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NOVEL ORAL ANTICOAGULANTS, A SUBJECT IN CONTINUING DEBATE

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Abstract
Coumarin anticoagulants era (warfarin, acenocumarol) seems to be coming to an end with the launch of the novel anticoagulants like dabigatran, rivaroxaban, apixaban and edoxaban. Dabigatran (Pradaxa) is a prothrombin (factor II) inhibitor that doesn't necessitate monitoring by coagulation tests, doesn't have food or drug interactions, except for P-gp inhibitors. Rivaroxaban (Xarelto) is a direct inhibitor of factor X and is approved for the prevention of thromboembolic events in patients with non-valvular atrial fibrillation and for the prevention of deep venous thrombosis in patients undergoing orthopaedic surgery (hip and knee prosthesis). Apixaban (Eliquis) is a direct inhibitor of factor X and is indicated for the prevention of venous thromboembolic events in patients undergoing hip or knee arthroplasty, the prevention of thromboembolic events in patients with non-valvular atrial fibrillation and treatment or prevention of recurrences in patients with deep vein thrombosis or pulmonary embolism. Edoxaban (Savaysa), recently approved is USA, is a direct inhibitor of factor X and is indicated for deep venous thrombosis, pulmonary embolism and for the prevention of thromboembolic events in patients with non-valvular atrial fibrillation. The most recent studies focus on antidotes specifically designed to bind and neutralise the anticoagulant activity of both direct thrombin inhibitors and direct factor Xa inhibitors. The drugs currently being studied are idarucizumab, a specific antidote, andexanet alfa, a class-specific antidote and ciraparantag, a universal antidote. Of these, only idarucizumab was approved by the FDA.
Keywords: *anticoagulation, dabigatran, rivaroxaban, apixaban, idarucizumab.*

Rezumat
Era anticoagulantelor cumarinice (warfarina, acenocumarolul) pare că se apropie de sfârşit odată cu lansarea noilor anticoagulante de tipul dabigatran, rivaroxaban, apixaban și edoxaban. Dabigatranul (Pradaxa) este un inhibitor al protrombinei (factorul II) care nu

necesită monitorizarea prin teste de coagulare, nu are interacţiuni alimentare sau medicamentoase cu excepţia inhibitorilor de P-gp. Rivaroxaban (Xarelto) este un inhibitor direct al factorului X şi este aprobat pentru prevenirea evenimentelor tromboembolice la pacientii cu fibrilație atrială non-valvulară și pentru prevenirea apariţiei trombozei venoase profunde la pacienţii supuşi unor intervenţii chirurgicale ortopedice (proteză de șold şi genunchi). Apixaban (Eliquis) este un inhibitor direct al factorului X şi este indicat pentru prevenirea evenimentelor tromboembolice venoase la pacienţii supuşi unor intervenţii chirurgicale de artroplastie a şoldului sau a genunchiului, prevenirea evenimentelor tromboembolice la pacienţii cu fibrilaţie atrială non-valvulară şi tratamentul sau prevenirea recurenţelor la pacienţii cu tromboză venoasă profundă sau a emboliei pulmonare. Edoxaban (Savaysa), recent aprobat în USA, este un inhibitor direct al factorului X şi este indicat pentru trombembolismul venos profund, embolia pulmonară şi pentru prevenirea evenimentelor tromboembolice la pacienţii cu fibrilaţie atrială non-valvulară.

Cele mai recente studii se axează pe antidoturile realizate special pentru a lega și neutraliza activitatea anticoagulantă atât a inhibitorilor direcți ai trombinei, cât și a inhibitorilor direcți ai factorului Xa. Medicamentele ce sunt în prezent studiate sunt idarucizumab, un antidot specific, andexanet alfa, un antidot specific de clasă și ciraparantag, un antidot universal. Dintre acestea, doar idarucizumab a fost aprobat de FDA.

Cuvinte cheie: *anticoagulare, dabigatran, rivaroxaban, apixaban, idarucizumab.*

Coumarin anticoagulants era (warfarin, acenocumarol) seems to be coming to an end with the launch of the novel anticoagulants like dabigatran, rivaroxaban, apixaban and edoxaban.

