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What role can dabigatran, rivaroxaban and apixaban play in the future?

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abstract

Objective: to evaluate the role of new anticoagulant agents in the treatment of non valvular atrial fibrillation. **Methods:** a critical appraisal was made based on the data from clinical trials available on Medline and the data bases of the FDA and EMA, updated up to November 30th, 2011. **Results and conclusions:** dabigatran, rivaroxaban and apixaban have shown to be non inferior to warfarin. However these drugs might not be indicated in a considerable group of patients, especially the elderly and those with important liver or renal impairment. The long-term safety profile is unknown and safety alerts have been published in different countries. The high cost of these agents may limit their use. Use of the new anticoagulants remains unjustified in those patients who tolerate warfarin treatment and whose monitoring is stable. Independent clinical trials are needed to define the role of new anticoagulant agents in the treatment of non valvular AF. **Key words:** atrial fibrillation, dabigatran, rivaroxaban, apixaban, oral anticoagulants.

Will the current anticoagulants be replaced by other new drugs?

Over the last few years a significant change has taken place with regard to the management of anticoagulant drugs. On the one hand, there has been an important increase in their prescription given that more patients are under anticoagulant therapy. On the other hand, the use of anticoagulants has passed from hospital based prescription to primary care, where most indications and monitoring takes place for the majority of patients.

Criteria for anticoagulation of patients with heart valves or for secondary prevention of embolic events have not changed. However, the indications for the prophylaxis of venous thromboembolism have increased after surgery, especially those interventions affecting the knee and hip. The use of anticoagulants for the prevention of stroke in patients with atrial fibrillation (AF) with non-valvular disease has also been approved increasing the age limit at which it is indicated.

With the aim of producing a beneficial anticoagulant effect, drugs such as heparin and derivatives are employed in the acute phase of some processes. After the acute phase, oral anticoagulants may be given to maintain this effect in the long term. The use of these drugs, their doses, contraindications, interactions, etc, are well known by the clinical physician. However, in recent years new drugs have been developed that may displace conventional anticoagulants in some of their current indications. With these new drugs it is expected to obtain a more convenient form of administration, a more foreseeable effect and better results with regard to safety for the patient.

To get an idea of the dimension of the issue, in Navarre, with a population of approximately 600,000 inhabitants, 11,637 patients received low molecular weight heparin during 2010, with a DHD = 4.4 (number of defined daily dose per 1000 inhabitant per day). On the other hand, 12,043 patients were treated with oral anticoagulants (warfarin and acenocumarol), DHD = 7.5. These figures do not account for hospital prescriptions of both drugs.

Indications for anticoagulant therapy. Current situation

Arterial or venous thromboembolic disease is an important cause of morbidity and mortality in our setting. In 2008, the National Institute of Statistics reported that in Navarre[1], there were 277 patients discharged from hospital with phlebitis, embolism and venous thrombosis as a first diagnosis, which generated 2,090 hospital days. On the other hand, 1,682 patients were discharged due to cerebrovascular disease, that generated 19,601 stays. The publication on pulmonary thromboembolism by the Society of Internal Medicine[2] reported that between 1999 and 2003 the number of patients discharged in Spain after pulmonary embolism was 39,805, and a first diagnosis of deep vein thrombosis was made in 30,120 patients, while as a second diagnosis, the figure reached 64,715 cases.

Stroke was the most important cause of disability given the residual injuries that may incur. When analysing aetiology, of the total number of ischemic stroke (20% of the causes of stroke are of undefined origin), 20% of them clearly identified emboli originating from the heart, while 50% are of atherothromboembolic origin[3]. Both the embolic and atherothrombotic strokes can be managed with prophylactic anticoagulant therapy, either temporary or permanent.

On the other hand, the classical indications for anticoagulation are maintained such as in patients with mechanical heart valves, or patients with heart valve disease, especially cases affecting the mitral valve, and patients presenting atrial fibrillation who have suffered a stroke[4]. In addition, those patients who have already suffered from a thromboembolic event are also candidates for antithrombotic therapy, at least for a period of time[5].

The coagulation process

The steps involved in hemostasis include platelet activation, the coagulation cascade per se and fibrinolysis. In this article we will concentrate on the intervention of the second process. In the appendix 1 a summary is given of the coagulation cascade and the sites at which anticoagulants act upon the process[6].

The effect of these drugs is based on partial or total inhibition of one of the proteins involved in the coagulation process. Oral antithrombotic therapy acts upon the initial steps (factors II, IV, IX and X). Both heparin and low molecular weight heparin sodium act by inhibiting prothrombin action. The new class of anticoagulants act at different sites during the phase of propagation of the thrombus. While rivaroxaban and apixaban act at factor Xa, dabigatran and ximelagatran act upon factor IIa, blocking the coagulation cascade as direct inhibitors of thrombin.

Drugs currently used and their most frequent indications.

