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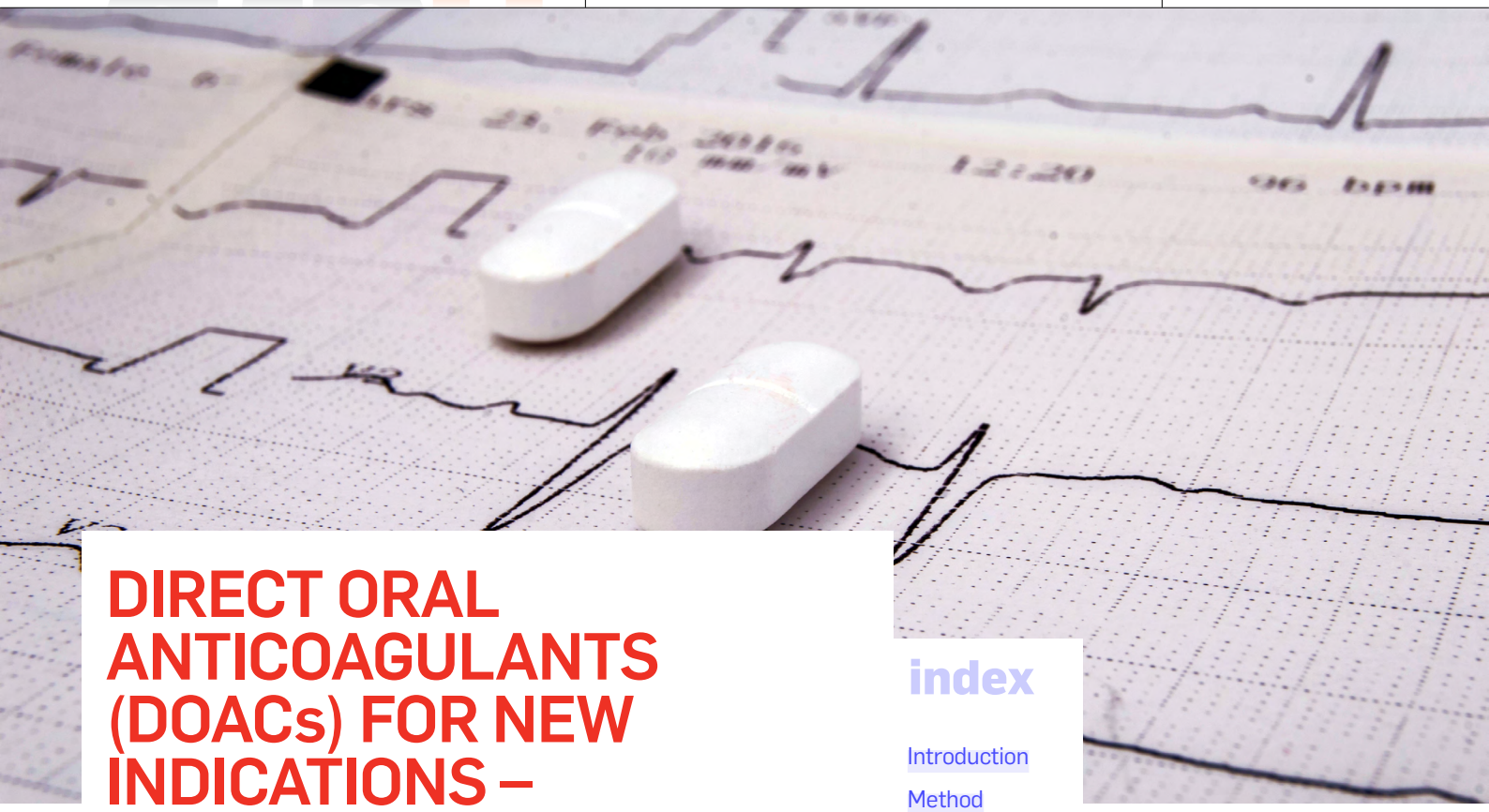

DIRECT ORAL ANTICOAGULANTS (DOACs) FOR NEW INDICATIONS – FROM BAD TO WORSE?

OBJECTIVE To evaluate the results of clinical trials in which direct oral anticoagulants are used for indications different from non-valvular atrial fibrillation and hip or knee replacement surgery. CONCLUSIONS Rivaroxaban had a higher incidence of thromboembolic events than warfarin in patients with antiphospholipid syndrome. The trial was terminated prematurely due to this fact. Three more trials were early stopped: the first one, because of increased mortality in the rivaroxaban group compared to clopidogrel in transcatheter aortic valve replacement; the second one, because of an unfavorable risk-benefit ratio compared to ASA in the prevention of recurrent stroke after embolic stroke of unknown origin; the third one, because of an increased risk of thromboembolism and bleeding with dabigatran compared to warfarin in patients with cardiac valve prostheses. ACODs' results were rather disappointing in the following situations: stable cardiovascular disease; acute coronary syndrome; patients with heart failure, sinus rhythm and coronary disease; patients hospitalized for acute medical illnesses; minor orthopedic surgery, and prevention of recurrent thromboembolism in cancer patients. Vitamin K antagonists should always be the first treatment option when patients need to be anticoagulated. DOACs should be restricted to cases where vitamin K antagonists are contraindicated, not tolerated, or where it is not possible to maintain INR levels within the therapeutic range.

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Introduction

In 2011, an article entitled *¿Cuál puede ser el papel de los nuevos anticoagulantes en la fibrilación auricular no valvular?* was published in DTB Navarre[1] ("What is the role of new anticoagulants for non-valvular atrial fibrillation?"). This article concluded that replacing the current standard oral anticoagulant therapy with the new anticoagulant drugs in stable patients who tolerate conventional therapy and was not justified. It also stressed that independent trials were needed to accurately define the role of new drugs in patients with non-valvular atrial fibrillation and the specific indication for each of them.

Five years later, in 2016, BTB Navarre published an article entitled *Incertidumbres sobre los nuevos anticoagulantes orales en fibrilación auricular: irregularidades y lagunas en su autorización*[2] ("Uncertainties about new oral anticoagulants for atrial fibrillation: deficiencies and irregularities in the authorization process"). This time, the conclusions highlighted that the pivotal clinical trials that led to the marketing of dabigatran, rivaroxaban, apixaban and edoxaban in atrial fibrillation had numerous irregularities, including concealment and falsification of data. It was also stated that they did not provide reliable information on the harm-benefit ratio of dabigatran, rivaroxaban, apixaban and edoxaban compared to warfarin for atrial fibrillation. Finally, it was mentioned that the regulatory agencies had ignored many problems and irregularities detected, revealing the need to make full data from clinical trials public, thus assuring transparency and access to truthful information. This would guarantee that patients receive the best treatment for their condition.

This article prompted the reaction of five scientific societies, whose letter of protest is available on DTB Navarre's website, along with the author's response to it. What is certain is that the content of this article is still considered valid today, and the controversy about the true usefulness of direct oral anticoagulants (DOACs) is more alive than ever.

Until then, new oral anticoagulants had been used in thromboembolism prophylaxis in patients with non-valvular atrial fibrillation and in those undergoing hip or knee replacement surgery. The potential use of these drugs in other indications has also been studied, especially since then.

The objective of this article is to evaluate the results of clinical trials in which direct oral anticoagulants are used for indications or clinical situations different from those mentioned above.

Method

A Medline search was performed, updated to 31/03/2020, for all clinical trials conducted for indications different from thromboembolism prophylaxis in patients with non-valvular atrial fibrillation and for those undergoing hip or knee replacement surgery. The comparator could be any anticoagulant, antiplatelet or placebo. In addition, the FDA and EMA registries were searched for additional public information on the identified trials.

Results

Table 1 below shows the list of trials identified with DOACs in indications different from thromboembolism prophylaxis in patients with non-valvular atrial fibrillation or following hip or knee replacement surgery. These trials will be discussed in this article.

Dabigatran versus warfarin in patients with heart valve prostheses

In 2013, the results of the phase II RE-ALIGN trial[3] were published, comparing the administration of dabigatran (150, 220 or 300 mg, twice a day) *vs* warfarin (target INR range between 2 and 3.5) in patients with heart valve prostheses. As for the patients included, they had either recently undergone a valve replacement or had undergone such replacement over three months before being included in the study. The primary endpoint was determining plasma concentrations of dabigatran. However, the secondary endpoints included estimates of clinical outcomes such as the incidence of stroke or transient ischemic attack, systemic embolism, valve thrombosis, bleeding, venous thromboembolism, myocardial infarction, and death. The trial was terminated prematurely after 252 patients of the 405 initially planned had been included, due to an excess of thromboembolic events and bleeding in patients in the dabigatran group (Table 2).

Once the results of the clinical trial were published, the Spanish Agency of Medicines and Medical Devices (AEMPS) issued an information note in December

Table 1. List of clinical trials identified with DOACs.