Both classes of anticoagulants, both the novel generation and coumarin, present a number of drawbacks. Although they are widely used and effective, coumarin anticoagulants have 4 major drawbacks:

1. are subject to medicinal interactions (diminished effect due to simultaneous administration of: barbiturates, carbamazepine, thiazide diuretics, oral contraceptives and effect boosted due to concomitant administration of: antibiotics, allopurinol, oral antidiabetic agents, thyroid hormones, antiarrhythmics),
2. food (cabbage, broccoli, spinach),
3. INR determination at least monthly and
4. longer half-life than novel generation anticoagulants (in the context of a required surgery).

Novel generation anticoagulants drawbacks are: the price, the impossibility of administration in the context of the presence of certain cardiac pathologies (eg: metal

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target		Xa factor	Xa factor	Xa factor
Administration	Oral	Oral	Oral	Oral
Hours up to c^{MAX}	1.25-3	2-4	3-4	1-2
Pro-drug	Yes	No	No	No
Food interactions	No	No	No	No
Bioavailability (%)	6.5	80-100	50	62
Drug interactions	Inhibitors and inducers of Gp P	Inhibitors and inducers of CYP3a4 Inhibitors and inducers of Gp P	Inhibitors and inducers of CYP3a4 Inhibitors and inducers of Gp P	Inhibitors and inducers of Gp P
Half-life (hours)	12-14	7-11 (11-13 in elders)	12	6-11
Renal clearance	85	33	27	37-50
Number of doses	2/day	1/day	2/day	1/day

Table 1. *Pharmacological characteristics of oral anticoagulants, except for antagonists of vitamin K.*
C^{max} = maximum concentration; CYP3A4 = enzyme of cytochrome P3a4; GP P = platelet glycoprotein.

valvular prosthesis and tight aortic stenosis). Often, patients undergoing anticoagulation therapy may experience bleeding with different locations due to an excess of anticoagulants. In the case of coumarin anticoagulants, the antidote is protamine sulphate.

Although the novel generation anticoagulants may have no antidote, 2014 ESC guidelines provide the patient, depending on the severity of bleeding, an approach that includes: postponing the next dose or discontinuation of treatment, symptomatic support treatment, mechanical compression, volumetric repletion, blood transfusion, medicinal charcoal per bone, if NOAC was recently administered, prothrombin or haemodialysis administration.

At present, the following are used as novel oral anticoagulants: dabigatran, rivaroxaban, apixaban, edoxaban. Their characteristics can be observed in table 1[(2)].

Dabigatran (Pradaxa) is a prothrombin (factor II) inhibitor that doesn't necessitate monitoring by coagulation tests, doesn't have food or drug interactions, except for P-gp inhibitors. It is approved for: prevention of stroke and peripheral embolism in patients with atrial fibrillation, venous thromboembolism and prevention of thrombotic events in orthopaedic surgery (after hip/knee prosthesis surgery). In patients with non-valvular atrial fibrillation, the recommended dosage is 150 mg 2 x/day for prevention of thromboembolic events, but it should be taken into account that creatinine clearance should be >30 mL/min. The recommended dose in patients who underwent elective surgeries for knee replacement is 110 mg x 2/day for 10 days, and in those who underwent elective surgery for hip replacement the dose is 110 mg x 2/day for 28-35 days. For the following groups of patients, the recommended daily dose is 150 mg (75 mg x 2/day):

- patients with creatinine clearance between 15-30 mL/min (provided that P-gp inhibitors are simultaneously administered it is prohibited from administering dabigatran).
- patients who are concurrently administered medications such as: verapamil, amiodarone, quinidine, ketoconazole, dronedarone and creatinine clearance between 30-50 mL/min.
- patients with age over 75 years.

Rivaroxaban (Xarelto) is a direct inhibitor of factor X and is approved for the prevention of thromboembolic events in patients with non-valvular atrial fibrillation and for the prevention of deep venous thrombosis in patients undergoing orthopaedic surgery (hip and knee prosthesis). The recommended

dose is 10 mg/day. It is not recommended for patients with creatinine clearance <15 mL/min.

Apixaban (Eliquis) is a direct inhibitor of factor X and is indicated for the prevention of venous thromboembolic events in patients undergoing hip or knee arthroplasty, the prevention of thromboembolic events in patients with non-valvular atrial fibrillation and treatment or prevention of recurrences in patients with deep vein thrombosis or pulmonary embolism. The recommended dose in the first 7 days in deep venous thrombosis and pulmonary embolism is 10 mg x 2/day with oral administration followed by reducing the dose to 5 mg x 2/day after that period. In patients with non-valvular atrial fibrillation, the recommended dose is 5 mg × 2/day with oral administration and reduction of the dose to 2.5 mg × 2/day in the case of those with non-valvular atrial fibrillation and at least 2 of the following features: age ≥80, body weight ≤60 kg, serum creatinine ≥1.5 mg/dl. In patients with hip arthroplasty, the recommended dose is 2.5 mg x 2/day for 32-38 days and in those with knee arthroplasty 2.5 mg x 2/day for 10-14 days.