Since the 1990s heparin has been employed as an anticoagulant[7]. It consists of a chain of polysaccharides with a molecular weight of between 4,000 and 40,000 daltons which organically acts as a cofactor of antithrombin III, the natural inhibitor of thrombin. It is found in the lung, liver, skin and mastocytes. Industrial extraction originates from bovine lungs and the intestinal mucosae of pigs. Besides its action on platelets[8] and on the system of fibrinolysis, this drug inhibits the action of various coagulation factors (IXa, Xa, XIa, XIIa). It is administered intravenously and requires monitoring. Only part of the molecule is active and can produce thrombocytopenia, especially if therapy is prolonged.

A few years later, the heparin molecule was modified maintaining its active structure but reducing the molecular weight by eliminating protein chains with no pharmacological effect. This led to a new class of low molecular weight heparin which maintains the same action mechanism with less collateral effects, and bears some more additional advantages including a more comfortable administration regimen, a subcutaneous route and no monitoring requirements.

Fondaparinux is a synthetic antithrombotic agent related to heparin, derived from short chain polysulphate polysaccharides that selectively block factor Xa and therefore the production of thrombin. It is administered by subcutaneous injection and does not have any direct effect on platelets.

The new anticoagulant agents have shown non-inferiority versus warfarin

Bivalirudin[9] is a specific and direct inhibitor of thrombin, similar to the natural anticoagulant hirudin, which reversibly inhibits the catalyst site of thrombin, neutralizing its effects, including the thrombin contained in already formed clots. By the reversible union with thrombin, the anticoagulant effect of bivalirudin disappears soon after interruption of its administration (half-life of approximately 25 minutes). Unlike heparin, bivalirudin does not require antithrombin III for its activation, nor is its effect inhibited by the platelets factor IV. It is indicated in patients undergoing coronary intervention in the course of unstable angina[10].

Conventional oral anticoagulants are widely used drugs, especially in primary care and are indicated as prophylaxis for venous thromboembolism (VTE) or arterial embolic phenomena. They have been administered orally since the 1960s. They act by inhibiting vitamin K and their inconveniences include the need to regularly monitor blood levels, the interaction with other drugs, and the need to establish anticoagulation with some other type of heparin when the patient is to undergo any surgical procedure or vascular intervention.

It is evident that each drug has its own advantages and inconveniences. The greatest advantage is that they are drugs with known action mechanisms and well known side effects. The most important inconveniences are related to variability in action, the need for monitoring, and interactions. Table 1 shows a summary of the advantages and inconveniences of each drug.

Risks of venous thromboembolism

When deciding on offering anticoagulant therapy in the prevention of venous thromboembolism (VTE), the clinician should evaluate the patient's risk of suffering from VTE, while also considering the increased risk of bleeding related to antithrombotic therapy.

Table 1. Advantages and inconveniences of the different anticoagulants.

DRUG	ADVANTAGES	INCONVENIENCES
Heparin sodium	Fast action Effective Use widely known	Can produce thrombocytopenia. Parenteral route. Risk of bleeding. Variable bioavailability (only 30% of the molecule presents anticoagulant effect) which can produce an unpredictable response. It is not inhibited by coagulation factors. Requires monitoring.
Low molecular weight heparins	Administered 1-2 times a day No monitoring required Effective Use widely known	Parenteral route. Risk of bleeding in case of renal impairment. Risk of thrombocytopenia (less than heparin sodium). Indirect action via antithrombin. Not inhibited by coagulation factors.
Fondaparinux	One daily dose No monitoring required Effective	Parenteral route. Risk of bleeding in case of renal impairment. Indirect action via antithrombin. Not inhibited by coagulation factors.
Bivalirudin	Rapid anticoagulation effect Indicated during coronary intervention Does not produce thrombocytopenia in patients who have suffered from heparin induced thrombocytopenia	Intravenous route. Monitoring of its effect on coagulation parameters required while administering. Antidote available. Dose adjustments required in patients with renal impairment.
Antivitamin K drugs	Oral route Effective Use widely known	Requires periodic dose monitoring. Presents interactions with drugs. Changes in management strategy required in case of surgery.

Table 2. Factors that increase VTE risk.

Active cancer condition or current treatment.
Age > 60 years.
Admission in critical condition.
Evidence of dehydration.
Known thrombophilia.
Obesity
Co-morbidity (heart failure, metabolic, endocrine or respiratory disorders, active infection)
Personal or first grade family history of VTE, estrogen contraceptive treatment, or hormone replacement therapy.
Varicose veins with phlebitis.

Table 3. Summary of some of the factors that may increase the risk of bleeding in patients under anticoagulant therapy.

Current active bleeding.
Suffer diseases that bear a risk of bleeding (eg, acute hepatic failure).
Patients under anticoagulant therapy and with a INR>2.
A lumbar puncture performed in the last 4 hours or an expected puncture during the next 12 hours.
Acute stroke.
Thrombocytopenia (platelet count < 75,000/mm^3).
Uncontrolled systolic high blood pressure (≥ 230/120 mmHg).
Untreated hereditary hemorrhagic disorders (eg, haemophilia or Von Willebrand disease).