Indication	Trial	Follow-up	DOAC	Comparator
Dabigatran in patients with heart valve prostheses	RE-ALIGN	12 weeks	Dabigatran	Warfarin
Rivaroxaban in high-risk patients with antiphospholipid syndrome	TRAPS	569 days (median)	Rivaroxaban	Warfarin
Rivaroxaban in antiphospholipid syndrome: a randomized non-inferiority trial	ANTIPHOSPHOLIPID SYNDROME	3 years	Rivaroxaban	Acenocumarol
Rivaroxaban in patients undergoing transcatheter aortic valve replacement	GALILEO	17 months (median)	Rivaroxaban	Clopidogrel / AAS
Rivaroxaban in the prevention of recurrent stroke after embolic stroke of unknown origin	NAVIGATE ESUS	11 months (median)	Rivaroxaban	ASA
Dabigatran in the prevention of recurrent stroke after embolic stroke of unknown origin	RE-SPECT ESUS	19 months (median)	Dabigatran	ASA
Dabigatran in the prevention of recurrent stroke after thromboembolic stroke	RE-SPECT CVT	24 weeks	Dabigatran	Warfarin
Rivaroxaban in patients hospitalized for an acute medical illness	MAGELLAN	25 days	Rivaroxaban	Enoxaparin
Betrixaban in patients hospitalized for an acute medical illness	APEX	42 days	Betrixaban	Enoxaparin
Rivaroxaban in patients after hospitalization for an acute medical illness	MARINER	45 days	Rivaroxaban	Placebo
Rivaroxaban in patients with heart failure, sinus rhythm, and coronary disease	COMMANDER-HF	21 months (median)	Rivaroxaban	Placebo
Rivaroxaban in patients with acute coronary syndrome	ATLAS ACS 2 - TIMI 51	13 months (median)	Rivaroxaban	Placebo
Rivaroxaban in patients with or without acetylsalicylic acid in stable cardiovascular disease	COMPASS	23 months	Rivaroxaban	ASA
Apixaban in outpatients with cancer and moderate to high risk of thromboembolism	AVERT	6 months	Apixaban	Placebo
Edoxaban in cancer patients who developed thromboembolism	Hokusai VTE	12 months	Edoxaban	Dalteparin
Apixaban in the treatment of thromboembolism in cancer patients	Caravaggio	6 months	Apixaban	Dalteparin
Rivaroxaban in outpatients with cancer at high risk of thromboembolism	CASSINI	6 months	Rivaroxaban	Placebo
Minor orthopedic surgery	PRONOMOS	Undefined	Rivaroxaban	Enoxaparin

ASA: Acetylsalicylic Acid. **DOAC:** Direct Oral Anticoagulant.

Table 2. Results of dabigatran (DAB) *vs* warfarin in patients with heart valve prostheses.

Variable	Population A		Population B		All patients		HR (95%CI)	p
	DAB (n=133) N (%)	WAR (n=66) N (%)	DAB (n=35) N (%)	WAR (n=18) N (%)	DAB (n=168) N (%)	WAR (n=84) N (%)		
Death	1 (1)	2 (3)	0 (0)	0 (0)	1 (1)	2 (2)	0.25 (0.02 - 2.72)	0.26
Stroke	9 (7)	0	0 (0)	0 (0)	9 (5)	0	–	–
Death, stroke, systemic embolism or myocardial infarction	11 (8)	2 (3)	2 (6)	0	13 (8)	2 (2)	3.37 (0.76 - 14.95)	0.11
Bleeding (any severity)	35 (26)	8 (12)	10 (29)	2 (11)	45 (27)	10 (12)	2.45 (1.23 - 4.86)	0.01

CI: Confidence interval. **HR:** Hazard ratio. **N:** Number of subjects with event. **Population A:** Recent valve prosthesis implantation.
Population B: Implantation >3 months before inclusion.

2012[4] contraindicating the use of dabigatran in patients with mechanical heart valve prostheses. It specifically stated that the data showed a higher number of cases of thromboembolism (mainly stroke and symptomatic or asymptomatic thrombosis in the valve prosthesis) and bleeding in the dabigatran group compared to the warfarin group. In the group of patients who had recently undergone valve replacement surgery, major bleeding events predominantly involved hemorrhagic pericardial effusion, specifically in patients who had started treatment with dabigatran within the first days of heart valve implantation. Consequently, dabigatran was contraindicated in patients with heart valve prostheses.

Rivaroxaban versus warfarin in high-risk patients with antiphospholipid syndrome

Antiphospholipid syndrome (APS) is an autoimmune disease with increased thromboembolic risk due to the production of autoantibodies directed against phospholipid-binding proteins in cell membranes. Acetylsalicylic acid (ASA) or vitamin K antagonists are often used for the prevention of thrombotic events. In pregnancy, the risk increases considerably and low-molecular-weight heparin is used.

A clinical trial (TRAPS) published in 2018 evaluated the efficacy and safety of rivaroxaban (20 mg/day) versus warfarin (target INR = 2.5) in high-risk patients with APS.[5] The primary endpoint was the combination of episodes of thromboembolism, major bleeding, or death from vascular disease. The trial was prematurely terminated due to an excess of events in the rivaroxaban arm. The median follow-up of patients was 569 days. The results of rivaroxaban were clearly worse than those of warfarin in this trial, mostly due to a higher incidence of thromboembolism (Table 3).

This trial presents limitations such as being open-label and having a small sample size (n=120). However, the hazard ratio obtained for the primary endpoint (HR = 7.4 [1.7-32.9]) was very high, thus the magnitude of the difference between both treatment groups could not be explained by potential confounding factors. The differences observed are mainly due to the higher number of arterial thromboses observed in the rivaroxaban arm. Therefore, it can be stated quite reliably that warfarin is a more effective and safer drug than rivaroxaban in this indication.

Following the results of this study, the Spanish Agency of Medicines and Medical Devices (AEMPS) issued an information note in which the use of DOACs was not recommended in patients with APS and a history of thrombosis.[6]

The conclusions of the AEMPS were the following:

- In patients with APS and a personal history of thrombosis, the use of DOACs, compared to the use of vitamin K antagonists, may increase the risk of thrombotic events.
- Rivaroxaban, apixaban, edoxaban or dabigatran are not recommended in patients with APS and a history of thrombosis.
- In patients with APS who are taking rivaroxaban, apixaban, edoxaban or dabigatran for the prevention of thromboembolic events, the convenience of maintaining the treatment should be assessed, and switching to a vitamin K antagonist should be considered.

Another open-label, non-inferiority clinical trial conducted in Spain and published in 2019 compares rivaroxaban versus warfarin in 190 patients with APS and a three-

Table 3. Results of rivaroxaban (RIV) vs. warfarin (WAR) in patients with antiphospholipid syndrome.

Variable	Protocol analysis				Intention-to-treat analysis			
	RIV (n=59) N (%)	WAR (n=61) N (%)	HR (95% CI)	p	RIV (n=59) N (%)	WAR (n=61) N (%)	HR (95% CI)	p
Primary endpoint. Thromboembolism, major bleeding or vascular death.	11 (19)	2 (3)	6.7 (1.5 - 30.5)	0.01	13 (22)	2 (3)	7.4 (1.7 - 32.9)	0.008
Arterial thrombosis. · Ischemic stroke · Myocardial infarction	7 (12) 4 (7) 3 (5)	0 0 0	–	–	7 (12) 4 (7) 3 (5)	0 0 0	–	–
Venous thromboembolism	0	0	–	–	1 (2)	0	–	–
Major bleeding	4 (7)	2 (3)	2.5 (0.5 - 13.6)	0.3	4 (7)	2 (3)	2.3 (0.4 - 12.5)	0.3
Death	0	0	–	–	1 (2)	0	–	–

CI: Confidence interval. **HR:** Hazard ratio. **N:** Number of subjects with event

year follow-up.[7] Its results confirm the conclusions of the TRAPS trial, as they found that patients receiving rivaroxaban developed twice as many thrombotic events as the warfarin group (12.6% *vs* 6.3%; HR=2.10 [0.79-5.59]), more arterial events (HR=3.84 [1.07-13.76]) and strokes (HR=20.01 [1.12-431.8]).

Rivaroxaban versus antiplatelet agents in patients undergoing transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) is usually performed in patients with aortic valve stenosis who are not suitable for open heart surgery because of a high risk of thromboembolism.

The GALILEO trial, a phase III, randomized, open-label trial, compared the efficacy of rivaroxaban versus clopidogrel in these patients.[8] The experimental group received rivaroxaban (10 mg/day) and ASA 75-100 mg/day for 90 days, followed by maintenance with rivaroxaban 10 mg/day. The comparator group was given clopidogrel 75 mg/day and ASA 75-100 mg/day for 90 days, followed by ASA monotherapy.

The primary efficacy endpoint was the combination of overall mortality, stroke, myocardial infarction, pulmonary or systemic embolism, deep vein thrombosis, and symptomatic valve thrombosis. The primary safety endpoint was the combination of life-threatening or disabling bleeding and major bleeding. Patients with atrial fibrillation were excluded from this clinical trial.

In August 2018, after a median follow-up of 17 months, the independent safety data monitoring committee recommended stopping the trial because of an increase in overall mortality and in the incidence of thromboembolism and major bleeding in patients treated with rivaroxaban. The results of the trial can be seen in Table 4.

Published data confirm the increase in mortality and thromboembolic events in the rivaroxaban group in patients undergoing transcatheter aortic valve replacement. Therefore, this drug should not be used in this indication, as recalled by Bayer Laboratories in a letter addressed to healthcare professionals in October 2018.[9]

The results of this trial are concerning and may jeopardize the development of a similar ongoing trial in patients with TAVR in which the drug under study is apixaban at a dose of 5 mg every 12 hours (ATLANTIS).[10] This trial has a similar sample size and is also open-label. The main differences are shown in Table 5.

Prevention of recurrent stroke after embolic stroke of unknown origin

Rivaroxaban

A randomized, phase III, open-label clinical trial (NAVIGATE ESUS) published in 2018 compared the use of rivaroxaban 15 mg/day versus ASA 100 mg/day in the prevention of recurrent stroke in patients with a recent stroke due to cerebral embolism without arterial stenosis or lacunar infarction and of unknown origin.[11] A total of 7213 patients were evaluated with a planned follow-up of 2 years (median follow-up was 11 months). The primary efficacy endpoint was the incidence of recurrent stroke (ischemic, hemorrhagic or undefined) or systemic

Table 4. Results of the GALILEO trial (intention-to-treat analysis).

