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New Oral Anticoagulants in Atrial Fibrillation

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<http://dx.doi.org/10.5772/53614>

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice with a strong impact on public health. The prevalence in the general population is 0.4% and their incidence increases markedly with age to reach 4-5% in patients over 65 years and 9% in patients older than 80 years [1]. The main complication associated with this disease is the development of an embolic event, peripheral or cerebral, strokes being caused by the AF the most serious and worse prognosis. The risk that a patient suffers a stroke with AF is related to the presence of other cardioembolic risk factors: hypertension, diabetes mellitus, heart failure or left ventricular systolic dysfunction, moderately severe, age over 75 years, female, vascular disease or stroke have shown a previous cerebral (transient or established). These risk factors are reflected in the scales CHADS₂ or CHA₂DS₂-VAS_C used today to evaluate this type of patient.

In the management of patients with AF, the most important to improve prognosis is correct indication of anticoagulant therapy. For over 60 years using vitamin K antagonists (VKAs), especially warfarin and acenocoumarol, have been shown in several studies a reduction of 70% risk of stroke in AF patients correctly anticoagulated compared with only 22% reduction of antiplatelet drugs, or a nonsignificant 19% reduction with acetylsalicylic acid. Thus, oral anticoagulants (OACs) are recommended in AF patients at moderate-high risk for stroke and thromboembolism [2]. The VKAs are drugs with proven efficacy, specific antidote in case of bleeding, possibility of discontinuing medication urgently and low cost. However, VKAs have limitations that affect the quality of life of patients and increase morbidity: narrow therapeutic window (International normalized ratio, INR 2.0-3.0) [3], unpredictable response, systematic control of bleeding, frequent dose adjustments and numerous food and drug interactions. Also, scenarios such as intercurrent infections and other medical conditions can also modify the values of the INR [4]. These results indicate that it is important to

stratify each patient, both the risk of stroke such as bleeding, to individually assess what the best therapeutic approach in each case.

Due to the complexity of the use of VKAs in routine clinical practice in the last decade has developed an extensive research activity and has seen the introduction of new oral anticoagulants (NOACs): The direct thrombin inhibitors (dabigatran) and factor Xa (rivaroxaban and apixaban) that do not possess the disadvantages of the VKAs. These drugs are characterized by rapid onset of action, low potential for drug and food interactions and a predictable anticoagulant effect that avoids the need to monitor coagulation (Table 1) [5-7].

Comparative features of VKAs and NOACs	
Advantage	Clinical implications
The rapid onset of action	No bridge therapy required
Predictable anticoagulant effect	No routine coagulation monitoring required
Diana enzymatic cascade specific clotting	Low risk of adverse effects related to its mechanism of action
Low potential for interactions with food	No dietary restrictions
Low potential for drug interactions	Few drugs restrictions

Table 1. Comparative features of VKAs and NOACs

2. Evaluation of the risk of tromboembolism and bleeding to recommend anticoagulant therapy in the AF

Currently, there have been scales for assessing the risk of stroke and bleeding in patients with AF. The risk of stroke is classified into low, moderate and high, depending on the factors set out in the CHADS₂ scale (Table 2) [8]. A higher score greater risk. Patients at high risk should receive OACs and low risk, acetylsalicylic acid or nothing (prefer no treatment). In intermediate-risk patients should consider any of the two treatments.

CHADS ₂ acronym	Score
Congestive Heart failure (CHF)	1
Hypertension	1
Aged ≥ 75 years	1
Diabetes mellitus	1
Stroke or transient ischemic attack (TIA)	2
Maximum score	6

Table 2. Stroke risk stratification with the CHADS₂ score

Given the limitations of CHADS₂ scale, a large proportion of patients are classified as intermediate risk and to the omission of potential risk factors for thromboembolism, there is the scale CHA₂DS₂-VASc [9,10]. This new scale is more comprehensive as additional risk factors: the presence of vascular disease, a younger age range than the CHADS₂ and female category (Table 3). The patients with a grade of 0 are at low risk and should not be treated. The rest should be considered for oral anticoagulation, establishing the risk of bleeding by HAS-BLED scale (Table 4) [11]. In patients with a HAS-BLED score ≥ 3 , caution and regular review are recommended and to correct the potentially reversible risk factors for bleeding. A high HAS-BLED score per se should not be used to exclude patients from OAC therapy.

CHA ₂ DS ₂ -VASc acronym	Score
CHF or LVEF \leq 40%	1
Hypertension	1
Aged \geq 75 years	2
Diabetes mellitus	1
Stroke / TIA / Thromboembolism	2
Vascular disease	1
Aged 65-74 years	1
Sex category (Female)	1
Maximum score	9

Table 3. Stroke risk stratification with the CHA₂DS₂-VASc score

HAS-BLED risk criteria	Score
Hypertension	1
Abnormal renal or liver function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (age > 65)	1
Drugs or alcohol (1 point each)	1 or 2

Table 4. HAS-BLED risk criteria

If a patient has a rating of less than 2 on the CHADS₂ scale, it also assesses the amendment CHA₂DS₂-VASc, although this could be applied directly: if the score is zero, who are at low risk, with none of the risk factors, no antithrombotic treatment is indicated and if the score is

1, is preferred to administer OACs (VKAs or NOACs) based upon an assessment of the risk of bleeding complications and patient preferences. If CHA₂DS₂-VASc score equal to or greater than 2, the treatment is with OACs (VKAs or NOACs) is recommended, unless contraindicated. When the patients refuse the use of OACs (VKAs or NOACs), antiplatelet therapy should be considered (combination therapy with acetylsalicylic acid plus clopidogrel).