In general terms we can define major risk for VTE in those patients who:
· present a clinical problem and whose mobility has been or will be limited for the next three or more days.
· undergo a surgical intervention or orthopedic procedure in which:
· the anaesthesia lasts for more than 90 minutes.
· surgery involves the pelvis or lower extremities and lasts for more than 60 minutes.

Along with the intrinsic risk of the surgical process involved, other additional risk factors should be taken into account and are related to the patient[11] (table 2). On the other hand, the decision process should be made on an individual basis when considering the risk of suffering from a hemorrhagic complication (table 3). The evaluation of these aspects: underlying disease, risk of VTE and risk of bleeding can help make a decision on initiating or not anticoagulant therapy, the choice of drug to be employed, and the duration of treatment.

New antithrombotic drugs. A brief description

A brief review of the pharmacological characteristics of some of these new agents is outlined below.

Direct inhibitors of factor Xa

At the moment there are a number of drugs in this class that are under the evaluation phase, others have approved indications or are also in the phase of extending their indications. These agents, given orally, are effective anticoagulants and include razaxaban, apixaban, and rivaroxaban. Some of them are in phase II of development (LY-517717, YM-150, etc)[12].

The bioavailability of **rivaroxaban** administered orally is approximately 80% with a half-life of about 9 hours. The habitual dose is 10 mg daily, and this drug does not require dose adjustments or monitoring of coagulation. It interacts with ketoconazole, macrolide antibiotics, and protease inhibitors.

In laboratory studies it has been observed that rivaroxaban does not produce platelet activation or aggregation in presence of antibodies that induce thrombocytopenia originating from cases of heparin induced thrombocytopenia. This advantage can support the use of these agents in patients presenting this problem[13].

Apixaban is absorbed orally and its average half-life is 12 hours, its renal elimination is 25% while the rest is excreted through the liver or in the form of meta-bolites[14].

Direct thrombin inhibitors

This class of drugs is also administered orally. Odiparcil was suspended in phase II and ximelagatran was also withdrawn due to safety issues. Currently, dabigatran is on the market for the prevention of VTE and its indication in patients with atrial fibrillation has just been approved.

Ximelagatran was the first commercialized drug to be administered orally. It is a prodrug which metabolizes rapidly to melagatran which binds reversibly to thrombin. Its clinical efficacy was evaluated in the prevention of thromboembolic phenomena after orthopedic surgery, but its commercialization was halted due to the adverse effects observed, especially liver toxicity[15].

Dabigatran is administered orally twice daily. It is eliminated unaltered mainly through the kidney (80%), and therefore its use is limited in patients with renal impairment[12].

Table 4 shows a summary of some of the most important pharmacokinetic characteristics of apixaban, dabigatran and rivaroxaban[6]. Some of the interactions observed are also described[16].

New anticoagulants for the prevention of stroke in relation to atrial fibrillation

In the previous section, we considered thromboembolic management in the acute phase and thus, short term treatments. Now we will look at different strategies and arguments that support long term antithrombotic therapy. Atrial fibrillation (AF) is the most prevalent arrhythmia in our context, present in 10.3% of patients over 65 years of age and who suffer from hypertension[17].

The clinical implications of AF are firstly hemodynamic, with the habitual symptoms that announce its apparition, and secondly AF presents the risk of embolic events. An estimation of the risk of embolism is made in those patients with structural heart disease (valvular or ischemic). If no structural cardiac disease exists, then the estimation of embolic risk is carried out with the CHADS2[18] score which evaluates age (older than 75 years), a history of heart failure, hypertension under treatment, diabetes, or history of embolism, the latter

The safety profile is unclear and safety alerts have been published in different countries

presenting twice the value assigned to the other variables. With this score a classification of six levels is established, where those who present ≥ 2 points bear a significant risk of embolism.

However, in the last guidelines issued by the European Society of Cardiology on the management of AF, this evaluation was modified, including a new estimation of risk[11]. This modification considers age ≥ 75 years, or history of embolism as "major" risk factors assigning them with twice the value of other factors. The other factors mentioned with regard to the CHADS2 also included as "not major" include: female, age between 65-74 years, ventricular ejection fraction ≤ 0.40 and presence of vascular disease[20,21]. The nomenclature of this index has also changed and is now denominated by its acronym, CHA2DS2-VASc. Based on this classification, we can estimate that patients with a score of ≥ 2 points present a risk higher than the 2.2% risk of embolic events per year. In this case, anticoagulant therapy is indicated in place of antiplatelet therapy (the theoretical annual risk of stroke or embolism is 2.2%, though it reaches 15.2% if the patients presents a maximum of 9 points). At this moment the use of the CHADS2 score is still widely employed and appears in the majority of the current publications.

