

Prevention of Stroke in Patients with Atrial Fibrillation, Anticoagulation and Beyond

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Coagulation is a physiological process that has fascinated scientists since the time of Hippocrates and Aristotle. In the 19th century, fibrin (Johannes Muller), fibrinogen (Rudolph Virchow) and thrombin (Alexander Schmidt) were described, as well as the cofactor role of calcium throughout the coagulation cascade (Arthus), with the biochemistry of coagulation becoming established [1]. The pharmacological basis for antithrombotic treatment was established in the first half of the 20th century with the isolation of heparin and subsequently from oral anticoagulants anti-vitamin K, which together with aspirin, constituted the treatment antithrombotic for more than 50 years. At the beginning of the 21st century, direct oral anticoagulants (ACOD) emerged with two basic mechanisms, thrombin inhibition and factor Xa. A count of medications available for the prevention of cerebral vascular disease (CVD) is offered.

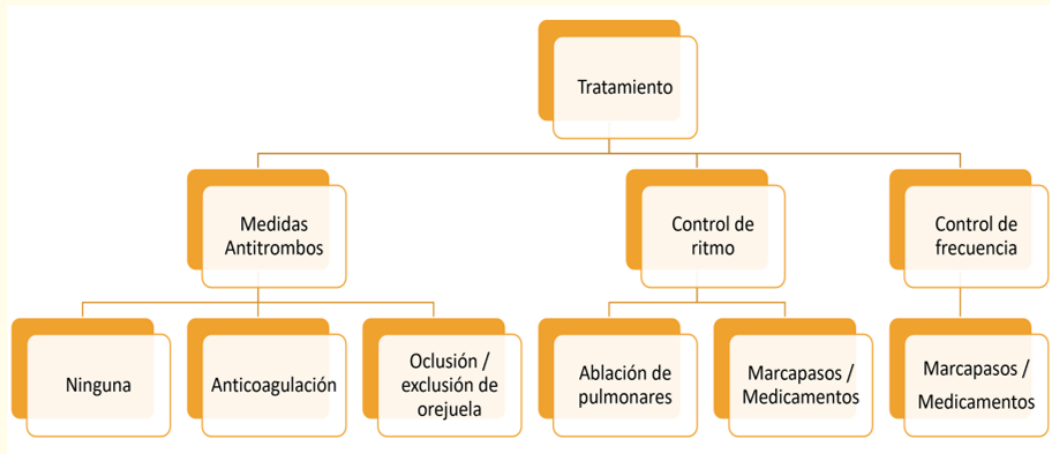


Figure 1: Treatment pillars in atrial fibrillation.

Aspirin

Discovered 2000 years ago, its antithrombotic effects by platelet inhibition were described in 1943 by Karl Link. Craven (1950) reported a series of 400 older men treated with AAS who did not develop heart attacks and a report [2] of 8,000 sick great results, including their mention to reduce stroke events. Between 1970 and 1980 the efficacy of SAA in the prevention of transient [3] cerebral infarction and ischemia was demonstrated. It is currently one of the most prescribed medicines worldwide, with AI indication in secondary prevention

of EVC in the absence of atrial fibrillation (FA), either alone or in combination with another antiplatelet anti-platelet. According to the European guide published in 2016 [4], in the patient with FA there is no recommendation to use antiplatelet agents since Warfarin showed greater efficacy than AAS alone and AAS + clopidogrel for prevention of VTe (annual risk 5.6% vs 3.9%) [5].

Oral anticoagulants anti-vitamin K (AVK)

A veterinarian reported in 1922 the prolongation of clotting times and severe bleeding in cattle consumed by Melilotus when spoiled and that the disease was cured by removing this forage from the diet. Karl Link then established the reversal ratio of the hemorrhage caused by *M. alba* with vitamin K. The Wisconsin Alumni Research Foundation (WARF) funded much of the first studies and Wright (1946) conducted the first clinical trial for treatment of myocardial infarction with warfarin. It was accepted for clinical use in 1955, the same year that U.S. President Eisenhower suffered a heart attack and was treated with Warfarin [6]. AVVs have shown in multiple studies to reduce the risk of CVD two-thirds and mortality by a quarter. 16% of patients with Warfarin have major bleeding and these lead to death, hospitalization and permanent disability up to 90% of cases. Despite their broad benefits, narrow therapeutic margin, the need for frequent monitoring and adjustment of doses, they have caused them to lose ground to ACOD, however they remain the only option of chronic anticoagulation in patients with valvular FA (moderate/severe mitral stenosis and/or mechanical valve prostheses) [4].