	Rivaroxaban (n = 826)	Antiplatelet agents (n = 818)	HR (95% CI)
	N (%)	N (%)	
Efficacy endpoints			
Primary endpoint*	105 (12.7)	78 (9.5)	1.35 (1.01 - 1.81)
Overall mortality	64 (7.7)	38 (4.6)	1.69 (1.13 - 2.53)
· of cardiovascular origin	35 (4.2)	27 (3.3)	1.30 (0.79 - 2.14)
· of non-cardiovascular origin	29 (3.5)	11 (1.3)	2.67 (1.33 - 5.35)
Stroke (ischemic or hemorrhagic)	30 (3.6)	25 (3.1)	1.20 (0.71 - 2.05)
Myocardial infarction	23 (2.8)	17 (2.1)	1.37 (0.73 - 2.56)
Safety endpoints			
Primary safety endpoint†	46 (5.6)	31 (3.8)	1.50 (0.95 - 2.37)
Net clinical benefit/harm**	137 (16.6)	100 (12.2)	1.39 (1.08 - 1.80)

HR: Hazard ratio. **CI:** Confidence interval. **N:** Number of subjects with event.
(*) Overall mortality, stroke, myocardial infarction, pulmonary or systemic embolism, deep vein thrombosis or symptomatic valve thrombosis.
(†) Life-threatening, disabling or major bleeding.
(**) Composite variable of the primary efficacy and safety endpoints.

Table 5. Main differences in the design of the GALILEO and ATLANTIS trials.

Variable	GALILEO	ATLANTIS
Primary	Overall mortality, stroke, myocardial infarction, pulmonary or systemic embolism, deep vein thrombosis or symptomatic valve thrombosis	Same, plus life-threatening, disabling or major bleeding
Duration	2 years	1 year
Comparator	ASA + clopidogrel for 3 months, and then ASA in monotherapy	Vitamin K antagonist, antiaggregant or both
Population	Patients without prior anticoagulation or with atrial fibrillation	With/without prior anticoagulation // includes a subset of patients with atrial fibrillation
Funding	Bayer and Janssen	Academic

ASA: Acetylsalicylic acid.

embolism. The primary safety endpoint was the incidence of major bleeding.

This trial was prematurely stopped due to the lack of benefit of rivaroxaban treatment in the prevention of recurrent stroke and the persistence of increased bleeding associated with the use of the anticoagulant.[12] The results of the trial can be seen in Table 6.

Once again, the data obtained with rivaroxaban are very concerning. The increase in hemorrhagic stroke observed in the rivaroxaban group is remarkable. On the other hand, there was also a non-significant increase in the incidence of thrombotic episodes and mortality, although the early termination of the trial makes it impossible to know if there is actually a difference in these outcomes.

Furthermore, this trial provides detailed information on bleeding by location. It can be seen that the risk of developing intracranial hemorrhage is four times higher in the rivaroxaban group compared to patients treated with ASA.

Table 6. Results of the NAVIGATE ESUS trial (intention-to-treat analysis).

	Rivaroxaban (n = 3,609)	ASA (n = 3,604)	HR (95% CI)
	N (%)	N (%)	
Efficacy endpoints			
Primary endpoint*	172 (5.1)	160 (4.8)	1.07 (0.87 - 1.33)
Secondary endpoints			
Total recurrent strokes	171 (5.1)	158 (4.7)	1.08 (0.87 - 1.34)
Ischemic stroke	158 (4.7)	156 (4.7)	1.01 (0.81 - 1.26)
Hemorrhagic stroke	13 (0.4)	2 (0.1)	6.50 (1.47 - 28.8)
Systemic embolism	1 (<0.1)	2 (0.1)	0.50 (0.05 - 5.51)
Recurrent stroke, myocardial infarction, cardiovascular death or systemic embolism	207 (6.2)	195 (5.8)	1.06 (0.87 - 1.29)
Disabling stroke	41 (1.2)	29 (0.8)	1.42 (0.88 - 2.28)
Myocardial infarction	17 (0.5)	23 (0.7)	0.74 (0.39 - 1.38)
Overall mortality	65 (1.9)	52 (1.5)	1.26 (0.87 - 1.81)
Cardiovascular mortality	34 (1.0)	23 (0.7)	1.48 (0.87 - 2.52)
Safety endpoints			
Primary safety endpoint†	62 (1.8)	23 (0.7)	2.72 (1.68 - 4.39)
Fatal or life-threatening bleeding	35 (1.0)	15 (0.4)	2.34 (1.28 - 4.29)
Symptomatic intracranial hemorrhage	20 (0.6)	5 (0.1)	4.02 (1.51 - 10.7)
Clinically relevant non-major bleeding	118 (3.5)	79 (2.3)	1.51 (1.13 - 2.00)

HR: Hazard ratio. **CI:** Confidence interval. N: number of subjects with event. (*) Recurrent stroke or systemic embolism. (†) Major bleeding.

Dabigatran

In addition, a clinical trial (RE-SPECT ESUS) assessing the effects of dabigatran in the same indication was published.[13]

It is a phase III, double-blind trial in which the efficacy and safety of dabigatran 150 mg or 110 mg every 12 hours was compared to ASA 100 mg per day in the prevention of recurrent stroke after stroke of unknown origin. The results are summarized in Table 7.

Dabigatran had a similar result to ASA in preventing recurrent stroke, but significantly increased the risk of major or clinically relevant bleeding.

Dabigatran in the prevention of recurrent stroke after thromboembolic stroke

A randomized, multi-center, open-label, exploratory clinical trial (RE-SPECT CVT) was published, comparing the efficacy and safety of dabigatran (150 mg/12h) versus warfarin in the prevention of recurrent thromboembolism in patients with previous cerebral thromboembolism.[14]

This trial evaluated 120 patients who were followed for 24 weeks. The primary endpoint was the incidence of a new thromboembolic event (recurrent cerebral thromboembolism, deep vein thrombosis in the limbs, pulmonary embolism, splanchnic venous thrombosis) or major bleeding.

The fact is that no conclusions can be drawn from this trial, given its exploratory nature. Only three events were recorded in the primary endpoint. Perhaps the most remarkable point is that, in the dabigatran group, seven patients (11.7%) abandoned treatment due to adverse effects, compared to zero cases in the warfarin group. However, this finding needs to be evaluated in a larger properly designed clinical trial.

Prevention of thromboembolism in patients hospitalized for an acute medical illness: the curious case of rivaroxaban and betrixaban

Rivaroxaban

A randomized, phase III, double-blind clinical trial (MAGELLAN) was published. It compared the efficacy and safety of rivaroxaban 10 mg/day for 35±4 days, with enoxaparin 40 mg/day for 10±4 days, in 8,101 patients hospitalized for an acute medical illness (15). The rivaroxaban group received subcutaneous placebo for 10±4 days, and the enoxaparin group oral placebo for 35±4 days, thus the trial was properly blinded.

The primary efficacy endpoint was the incidence of asymptomatic proximal thromboembolism, symptomatic proximal or distal thromboembolism, non-fatal symptomatic pulmonary embolism, or fatal thromboembolism. Data at day 10 were used for the non-inferiority test, and results at day 35 for the superiority test. The primary safety endpoint was the incidence of major bleeding or clinically relevant non-major bleeding.

A summary of the efficacy and safety results of the trial can be seen in Table 8.

Thirty-five days after the start of treatment, the rivaroxaban group showed a 1.3% [NNT=77][a] reduction in the episodes included in the primary endpoint and a 2.4% [NNH=42][b] increase in clinically relevant bleeding. Thus, the use of rivaroxaban instead of enoxaparin does not seem to have any overall advantages in this population.

Table 7. Results of the RE-SPECT ESUS trial (intention-to-treat analysis).

	Dabigatran (n = 2,695)	ASA (n = 2,695)	HR (95% CI)
	N (%)	N (%)	
Efficacy endpoints			
Primary endpoint*	177 (4.1)	207 (4.8)	0.85 (0.69 - 1.03)
Secondary endpoints			
Ischemic stroke	172 (4.0)	203 (4.7)	0.84 (0.68 - 1.03)
Recurrent stroke, myocardial infarction or cardiovascular death	207 (4.8)	232 (5.4)	0.88 (0.73 - 1.06)
Safety endpoints			
Major bleeding	77 (1.7)	64 (1.4)	1.19 (0.85 - 1.66)
Clinically relevant non-major bleeding	70 (1.6)	41 (0.9)	1.73 (1.17 - 2.54)
Major or clinically relevant bleeding	145 (3.3)	101 (2.3)	1.44 (1.12 - 1.85)

HR: Hazard ratio. **CI:** confidence interval. **N:** number of subjects with event. **ASA:** Acetylsalicylic acid. **(*)** Recurrent stroke.

In a decision difficult to understand, in October 2019 the FDA approved the use of rivaroxaban in patients hospitalized for an acute medical illness, based on data from the MAGELLAN trial and a post-hoc analysis of the MARINER trial (rivaroxaban after discharge from hospital in patients hospitalized for an acute medical illness). This trial failed in the primary endpoint, as discussed below.

On the other hand, in the MAGELLAN trial, a non-statistically significant higher incidence bleeding at critical location was observed in the rivaroxaban group. Locations considered as critical in the trial protocol included the following bleeding: intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or compartment syndrome. The location of the observed events was not specified in the publication.