Clinical decisions are becoming more complex and health care professionals are facing the dilemma of evaluating on the one hand the risk of embolism for their patients and on the other hand the risk of haemorrhage that chronic oral anticoagulation bears. In order to estimate the risk of bleeding in patients with atrial fibrillation in the last few years different models based on scores have been designed. Recently the HAS-BLED[22] bleeding risk score was published (acronym for hypertension, abnormal kidney and/or liver function, stroke, bleeding history, labile INR, elderly >65 years, and drugs and/or alcohol).

A point is assigned to each of the factors and a maximum of two points is assigned to the combined factors (abnormal kidney and/or liver function, antiplatelet or non steroid anti-inflammatory drugs, and /or alcohol abuse). It is estimated that patients with ≥ 3 factors present a high risk of bleeding. Once the estimated risk of embolism and that of bleeding is known, then we should decide on introducing antithrombotic therapy to our patients. Possibly age represents the main factor to bear in mind, especially with regard to the risk of intracranial bleeding, which is estimated as an increase by 1.1% per year in patients over 75 years, or an increase in relative risk of 2.5 in those patients over 85 years of age[23].

When indicating oral anticoagulation with conventional drugs, the aim is to maintain INR levels between 2 and 3. As mentioned earlier, the use of oral anticoagulants has two main inconveniences. On the one hand, periodic INR monitoring is re-

Table 4. Pharmacokinetic characteristics of anticoagulant drugs.

	APIXABAN	DABIGATRAN	RIVAROXABAN
Habitual dose	2.5 to 5 mg b.i.d.	110 to 150 mg b.i.d.	10 mg once daily
Oral bioavailability	50%	5 to 6%	60 to 90 %
Half-life (hours)	10 - 15	7 -16	6 - 9
Elimination	Renal: 25%	Renal:80%	Biliar or feces: 28%. Renal 66%
Dose adjustments according to age and weight	NO	NO	NO
Coagulation monitoring	NO	NO	NO
Interactions	Potent inhibitors of CYP3A4*	Inhibitors /inducers glycoprotein (P-gp)**	Potent inhibitors /inducers of CYP3A 4***

(*) Ketonazole and diltiazem reduces the bioavailability of apixaban; rifampicin increases it.
(**) Includes verapamil, clarithromycin, amiodarone, rifampicin and quinin. Quinidine is contraindicated in patients taking dabigatran.
(***) Includes ketoconazole, macrolides, and protease inhibitors. Both rivaroxaban and possibly apixaban are contraindicated with drugs that simultaneously inhibit CYP3A4 and P-gp, such as triazole antifungal agents, ritonavir or clarithromycin.

quired, where up to now patients with a correct therapeutic range reached lies between 58-65%[24]. On the other hand, patient adherence to treatment is not always the desired one (about 30% of patients abandon treatment).

Rivaroxaban

A **non-inferiority** clinical trial, the ROCKET-AF[25], that compares rivaroxaban 20 mg with warfarin at required doses to attain INR levels between 2 and 3 was published. A total of 14,264 patients diagnosed with AF were included (age range, 65-78 years; women, 39.7%; hypertension, 90.5%, heart failure, 62.5% and previous stroke, embolism or transient ischaemic attack, 54%). The average $CHADS_2$ score was 3.5 in both groups. Table 5 shows the results of the ROCKET-AF trial.

The rate of bleeding was similar in both groups, either total bleeding (14.9%/year vs 14.5%/year) or major bleeding (3.6% *vs* 3.4%, rivaroxaban and warfarin, respectively). A small lower incidence of intracranial haemorrhage was observed in the rivaroxaban group (ARR = 0.4% at the end of the trial, NNT = 250). The authors conclude that rivaroxaban was non-inferior to warfarin with a similar bleeding rate. An editorial[26] published in the same journal raises the question on whether trials to test superiority versus warfarin or non-inferiority versus dabigatran will be carried out.

FDA experts raised concerns on two different aspects of the ROCKET-AF trial. They stated there is a lack of substantial evidence that rivaroxaban will have its desired effect when used as recommended on the labelling. The data from the ROCKET-AF trial comparing rivaroxaban to warfarin are not adequate to determine whether rivaroxaban is as effective for its proposed indication as warfarin when the latter is used skilfully. In order for atrial fibrillation patients to be protected from the risk of thrombotic events, any new drug for this indication should be demonstrated as effective as warfarin when it is used skilfully.

Patients who do not tolerate warfarin or those with INR levels out of control could be prescribed the new anticoagulant agents

In the ROCKET study there was an excess of strokes in the rivaroxaban arm during the transition from blinded study drug to open label warfarin at the end of the study. The instructions proposed by the sponsor after the ROCKET trial was completed for the transition from rivaroxaban to warfarin, have not been evaluated or shown to be safe in terms of bleeding risk or embolic risk in any clinical study. Such a study must be performed prior to approval in this case. Despite the recommendations of the FDA's experts, the drug has recently been granted approval.