X-factor inhibitors

Xabanes are small synthetic molecules that inhibit reversible activated X-factor. They have a linear pharmacokinetics, lack interaction with food and have little or no interaction with other medicines, therefore do not require systematic monitoring. They achieve adequate bioavailability orally with a peak effect at 2 hours of [7] ingesting and a half-life of 10hours. In the context of the prevention of cerebral vascular disease (CVD) in patients with non-valvular atrial fibrillation rivaroxaban, apixaban and edoxaban [4] are accepted.

ROCKET AF is a double-blind, double-placebo clinical study, using Rivaroxaban 20 mg/day with a non-inferiority target compared to Warfarin [8] (INR 2.5), to prevent embolic events in patients with non-valvular FA. Rivaroxaban was no lower than Warfarin in prevention of VCV and systemic embolism, with a significant reduction in intracerebral hemorrhages.

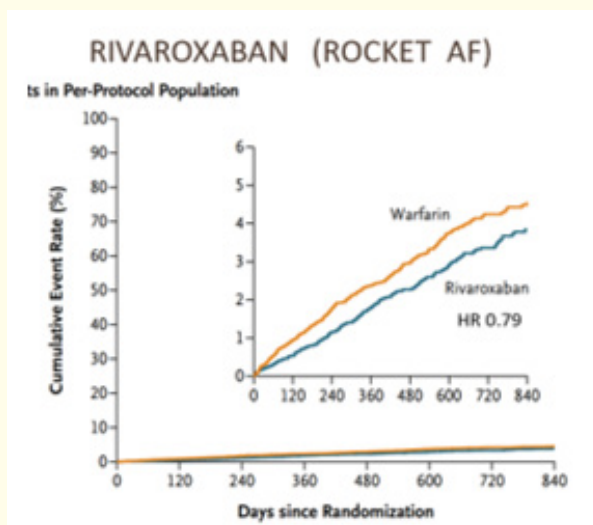


Figure 2

ARISTOTLE, double-blind, double-placebo, event-based clinical trial, where the non-inferiority of Apixaban 5mg was evaluated every 12 hrs against Warfarin (INR 2-3) for stroke prevention and systemic embolism in patients with FA. Apixaban demonstrated no inferiority for prevention of CVD (HR 0.92; 95% CI, 0.74 - 1.13; p=0.42), with a 31% decrease in major [9] bleeding, with 49% fewer brain haemorrhagic events. The AVERROES study compared Apixaban 5mg twice daily with Ac. Acetylsalicylic 81 to 324mg once daily (patients who did not tolerate or could not use AVK) and was suspended for the extensive benefits of apixaban in reducing stroke events and systemic embolism (55%), without excess bleeding [10] rate.

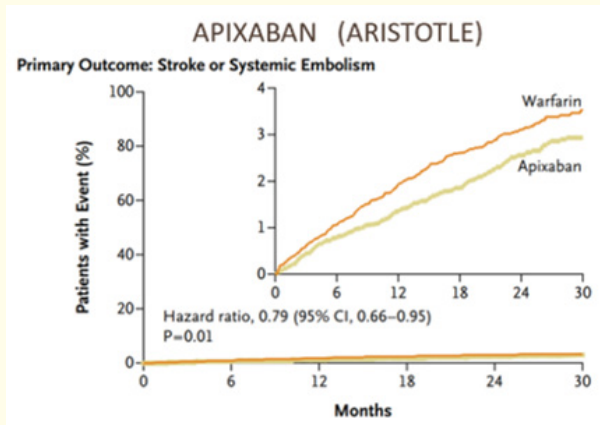


Figure 3

ENGAGE AF TIMI 48, explored the daily doses of 30 and 60 mg of Edoxaban vs Warfarin (INR 2-3), in a double-blind, double-placebo design, with more than 16,000 patients with non-valvular FA and CHA₂DS₂VASc s2. Edoxaban 60 mg daily, reduced VCV and systemic embolism by 21% and reduced major bleeding 20% compared to Warfarin. Edoxaban 30 mg daily, was no lower than Warfarin in preventing embolic events, but reduced major bleeding by 53% [11]. Only the 60 mg dose is accepted for prevention in atrial fibrillation [4].