Edoxaban (Savaysa), recently approved is USA, is a direct inhibitor of factor X and is indicated for deep venous thrombosis, pulmonary embolism and for the prevention of thromboembolic events in patients with non-valvular atrial fibrillation. The recommended dose is 60 mg 1/day with oral administration and the dose is reduced to 30 mg 1/day for patients with creatinine clearance between 15-50 mL/min, weight ≤60 kg, and simultaneous administration of P-gp inhibitor (verapamil, quinidine, dronedarone). It is contraindicated in patients with creatinine clearance >95 mL/min.

The main studies of novel oral anticoagulants:

RE-LY study (the Randomized Evaluation of Long-term Anticoagulation Therapy) is a randomized trial, conducted in the period 22.12.2005-15.03.2009, on a batch of 18,113 patients from 44 countries with non-valvular atrial fibrillation; patients were divided into 2 subgroups: a subgroup treated with warfarin, and the other with dabigatran 110/150 mg × 2/day. RE-LY study results reveal that etexilate dabigatran of 150 mg × 2/day administered to patients with non-valvular atrial fibrillation significantly reduces the risk of stroke and systemic embolism by 34% (p = 0.01) compared to the tightly controlled treatment with warfarin. 110 mg dose of dabigatran administered 2/day showed a similar reduction of stroke and a reduction in the rate of bleeding by 20% in the case of major ones (p = 0.03) compared to warfarin. As secondary objectives of the study compared with warfarin a reduction in the rate of death, a significant reduction in hemorrhagic stroke and an increase in the rate of myocardial infarction for both doses were proven. The only adverse effect, which was significantly more frequent in patients treated with dabigatran, was represented by dyspeptic syndrome (11.8 vs. 5.8%)[3,4].

In 2014, a review of RE-LY study is published for the reevaluation of additional events in view of the large number of deaths during the study (1387 patients) and after its completion, which resulted in reevaluation > 1500 cases. Comparing the subsequent results with previous ones of this review, they added 2 new cases of stroke (1 case treated with dabigatran 150 mg × 2/day and 1 case treated with warfarin), and 20 episodes of major bleeding of which: 10 cases treated with dabigatran 150 mg × 2/day, 5 cases

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treated with dabigatran 110 mg × 2/day and 5 cases treated with warfarin. Of these previously presented events, they considered to be fatal in 2 patients treated with dabigatran 150 mg × 2/day, in 3 patients treated with dabigatran 110 mg × 2/day and in 3 patients treated with warfarin.

After including these events in the RE-LY study, the effect of therapy with dabigatran compared to warfarin on the incidence of stroke, systemic embolism and major bleeding suffered minimal changes and therefore RE-LY study's findings has not undergone changes[5].

The ARISTOTLE study (Apixaban for the Prevention of Stoke in Subjects With Atrial Fibrillation) is a randomised study conducted from 19 December 2006 to 2 April 2010 on a batch of 18,201 patients from 39 countries with non-valvular atrial fibrillation. Patients are divided into 2 subgroups: a subgroup treated with apixaban (5 mg × 2/day) and the other with warfarin.

As primary results, a decrease of events (ischaemic or haemorrhagic stroke and systemic embolism) in patients treated with apixaban: 1.27%/year (the subgroup with apixaban) vs. 1.60% per year (the subgroup with warfarin). In the group treated with apixaban, a decrease of 49% of hemorrhagic stroke and a 8% reduction in the rate of stroke of ischaemic type or of unknown cause. The rate of major bleeding was also lower in those treated with apixaban compared to those treated with warfarin (2.13%/year vs. 3.09%/year). As secondary objectives, a reduction in all-cause death in the group treated with apixaban 3.52%/year vs. 3,.94% per year and a reduction in death from cardio-vascular cause, including hemorrhagic stroke (1.80% per year vs. 2.02% per year) were observed. Regarding RE-LY study, the rate of myocardial infarction was lower in the group treated with apixaban, however the difference between the 2 groups (apixaban versus warfarin) is insignificant[6].