Betrixaban

Betrixaban is a direct factor Xa inhibitor anticoagulant that was approved in the USA in June 2017, but has not been authorized in Europe for the prevention of venous thromboembolism in adult patients hospitalized for an acute medical illness. It is a drug marketed by a small American pharmaceutical company called Portola. The EMA issued a ruling unfavorable to its authorization and, after a re-evaluation at the company's request, in July 2018 it reaffirmed its decision not to authorize this drug because the benefits of betrixaban did not outweigh the risks of its use in this population.[16] It is noteworthy that, in the light of the same scientific evidence, the FDA and the EMA come to completely different conclusions.

The APEX trial[17] has a very similar design to the MAGELLAN trial. The population included is similar, as is the comparator –enoxaparin– used in both studies. The APEX trial evaluated the effects of betrixaban 80 mg/day for 35-42 days with enoxaparin 40 mg/day for 10±4 days in 7,513 patients. Double blinding with placebo was also carried out, as in the MAGELLAN trial. Two patient cohorts were distinguished: those with a D-dimer value at least two-fold higher than the baseline –cohort 1–, and those who met this condition and were older than 75 years –cohort 2–. Overall patient data were also provided.

Patients hospitalized for an acute medical illness (e.g. heart or respiratory failure, infection, rheumatic disease or stroke) with reduced mobility and presence of additional risk factors for venous thrombosis were included.

The primary endpoint was asymptomatic proximal deep vein thrombosis, symptomatic proximal or distal deep vein thrombosis, non-fatal symptomatic pulmonary embolism, or mortality from deep vein thrombosis. The primary safety endpoint was the incidence of major bleeding.

Table 8. Results of the MAGELLAN trial (day 35).

	Rivaroxaban	Enoxaparin	RR (95% CI)
	N (%)	N (%)	
Efficacy endpoints (analyzed in the modified intention-to-treat population: n=2,967 [rivaroxaban]; n=3,057 [enoxaparin])			
Primary endpoint*	131 (4.4)	175 (5.7)	0.77 (0.62 - 0.96)
Asymptomatic proximal DVT	103 (3.5)	133 (4.4)	0.80 (0.62 - 1.03)***
Symptomatic proximal or distal DVT	13 (0.4)	15 (0.5)	0.89 (0.43 - 1.87)***
Non-fatal symptomatic pulmonary embolism	10 (0.3)	14 (0.5)	0.74 (0.33 - 1.65)***
Fatal venous thromboembolism	19 (0.6)	30 (1.0)	0.65 (0.37 - 1.16)***
Safety endpoints (analyzed in the safety population: n=3,997 [rivaroxaban]; n=4,001 [enoxaparin])			
Primary safety endpoints†	164 (4.1)	67 (1.7)	2.5 (1.85 - 3.25)
Major bleeding	43 (1.1)	15 (0.4)	2.9 (1.60 - 5.15)
Major bleeding at critical location	9 (0.2)	4 (0.1)	2.32 (0.71 - 7.52)***
Net clinical benefit/harm**	284/3,042 (9.4)	240/3,082 (7.8)	1.21 (1.03 - 1.43)

CI: Confidence Interval. **n:** Number of subjects with event. **RR:** Risk ratio. **DVT:** Deep vein thrombosis.
(†) Clinically relevant bleeding (major bleeding or clinically relevant non-major bleeding)
(*) Asymptomatic proximal thromboembolism, symptomatic proximal or distal thromboembolism, non-fatal symptomatic pulmonary embolism or fatal thromboembolism.
(**) Composite variable of the primary efficacy and safety endpoints.
(***) Calculated by the authors.

(a) Number of patients to be treated for one patient to avoid an adverse event

(b) Number of patients to be treated for one patient to suffer an adverse event

Results were evaluated with a modified intention-to-treat analysis, excluding 609 patients with betrixaban and 546 patients with enoxaparin, because no ultrasound data were available and no fatal or symptomatic thromboembolic events were observed.

A summary of the efficacy and safety results of the trial can be seen in Table 9.

At 32-47 days after the start of treatment, in the betrixaban group there was a 1.7% reduction in the episodes included in the primary endpoint, and a 1.5% increase in clinically relevant bleeding. The data are practically superimposable with those observed in the case of rivaroxaban for this same indication.

If we make an indirect adjusted comparison between rivaroxaban and betrixaban based on data from the MAGELLAN and APEX trials, we find that there is no statistically significant difference in the primary efficacy endpoint (RR = 1.01 [0.76-1.35]) nor in the incidence of clinically relevant bleeding (RR = 1.27 [0.83-1.93]).

The EMA decided to reject the authorization of betrixaban mainly because of the results of the APEX trial. Nevertheless, it appears that rivaroxaban and betrixaban are drugs with a similar efficacy and safety profile.

Rivaroxaban in the prevention of thromboembolism after hospitalization for an acute medical illness

A randomized, double-blind clinical trial (MARINER) was carried out to evaluate the efficacy and safety of rivaroxaban 10 mg/day compared with placebo in the prevention of thromboembolic events after hospitalization in patients at high risk of venous thromboembolism.[18] A total of 12,024 patients were randomized to receive treatment for 45 days after discharge from hospital. The primary efficacy endpoint was the incidence of symptomatic venous thromboembolism or death due to venous thromboembolism. The primary safety endpoint was the incidence of major bleeding.

The use of rivaroxaban was associated with a statistically significant decrease in the incidence of symptomatic venous thromboembolism. However, no difference in mortality from this cause was found, leading to no difference in the primary efficacy endpoint. On the other hand, a significant increase in the incidence of clinically relevant bleeding was observed.

In this trial, three cases of bleeding at critical location in the rivaroxaban group and two cases in the placebo group were registered. Bleeding locations considered as critical in the trial protocol included the following: intracranial,

Table 9. Results of the APEX trial (total population).

	Betrixaban	Enoxaparin	RR (95% CI)
	N (%)	N (%)	
Efficacy endpoints (analyzed in the total population: n=3,112 [betrixaban]; n=3,174 [enoxaparin])			
Primary endpoint*	165 (5.3)	223 (7.0)	0.76 (0.63 - 0.92)
Asymptomatic proximal DVT	133 (4.3)	176 (5.5)	0.77 (0.62 - 0.96)***
Symptomatic proximal or distal DVT	14 (0.4)	22 (0.6)	0.65 (0.33 - 1.27)***
Non-fatal symptomatic pulmonary embolism	9 (0.2)	18 (0.5)	0.51 (0.23 - 1.13)***
Mortality by DVT	13 (0.3)	17 (0.5)	0.78 (0.38 - 1.60)***
Symptomatic episodes	35 (0.9)	54 (1.5)	0.64 (0.42 - 0.98)
Safety endpoints (analyzed in the safety population: n=3,716 [betrixaban]; n=3,716 [enoxaparin])			
Primary safety endpoints†	25 (0.67)	21 (0.57)	1.19 (0.67 - 2.12)
Clinically relevant non-major bleeding	91 (2.45)	38 (1.02)	2.39 (1.64 - 3.49)
Clinically relevant bleeding**	116 (3.12)	59 (1.59)	1.97 (1.44 - 2.68)

CI: Confidence Interval. **n:** Number of subjects with event. **RR:** Risk ratio. **DVT:** Deep vein thrombosis.
(*) Asymptomatic proximal deep vein thrombosis, symptomatic proximal or distal deep vein thrombosis, non-fatal symptomatic pulmonary embolism or mortality by DVT.
(**) Sum of major bleeding and clinically relevant non-major bleeding.
(***) Calculated by the authors.
(†) Major bleeding.

intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or compartment syndrome. The location of the observed events was not specified in the publication.

For all the above reasons, the use of rivaroxaban in the prevention of thromboembolism after hospitalization for an acute medical illness is not recommended.

Rivaroxaban in patients with heart failure, sinus rhythm, and coronary disease

A randomized, double-blind clinical trial (COMMANDER-HF) was performed to evaluate the efficacy of rivaroxaban in the prevention of thromboembolism in patients with heart failure, sinus rhythm, and coronary disease.[19] A total of 5,022 patients diagnosed with chronic heart failure with an ejection fraction of ≤40%, coronary artery disease and elevated plasma natriuretic peptides were included. Patients were required to be free of atrial fibrillation, and they were randomized to receive rivaroxaban 2.5 mg/12h or placebo. The primary endpoint was overall mortality, myocardial infarction or stroke. The primary safety endpoint was the incidence of fatal bleeding or bleeding at critical location with the potential to cause permanent disability. Median follow-up was 21 months. The results of this trial are summarized in Table 11.

No statistically significant differences were observed between rivaroxaban 2.5 mg/12h and placebo in the primary efficacy endpoint. However, a higher incidence of major bleeding was observed in the rivaroxaban group, so the use of this drug in the indication evaluated is not recommended.

Rivaroxaban in patients with recent acute coronary syndrome

A randomized, double-blind, placebo-controlled clinical trial (ATLAS ACS 2-TIMI 51) was conducted to investigate the potential improvement in cardiovascular parameters with the administration of rivaroxaban in patients with recent acute coronary syndrome. A total of 15,526 patients were randomized to receive 2.5 or 5 mg/12h of rivaroxaban or placebo.[20]

The duration of the trial was 13 months on average, with a maximum follow-up of 31 months. The primary safety endpoint was major bleeding according to TIMI criteria (risk score for acute coronary syndrome), not related to aorto-coronary bypass graft. The main results of this trial are shown in Table 12.

Data show a statistically significant reduction in the incidence of the primary endpoint with rivaroxaban but, at the same time, an increased incidence of major bleeding and intracranial hemorrhage. When different strategies of analysis are considered or the two explored doses of rivaroxaban are assessed, no consistent differences in overall or cardiovascular mortality are seen. Considering all aspects together, this new anticoagulant cannot be recommended in the clinical setting of recent acute coronary syndrome.