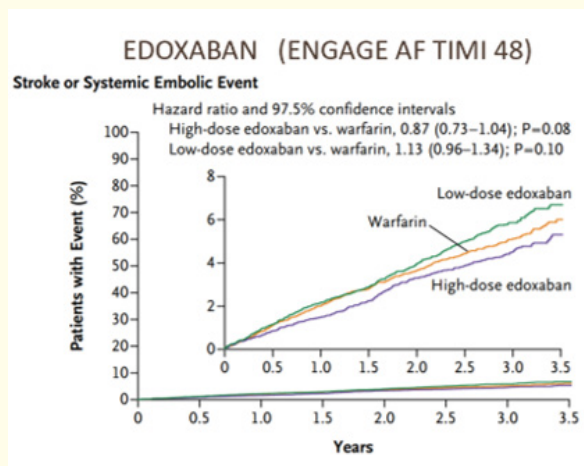


Figure 4

Direct thrombin inhibitors

Dabigatran (the only drug in the group accepted for VSE prevention) is a prodrug of intestinal, plasma and hepatic activation, with a predictable pharmacokinetics and does not require regular monitoring. It is characterized by a bioavailability of less [12] than 10%, with predominant renal excretion. It binds univally and reversibly to F IIa (thrombin). The use of dabigatran in VSE prophylaxis in faFA patient was assessed with >18,000 patients in the RE-LY study, which randomized patients at doses of 110 and 150mg twice daily vs Warfarin in blind [13] design. At low dose (110 mg x 2) dabigatran was no lower than Warfarin for prevention of vascular events (RR 0.91; 95% CI, 0.74 - 1.11; $p < 0.001$) with a better safety profile, a bleeding rate greater than 2.71 vs 3.36% Warfarin (reduction of 20%, $p < 0.003$). At the high dose (150 mg x 2), Dabigatran was more effective than Warfarin in preventing EVC (RR 0.66; 95% CI, 0.53 - 0.82; $p < 0.001$), with a similar bleeding rate (3.36% vs 3.11%), although with fewer intracranial bleeding. The mortality rate was also better with dabigatran in both groups (12%) warfarin [12].

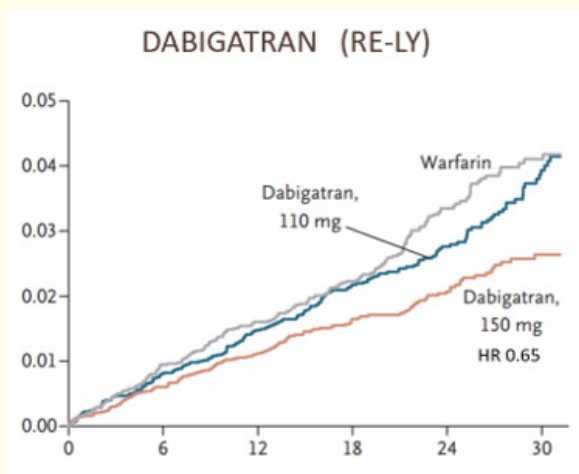


Figure 5

Corey (2012) reported a concentration of studies that includes the 3 ACODs approved at the time, with a significant decrease in any type of VSE and systemic embolism (22%), brain bleeding (51%), mortality from any cause (12%), when compared to as a group [14] vs Warfarin. Another meta-analysis with more than 42,000 patients receiving ACOD and more than 29,000 with Warfarin reports reduction of VSE and peripheral thrombosis with the use of ACOD (RR 0.81; CI 0.73 - 0.91; $p < 0.001$), reduction of intracranial bleeding 51% and a decrease in mortality of 10% in favor of ACOD [15]. There are no direct comparisons between ACLs at the moment, but there are meta-analyses that have indirectly compared them. It should be remembered that current guidelines recommend the use of ACOD above Warfarin with AI indication, for non-valvular atrial fibrillation [4,16].

Chronic kidney disease (CKD) is linked to increased risk of bleeding and thrombotic events. In patients with atrial fibrillation and CKD oral anticoagulation can be used safely with any of the approved medications and without modifying doses with leaks greater than 50 ml/min. Between 30 - 49 ml/min the main restriction is for dabigatran due to its renal elimination and it is recommended to decrease rivaroxaban to 15 mg/day, apixaban 2.5 mg x2 and edoxaban 30 mg/day [14]. In stage IV the same doses are recommended with special caution and below 15 ml/min (stage V) no ACOD is recommended, they are patients candidates for warfarin, as there are no studies controlled with ACOD in this group, nor in patients already in place with dialysis or hemodialysis [4].