Dabigatran

The most ample study evaluating the impact of dabigatran is the RE-LY trial[27]. This is an **unblinded** randomized trial designed to evaluate the non inferiority of dabigatran at fixed doses to warfarin at adjusted doses in patients with AF. The patients included presented no valvular disease and events such as stroke, systemic embolism or its recurrence were recorded. The primary endpoint was stroke or systemic emboli.

Patients with a documented history of AF were enrolled [including those patients with permanent or

Table 5. Stroke or systemic embolism outcomes in the ROCKET-AF trial.

	RIVAROXABAN		WARFARINA		ARR	NNT
	PATIENTS	% EVENTS/YEARS	PATIENTS	% EVENTS/YEARS	%	
Treated patients	6,958	1.7	7,004	2.2	0.5	200
Safety in treated population	7,061	1.7	7,082	2.2	0.3	333
ITT population	7,081	2.1	7,090	2.4	0.3	333

ARR: absolute risk reduction. NNT: number needed to treat to prevent one event.

Table 6. Clinical follow-up of primary endpoints (stroke or embolism) and severe bleeding. The calculation of events comprehends the whole follow-up period[29].

COMPARISON	EVENT UNDER ANALYSIS	RELATION OF EVENTS	ARR	RRR	NNT
Dabigatran 110 mg/12h compared to warfarin	Stroke or systemic embolism Severe bleeding Stroke Death	3.0% *vs* 3.3% 5.5% *vs* 6.6% 2.8% *vs* 3.1% 7.4% *vs* 8.1%	0.3 % n.s. 1.2% 0.3% n.s. 0.7% n.s.	9% (-11 to 26) 20% (7 to 31) 8% (-13 to 26) 9% (-3 to 20)	- 76 (49 to 217) - -
Dabigatran 150 mg/12h compared to warfarin	Stroke or systemic embolism Severe bleeding Stroke Death	2.2% *vs* 3.3% 6.2% *vs* 6.6% 2.0% *vs* 3.1% 7.2% *vs* 8.1%	1.1% 0.4% n.s. 1.1 % 0.9% n.s.	34% (18 to 47) 7% (-7 to 19) 34% (19 to 49) 12% (0 to 23)	90 (65 to 169) - 90 (66 to 170) -
Dabigatran 150 mg/12h compared to dabigatran 110 mg/12h	Stroke or systemic embolism Stroke Death	2.2% *vs* 3% 2.0% *vs* 2.8% 7.2% *vs* 7.4%	0.8% 0.8% 0.2% n.s.	27% (9 to 42) 30% (11 to 44) 3% (-11 to 15)	124 (80 to 371) 120 (82 to 325) -
				IRR (95% CI)	
	Severe bleeding	6.2% *vs* 5.4%		16% (0 to 34)	-

ARR: absolute risk reduction.
RRR: relative risk reduction (95% confidence interval).
NNT: number of patients needed to treat.
IRR: increment in relative risk.

persistent AF (appendix II),] and paroxysmal AF with a duration ≥ 30 seconds) in addition to the following events:

· stroke, transitory ischemic attacks or systemic embolism.
· left ventricle ejection fractions under 0.40 recorded in the last six months.
· patients ≥ 75 years or ≥ 65 years with one of the following circumstances: diabetes, significant coronary disease, or surgical treatment or percutaneous coronary intervention.
· hypertension requiring medication.

We can therefore verify that in this trial the patients included presented at least 1 point of the CHADS2 score and both persistent or paroxysmal AF. Three branches of the study were randomly assigned with dabigatran 110 mg b.i.d, dabigatran 150 mg b.i.d and warfarin. Of all the patients, 40% received aspirin (up to 100 mg daily). The average age was 71 years, and 63.6% were male, and the average CHADS2 score was 2.1. The average follow-up period was 2 years[28]. The overall results showed the non inferiority of dabigatran 110 mg twice daily compared to warfarin with regard to the primary endpoints (stroke and embolism) and a slight advantage of the 150 mg dose compared to warfarin (table 6).

As can be observed in the table, it can be concluded that there is no inferiority when comparing warfarin with dabigatran, and that the 150 mg dabigatran dose is more effective than 110 mg. Other important aspects of this trial is the analysis of the side effects. The rate of major bleeding are similar (6.2% compared to 5.4%, the rate of haemorrhagic stroke is favourable for dabigatran (0.36% with warfarin, compared to 0.12% or 0.1% with dabigatran), maximum ARR = 0.26%. The fact that **intracranial haemorrhage rates** in the RELY trial were 3-fold higher than those in similar studies deserves consideration. However, the authors do not offer any explanation about it. Another difference expressed in the results is the **higher rate of myocardial infarctions** in the two groups under dabigatran (0.72% and 0.74%) in comparison to warfarin (0.53%). The NNH to suffer an infarction is 500 approximately.

It is interesting to know other aspects derived form the follow-up of this study. On the one hand, in the group under oral anticoagulation the estimated time in which they presented desired therapeutic ranges of INR is 64%. Although it is true that this figure is similar to that observed in other studies, one cannot avoid asking whether the results would have been the same if the desired therapeutic range was greater.