Rivaroxaban in patients with or without ASA in stable cardiovascular disease

A randomized, double-blind clinical trial (COMPASS) was conducted to evaluate the efficacy of rivaroxaban in preventing cardiovascular events in patients with stable cardiovascular disease[21] we randomly assigned

Table 10. Results of the MARINER trial (intention-to-treat analysis).

	Rivaroxaban	Placebo	HR (95% CI)
	N (%)	N (%)	
Efficacy endpoints (intention-to-treat population: n=6,007 [rivaroxaban]; n=6,012 [placebo])			
Primary endpoint*	50 (0.83)	66 (1.10)	0.76 (0.52 - 1.09)
Death by thromboembolism	43 (0.72)	46 (0.77)	0.93 (0.62 - 1.42)
Symptomatic thromboembolism	11 (0.18)	25 (0.42)	0.44 (0.22 - 0.89)
Safety endpoints (safety population: n=5,982 [rivaroxaban]; n=5,980 [placebo])			
Primary endpoint (major bleeding)	17 (0.28)	9 (0.15)	1.88 (0.84 - 4.23)
Clinically relevant non-major bleeding	85 (1.42)	51 (0.85)	1.66 (1.17 - 2.35)
Other bleeding	54 (0.90)	34 (0.57)	1.59 (1.03 - 2.44)

HR: Hazard ratio. **CI:** Confidence interval. **n:** Number of subjects with event.
(*) Symptomatic venous thromboembolism or death by venous thromboembolism.

Table 11. Results of the COMMANDER-HF trial (total population).

	Rivaroxaban	Placebo	HR(95% CI)
	N (%)	N (%)	
Efficacy endpoints (analyzed in the total population: n=2,507 [rivaroxaban]; n=2,515 [placebo])			
Primary endpoint*	626 (25.0)	658 (26.2)	0.94 (0.84 - 1.05)
Overall mortality	546 (21.8)	556 (22.1)	0.98 (0.87 - 1.10)
Myocardial infarction	98 (3.9)	118 (4.7)	0.83 (0.63 - 1.08)
Stroke	51 (2.0)	76 (3.0)	0.66 (0.47 - 0.95)
Safety endpoints (n=2,499 [rivaroxaban]; n=2,509 [placebo])			
Primary endpoint**	18 (0.7)	23 (0.9)	0.80 (0.43 - 1.49)
Major bleeding	82 (3.3)	50 (2.0)	1.68 (1.18 - 2.39)
Bleeding at critical location	25 (1.0)	23 (0.9)	1.12 (0.63 - 1.97)

HR: Hazard ratio. **CI:** Confidence interval. **n:** Number of subjects with event.
(*) Overall mortality, myocardial infarction or stroke. (**) Fatal bleeding or bleeding at critical location with the potential to cause permanent disability.

Table 12. Results of the ATLAS ACS 2-TIMI 51 trial.

	Rivaroxaban 2.5 and 5 mg /12h+ASA combined (n = 10,229)	Placebo (n = 5,113)	HR (95% CI)	P	
	N (%)	N (%)		Modified ITT	ITT
Efficacy endpoints					
Primary endpoint (cardiovascular mortality, myocardial infarction, stroke)	626 (8.9%)	376 (10.7%)	0.84 (0.74 - 0.96)	0.008	0.002
CV mortality	226 (3.3%)	143 (4.1%)	0.80 (0.65 - 0.99)	0.04	0.05
Myocardial infarction	384 (5.5%)	229 (6.6%)	0.85 (0.72 - 1.00)	0.047	0.01
Stroke	100 (1.6)	41 (1.2)	1.24 (0.86 - 1.78)	0.25	0.19
Overall mortality	245 (3.7%)	153 (4.5%)	0.81 (0.66 - 1.00)	0.04	0.08
Safety endpoints					
Primary endpoint (major TIMI bleeding not associated with bypass graft)	147 (2.1)	19 (0.6)	3.96 (2.46 - 6.38)	<0.001	
TIMI bleeding requiring medical attention	1129 (14.5)	282 (7.5)	2.09 (1.83 - 2.38)	<0.001	
Intracranial hemorrhage	32 (0.6)	5 (0.2)	3.28 (1.28 - 8.42)	0.009	
Fatal bleeding	21 (0.3%)	9 (0.2%)	1.19 (0.54 - 2.59)	0.66	

HR: Hazard ratio. **CI:** Confidence interval. **CV:** Cardiovascular. **ITT:** Intention-to-treat analysis. **N:** Number of subjects with event.
TIMI: Thrombosis in myocardial infarction. **ASA:** Acetylsalicylic acid.

27,395 participants with stable atherosclerotic vascular disease to receive rivaroxaban (2.5 mg twice daily. Two experimental groups were established, rivaroxaban 2.5 mg/12h + ASA 100 mg/day and rivaroxaban 5 mg/12h, both versus ASA 100 mg/day. Double-blinding with placebo was performed.

A total of 27,395 patients participated in this trial and were followed for an average of 23 months. The primary endpoint was cardiovascular mortality, myocardial infarction or stroke. The primary safety endpoint was the incidence of major bleeding. Another variable was the net clinical benefit, i.e. composite variable of cardiovascular mortality, myocardial infarction, stroke, fatal bleeding or symptomatic bleeding in a critical organ. Results are summarized in Table 13.

As shown in the table, the association of rivaroxaban 2.5 mg/12h with ASA seems to have a slight clinical benefit over the use of ASA in monotherapy, which can be quantified as a 0.6% annual reduction in the incidence of events in the combined variable of cardiovascular mortality, myocardial infarction, stroke, fatal bleeding or symptomatic bleeding in critical organ. The fact that the effect size is so low makes us question the efficacy of the intervention.

On the other hand, when comparing rivaroxaban at high doses in monotherapy (5 mg/12h) versus ASA, no statistically significant differences in efficacy endpoints are found. Conversely, a statistically significant increase in major bleeding and no net clinical benefit are observed. Therefore, the use of rivaroxaban in stable cardiovascular disease is highly questionable.

Cancer patients and thromboembolism

Apixaban

A randomized, double-blind, placebo-controlled clinical trial (AVERT) evaluating the efficacy and safety of apixaban 2.5 mg/12h in the prevention of thromboembolism in outpatients with cancer and at moderate to high risk of thromboembolism at the beginning of chemotherapy was published.[22]

A total of 574 patients were randomized, of which 563 were included in the modified intention-to-treat analysis. Follow-up was 180 days. The main efficacy endpoint was the incidence of objectively documented venous thromboembolism. The primary endpoint was the incidence of major bleeding. Table 14 shows the most important results of the trial.

Apixaban reduced the incidence of objectively documented venous thromboembolism and led to an increase in major bleeding, both statistically significant. In this patient setting, mortality is particularly relevant given that this condition entails a significant mortality risk. Accordingly, mortality is approximately 10% at 6 months. The use of apixaban was not associated with a benefit in mortality.

On the other hand, a randomized, open-label, non-inferiority trial on the efficacy and safety of apixaban versus dalteparin in the treatment of thromboembolism in cancer patients (Caravaggio) has been published.[23] Apixaban was administered at a dose of 10 mg/12h during the first 7 days and then at a dose of 5 mg/12h for the rest of the time. Dalteparin was administered at a dose of 200 IU/kg/day during the first month and then 150 IU/kg/day. The duration of treatment was 6 months.

A total of 1,155 patients were included. The incidence in the recurrence of venous thromboembolism (primary efficacy endpoint) with apixaban versus dalteparin was 5.6% *vs* 7.9% (HR= 0.63 [0.37-1.07]), respectively. The incidence of major bleeding (primary safety endpoint) with apixaban versus dalteparin was 3.8% *vs* 4.0% (HR=0.82 [0.40-1.69]). Apixaban was considered to be not inferior to dalteparin in this trial.

Edoxaban

A randomized, open-label, non-inferiority clinical trial (Hokusai VTE) was conducted to evaluate the efficacy and safety of edoxaban 60 mg/day versus dalteparin (150 IU/kg/day) in cancer patients with an acute symptomatic or incidental episode of thromboembolism.[24]

A total of 1,050 patients were randomized, of which 1,046 were included in the intention-to-treat analysis. Patients were treated for 6 to 12 months. The primary

Tabla 13. Results of the COMPASS trial.

	Rivaroxaban 2.5 mg/12h+ASA (n = 9,152)	Rivaroxaban 5 mg/12h (n = 9,117)	ASA (n = 9,126)	Rivaroxaban 2.5 mg/12h+ASA *vs.* ASA HR (95% CI)	Rivaroxaban 5 mg/12h *vs.* ASA HR (95% CI)
	N (%)	N (%)	N (%)		
Efficacy endpoints					
Primary endpoint*	379 (4.1)	448 (4.9)	496 (5.4)	0.76 (0.66 - 0.86)	0.90 (0.79 - 1.03)
CV mortality	160 (1.7)	195 (2.1)	203 (2.2)	0.78 (0.64 - 0.96)	0.96 (0.79 - 1.17)
Myocardial infarction	178 (1.9)	182 (2.0)	205 (2.2)	0.86 (0.70 - 1.05)	0.89 (0.73 - 1.08)
Stroke	83 (0.9)	117 (1.3)	142 (1.6)	0.58 (0.44 - 0.76)	0.82 (0.65 - 1.05)
Safety endpoints					
Primary endpoint (major bleeding)**	288 (3.1)	255 (2.8)	170 (1.9)	1.70 (1.40 - 2.05)	1.51 (1.25 - 1.84)
Intracranial hemorrhage	28 (0.3)	43 (0.5)	24 (0.3)	1.16 (0.67 - 2.00)	1.80 (1.09 - 2.96)
Net clinical benefit/harm***	431 (4.7)	504 (5.5)	534 (5.9)	0.80 (0.70 - 0.91)	0.94 (0.84 - 1.07)

HR: Hazard ratio. **CI:** Confidence interval. **N:** Number of subjects with event. **ASA:** Acetylsalicylic acid.
(*) Cardiovascular mortality, myocardial infarction or stroke.
(**) Includes: fatal bleeding, symptomatic critical organ bleeding, bleeding at surgical site leading to hospitalization, and bleeding leading to hospitalization.
(***) Cardiovascular mortality, myocardial infarction, stroke, fatal bleeding or symptomatic bleeding in critical organ.