In patients with CHA₂DS₂-VASc score of 1, apixaban and both doses of dabigatran (110 mg twice daily and 150 mg twice daily) had a positive net clinical benefit while, in patients with CHA₂DS₂-VASc score ≥ 2 , all three NOACs were superior to warfarin, with a positive net clinical benefit, irrespective of bleeding risk. The patients with CHA₂DS₂-VASc equal to 0 have a lower risk of stroke and could be left with acetylsalicylic acid or no treatment, preferring the latter option, as it has not shown any benefit in this group without treatment.

When using dabigatran, the dose is 150 mg administered twice daily in patients with low risk of hemorrhage (HAS-BLED scale of 0 to 2) and 110 mg twice daily in patients with increased risk hemorrhage (HAS-BLED ≥ 3), elderly patients, concomitant use of interacting drugs and moderate renal impairment (creatinine clearance (CrCl) 30-49 mL/min) [12]. When using rivaroxaban, the dose is 20 mg daily in the most patients and 15 mg daily in high bleeding risk (HAS-BLED ≥ 3) and moderate renal impairment (CrCl 30-49 mL/min) [13].

3. Objectives of anticoagulant therapy

Anticoagulant therapy is recommended in patients with AF with risk factors for systemic embolism. The choice of treatment is based on the absolute risk of stroke, the risk of bleeding and the risk/benefit ratios for each patient [14]. The recent development of NOACs, with innovative mechanisms of action of therapeutic targets in the coagulation could change the current standard anticoagulant drug treatment [15]. The NOACs are orally administered drugs that directly inhibit the coagulation steps defined by decreasing or inhibiting thrombin generation of the final enzyme, thrombin. Thrombin (factor IIa) is the end effector of the coagulation cascade that catalyzes the formation of fibrin from plasma fibrinogen. Is the most potent physiological agonist of platelet activation, so it is considered a key therapeutic target in the development of NOACs. The Factor Xa acts as a point of convergence of the intrinsic and extrinsic pathways of coagulation and catalyzes the conversion of prothrombin to thrombin [16,17]. A single molecule of factor Xa can generate more than 1.000 molecule of thrombin, as a consequence the inhibition of factor Xa can block this process by reducing the activation of coagulation and platelet thrombin mediated. Whether the coagulation cascade is inhibited at the level of thrombin and factor Xa, or even above the sequence, the net result is a decreased activity of thrombin.

The NOACs are characterized by specific inhibition of one of the two key factors in the coagulation system, factor Xa and thrombin. Dabigatran, MCC977 and AZD0837 acts by directly inhibiting thrombin thus interfere with the first phase (initial phase) and late (amplification / propagation phase) the model based on the coagulation system. Rivaroxaban, apixaban, edoxaban, betrixaban, eribaxaban, LY517717, YM150, TAK-442 and bind to either factor Xa or factor Xa without bound in the prothrombinase complex thus blocking the conversion of

prothrombin to thrombin in the early stage (stage start) and end (amplification / propagation phase) the model based on the coagulation system.

4. New oral anticoagulants

The search of ideal anticoagulant is one of the most active fields of investigation in lasts years. The ideal anticoagulant would be one that fulfilled the following characteristics: Oral administration, effective in the treatment of AF and low bleeding risk, predictable kinetics, which does not require monitoring of coagulation and platelet count, which is not necessary to adjust the dose, wide therapeutic range, low drug interaction, cost effective and availability of an effective antidote.

With these premises have been developed more specific inhibitors of coagulation factors: factor Xa and factor II (thrombin). In Table 5, inspired by Phillips and Ansell collected some of the most relevant pharmacological characteristics of NOACs (dabigatran, ribaroxaban and apixaban) compared with VKAs (warfarin and acenocoumarol) [18].

	Warfarin	Acenocoumarol	Dabigatran	Rivaroxaban	Apixaban
Target	VKOR and factors II, VII, IX, X	VKOR and factors II, VII, IX, X	Factor IIa (Thrombin)	Factor Xa	Factor Xa
Time to peak concentration	72-96 h		1,5-3 h	2-4 h	1-3 h
Vol. of dist.			60-70 l	50 l	Reported as low
Half-life	40 h	8-11 h	12-14 h	9-13 h	9-14 h
Metabolism	Liver-CYP2C9	Liver- CYP2C9	Conjugation	Liver-CYP3A4 and CYP2J2	Partially through CYP3A4
Elimination	Bile and urine	Bile and urine	80% renal, 20% faecal	66% faecal, 33% renal	75% faecal, 25% renal
Administration	Once Daily	Once Daily	Once or Twice daily	Once daily	Twice daily
Monitoring	INR	INR	Not needed	Not needed	Not needed
Antidote or potential therapy for bleedind	Vitamin K, FFP, PCC or rFVIIa	Vitamin K, FFP, PCC or rFVIIa	FFP, PCC or rFVIIa	FFP, PCC or rFVIIa	FFP, PCC or rFVIIa
Assay	PT/INR	PT/INR	Experimental	Experimental	Experimental
Drug interactions	CYP2C9		PPIs decrease absorption and potent P-gp inhibitors	Potent CYP3A4 inhibitors and P-gp inhibitors	Potent CYP3A4 inhibitors

VKOR: vitamin K oxidase reductase; CYP: cytochrome P450; PCC: prothrombin complex concentrates; PPIs: proton pump inhibitors; P-gp: P-glycoprotein; h: hour.