From the data presented in the two previous studies, there is a possibility of association between dabigatran or apixaban and antiplatelet medication (aspirin) but only in a subgroup with well-defined indications (coronary stent implantation, acute coronary syndrome, atherothrombotic events) as there is a risk of major bleeding and intracranial haemorrhage according to APPRAISE studies II[7] and ATLAS-ACS2-TIMI 51[8].

Through these studies no proven antithrombotic benefit was highlighted.

The ROCKET-AF study (The Rivaroxaban Once Daily Compared with Vitamin K Antagonist for Prevention of Stoke and Embolism Trial in Atrial Fibrillation) is a randomised study conducted from 18 December 2006 to 28 May 2010, on a batch

of 14,264 patients in 45 countries with non-valvular atrial fibrillation. Patients were divided into 2 subgroups: a subgroup treated with rivaroxaban 20 mg/day or 15 mg/day rivaroxaban (in patients with creatinine clearance between 30 and 49 mL/min) and the other treated with warfarin. As primary results, a decrease in stroke and systemic embolism by 2.1% per year in patients treated with rivaroxaban versus 2.4 percent per year in those treated with warfarin was noticed.

The rate of major bleeding was about the same in the two subgroups (3.6% vs. 3.4%). As secondary objectives, a reduction of death regardless of its cause was observed during treatment in the subgroup treated with rivaroxaban by 1.9%/year vs. 2.2%/year in the subgroup treated with warfarin. The rate of myocardial infarction was also lower than in the subgroup treated with rivaroxaban (0.9%/year vs. 1.1%/year)[9].

The Engage AF-TIMI 48 study (The Effective Anticoagulation with Factor Xa Generation Next in Atrial Fibrillation-Thrombolysis in Myocardial Infaction 48). Patients were divided into 3 subgroups (warfarin, 60 mg edoxaban, 30 mg edoxaban).

As primary results, a decrease in events (stroke or systemic embolism) is observed in patients treated with 60 mg edoxaban (1.18% vs. 1.50%) and an increase in such events in patients treated with 30 mg edoxaban (1.61% vs. 1.50%). The rate of hemorrhagic stroke was lower in patients treated with edoxaban (0.16%/year for 30 mg edoxaban; 0.26%/year for 60 mg edoxaban and 0.47%/year for warfarin). The rate of ischaemic stroke was similar in the group treated with 60 mg edoxaban and warfarin (1.25%/year) and higher in patients treated with 30 mg edoxaban (1.77%/year). The rate of major bleeding was lower in patients treated with 30 mg edoxaban compared to patients treated with 60 mg edoxaban and with patients treated with warfarin (1.61%/year vs. 2.75%/year vs. 3.43%/year). The rate of myocardial infarction was lower in patients treated with 60 mg edoxaban compared to patients treated with 30 mg edoxaban and warfarin (0.70%/year vs. 0.75%/year vs. 0.89%/year). As secondary objectives, a reduction in all-cause death at 30 mg endoxaban, 60 mg edoxaban and warfarin and major cardiac events 60 mg, 30 mg-edoxaban and warfarin was noticed (4.41%/year for 30 mg edoxaban vs. 4.90%/year for 30 mg edoxaban vs. 4.98%/year) for warfarin)[10].

Considering the data submitted through the 4 studies, the choice of anticoagulant belongs to the attending physician; the only aspect that could influence this choice remains the rapidity with which the antidote will be marketed. The company producing Xarelto (rivaroxaban) conducted a study entitled Annexa-R whose final data have not yet been published, but they published partial results. Annexa-R study is a randomised, double-blind, placebo-controlled, phase 3 study, which assesses the safety and efficacy of reversal of rivaroxaban effect using Andexanet Alfa. To neutralise the effect (Xarelto-rivaroxaban) they used an i.v. bolus of 800 mg Andexanet Alfa (27 patients) or placebo (14 patients) or i.v. bolus of 800 mg Andexanet Alfa, followed by i.v. administration of 8 mg/minute for 120 minutes of Andexanet Alfa. It was demonstrated that Alpha Andexanet was well tolerated; its use in administering an i.v. bolus has an immediate reversion of anticoagulant effect, but to continue to administer the antidote subsequently after those 120 minutes, the producing company has not made public any results[11].