Another aspect to bear in mind is that 20% of patients **abandoned** treatment (one of the most frequent adverse effects of dabigatran is dyspepsia, which develops into gastrointestinal intolerance in some patients). This could play a relevant role when addressing long-term treatment with this drug

which involves prolonged treatment taken twice daily (table 7).

From the data given the results of the trial can open a gateway to establish the reality of the anticoagulants that come close to the ideal drug that avoids embolism in patients with atrial fibrillation (now only employed in patients with no valvular disease or equivalent). However, this same trial also leads to questions which are not sufficiently answered: is anticoagulation equally effective in all patients, independent of their **risk profile**? Are patients aware that they should not **abandon** treatment, given that there is no need for monitoring? Is the mild increase in the incidence of myocardial **infarctions** a trivial finding or should further studies be carried out? Is the two-year study period of dabigatran 150 mg sufficient to consider it **safe**?

The EMA approved both the low **dose** (110 mg/12h) and the high dose (150 mg/12h) for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation. However the FDA approved the higher dose only on the grounds that the non-inferiority finding for the lower dose was somewhat less compelling. They also state they were unable to find any population for whom the availability of a lower dose would improve dabigatran's benefit-risk profile. They also point out that the rate of stroke or systemic embolism was lower with 150 mg of dabigatran 1.4 vs 1.9 per 100 patient-years) though the rate of bleeding was higher (5.1 vs 4.4 per 100 patient-years). If stroke or systemic embolism and major haemorrhage were considered equally undesirable, these rates would indicate similar benefit-risk assessments for the two doses. However, the FDA considers that most people would agree that the irreversible effects of strokes and systemic emboli have greater clinical significance than nonfatal bleeding[30].

In a recent reanalysis of the risk of bleeding with both doses of dabigatran in the RE-LY trial, the authors conclude that both doses have lower risks compared to warfarin of both intracranial and extracranial bleeding in patients under 75 years. In patients over 75 years, intracranial bleeding risk was lower but extracranial bleeding risk was similar or higher with both doses of dabigatran compared with warfarin[31].

Independent clinical trials are needed to define the role of new anticoagulant agents in the treatment of non valvular AF

Safety alerts have been published in Japan and Australia only just a few months after approval. In Japan 5 deaths and 81 severe adverse reactions have been registered between January and August 2011. In Australia, 7 deaths and 124 severe adverse reactions have been reported between April and October 2011. Also the Spanish Medicines Agency published a safety alert before dabigatran was granted approval for use in AF in Europe, on increased bleeding risk and the importance of monitoring renal function in patients under this drug. Most adverse reactions were seen in elderly patients[32], especially those over 75 years, with impaired renal function or low body weight. On 6 November 2011 a worldwide total of 256 spontaneous case reports of serious bleeding resulting in death were recorded in the EudraVigilance database in association with the use of dabigatran since March 2008. Of these 256 cases, 21 were reported in the EU. Over the first three years dabigatran was used at low doses (75 mg)

Table 7. Withdrawal of treatment during follow-up.

DURATION	DABIGATRAN 110 MG	DABIGATRAN 150 MG	WARFARIN
1 year	14.5%	15.5%	10.2%
2 years	20.7%	21.2%	16.6%
MOTIVE FOR DISCONTINUATION	**DABIGATRAN 110 MG**	**DABIGATRAN 150 MG**	**WARFARIN**
Decision of the patient	7.3%	7.8%	6.2%
Severe adverse effects	2.7%	2.7%	1.7%*
Gastrointestinal bleeding	1.0%	1.3%	0.9%

(*) p<0.001 comparing both doses of dabigatran with warfarin.

during a short period for the prevention of thromboembolism after knee replacement. Worldwide use of dabigatran at higher doses for the long-term was begun just a few months ago. Thereby the risk of bleeding associated with dabigatran should be a matter of great concern.

Cost-effectiveness analysis

Another aspect to take into account when prescribing dabigatran is its cost. The cost-effectiveness study after the publication of RE-LY[33] concluded that dabigatran could be an alternative to warfarin in this group of patients with respect to the selling price. However, with the current price, the cost efficiency does not support the systematic use of dabigatran as a substitute of warfarin. In Navarre, the annual cost of acenocumarol and warfarin for over 12,000 patients treated with these drugs is some 400,000 euros. If all these patients were switched to dabigatran, the annual cost would be increased to some 14 million euros. Although the use of dabigatran could reduce acenocumarol and warfarin monitoring costs, widespread use of dabigatran **may not be affordable** for the public health system.

Current situation

As mentioned above, in September 2010 the FDA[34] approved the use of dabigatran 150 mg in the prevention of embolism in patients with AF (with non-valvular disease), while not approving the 110 mg dose. After approval of the 150 mg dose twice daily, the new guidelines edited by the American Heart Association[35] proposed dabigatran as an alternative to warfarin in the prevention of stroke and systemic embolism both in patients at risk with paroxysmal or permanent AF with a class I recommendation, and a level of evidence B.

