombotic) cardiovascular events in patients with acute coronary syndrome (32).

The application for the supplemental NDA in acute coronary syndrome is based on the results of phase III clinical trial ATLAS ACS 2 - TIMI 51 (n=15.526) which compared rivaroxaban (2.5 and 5 mg twice daily) with placebo in patients with acute coronary syndrome who are receiving standard antiplatelet therapy (aspirin and clopidogrel). The primary efficacy end point was a composite of death from cardiovascular causes, myocardila infarction, or stroke, while the secondary efficacy end point was death from any cause, miocardial infarction, or stroke. The primary safety end point was major bleeding not related to coronary-artery bypass grafting. The results of the study showed that 2.5 mg dose of rivaroxaban reduces the rates of death from cardiovascular causes (p=0.002) and the rates of death from any cause (P=0.002). However, rivaroxaban (2.5 and 5 mg twice daily) increases the rates of major bleeding (p<0.001), without a significant increase in fatal bleeding (p=0.66) (33).

Apixaban

Apixaban, as an active drug, is absorbed rapidly, and maximal plasma concentration are achieved three hours after oral aministration. Concomitant treatment with potent inhibitors of CYP3A4 is contraindicated (10).

Apixaban is the first new oral anticoagulant studied in patients with acute coronary syndrome. Apixaban (5-20 mg daily) was studied in the phase of the II clinical trial (APRAISE-2) involving 1.715 patients with acute coronary syndrome who were receiving standard antiplatelet therapy, aspirin, or a combination of aspirin and clopidogrel. The primary outcome was major or clinically relevant nonmajor bleeding. A secondary outcome was cardiovascular death, myocardial infarction, severe recurrent ischemia, or ischemic stroke. By the recommendation of the Data Monitoring Committee, the 2 higher-dose (10 mg twice daily and 20 mg once daily) of apixaban were discontinued early because of excess total bleeding.

The results of this trial showed that apixaban (2.5 mg twice daily and 10 mg daily) dose-dependently increased the major or clinically relevant nonmajor bleeding (p=0.09 and p=0.005) and reduced, though not significantly, ischemic events compared with placebo (7.6% and 2.5% compared with 8.7% placebo) (34).

Based on the results of phase II APPRAISE-2 trial, the phase III of the same trial has been carried. APPRAISE-2 (n=7392) enrolled patients who were at high risk for recurrent ischemic events following acute coronary syndrome and on standard antiplatelet therapy. The trial randomized patients to either placebo or two 5-mg daily doses of apixaban. Unfortunately, phase III clinical trial was terminated prematurely because of increased risk of major bleeding (p<0.001), without a significant reduction in recurrent ischemic events (p=0.51) (35).

Apixaban at a dose of 5 mg twice daily was compared to aspirin (81-324 mg daily) for stroke prevention in atrial fibrillation (AVERROES trial). This study included 5.599 patients who were deemed unsuitable for warfarin; it was stopped early because of a clear benefit in favour of apixaban. The primary efficacy outcome was the occurence of stroke or systemic embolism. The primary safety outcome was the occurence of major beedeing. In this study, apixaban significantly reduced the risk of stroke or systemic embolism (p<0.001), without a significant increase in the risk of major or intracranial bleeding (p=0.66) (36).

In addition to rivaroxaban and apixaban, edoxaban should be also mentioned, which is currently being applied in phase III clinical trials for the prevention of stroke. The scope of this study is to compare the effects of edoxaban (30 and 60 mg once daily) with warfarin in 16.500 patients with atrial fibrillation (11 ).

**Conclusion**

The standard anticoagulant therapy, although effective, has significant disadvantages, so it is necessary to introduce new oral anticoagulants in therapy of patients with atrial fibrillation and acute coronary syndrome. For the present, dabigatran etexilate and rivaroxaban have gained approval for the prevention of stroke and systemic embolism in patients with atrial fibrillation, while rivaroxaban has successfully completed a phase III clinical trial in patients with acute coronary syndrome. However, the new anticoagulants could not completely replace the standard anticoagulant treatment until the results of the study demonstrate a satisfactory relation-ship between the efficacy and safety of these drugs, as well as the economic feasibility of their application.)

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# NOVI ORALNI ANTIKOAGULANTNI LEKOVI KOD ATRIJALNE FIBRILACIJE I AKUTNOG KORONARNOG SINDROMA

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Nakon akutnog koronarnog sindroma, kod bolesnika postoji povećan rizik od rekurentnih ishemičnih događaja, uprkos primeni antiagregacione terapije. U cilju smanjenja rizika od rekurentne ishemije, u terapiju visokorizičnih bolesnika sa akutnim koronarnim sindromom uvode se standardni oralni antikoagulansi, kao što su antagonisti vitamina K. Ovi lekovi imaju važnu ulogu u prevenciji moždanog udara i sistemskog embolizma kod bolesnika sa atrijalnom fibrilacijom. Antagonisti vitamina K (varfarin) smanjuju rizik od nastanka ponovnih kardiovaskularnih događaja i moždanog udara, ali povećavaju rizik od krvarenja. Pored toga, antagonisti vitamina K poseduju i druge, značajne nedostatke, tako da modulacija procesa koagulacije danas predstavlja značajnu metu za razvoj novih oralnih antikoagulanasa.

Novi oralni antikoagulansi deluju selektivno na trombin (dabigatran eteksilat) ili na faktor koagulacije Xa (rivaroksaban, apiksaban, edoksaban). Za razliku od standardnih antikoagulanasa, imaju brz početak dejstva i relativno veliku terapijsku širinu, ne zahtevaju laboratorijsku kontrolu protrombinskog vremena (PT) i retko stupaju u interakcije sa hranom i lekovima.

Dabigatran eteksilat i rivaroksaban su već registrovani u mnogim zemljama za prevenciju moždanog udara i sistemskog embolizma kod bolesnika sa atrijalnom fibrilacijom. Treća faza kliničke studije u okviru koje je ispitivan rivaroksaban kod bolesnika sa akutnim koronarnim sindromom uspešno je završena. *Acta Medica Medianae 2013; 52(3):42-48.*

***Ključne reči:*** *novi oralni antikoagulansi, akutni koronarni sindrom, atrijalna fibrilacija, trombin, faktor Xa*