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Andexanet Alfa is proposed as the antidote for apixaban according to a study titled Annexa A; Annexa R and Annexa A studies have the same principles and similar results.

A study on edoxaban reversion using as antidote PER 977, of phase 1, double-blind, placebo-controlled on a batch of 80 healthy people, uses PER 977 with doses between 100 and 300 mg administered intravenously, counteracts the anticoagulant effect of edoxaban in 10-30 minutes and maintains the effect for 24 hours[12].

The company producing dabigatran proposes as antidote, which is still under study, the use of idarucizumab; as information about its effectiveness, they are presented only under a substudy that includes 35 healthy volunteers. It proves both the anticoagulant effect of dabigatran by completely inhibiting the formation of fibrin at cutaneous level, where it caused a minor bleeding and the antidote effect through the process of restoration of fibrin at this level. It is the first company that initiates a study aiming at the effectiveness of the antidote on a batch of patients; the study is being conducted in more than 35 countries and is called Re-verse AD^{tm}, and the final results will be published according to the information provided by the manufacturer in 2017[13].

A study aiming at the improvement of efficiency of elective electric cardioversion for atrial fibrillation or atrial flutter, using dabigatran or wafarin as anticoagulant agent, study which was conducted during 2010-2013 and which appeared in January-March 2014 in "The British Journal of Cardiology, monitored 193 patients divided into two groups (group 1-being treated with warfarin, and group 2 - 48% have received dabigatran). The study demonstrated a 70% reduction in reprogramming for cardioversion due to therapeutic values of INR and a significant reduction in the time required to perform elective electrical cardioversion (24 days less in group 2 versus group 1, $p < 0.001$ and with 22 days less for those with dabigatran versus those with warfarin).

After cardioversion, the sinus rhythm and its maintenance were similar in the two groups ($p > 0.05$), and the rate of transient ischaemic event (2 cases in group 1 - treated with warfarin and 1 case in group 2 - treated with dabigatran)[14]. A study published a few months later called X-VErT (eXplore the efficacy and safety of once-daily oral riVaroxaban for the prevention of caRdiovascular events in patients with nonvalvular a Trial fibrillation scheduled for cardioversion), shows similar data of treatment with rivaroxaban in patients scheduled for cardioversion in comparison with the previously presented study in which it uses dabigatran[15].

A study appearing in the American College of Cardiology on 30 March 2014, conducted on a batch of 129 patients with non-valvular atrial fibrillation concluded that the value of APTT < 35 seconds, low body mass index and a CHADS2 increased score are predictive factors independent of the occurrence of stroke and brings back into discussion the determination of APTT as being required for the anticoagulant effect of dabigatran[16].

The most recent studies focus on antidotes specifically designed to bind and neutralise the anticoagulant activity of both direct thrombin inhibitors and direct factor Xa inhibitors. The drugs currently being studied are idarucizumab, aspecific antidote, andexanet alfa, a class-specific antidote and ciraparantag, a universal antidote. Of these, only idarucizumab was approved by the FDA[17,18].

A phase III, RE-VERSE AD study, examined the efficacy and safety of idarucizumab in patients treated with dabigatran that presented significant bleeding or required surgery. Recent studies assert that resuming the anticoagulant therapy after major bleeding is associated with better outcomes (including mortality) versus not resuming anticoagulants. Idarucizumab appears to be effective as the antidote for dabigatran, but additional data are required and the lack of a batch of comparison makes it difficult to make a final decision[19].

Two phase III trials have demonstrated a good safety and efficacy for andexanet alfa as the antidote of apixaban and rivaroxaban in healthy adult volunteers with age between 50 and 75 years compared with placebo. In the phase II double blind study, placebo-controlled trial on 80 healthy adults, ciraparantag presented a complete, immediate and consistent reversibility of edoxaban. Similar results have been reported for enoxaparin. Even if these results are encouraging, additional data are required from subsequent phases of trials related to clinical outcomes occurring in patients with active bleeding complications and receiving repeated doses of these medications. A potential advantage of ciraparantag compared to idarucizumab and andexanet alfa is its universal applicability on all novel oral anticoagulants, which can thus hasten the selection and administration of antidote[20,21].

Clinical studies confirm the efficacy of novel oral anticoagulants. These ideal anticoagulants have outstanding qualities, but indications of guidelines are limited. The results of trials are expected for the other two antidotes, whose effectiveness is not yet confirmed.

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