Table 14. Results of the AVERT trial (modified intention-to-treat analysis).

	Apixaban N= 288	Placebo N= 275	HR (95% CI)
	N (%)	N (%)	
Venous thromboembolism	12 (4.2)	28 (10.2)	0.41 (0.26 - 0.65)
Major bleeding	10 (3.5)	5 (1.8)	2.00 (1.01 - 3.95)
Clinically relevant non-major bleeding	21 (7.3)	15 (5.5)	1.28 (0.89 - 1.84)
Overall mortality	35 (12.2)	27 (9.8)	1.29 (0.98 - 1.71)

HR: Hazard ratio. **CI:** Confidence interval. **N:** Number of subjects with event.

Table 15. Results of the Hokusai VTE trial (modified intention-to-treat analysis).

	Edoxaban N= 522	Dalteparin N= 524	HR (95% CI)
	N (%)	N (%)	
Primary endpoint			
Recurrent venous thromboembolism or major bleeding	67 (12.8)	71 (13.5)	0.97 (0.70 - 1.36)
Secondary endpoints			
Recurrent venous thromboembolism	41 (7.9)	59 (11.3)	0.71 (0.48 - 1.06)
Major bleeding	36 (6.9)	21 (4.0)	1.77 (1.03 - 3.04)
Clinically relevant non-major bleeding	76 (14.6)	58 (11.1)	1.38 (0.98 - 1.94)
Major or clinically relevant bleeding	97 (18.6)	73 (13.9)	1.40 (1.03 - 1.89)
Overall mortality	206 (39.5)	192 (36.6)	1.12 (0.92 - 1.37)

HR: Hazard ratio. **CI:** Confidence interval. **N:** Number of subjects with event.

efficacy endpoint was the incidence of recurrent venous thromboembolism or major bleeding during the 12 months following randomization, regardless of the duration of treatment. The most relevant results of the trial are shown in Table 15.

No statistically significant differences were found in the primary endpoint. Regarding the secondary endpoints, no significant differences were found between the two drugs in the incidence of recurrent venous thromboembolism or in overall mortality. Edoxaban showed a higher incidence of major bleeding.

Rivaroxaban

A randomized, double-blind, placebo-controlled clinical trial (CASSINI) was published. This trial evaluated the efficacy and safety of rivaroxaban 10 mg/day in the prevention of thromboembolism in cancer outpatients who were at high risk of thromboembolism.[25]

The primary efficacy endpoint was composed of objectively confirmed proximal venous thrombosis, deep vein thrombosis in the lower limb, pulmonary embolism, symptomatic deep vein thrombosis in the upper limb, distal deep vein thrombosis in the lower limb and death by venous thromboembolism. The primary safety endpoint was the incidence of major bleeding.

A total of 1,080 were recruited, but only 841 of them were eventually randomized. The primary endpoint was evaluated at 180 days. Table 16 shows the main results of the trial.

Rivaroxaban showed no statistically significant differences in efficacy and safety endpoints compared to placebo.

Patients undergoing minor orthopedic surgery

A randomized, double-blind, non-inferiority clinical trial (PRONOMOS) evaluating the efficacy and safety of rivaroxaban 10 mg/day versus enoxaparin 40 mg/day in minor surgery of the lower limbs has been published.[26] A total of 3,604 patients were randomized. The incidence of major thromboembolism (primary efficacy endpoint) with rivaroxaban versus enoxaparin was 0.2% *vs* 1.1% (HR= 0.25 [0.09-0.75]), respectively. The incidence of major or clinically relevant bleeding (safety endpoint) with rivaroxaban versus enoxaparin was 1.1% *vs* 1.0% (HR = 1.04 [0.55-2.00]), respectively.

The trial was stopped early due to slow recruitment of the anticipated 4,400 patients. Because the number of events recorded was very low (4 cases in the rivaroxaban group and 18 in the enoxaparin group), the results of this trial should be interpreted with caution. Patients were

stratified into three groups, depending on whether they received treatment for 2 weeks to 1 month; 1-2 months; or over 2 months. Better results were achieved with rivaroxaban only when it was given for 1-2 months, which is difficult to explain. The fact that the median time to event was 26 days with rivaroxaban versus 40 days with enoxaparin is also inconsistent with the claimed better efficacy of rivaroxaban.

On the other hand, the incidence of major bleeding was clearly higher than the reduction of thromboembolic episodes. This single trial is insufficient to recommend rivaroxaban in this setting.

Final thoughts

The clinical trials included in this article address the use of DOACs for long or short periods of time, for different indications. In almost all of the analyzed trials comparing the long-term use of DOACs versus other agents, DOACs showed poorer results. The only exception was the Caravaggio trial (apixaban versus dalteparin), in which no significant differences were observed. In the cases of possible new indications where DOACs were compared with placebo, the risk-benefit ratio did not favor their use (Table 17).

Three of these trials had to be stopped early: one because of increased mortality in the rivaroxaban group compared to clopidogrel (GALILEO), one because of an excess of arterial thromboses with rivaroxaban compared to warfarin (TRAPS), and one because of an unfavorable risk-benefit ratio compared to ASA (NAVIGATE ESUS). Based on the results of the trial comparing rivaroxaban with warfarin in antiphospholipid syndrome, the AEMPS explicitly recognizes that vitamin K antagonists are safer and more effective than rivaroxaban in this setting of high thromboembolic risk. It even proposes that, if the patient is being treated with a DOAC, the switching to a vitamin K antagonist should be considered.

When the potential benefit of rivaroxaban versus placebo was investigated in patients with recent acute coronary syndrome (ATLAS ACS 2-TIMI 51), a statistically significant reduction in the combined endpoint was found. However, there was an increased risk of major bleeding with the anticoagulant and no consistent benefit in mortality was observed with different doses and types of analysis.

In a trial in stable cardiovascular disease (COMPASS), a clinically irrelevant benefit of rivaroxaban+ASA versus ASA, and no benefit of rivaroxaban in monotherapy versus ASA was observed. In addition, both rivaroxaban regimens showed an increased incidence of major bleeding with rivaroxaban.

In a trial of patients with heart failure, sinus rhythm and coronary disease (COMMANDER-HF), rivaroxaban was compared versus placebo. Rivaroxaban caused a significant increase in the incidence of major bleeding, and did not provide any benefit in preventing thromboembolism.

In cancer patients, edoxaban showed less net clinical benefit than dalteparin in the prevention of recurrent thromboembolism (Hokusai VTE). In the prevention of thromboembolism in patients at risk, both apixaban (AVERT) and rivaroxaban (CASSINI) showed inconclusive or no clinical benefit versus placebo.

Regarding the use of dabigatran or rivaroxaban in short-term trials (Table 18), it was observed that, in patients with cardiac valve prostheses, the results for dabigatran were not favorable (RE-ALIGN) what prompted the early termination of the trial. Similarly, in hospitalized patients with acute medical illnesses, enoxaparin reduced outcomes better than rivaroxaban (MAGELLAN). Compared to placebo, the use of rivaroxaban after hospitalization for acute medical illnesses (MARINER-HF) was not associated with any benefit in the reduction of symptomatic venous thromboembolism or in mortality. However, rivaroxaban caused a significant increase in the incidence of bleeding.

Table 16. Results of the CASSINI trial ("intention-to-treat" analysis).

	Placebo	Rivaroxaban	HR (95% CI)
	N (%)	N (%)	
Efficacy endpoints (intention-to-treat population: n=421 [placebo]; n=420 [rivaroxaban])			
Primary endpoint*	37 (8.8)	25 (6.0)	0.66 (0.40 - 1.09)
Safety endpoints (n=404 [placebo]; n=405 [rivaroxaban])			
Major bleeding (primary)	4 (1.0)	8 (2.0)	1.96 (0.59 - 6.49)
Clinically relevant non-major bleeding	8 (2.0)	11 (2.7)	1.34 (0.54 - 3.32)
Major or clinically relevant bleeding	12 (3.0)	19 (4.7)	1.54 (0.75 - 3.17)

HR: Hazard ratio. **CI:** Confidence interval. **N:** Number of subjects with event.
(*) Objectively confirmed proximal venous thrombosis, deep vein thrombosis in the lower limb, pulmonary embolism, symptomatic deep vein thrombosis in the upper limb, distal deep vein thrombosis in the lower limb and death by venous thromboembolism.

Table 17. Results of long-term use of DOACs in different situations.