Table 5. Summary of pharmacokinetics and pharmacodynamics of VKAs and NOACs

The following describes the characteristics of each one of them:

4.1. Dabigatran

It is a potent, selective and reversible thrombin [19]. Has been authorized, among other indications, in preventing stroke and systemic embolism in adult patients with non-valvular AF with one or more risk factors: stroke, transient ischemic attack or previous systemic embolism, left ventricular ejection fraction $<40\%$, symptomatic heart failure class ≥ 2 scale New York Heart Association (NYHA), age ≥ 75 years, age ≥ 65 years associated with diabetes mellitus, coronary artery disease or hypertension.

It is administered orally as a prodrug (dabigatran etexilate), which is rapidly transformed by intestinal bioconversion by esterases to its active form. With a bioavailability of 6.5% for adequate absorption requires an acidic microenvironment, provided by multiple tartaric acid microspheres present in the composition of the capsules. It reaches its peak plasma concentration 2 hours after administration, with slight delays in the presence of food (up to 4 hours) or in the postoperative period (up to 6 hours). Elimination half life is about 12-14 hours. Approximately 20% of the drug is metabolized in the liver and excreted by the biliary system, independent of cytochrome P450. Most of dabigatran (about 80%) is eliminated renally as unchanged, so that its administration is contraindicated in patients with severe renal impairment ($\text{CrCl} < 30 \text{ mL/min}$), requiring administered with caution (setting dose) in patients with $\text{CrCl} 30\text{-}49 \text{ mL/min}$. No other adjustments are required, except in patients over 75 years, which should decrease the dose. Administration is not recommended if liver enzymes are elevated (transaminases 2 times baseline). Are recommended a baseline measurement before starting treatment, in patients with severe renal impairment ($\text{CrCl} < 30 \text{ mL/min}$) or in cases of concomitant quinidine. The main adverse event of dyspepsia is related to the pharmaceutical formulation. Dabigatran need a daily oral dose and fixed (in two doses), independent of age, weight and race, with predictable effects and constant, without significant interactions with food or other drugs without coagulation controls. The absorption of dabigatran administration is reduced by approximately 25% with the co-administration of proton pump inhibitors. Dabigatran is contraindicated if the patient is treated with systemic ketoconazole, cyclosporine, itraconazole and tacrolimus, and should be used with caution if the patient is receiving other potent inhibitors of P-glycoprotein (P-gp): amiodarone, quinidine or verapamil.

4.2. Rivaroxaban

It is a potent and selective inhibitor of factor Xa [20], having peak plasma levels approximately 3 hours after oral ingestion. As dabigatran, is indicated for the prevention of stroke and systemic embolism in adult patients with non-valvular AF, with one or more risk factors: congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or attack transient ischemic. Bioavailability is 80-100% for the dose of 10 mg. Rapidly absorbed and reaches peak concentrations at 2-4 hours after ingestion. Its plasma half-life is 5 to 9 hours but increases markedly in people over 75 years from 9 to 13 hours. Not recommended for use in patients with $\text{CrCl} < 15 \text{ mL/min}$. The intensity of inhibition and, therefore, the genera-

tion of thrombin, is dose dependent, meaning that high doses could compromise coagulation. Has a dual route of elimination: 1/3 of the drug is eliminated via the kidney and 2/3 of the drug has hepatic metabolism. No interaction was observed with drugs such as acetylsalicylic acid, aluminum hydroxide and magnesium, ranitidine or naproxen. Its bioavailability increases with inhibitors of CYP3A4 and P-gp, such as ketoconazole and ritonavir, and diminishes with rifampicin. The bioavailability increases only marginally with food.

4.3. Apixaban

It is an oral potent inhibitor reversible and highly selective direct factor Xa [21]. Has greater affinity for factor Xa attached to clot which is free. Inhibits and delays the generation of thrombin without significantly affecting platelet aggregation. The oral bioavailability is approximately 50%. Rapidly absorbed and reaches peak concentrations at 3-4 hours after ingestion. Food intake does not affect the area under the curve or maximum concentration, and can be taken with or without food. The binding to plasma proteins is 87%. The half-life is 12 hours and is metabolized with CYP3A4/5. It is also a substrate binding proteins, P-gp. Not recommended for use with potent CYP3A4 inhibitors and P-gp and that may increase exposure to apixaban twice. With the administration of inductors opposite happens. Approximately 25% of the drug is excreted in the urine and more than 50% in the feces. The multiple elimination pathways suggest that even patients with moderate hepatic or renal impairment may be suitable for this anticoagulant. No need to monitor renal function.

4.4. Oral anticoagulants under investigation

Currently, there are other investigational drugs: direct thrombin inhibitor (AZD0837 and MCC977), direct inhibitors of factor Xa (betrixaban, YM150, edoxaban, eribaxaban, LY517717, TAK-442, otamixaban (parenteral) [22].

5. Monitoring of NOACs

The NOACs not require routine monitoring. However, there are situations where it is advisable to monitor selected patients as those with extreme weights, kidney failure or those who suffer thrombotic complications being treated with these drugs.

As a result of the occurrence of serious adverse effects, including severe gastrointestinal bleeding (81 cases) and deaths (260 cases) of bleeding in patients treated with dabigatran were published safety ratings by the rating agencies worldwide drug advising monitoring of renal function in patients with moderate renal impairment (30-50 mL/min) receiving dabigatran and in patients over 75 years. Rivaroxaban is contraindicated if CrCl <15 mL/min, and should be used with caution if is 15-30 mL/min.

Monitoring is also useful to evaluate the adherence to treatment (the omission of one or more doses puts the patient at risk of complications at an early stage) or when the patient needs to undergo an invasive procedure. When subjecting a patient to an invasive proce-

dures, it is important to note that the drug half-life (12-14 hours dabigatran, rivaroxaban 9-13 hours and apixaban 9-14 hours). If the invasive procedure has a low bleeding risk, it is sufficient to suspend the drug 24-36 hours before surgery and if no complications arise, resume anticoagulant treatment at 36-48 hours [23].