The recommendation includes those patients with hemodynamic repercussion, kidney impairment with a creatinine clearance of less than 15 mL/min or important liver impairment that can provoke baseline coagulation disorders. The CEDAC also recently approved the 110 mg dose reserving it for patients over 80 years or with a risk of bleeding and the 150 mg dose for the rest of the population. In the last clinical guidelines issued by the Canadian Cardiovascular Society[36] on AF, dabigatran was included at the same level as warfarin, with a high degree of recommendation and with an established indication for patients with a CHADS2 score of ≥ 2, and even in patients with CHADS2 score of 1, but with precaution and only after an individual risk benefit analysis. The EMA has just approved dabigatran in the prevention of stroke or embolism in patients with non valvular related AF.

In Spain, dabigatran for AF is a controlled drug with special requirements for prescription under the Spanish Public Health System. The cost per patient-month is 98.35 euros regardless of the dose.

Apixaban

In the last few months two clinical trials have been published with respect to apixaban: AVERROES[37], which included 5,599 participants comparing patients with AF under apixaban 5 mg b.i.d (some patients, apixaban 2.5 mg b.i.d.) to patients with acetylsalycilic acid (ASA) 81-324 mg daily. The patients presented at least one risk factor for stroke and did not tolerate treatment with warfarin (40% were previously under warfarin). The study was discontinued when benefits were confirmed for apixaban with respect to ASA. Table 8, shows a summary of some of the results of the trial. The results of the outcome with most of the variables (stroke, systemic embolism, myocardial infarction, death due to vascular causes, or important bleeding) are excluded given the difficulty in evaluating the results with these variables.

The ARISTOTLE[38] trial enrolled 18,026 patients with AF to demonstrate **non inferiority**, of apixaban compared to warfarin in the incidence of stroke, embolism and haemorrhage. Patients diagnosed with flutter or more than two AF events were included (age range, 63-76 years; mean age, 70 years; women, 35%; previous stroke, embolism or transient ischaemic attack, 19,7%). The average $CHADS_2$ score was 2.1 in both groups. Some 66% warfarin patients achieved INR levels within the therapeutic range and time within therapeutic range was 62% on average. Table 9 shows the results of the ARISTOTLE trial.

Apixaban showed a decrease in the incidence of total bleeding (ARR = 0.96%/year, p<0.001, NNT = 104). Incidence of gastrointestinal haemorrhage was similar in both groups.

The outcomes in the ARISTOTLE trial were more favourable to apixaban in the **Asian population** compared to the European or American patients. It could be hypothesized that Asians patients respond to the drug in a different way or maybe some elements related to the implementation of the trial in Asia could account for the differences. However, the authors do not discuss on this issue. Also, some 35% warfarin patients had INR levels out of therapeutic range, meaning **warfarin management** in this trial was not skilful.

Table 8. Main results of the AVERROES[37] trial (apixaban vs ASA).

	APIXABAN (% PER YEAR)	ASPIRIN (% PER YEAR)	RRA	NNT
Stroke or systemic embolism	1.6 %	3.7 %	2.1 %	47
Stroke, embolism or death	4.6 %	7.2 %	2.6 %	38
Stroke	1.6 %	3.4 %	1.7 %	59
Ischemic	1.1 %	3.0 %	1.9 %	53
Hemorrhagic	0.2 %	0.3 %	0.1 %	1,000
Systemic embolism	0,1 %	0.4 %	0.3 %	333
Myocardial infarction	0.8 %	0.9 %	0.1 %	1,000
Important bleeding	1.4 %	1.2 %	-	-
Intracranial haemorrhage	0.4 %	0.4 %	-	-
Gastrointestinal bleeding	0.4 %	0.4 %	-	-

ARR: absolute risk reduction. NNT: number needed to treat to prevent one event.

Indications of the new drugs in acute coronary syndrome

Acute coronary syndrome includes two main groups of clinical processes: myocardial infarction, with or without Q wave, and unstable angina. These situations share a common physiological process, thrombosis of one or more coronary lesions. Management mainly includes anti-ischemic drugs and antithrombotic therapy (antiplatelet and anticoagulant therapies).

Conventional drugs employed in the acute phase include heparin, low molecular weight heparin or fondaparinux. The new drugs such as rivaroxaban[39,40] or dabigatran[41] reduce the number of episodes included as primary endpoints, but also increase the incidence of bleeding. With respect to similar findings, it has been announced that the APPRAISE-2 ACS trial has been suspended. This trial aimed to compare apixaban 5 mg b.i.d. with placebo added to one or two antiplatelet drugs, but was discontinued due to the increase in the incidence of bleeding in the apixaban group[42]. The results showed no benefit of adding apixaban to one or two antiplatelet drugs while bleeding risk significantly increased[43].