Trial	Indication	DOAC	Comparator	Duration	Results	Comments
COMMANDER-HF[19]	Heart failure, sinus rhythm and coronary disease	Rivaroxaban 2.5 mg/12h	Placebo	21 months (median)	No benefit in preventing thromboembolism and significant increase in major bleeding.	Risk-benefit ratio unfavorable to intervention.
GALILEO[8]	Transcatheter aortic valve replacement	Rivaroxaban 10 mg/d	Clopidogrel 75 mg/d	17 months (median)	Increased mortality with rivaroxaban.	Trial suspended due to increased mortality associated with rivaroxaban.
TRAPS[5]	Antiphospholipid syndrome	Rivaroxaban 20 mg/d	Warfarin	569 days (median)	Significant increase in thromboembolism and major bleeding in the rivaroxaban group.	Trial prematurely suspended due to excessive events with rivaroxaban. Small sample size, but significantly increased risk with rivaroxaban.
SÍNDROME ANTIFOSFOLÍPIDO[7]	Antiphospholipid syndrome	Rivaroxaban 20 mg/d	Acenocumarol	3 years	Rivaroxaban failed to demonstrate non-inferiority to acenocoumarol	Acenocoumarol showed better net clinical benefit than rivaroxaban.
NAVIGATE ESUS[11]	Prevention of recurrent stroke after embolic stroke of unknown origin	Rivaroxaban 15 mg/d	ASA 100 mg/d	11 months (median)	Lack of efficacy and significant increase in bleeding.	The trial was suspended due to unfavorable risk-benefit ratio.
RE-SPECT ESUS[13]	Prevention of recurrent stroke after embolic stroke of unknown origin	Dabigatran 150 mg or 110 mg/12h	ASA 100 mg/d	19 months (median)	No benefit in preventing thromboembolism and significant increase in major or clinically relevant bleeding.	ASA showed improved net clinical benefit.
ATLAS ACS 2 – TIMI 51[20]	Recent acute coronary syndrome	Rivaroxaban 2.5 mg or 5 mg/12h	Placebo	13 months (mean)	Reduced risk in the primary composite variable and increased major bleeding and intracranial hemorrhage.	Inconclusive net clinical benefit versus placebo. No consistent effect on mortality with different doses and type of analysis.
COMPASS[21]	Stable cardiovascular disease	Rivaroxaban 5 mg/12h Rivaroxaban 2.5 mg/12h + ASA 100 mg/d	ASA 100 mg/d	23 months	Non-significant benefit of rivaroxaban+ASA; no net clinical benefit with rivaroxaban 5 mg/12h	Non-significant or absent net clinical benefit.
AVERT[22]	Apixaban in outpatients with cancer and moderate to high risk of thromboembolism	Apixaban 2.5 mg/12h	Placebo	6 months	Apixaban reduced the incidence of objectively documented venous thromboembolism, but increased major bleeding.	Inconclusive net clinical benefit versus placebo. No effect on mortality.
Hokusai VTE[24]	Edoxaban in cancer patients with thromboembolism	Edoxaban 60 mg/d	Dalteparin 150 IU/day	12 months	Edoxaban did not show advantages in thromboembolism and increased major bleeding.	Dalteparin has better net clinical benefit. No effect on mortality.
Caravaggio[23]	Apixaban in the treatment of thromboembolism in cancer patients	Apixaban 5 mg/12h	Dalteparin 150 IU/Kg/day	6 months	No differences were observed between the drugs investigated nor in the incidence of recurrent thromboembolism or bleeding.	Apixaban is non-inferior to dalteparin.
CASSINI[25]	Rivaroxaban in cancer outpatients at high risk of thromboembolism	Rivaroxaban 10 mg/day	Placebo	6 months	Rivaroxaban showed no statistically significant differences in efficacy and safety compared to placebo.	No net clinical benefit over placebo.

ASA: Acetylsalicylic acid.

All trials found with the search criteria used in this review studying new indications for rivaroxaban showed worse outcomes or no benefit versus placebo, antiplatelets and anticoagulants, including warfarin. This should lead to many questions about these drugs. However, there is a lack of critical thinking among most healthcare stakeholders. Many years have passed since these medicines were marketed, but despite that we have not been able to obtain full access to the clinical trial data in order to determine what their place in therapy should be.

The EMA authorized dabigatran and rivaroxaban in 2009, apixaban in 2011, and edoxaban in 2015. In 2019 the EMA refused to authorize the marketing of betrixaban, which has been authorized by the FDA in the USA.

In 2011, DTB Navarre published an article highlighting logical and necessary cautions with the emergence of this new class of drugs, for which there was particularly limited evidence. They had been authorized under an accelerated procedure on the grounds that they were supposed to meet an "unsatisfied medical need". The first of these drugs in the European series, dabigatran, was authorized while the pivotal trial (RE-LY)[27] was still underway.

In 2016, DTB Navarre published a further article entitled *Incertidumbres sobre los nuevos anticoagulantes orales en fibrilación auricular: irregularidades y lagunas en su autorización* ("Uncertainties about new oral anticoagulants in atrial fibrillation: deficiencies and irregularities in the authorization process"). This paper described serious irregularities in notable trials with the new anticoagulants, such as the concealment and falsification of data from the pivotal trials that led to the authorization of the first indications for these drugs.

Important figures in the world of healthcare have drawn a veil over this matter, ignoring the alerts issued about these drugs. The pharmaceutical industry refuses to provide complete information on clinical trials with DOACs, leading to a great deal of mistrust in the reliability of the results they once published. For their part, scientific journals and some scientific societies have clearly fallen short in their role as guarantors of quality scientific production. They have uncritically taken on board the messages about the supposed efficacy and safety of these medicines and have not shown the minimum effort required to seek out and claim the real available information. Regulatory agencies around the world, including the EMA, have also looked the other way by not giving due weight to the warning signals given by their own reviewers. It would be particularly important for the agencies to truly defend the interests of patients and to move towards greater transparency about the data they hold.

As a result, there is a widespread belief that the new oral anticoagulants are safe and effective, and that no monitoring of coagulation parameters is required for their use. At the same time, the idea that it is necessary to increase the number of anticoagulated patients is also being promoted, in line with the mantra present in many other medical fields that the more aggressive we are in dealing with diseases or risk factors, the better the outcome for the population.

For instance, the European Society of Cardiology (ESC) Guidelines for the Management of Atrial Fibrillation[28] propose anticoagulation for men with a CHA_2DS_2-Vasc score ≥1 and women with a CHA_2DS_2-Vasc ≥2. This is based on a study commissioned by the ESC itself, which was carried out with information from an English database (CALIBER). This database includes information from four other sources: some from the primary care information from the CPRD GOLD database, the hospital episode database (Hospital Episode Statistics, HES), data on hospital admissions due to acute coronary syndrome from the Myocardial Ischaemia National Audit Project (MINAP), and mortality data from the Office National Statistics.

Table 18. Results of the short-term use of DOACs in different settings.

Trial	Indication	DOAC	Comparator	Duration	Results	Comments
RE-ALIGN[3]	Mechanical heart valve prosthesis	Dabigatran (150, 220, 300 mg/d)	Warfarin	12 weeks	Increased number of thromboembolic and haemorrhagic events in the dabigatran group	Risk-benefit ratio unfavorable to dabigatran
MAGELLAN[15]	Patients hospitalized for acute medical illness	Rivaroxaban 10 mg/d, 35±4 days	Enoxaparin 40 mg/d, 10±4 días	45 days	Reduction of 1.3% in the primary endpoint and increase of 2.4% in significant bleeding	Risk-benefit ratio unfavorable to rivaroxaban
APEX[17]	Patients hospitalized for acute medical illness	Betrixaban 80 mg/d	Enoxaparin 40 mg/d, 10±4 days	42 days	Reduction of 1.7% in the primary endpoint and increase of 1.5% in significant bleeding	Neutral risk-benefit ratio
MARINER[18]	After hospitalization for acute medical illness	Rivaroxaban 10 mg/d,	Placebo	45 days	No benefit in symptomatic venous thromboembolism or in mortality and significantly increased bleeding	Risk-benefit ratio unfavorable to rivaroxaban
RE-SPECT CVT[14]	Prevention of recurrent stroke after thromboembolic stroke	Dabigatran 150 mg/12h	Warfarin	24 weeks		This is an exploratory trial
PRONOMOS[26]	Minor orthopedic surgery	Rivaroxaban 10 mg/day, duration based on clinical assessment	Enoxaparin 40 mg/day	Undefined	Lower incidence of thromboembolism in the rivaroxaban group and similar incidence of bleeding	Trial with many methodological limitations. The incidence of major bleeding is much higher than the reduction of thromboembolism. Risk-benefit ratio unfavorable to intervention

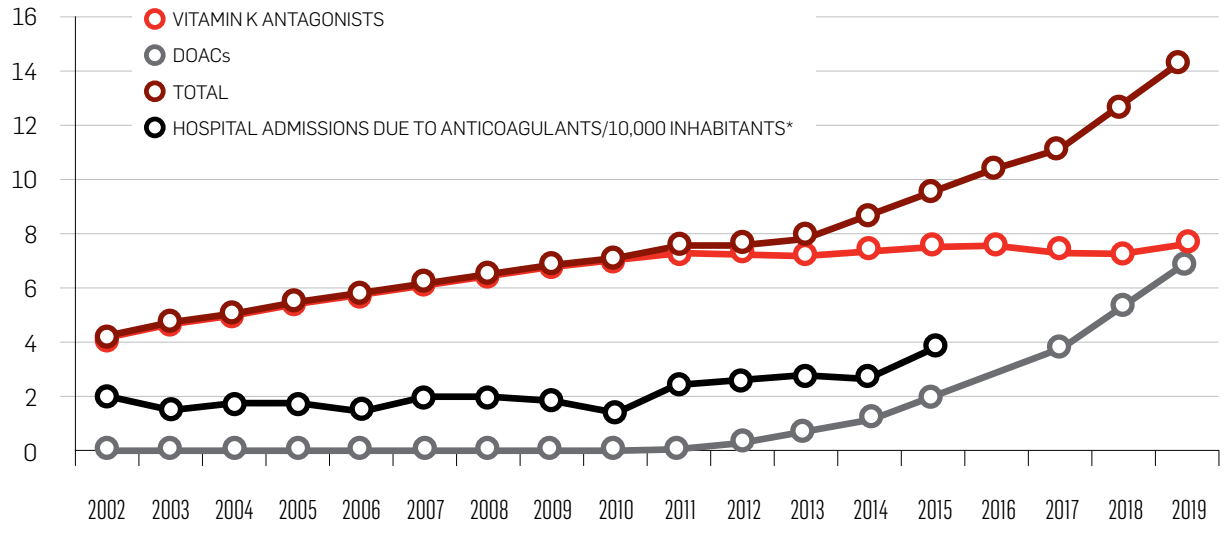
When the ESC published this recommendation, the research that was supposed to support it had not even been published – it was done a year later.[29] In this article it can be seen that, in the general population, some net benefit is beginning to be obtained from treatment with anticoagulants from a CHA_2DS_2-Vasc ≥3. Below this threshold, there are no statistically significant differences between treating and not treating. In the case of men, some net benefit from a CHA_2DS_2-Vasc ≥2 (although those scoring "2" have clinically irrelevant benefits) can be observed. In women, the only benefit is seen with a CHA_2DS_2-VASc ≥3. Therefore, the ESC Guidelines recommendation is not justified by the data from the study to which it refers.