The ideal test for monitoring of direct thrombin inhibitors is the coagulation time of ecarin, with a linear relationship, and a good slope and discriminate levels of dabigatran in plasma. The problem is that it is non-standardized and few laboratories possess it.

The studies suggest that dabigatran monitoring will be done with a variant of thrombin time (TT). TT is very sensitive, with a linear relationship, but with a high slope, so that at low concentrations of dabigatran, TT extends above the detection limit of the coagulometer. It is a very good from a qualitative point of view, to assess adherence to treatment, but cannot quantify levels. The thrombin time will be a diluted thrombin time, marketed as Hemoclot®, which manages to improve the linear relationship with respect to TT and discriminate between low, intermediate and high dabigatran in plasma [24].

Monitoring of rivaroxaban will be done by a method chromogenic anti-factor Xa. This test is marketed as anti-Xa assay. Is a sensitive and accurate, useful to measure the maximum and minimum plasma concentrations of rivaroxaban [25,26].

6. Bleeding complications and antidotes

The fear of bleeding complications is one of the most prevalent obstacles in anticoagulant treatment in AF, especially cerebral hemorrhage.

These drugs have no specific antidotes which is a problem in patients who are at high risk of bleeding or hemorrhagic. Dabigatran is a dialyzable drug, which can eliminate up to 60% of the molecule in serum. Other possibilities include the use of activated coal and of neutralizing antibodies but are lacking in vivo experience. With respect to rivaroxaban is working in a variant of factor Xa would compete with the normal to factor Xa when joining rivaroxaban and thus the effect would be reversed.

In order to reverse the effect of NOACs designed a crossover trial, randomized, double-blind, placebo-controlled study included 12 healthy male volunteers. Received rivaroxaban 20 mg/12h or dabigatran 15 mg/12h for 2.5 days followed by a single bolus of 50 IU/kg of prothrombin complex concentrate (PCC) or similar volume of saline. The results concluded that the PCC completely and immediately reversed the anticoagulant effect of ribaroxaban but had no influence on the effect of dabigatran at the doses used in this study. These results should be analyzed with caution due to small sample size (12 patients) and the characteristics of the population that was part of the study (only male patients and healthy). [27]. Another study found the low doses of non-specific reversal agents (anticoagulant anti-inhibitor complex with non-activated factors II, IX and X and activated factor VII) appear to be able to reverse the anticoagulant activity of rivaroxaban or dabigatran. However, clinical evaluation is needed regarding haemorrhagic situations, and a meticulous risk-benefit evaluation [28]. The absence of normalization of coagulation tests not necessarily correlate with the absence of anti-haemorrhagic effect, as demonstrated in animal models [24].

Thus, in a patient treated with dabigatran and rivaroxaban that presents a mild bleeding complication, it is advisable to delay the next drug administration or discontinuation. If bleeding is moderate or severe, symptomatic treatment is indicated as mechanical compression standard, surgical hemostasis bleeding control procedure, blood products and hemodynamic support (packed red cells or fresh frozen plasma). In the case of very severe bleeding will require charcoal filtration or haemodialysis or administration of an agent for reversing the specific procoagulant effect, such as prothrombin complex, the prothrombin complex concentrate or activated recombinant factor VIIa. In this case, experience is limited.

7. Evaluation of scientific evidence, relevance and limitations of the study

It will analyze the scientific evidence, the limitations of design and the clinical relevance of the results of published clinical trials (RE-LY, ROCKET AF, AVERROES and ARISTOTLE). In general, these new drugs are at least equally effective and safer than warfarin, with the advantage of inducing a lesser extent intracerebral hemorrhages (Table 6).

	Dabigatran	Rivaroxaban	Apixaban	
	(RE-LY)	(ROCKET AF)	(AVERROES)	(ARISTOTLE)
Study design	Randomized open label	Multicenter, randomized, double-blind, double-dummy	Multicenter, randomized, double-blind, double-dummy	Multicenter, randomized, double-blind, doble-dummy
Number of patients	18.113	14.264	5.599	18.201
Mean age	71.5 years	73 years	70 years	70 years
Male:female ratio	63.6%: 36.4%	60%:40%	58.5%: 41.5%	64.7%: 35,30%
Follow-up period, years	2 years	1.9 years	1.1 years	1.8 years
Randomized groups	Dose-adjusted WA vs. blinded doses of DA (150 mg BID, 110 mg BID)	Dose-adjusted WA vs. RI 20 mg OD	AAS 81-324 mg OD vs. API 5 mg BID	Dose-adjusted WA vs. API 5 mg BID
Mean CHADS ₂ score	2.1	3.5	2.1	2.1
Primary endpoint: stroke and systemic embolism (in % per year)	1.71% WA 1.54% DA 110mg 1.11% DA 150mg	2.42% WA 2.12% RI	3.9% AAS 1.7% API	1.60% WA 1.27% API
Major bleeding events	3.57% WA 2.87% DA 110mg 3.32% DA 150mg	3.45% WA 3.6% RI	1.2% AAS 1.4% API	3.09% WA 2.13% API

BID: twice daily; OD: once daily; WA: warfarin; DA: dabigatran; RI: rivaroxaban; API: apixaban; AAS: acetylsalicylic acid

Table 6. Summary of the main clinical trials with NOACs

7.1. Dabigatran

The RE-LY is the largest study of AF (Randomized Evaluation of Long term anticoagulant therapy) [29]. The primary endpoint was to establish non-inferiority of dabigatran etexilate compared with warfarin for a minimum of 1 year follow-up to a maximum 3 years, median follow-up of 2 years in 18,113 patients with nonvalvular AF (mean age 71 years) with at least one of the following risk factors for stroke: previous stroke or transient ischemic attack, left ventricular ejection fraction <40%, symptoms of heart failure class 2 or higher NYHA, age >75 years or 65-74 years associated with diabetes mellitus, hypertension or coronary artery disease. Meanwhile, we excluded patients with: severe valvular disease, recent stroke, (a condition that increases the risk of bleeding), CrCl <30mL/min, active liver disease and pregnancy.