Additional aspects related to safety

There are three notable safety concerns on the new oral anticoagulant agents: there is no readily available means for assessing the degree of anticoagulation, there is no readily available reversal strategy, and life-threatening bleeding complications can occur after an injury in patients taking this drug. Several cases of injured patients receiving dabigatran have been reported, all of whom had poor outcomes. In these cases all values except activated clotting time were normal. Unfortunately, even with the aid of rTEG, supportive care is all that is available in the emergency setting[44].

Whenever a new drug is employed, its efficacy and its safety margins are well known within the period of study, although in many cases the mid to long-term safety profile of the drug remains unknown. This issue causes uncertainty, which increases because clinicians do not have any available information to draw any conclusions.

It is surprising that after the publication of the RE-LY[24] study, the authors presented corrections to the initial data[45]. While they did not change the global results, this modification raises doubts on whether

Table 9. ARISTOTLE trial main outcomes.

	APIXABAN (%/ year)	WARFARINA (%/year)	p-VALUE	ARR	NNT
Stroke or systemic embolism	1.27	1.60	0.01	0.33	303
Stroke	1.19	1.51	0.01	0.32	312
Hemorrhagic stroke	0.24	0.47	<0.01	0.23	434
Systemic embolism	0.09	0.10	0.70	0.01	-
All cause death	3.52	3.94	0.047	0.43	232

ARR: absolute risk reduction.
NNT: number needed to treat to prevent one event.

the other results are incorrect or incomplete. The incidence of myocardial infarction and gastrointestinal bleeding is too considerable to leave unmentioned. More so, some of the data from this trial still remains reserved. The company stated that this information would be released only in the setting of a formal review by a hospital considering dabigatran for its formulary. In that case, a confidentiality agreement forbidding sharing the data with anyone but the hospital decision makers had to be signed[46]. **Why so?** Independent clinical trials are needed to define the role of dabigatran in atrial fibrillation[47].

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Conclusions

Up to now well known conventional anticoagulant drugs have been employed. They are effective but do have limitations: require monitoring, interactions with food and other drugs and present irregular efficacy.

New drugs are under development and evaluation that do not bear the majority of the inconveniences that conventional drugs present. This could prove a significant advancement in the management of some of these patients, although none of these new agents are free from secondary effects.

The efficacy of the new anticoagulants in the initial management of acute coronary syndrome is limited. Moreover, its use is more complicated given the increased risk of bleeding with the combination of antiplatelet and anticoagulant therapy (frequently patients are under both anticoagulant and antiplatelet therapy simultaneously).

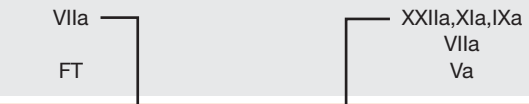
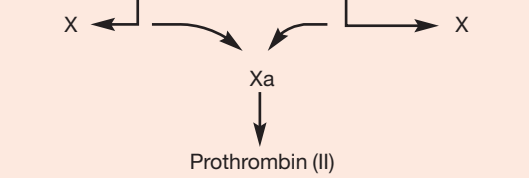
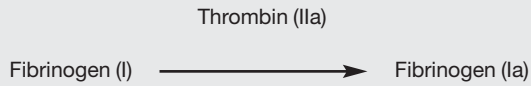
There is data available on the efficiency of dabigatran in the prophylaxis of embolic events in patients with non-valvular AF but no conclusive data is available on the long-term safety profile of this drug at high doses. Widespread use of these drugs may not be affordable for the public health system.

These drugs might not be indicated in a considerable group of patients, especially the elderly and those with important liver or renal impairment.

Until the pending issues are not clarified, any substitution of current oral anticoagulation by the new anticoagulants remains unjustified in those patients who tolerate conventional treatment and whose monitoring is stable.

Independent clinical trials are needed to define the role of new anticoagulant agents in the treatment of non valvular AF.

Appendix I

PHASE	COAGULATION CASCADE	DRUGS AND LEVEL OF ACTION
Initiation		Warfarin: II, VII, IX, X Alpha dotrecogin C Protein
Propagation		Rivaroxaban Apixaban: Xa Fondaparinux: Xa+ATIII Non fractioned heparin: ATIII+Xa+IIa Low molecular weight heparin: ATIII+Xa>>IIa
Thrombin activation		Dabigatran: IIa Ximelagatran: IIa

TF: Tissue factor.
(I-XII): coagulation factors.
(Ia-XIIa): activated coagulation factors.

Appendix II. Classification of atrial fibrillation. European Society of Cardiology[20].

Paroxsymal AF	Self terminating usually within 48 hours. Paroxysmal AF can last upto 7 days, but if it lasts more than 48 hours, then anticoagulation should be considered.
Persistent AF	Lasts more than 7 days, and terminates with pharmacological or direct current cardioversion.
Long-lasting persistent AF	Lasts for more than one year and when it is decided to adopt a rhythm control strategy.
Permanent AF	Presence of AF is accepted by the patient and physician. Management directed at controlling heart rate.

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