On the other hand, other studies suggest that the use of the $CHADS_2$ score has a better predictive value than the CHA_2DS_2-VASc score in elderly patients with atrial fibrillation, which is the main population for this condition.[30] At least, one would expect that scientific societies would be rigorously evaluating these issues, but this seems not to be the case.

Over the last few years, numerous observational and real-life studies have been published attempting to provide complementary information about the efficacy and safety of DOACs. A detailed analysis of these studies would require a separate article. However, it should be noted that the vast majority of these studies have been conducted in non-validated databases and use methodologies with significant weaknesses and biases that tend to favor the results of DOACs.

In the Navarre Health Service (Servicio Navarro de Salud-Osasunbidea, SNS-O) we studied the evolution of hospital admissions caused by anticoagulants and the use of anticoagulants from 2002 to the present (Figure 1). It can be seen that, since the commercialization of DOACs, the increase in the use of vitamin K antagonists has stagnated, while the overall increase in the use of anticoagulants is due to the increase of DOACs. An increase in hospital admissions caused by anticoagulants is also observed after 2010, which coincides with the increase in the use of DOACs. This data should be taken with caution, as it is an ecological study and, therefore, it would be imprudent to assign causality. However, it must be recognized that the evidence observed is important, and it would be irresponsible not to explore the hypothesis that the use of DOACs was associated with an increase in hospital admissions.

Figure 1. Use of anticoagulants and admissions due to anticoagulants in Navarre.



(*) Admissions due to ADRs of DOACs are shown until 2015 because the ICD-9 was changed to the ICD-10 in 2016 and the ICD-9 code E934.2 has no equivalent in the ICD-10.

Figure 2 shows the evolution of the rate of hospital admissions in the population of Navarre >70 years of age due to ischemic stroke and major bleeding, with a certain upward trend from 2011 to 2015 that seems to be reduced, at least partially, from 2016 onwards.

In November 2019 the protocol for the first randomized clinical trial to evaluate the safety of replacing a vitamin K antagonist with a DOAC in elderly patients with atrial fibrillation was published.[31] It is funded by *The Netherlands Organisation for Health Research and Development (ZonMw)* and results are expected in 2022. In fact, this is a common practice that is becoming established in many patients, but, unfortunately, without data to support it. However, the information from this relevant clinical trial will be accessible more than a decade after the start of use of these drugs, when their patent has expired.

Finally, the public healthcare system does not seem to perceive the need to play a major role in this controversy. Public healthcare systems should be more involved in promoting independent clinical trials to answer the urgent and important questions that need to be answered and that pharmaceutical companies do not even want to pose. They also have an important responsibility to train their healthcare professionals through activities that are free of conflict of interest with the companies that market medicines. There is clearly still a great opportunity for improvement in these areas.

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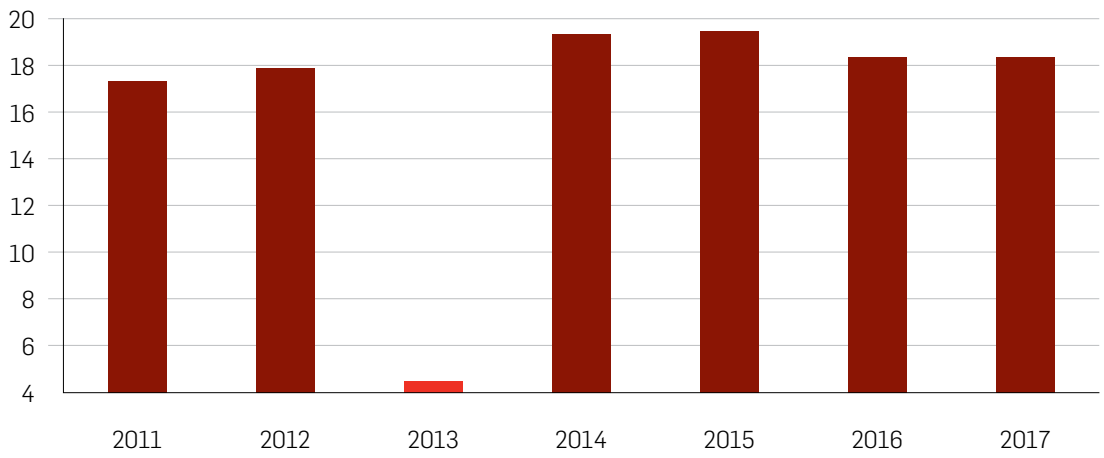
Figure 2. Hospital admission rate for ischemic stroke + major bleeding in patients over 70 years of age in Navarre.



Source: Basic Minimum Data Set (Navarre).
Note: The figure for 2013 suggests a problem in coding the diagnoses of interest in that period and should not be considered valid.

Conclusions

Rivaroxaban had a higher incidence of thromboembolic events than warfarin in patients with antiphospholipid syndrome. The trial was terminated prematurely due to this fact. The AEMPS proposes that, in these patients treated with a DOAC, switching to a vitamin K antagonist should be considered.

Three other clinical trials have been stopped early: the first one because of increased mortality in the rivaroxaban group compared to clopidogrel in transcatheter aortic valve replacement; the second one because of an unfavorable risk-benefit ratio compared to ASA in the prevention of recurrent stroke after embolic stroke of unknown origin; the third one because of an increased risk of thromboembolism and bleeding with dabigatran compared to warfarin in patients with cardiac valve prostheses.

In a trial in patients with stable cardiovascular disease, a non-significant clinical benefit of rivaroxaban+ASA versus ASA and no benefit of rivaroxaban in monotherapy versus ASA were observed. In acute coronary syndrome, the net clinical benefit of rivaroxaban versus placebo is unclear because of an increased risk of major bleeding with rivaroxaban.

In one trial in patients with heart failure, sinus rhythm and coronary disease, rivaroxaban provided no benefit in preventing thromboembolism compared to placebo, while significantly increased the incidence of major bleeding.

Regarding the use of rivaroxaban for a short period of time in patients hospitalized for acute medical illnesses, the results were worse than with enoxaparin. When used after hospitalization for acute medical illnesses, no benefit in reducing symptomatic venous thromboembolism nor in mortality compared to placebo was observed. However, a significant increase in the incidence of bleeding was observed. In minor orthopedic surgery, the rivaroxaban trial had major methodological limitations.

In cancer patients, in prevention of recurrent thromboembolism, edoxaban showed worse clinical benefit as compared to dalteparin and apixaban – it has only been shown to be not inferior. In the prevention of thromboembolism in patients at risk, both apixaban and rivaroxaban showed doubtful or no clinical benefit over placebo.

Vitamin K antagonists should always be the first treatment option when patients need to be anticoagulated. DOACs should be restricted to cases where vitamin K antagonists are contraindicated, not tolerated, or where it is not possible to maintain INR levels within the therapeutic range.

THE PATIENT'S CORNER

MIGUEL ÁNGEL IMÍZCOZ

CARDIOLOGIST MEMBER OF THE EDITORIAL COMMITTEE OF DTB NAVARRE

One day, a patient with a mechanical aortic prosthesis, who requires permanent anticoagulation treatment, asked me a question. He knew from a friend that a type of anticoagulant medication had been marketed with the advantage that regular controls were not necessary and, furthermore, it was not necessary to be careful with certain foods, alcohol, etc. Why was this medication not indicated for him, rather than the one he was taking and which he needed to monitor periodically? In addition, he had the experience that, many times, when other medications were prescribed to him –especially antibiotics–, the anticoagulant was out of control.

I replied that patients wearing mechanical heart prostheses, even in the aortic position and sinus rhythm, who theoretically have a lower incidence of thromboembolic phenomena, were not prescribed this type of drug because of the results observed in a study.[3] This was a clinical trial that was stopped earlier than planned because the number of embolisms and bleeding complications was higher among patients taking the new drug than those on the same anticoagulant treatment as him.

The patient, surprised, asked me about the reason for this, and I did not know how to answer him... Would the mechanisms of thrombosis be different? Would the doses of the drug to be tested not be the right ones? But I could not explain why these "inadequate" doses produce, at the same time, more thromboses and more bleeding complications.

In short, I still do not know what to say to the patient.

Note: we remind the obligation to report suspected adverse reactions associated with these medicines at www.RAM.navarra.es and, above all, the obligation to report suspected adverse reactions under conditions other than those authorized in Spain (Royal Decree 1015/2009, of 19 June, regulating the availability of medicines in special situations).

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