Patients were randomized into three treatment arms: 110 mg dabigatran twice daily, dabigatran 150 mg twice daily and adjusted dose warfarin (INR 2.0-3.0). In patients randomized to receive warfarin, the average percentage of time within therapeutic range (INR = 2.0-3.0) were 64.4%. Dabigatran was administered in a blinded fashion in both treatment arms; the administration of warfarin was opened. In all branches were allowed concomitant use of acetylsalicylic acid or other antiplatelet agent. Also allowed the concomitant use of quinidine with dabigatran during the first two years of the study, when it was prohibited by the possibility of interaction with dabigatran.

The primary endpoint studied was the appearance of stroke or systemic embolic event and the primary safety outcome was the occurrence of serious bleeding. The criterion for non-inferiority was established that the upper limit of confidence interval (CI) 97.5% of the relative risk of occurrence of stroke or systemic embolism with dabigatran compared to warfarin was <1.46. The non-inferiority margin was established from the results of a meta-analysis with VKAs against a control treatment in patients with AF. The value of 1.46 represents half of the 95% CI relative risk estimated effect on warfarin control. All analyzes were by intention to treat (ITT).

The results for the primary endpoint were: onset of stroke or systemic embolism in 182 patients in the group treated with dabigatran 110 mg (1.53% per year), in 134 patients with dabigatran 150 mg (1.11% per year) and 199 patients with warfarin (1.69% per year). The two treatment groups dabigatran meet the criteria for non-inferiority to be the upper limit of 95% relative risk less than 1.46 (1.11 in the first case and 0.82 in the second), but only dabigatran 150 mg was associated with lower rate of stroke and embolic events than warfarin (RR = 0.66, 95% CI 0.53 to 0.82), dabigatran 110 mg was similar to warfarin.

Regarding security, in the RE-LY study, the treatment with dabigatran was associated with an "annual rate" of major bleeding (defined as bleeding associated with a decrease in hemoglobin of at least 2g/dL, transfusion of at least 2 units of whole blood or symptomatic bleeding in a critical organ or area (intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, bleeding or intra-articular pericardial bleeding). Severe bleeding was divided in turn into intracranial hemorrhage (intracerebral or subdural) and extracranial (gastrointestinal or not gastrointestinal). The major bleeds

were categorized as critical if they met one or more of the following criteria: fatal bleeding, symptomatic intracranial bleeding, reduced hemoglobin of at least 5g/dL, transfusion of at least 4 units of whole blood or packed red cells, bleeding associated with hypotension requiring the use of intravenous inotropic agents, bleeding required surgery) of 2.71% for dabigatran 110 mg, 3.11% for dabigatran 150 mg and 3.36% for warfarin. No significant difference in major bleeding between dabigatran 150 mg twice daily and warfarin; on the contrary, dabigatran 110 mg twice daily resulted in less major bleeding, RR 0.80 (95% CI: 0.69 to 0.93) $p = 0.003$. As for minor bleeding (defined as all non-major bleeding definition, previously expressed) annual rates were 13.16%, 14.84% and 16.37% for dabigatran 110 mg, dabigatran 150 mg and warfarin, respectively. In this case, the risk was significantly lower for dabigatran 110 mg [RR = 0.79 (95% CI: 0.74 to 0.84)] and dabigatran 150 mg [RR = 0.91 (95% CI: 0.85 to 0.97)] with respect to warfarin and was higher for dabigatran 150 mg versus dabigatran 110 mg [RR = 1.16 (95% CI: 1.08 to 1.24)]. Similarly, the risk of intracranial hemorrhage was significantly lower for dabigatran 110 mg [RR = 0.31 (95% CI: 0.20 to 0.47)] and for dabigatran 150 mg [RR = 0.40 (95% CI: 0.27 to 0.60)] against warfarin and no significant differences between the two doses of dabigatran. However, the risk of bleeding severe gastrointestinal was significantly higher in the group treated with dabigatran 150 mg versus warfarin [RR = 1.50 (95% CI: 1.19 to 1.89)] and versus dabigatran 110 mg [RR = 1.36 (95% CI: 1.09 to 1.70)]. The overall mortality (4%) showed no significant differences ($p=0.051$) between dabigatran 150 mg twice daily and warfarin, although the rate of deaths from vascular causes was significantly lower in the group treated with dabigatran 150 mg twice daily ($p=0.04$).

The results of dabigatran 150 mg dose showed that the benefit is somewhat larger than warfarin in $\text{CHADS}_2 \geq 2$ while the hemorrhagic risk is similar in both groups. In $\text{CHADS}_2 = 0-1$ the benefit is also somewhat higher than warfarin while the hemorrhagic risk is somewhat lower. A dose of 110 mg the benefit and bleeding risk is similar in every category of CHADS_2 except for the category $\text{CHADS}_2 = 0-1$ where the risk is somewhat lower.

Dropout rates were higher with dabigatran: 14.5% with dabigatran 110 mg, 15.5% with 150 mg dabigatran and 10.2% with warfarin the first year and 20.7% with dabigatran 110 mg, 21.2% with dabigatran 150 mg and 16.6% with warfarin the second year. There were more withdrawals due to serious adverse events with dabigatran (2.7%) than with warfarin (1.7%).