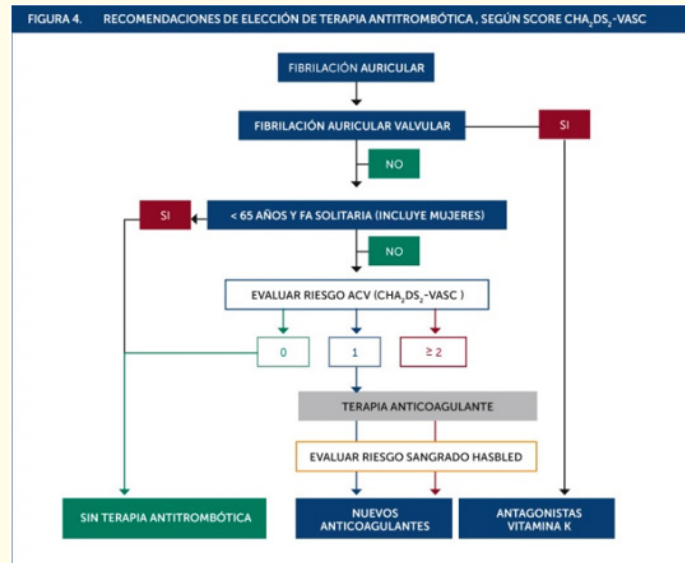


Figure 6

Traducido de Cam J, *et al.* Focussed update on the ESC Guidelines for the management of atrial fibrillation European Heart Journal 2012; 33: 2719-274.

Occluder ore devices

Surgical occlusion and percutaneous ligation of the left orejuela have been reported in observational studies and records only. Only one device (Watchman®) has been compared against Warfarin in randomized studies:

1. **+ PROTECT AF:** Non-inferiority study that compared the mechanical closure of the orejuela vs Warfarin, under a randomized 2:1, multicenter design. Patients with non-valvular FA (707), with CHADS₂ x1, with 4 years of follow-up. The Watchman group events were presented at 8.4%, with a rate of 2.3 events per 100 years/patient, in the Warfarin group 13.9% of vascular events were presented, with a rate of 3.8 per 100 years/patient, with RR 0.60; 95% (0.41 - 1.05). Lower cardiovascular mortality and mortality from any [17] cause. The study met non-inferiority targets in preventing CVD, rich perif é embolismand cardiovascular death and even met superiority criteria for cardiovascular death and death from any cause.

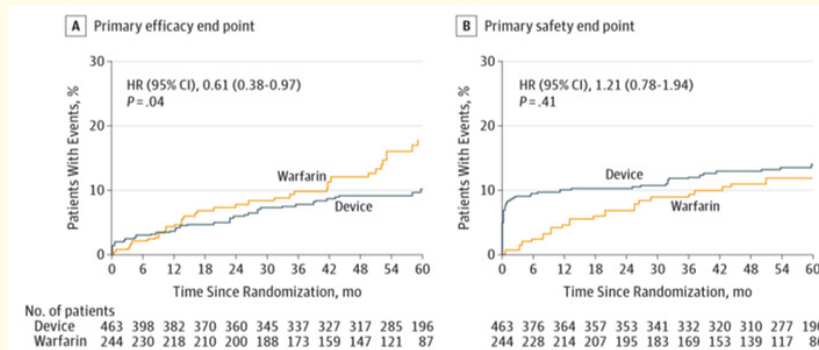


Figure 7

- 2. + **PREVAIL**: Randomized, parallel study. Patients with FA (CHADS₂). The safety objective evaluated death, VTE, systemic embolism, complications of the procedure/device at 7 days (2.2%). Efficacy compared to Warfarin was similar to 18 months (without statistically significant difference) to prevent cardiovascular death, VSE, embolism. Complications such as cardiac perforation, pericardial effusion with tamponade, ischemic EVC, device embolization and vascular complications reached 4.4% [18].