The incidence of myocardial infarction was higher with dabigatran 110 mg twice daily (0.72%, $p = 0.07$) and dabigatran 150 mg twice daily (0.74%, $p = 0.048$) than warfarin (0.53%), having calculated that myocardial infarction could occur for every 500 patients treated with dabigatran. With the correction of the results of RE-LY study the differentiation in the apparition of the myocardial infarction no longer statistically significant. However, a meta-analysis of 7 trials published recently concluded that the use of dabigatran is associated with an increased risk of myocardial infarction or acute coronary syndrome in a broad spectrum of patients compared with VKAs, antiplatelet or placebo [30]. Although the absolute risk may be low, it is necessary to closely monitor patients and the importance of improving pharmacovigilance systems [31].

7.2. Rivaroxaban

The ROCKET AF study (Rivaroxaban Once daily, oral, direct factor Xa inhibition Compared with vitamin K for prevention of stroke Antagonism and Embolism Trial in Atrial fibrillation) compared the clinical outcomes of rivaroxaban at doses of 20 mg/day (15 mg/day for those with estimated CrCl 30-49 mL/min) with warfarin dose-adjusted INR in patients with AF. It is a prospective, randomized, double-blind, parallel group, multicenter, event-based and non-inferiority which involved 14,264 patients. The patients had high risk of stroke (CHADS₂ score >2 in 90%) [32, 33]. It was shown that the new anticoagulant was non-inferior to warfarin in the combined primary endpoint, which included stroke and systemic embolism. Embolic events were presented to the central nervous system or systemic 1.7% per year in the rivaroxaban group compared with 2.2% in the warfarin group, which has met the criterion for non-inferiority. However, ITT analysis showed that superiority failed. The incidence rates of primary safety outcome (major bleeding episodes and no clinically relevant non-major bleeding) were similar in both treatment groups but, with rivaroxaban, there was a significant reduction in fatal bleeding, as well as an increase in gastrointestinal bleeds and bleeds requiring transfusion. Premature discontinuation of treatment was more common with rivaroxaban (23.9%) than with warfarin (22.4%). The duration of follow-up was 12-32 months.

7.3. Apixaban

The AVERROES study is a multicenter, randomized, double-blind and double-dummy (Apixaban Versus Stroke Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) comparing apixaban 5 mg twice daily (2.5 mg twice daily in patients ≥80 years, weight ≤60 kg or with a serum creatinine ≥1.5 mg/dL) versus acetylsalicylic acid 81-324 mg daily in 5,599 patients with AF at high risk of stroke and without indication for treatment with VKAs or by difficulties in anticoagulation or because the patient refused anticoagulation therapy.

The trial was stopped early, after about a year after intermediate analysis showed a significant reduction of 50% in the risk of stroke. There were 1.6% of cerebral and systemic embolic events in the apixaban group compared to 3.5% in the acetylsalicylic acid group. The frequency of bleeding was similar (1.4 versus 1.2% per year); there was no difference between patients treated with apixaban and acetylsalicylic acid on the incidence of major bleeding, intracranial hemorrhage, or gastrointestinal bleeding even if appreciate a significant increase of the total number of bleeding (major and minor). Mortality was lower in the apixaban group (3.5% per year) than acetylsalicylic acid (4.4% per year), results that corroborate the greatest benefit of anticoagulant therapy in AF. In patients with AF for whom therapy is inadequate VKAs, apixaban reduces the risk of stroke or systemic embolism without increasing the risk of major bleeding or intracranial hemorrhage [34].

The ARISTOTLE study is a multicenter, randomized, double-blind and double-dummy (Apixaban for Reduction in Stroke and Other Events in Atrial Fibrillation thromboembolic) comparing apixaban 5 mg orally twice daily (2.5 mg twice daily in patients ≥80 years, weight ≤60 kg or with a serum creatinine ≥1.5 mg/dL) versus adjusted-dose warfarin (INR

2.0-3.0). The study was designed to demonstrate non-inferiority of apixaban compared to warfarin. Analysis is performed of non-inferiority trial and after an analysis of superiority. The primary efficacy endpoint was the composite of stroke and systemic embolism. The primary safety outcome was major bleeding. The mean duration of follow-up was 1.8 years. The study included 18,201 patients with AF at high risk of systemic and cerebral embolism. Cerebrovascular events were 1.27% per year in the apixaban group versus 1.60% in the warfarin group ($p < 0.001$ for non-inferiority and $p = 0.01$ for superiority), bleeding of 2.13% versus 3.09% for year ($p < 0.001$), respectively. Significantly decreased the incidence of any type of bleeding, major bleeding and intracranial bleeding and not change the frequency of appearance of gastrointestinal bleeding. Mortality from all causes was 3.52% versus 3.94%, demonstrating the superiority of apixaban compared to warfarin in preventing stroke or central nervous system systemic fewer bleeding complications and lower mortality. Cerebrovascular events in patients with $\text{CHADS}_2 \geq 3$ were 1.9% per year in patients treated with apixaban compared to 2.8% per year in patients treated with warfarin; $\text{CHADS}_2 = 0-1$, 0.7% per year versus 0.9% per year and $\text{CHADS}_2 = 2$, 1.2% per year versus 1.4% per year. In patients under 65 years no difference in efficacy between both groups, but in patients over 65 years the difference is 0.9%.

In conclusion, treatment with apixaban compared to warfarin in AF patients with more than one risk factor reduces the incidence of stroke and systemic embolism by 21% ($p = 0.01$), reduced major bleeding by 31% ($p < 0.001$) and reduces mortality by 11% ($p = 0.047$) [35].

7.4. Methodological limitations of studies

Taking into account the results of the studies so far mentioned, there are some differences in patients enrolled in the RE-LY, the ROCKET AF, the AVERROES and the ARISTOTLE. The study population ARISTOTLE included subjects both with a CHADS_2 score of 1 point and those of scores. In the RE-LY incorporated population according to the CHADS_2 score was mild-moderate risk (32% of patients with a CHADS_2 of 3 to 6 points) and the ROCKET-AF population included was moderate to severe (87% patients had a CHADS_2 risk score (of 3 to 6 points) which makes comparisons difficult between these studies. RE-LY and ARISTOTLE have similar characteristics on patient demographics (age, gender...) and in the risk of stroke (average CHADS_2 score of 2.1). However, ROCKET AF patients were slightly older (median age 73 years), were at high risk of stroke (mean CHADS_2 score of 3.5), and 55% were a secondary prevention population [36]. Exclusion criteria of patients pose leave out AF patients eligible for treatment with VKAs, as those who have suffered a recent stroke or those with liver enzyme elevations 2 times the upper limit of normal.

They are non-inferiority studies. The European Medicines Agency (EMA) recommended in these studies an ITT and per protocol analysis (PP). In the RE-LY is not a PP (which could favor dabigatran) and also the non-inferiority margin has questionable clinical relevance. The superiority analysis showed more effectively to the highest dose of dabigatran. The ROCKET AF results PP were slightly significant in favor of rivaroxaban while ITT results demonstrate the non-inferiority of rivaroxaban with warfarin. ARISTOTLE and AVERROES studies also reflect the non-inferiority of apixaban versus warfarin however, the results were

better in the Asian population and whether they may be due to different effectiveness of the drug in this population or whether there was any element related to the study design to justify these differences. In addition 35% of patients with warfarin were outside the therapeutic range, implying poor control within the clinical trial.

In the RE-LY treated with warfarin branch has an open design which favors the appearance of bias. It would be necessary to make a double-blind design with warfarin (this limits the internal validity of the test. Both the ROCKET AF as ARISTOTLE was double blind). Dabigatran is necessary to take it twice a day. This helps to foster low compliance. Only in the RE-LY study, where patients are monitored closely, the dropout rate was 20.7% with dabigatran 110 mg and 21.2% with dabigatran 150 mg at two years. The same can happen with rivaroxaban and apixaban, the absence of regular checks can relax patients. Poor adherence to treatment would leave the patient exposed because the anticoagulant effect almost completely disappear (are drugs with short half-life). Unlike NOACs, with VKAs is necessary to periodically checks to confirm that are within the therapeutic range, a fact that is achieved in 58-65% of cases. The compliance rate is not always the desired (30% dropout) [37]. A subgroup analysis and an FDA report further notes that the benefit of dabigatran is significant only in those centers where patients have poorer control with warfarin. The results of the centers with better INR control with warfarin did not show superiority of dabigatran 150 mg versus warfarin. Improving the monitoring of the INR, the benefits seen for dabigatran compared to warfarin decreased. The ARISTOTLE study showed no superiority of apixaban in terms of INR control. The ROCKET AF study the level of INR of warfarin group was very low which has reduced the conviction to conclusions (55% versus 64.4% of RE-LY and 62% of ARISTOTLE).

Regarding the dose to be administered there are disputes between the position of the FDA (Food and Drug Administration) and EMEA. FDA has approved only high doses of dabigatran (150 mg/12h). Argued that low doses of dabigatran (110 mg/12h), the demonstration of non-inferior to warfarin, is not as conclusive as with higher doses. In addition to high doses reduces episodes of stroke but increase bleeding. The lower dose may be indicated in patients with increased risk of bleeding. The RE-LY study could not identify a subgroup of patients who would benefit from low dose.

Recently has been published a study that try to perform an indirect comparison analysis of NOACs regarding its efficacy and safety [36]. Despite the limitations of indirect comparison study (differences in patient population, differences in definition of major bleeding and unblinded versus nonblinded/double-blinded comparisons), no profound significant differences were found in efficacy between apixaban and dabigatran (both doses) or rivaroxaban. Dabigatran 150 mg twice daily was superior to rivaroxaban for efficacy (with less stroke and systemic embolism (by 26%), as well as less hemorrhagic stroke (by 56%, $p=0.039$ and non-disabling stroke (by 40%, $p=0.038$). There were no significant differences in preventing stroke and systemic embolism for apixaban versus dabigatran (both doses) or rivaroxaban, or rivaroxaban versus dabigatran 110 mg twice daily. For the ischemic stroke, there were no significant differences between the NOACs. Major bleeding was significantly lower with apixaban versus dabigatran 150 mg twice daily (by 26%) and rivaroxaban (by 34%), but was

not significantly different from dabigatran 110 mg twice daily. There were no significant differences between apixaban and dabigatran 110 mg twice daily. Apixaban had lower major or clinically relevant bleeding (by 34%) versus ribaroxaban. When compared with rivaroxaban, dabigatran 110 mg twice daily was associated with less major bleeding (by 23%) and intracranial bleeding (by 54%). No significant differences myocardial infarction events between dabigatran (both doses) and apixaban. However, only a head-to-head direct comparison of the different NOACs would be able to answer the question of efficacy/safety differences between them in the prevention of stroke in AF.

An advantage of the NOACs proposes absence monitoring. Instead, experts recommend that in chronic treatment with narrow therapeutic window and potentially serious complications (stroke/hemorrhage), lack of control is much more harmful than adequate control. The regular monitoring to adjust and correct the treatment regimen and distinguish, if complications, treatment failure or lack of adherence.