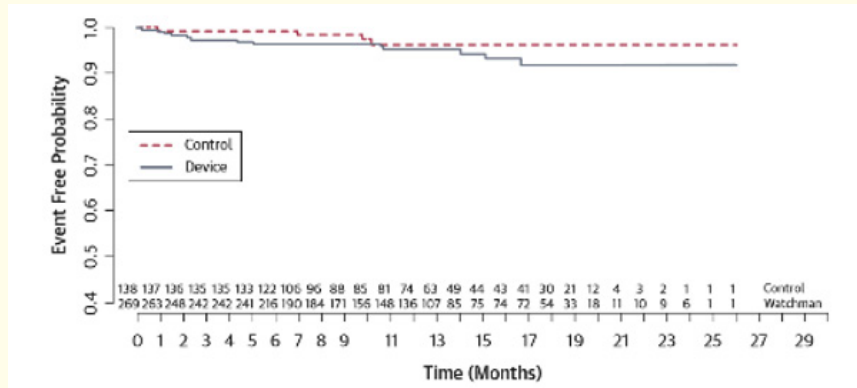


Figure 8

Left orengo occlusion reduces the risk of VSE in patients with some contraindication for oral anticoagulation. A European registry reports implant success at 98%, with a complication rate of 4% to 30 days. It has the experience of monitoring events 5 years from the two studies, which concludes good protection with decreased bleeding, especially intracranial and [19] mortality. Even higher-weight controlled studies are required, in patients who have undergone VSE, even taking anticoagulants, aimed at comparing occluders with ACOD, or by assessing post-implant platelet anti-aggregation to have more certainty in the use of occluder ore devices. Currently the guidelines give you an IIb recommendation in patients not candidates for oral anticoagulant use [4].

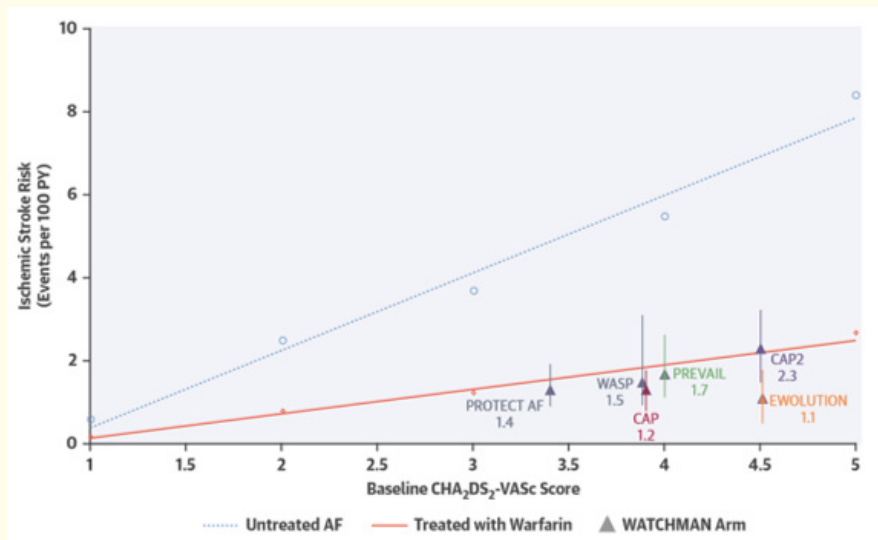


Figure 9

Watchman® (Boston Scientific) is the most clinically experienced percutaneous device, more than 30,000 patients in more than 75 countries and with the most extensive clinical evidence by studies, with more than 3,000 patients studied, although there are still questions to be answered [20]. Studies are running in patients ineligible for oral anticoagulation (ASAP TOO; NCT02928497) and Watchman in patients with atrial fibrillation after intracerebral hemorrhage (STROKE-CLOSE; NCT02830152). Perhaps the most important study, as it would be the comparison with the current gold standard is the PRAGUE-17 (Left atrial appendage closure vs novel oral anticoagulation agents in atrial fibrillation; NCT02426944). No doubt the results of these studies will resolve some doubts regarding the effectiveness and safety of the orejuela occluders in some specific contexts and in the vs ACOD which has been one of its most criticized points.

Occlusion or surgical exclusion of the left-hand erf

Mechanical occlusion strategies have been tried for decades as the complete and incomplete exclusion, which is accompanied by high VSE rates. Currently the complete exclusion of left orejuela, is used as a concomitant procedure to other cardiac surgeries, recently done together with surgical ablation. There is little information from controlled studies, the reported comes from observational studies. The benefit of surgical exclusion was marginal in the only randomized study available [21].

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