Are emerging post-marketing data on major bleeding and death with dabigatran: Japan (5 deaths and 81 cases of severe reactions), Australia (7 deaths and 24 serious reactions) and Europe (21 deaths). In the subsequent reanalysis of data from the RE-LY was a higher incidence of stroke, myocardial infarction and major bleeding compared to those initially reported, in those over 75 years more extracranial bleeding [38].

No specific antidote proved effective, which hinder the resolution of bleeding emergencies. In addition, the high cost compared to VKAs is a major limitation. Have been published some cost-effectiveness data for dabigatran, and dabigatran appears to be cost-effective for most patients, except in those with very well-controlled INRs [39,40].

8. Current recommendations - Caution

With the entry into force of the NOACs is emerging a new era in anticoagulant therapy. These drugs are proving to be at least as effective as VKAs without coagulation monitoring, with a reduction of more serious bleeding (intracranial) and with far fewer potential drug interactions and food.

But not all advantages. These drugs also have drawbacks and uncertainties about their safety, and to their clinical evaluation is needed before definitive recommendations on its use. Lack of specific antidotes which is a problem in patients who are at high risk of bleeding or hemorrhage (to negate the effect is included prothrombin complex or factor specifying of hospitalization and increasing costs associated with treatment), contraindicated in patients with renal impairment, short half-life (limits its use in patients with poor adherence), with higher incidence of gastrointestinal bleeding and high cost. In addition, there are no safety data long-term selected populations and are generating security alerts.

In the initial euphoria, with the placing on the market NOACs, it is necessary to proceed with caution. A few years ago, another promising thrombin inhibitor, ximelagatran, which

showed that it was at least as effective and safe as warfarin for stroke prevention in AF patients, had to be withdrawn by its liver toxicity after creating many expectations [41].

All this raises questions: Is it appropriate to change oral anticoagulation with warfarin or acenocoumarol to a patient controlled? Can these NOACs impact in preventing thromboembolism, especially stroke, in patients with AF? Will we monitor patients? Is it acceptable despite the cost of not requiring monitoring? How do we assess adherence?

The Canadian Cardiovascular Society (CCS) [41], the European Society of Cardiology (ESC) [13,42,43], the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA) and the Heart Rhythm Society (HRS) recently updated their guidelines for the treatment of patients with AF. The guidelines report that when OAC is recommended, one of NOACs should be considered rather than adjusted-dose VKAs (INR 2.0-3.0) for most patients with AF, when studied in clinical trials to date. The NOACs provide better efficacy, safety and comfort compared to the OAC with VKAs. There is insufficient evidence to recommend one over another NOACs, although some patient characteristics, drug tolerability and compliance and the cost may be important factors in the choice of agent. As experience with NOACs is still limited, strict adherence to the recommended indications approved and aftercare marketing.

The short half-lives of NOACs compared with that do not require routine monitoring of coagulation, causes adherence is very relevant. Poor adherence increase morbidity, mortality, and in turn, overall health costs. Poor compliance can be a particular problem in patients with AF who often has no symptoms. Warfarin has a half life of 40 hours, so that a slight failure of the patient will have a negligible effect on clotting compared to a drug with short half life.

In this context it is useful to provide a meta-analysis of clinical trials in patients treated with VKAs. The results showed that patients who achieved a treatment well stabilized, the determination home ("self") for the same patient resulted in a significant reduction in mortality and morbidity from thromboembolism without increasing the risk of serious bleeding in a selected group of motivated adults [44]. The results of a subsequent meta-analysis showed a reduced risk of thromboembolic disease, but no major bleeding or mortality [45].

The NOACs will not replace the classical therapy of oral anticoagulant therapy automatically. As a general rule, you should not change the anti-clotting drug to patients who are currently well controlled with acenocoumarol or warfarin and have an INR within the therapeutic range. The NOACs be reserved for those who have not attained regular values (between 2.0 and 3.0) the INR by more than 60% of the determinations despite good adherence to the prescription by the patient (for drug interactions that hinder the anticoagulation control, special dietary or digestive disorders that affect the pharmacokinetics of VKAs. Should not switch to dabigatran in patients with inadequate control of INR and nonadherence) [46], for those with mobility problems or difficulties traveling to determine the INR and for which have allergies or intolerance to the adverse effects of OACs. An anticoagulant is, by definition, a drug of high risk. And a patient with AF generally well. The fact that new drugs is involved uncertainty about their safety in the short and long term. You have to define more precisely the role of new drugs, considered as therapeutic innovations, and they are accompanied by a careful evaluation of their efficacy and toxicity in actual practice.

The experience of use and new studies will determine the profile of patient who may benefit most from these new therapies. Be taken into account: stage of disease, the left atrial size, presence and severity of underlying disease, therapeutic approaches and patient preferences. It also assessed the patients' age, presence of comorbidities and polypharmacy. Advanced age increases the impact of AF on the embolic risk. The elderly population is particularly vulnerable to stroke in AF. In addition, stroke patients with AF have increased mortality and the consequences are devastating.

9. Conclusions

Clinical trials available to date show that NOACs are at least as effective and safe as VKAs. However, although the evidence is a useful tool, it should await the development of major clinical studies in different populations to see the real benefit of these drugs. The main problems are lacking proven methods of monitoring, so that in certain patients (elderly, low weight, renal or liver impairment...) fixed dose may not be therapeutic. There are no conclusive data on its long-term safety and are already generating security alerts in different countries. No studies support the use of an antidote in case of overdose with bleeding. There is no justification to replace the current oral anticoagulant treatment by the NACOs in patients that conventional treatment is well tolerated and its controls are stable. Its high cost limits the use of these drugs. Independent trials are needed to precisely define the role of new drugs in patients with non-valvular AF.

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Not have any conflict of interest relating to the information in this article.

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