Apixaban

▼Eliquis® for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation Now we have three anticoagulants where the degree of anticoagulation is unknown

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ABSTRACT

This is an oral anticoagulant that lacks an antidote, and does not require INR monitoring which implies uncertainty with regard to the degree of anticoagulation.

In one trial, apixaban showed superiority when compared to warfarin in the composite primary endpoint of stroke or systemic embolism. However, this superiority was not observed in patients with adequate INR control under warfarin.

It presented a lower incidence of severe bleeding compared to warfarin and no differences in relation to gastrointestinal bleeding.

No comparative studies are available *versus* acenocumarol, dabigatran or rivaroxaban and its long-term safety profile is unknown.

Apixaban, dabigatran and rivaroxaban are only alternatives to vitamin K antagonists when it is not possible to achieve adequate anticoagulation.

Indications[1]

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, with one or more risk factors, such as prior stroke or transient ischaemic attack; age ≥75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).

Mechanism of action[1]

Apixaban is a selective inhibitor of Factor Xa. It indirectly inhibits platelet aggregation induced by thrombin.

Posology and administration[1]

Dose: 5 mg/12h. It can be reduced to 2.5 mg/12h when at least two of the following characteristics are present: age ≥80 years, body weight ≤60 kg or serum creatinine ≥1.5 mg/dL.

Clinical efficacy

The ARISTOTLE[3] study compared apixaban (n=9,120; 2.5-5 mg/12h) to warfarin (n=9,081; dose adjusted for INR 2-3) in adult patients with non-valvular atrial fibrillation. The median follow-up period was 1.8 years. Apixaban performed better than warfarin in the reduction of stroke or systemic embolism (primary endpoint), 212 patients under apixaban (1.27%/year) compared to 265 with warfarin (1.60%/year), HR=0.79 (95%CI, 0.66-0.95). Fatal or disabling stroke occurred in 84 patients under apixaban (0.5% per year) compared to 117 under warfarin (0.71% per year), HR=0.71 (95%CI, 0.54-0.94). The incidence of death from any cause (secondary endpoint) was inferior in the case of apixaban, 3.52% per year versus 3.94% per year, HR=0.89 (CI95%, 0.80-0.998; p=0.047). There were no significant differences in the incidence of myocardial infarction.[3]

Apixaban was not superior to warfarin in overall mortality in patients with adequate INR control under warfarin.[2]

Safety

Adverse reactions[1]

The incidence of major bleeding (primary safety outcome) was lower with apixaban (2.13% per year) compared to warfarin (3.09% per year), HR=0.69 (95%CI, 0.60-0.80).[3] The incidence of any bleeding was 18.1% and 25.8% per year in the apixaban and warfarin groups, respectively.[2]

Apixaban produced less major bleeding, intracraneal or in any other locations compared to warfarin, and no differences were observed in the case of gastrointestinal bleeding. This superiority in the bleeding profile was not observed in the subgroup of patients with adequate INR control.[2]

Although with some uncertainty, use only when vitamin K antagonists do not work.

Contraindications[1]

Clinically significant active bleeding; liver disease associated with coagulation and clinically relevant bleeding; injury or disease with significant risk of major bleeding such as existing or recent gastrointestinal ulcer; presence of malign neoplasm with high risk of bleeding; recent brain or spinal damage; recent brain, spinal or eye surgery, recent intracraneal hemorrhage, suspicion or knowledge of oesophageal varicose veins, arteriovenous malformations, grand intraspinal or intracebrebral vessel anomalies; concomitant treatment with heparin, oral anticoagulants except if switching from another anticoagulant to apixaban or viceversa, or when non-fractioned heparins are administered to maintain the permeability of a central venous or arterial catheter.

Warnings and precautions[1]

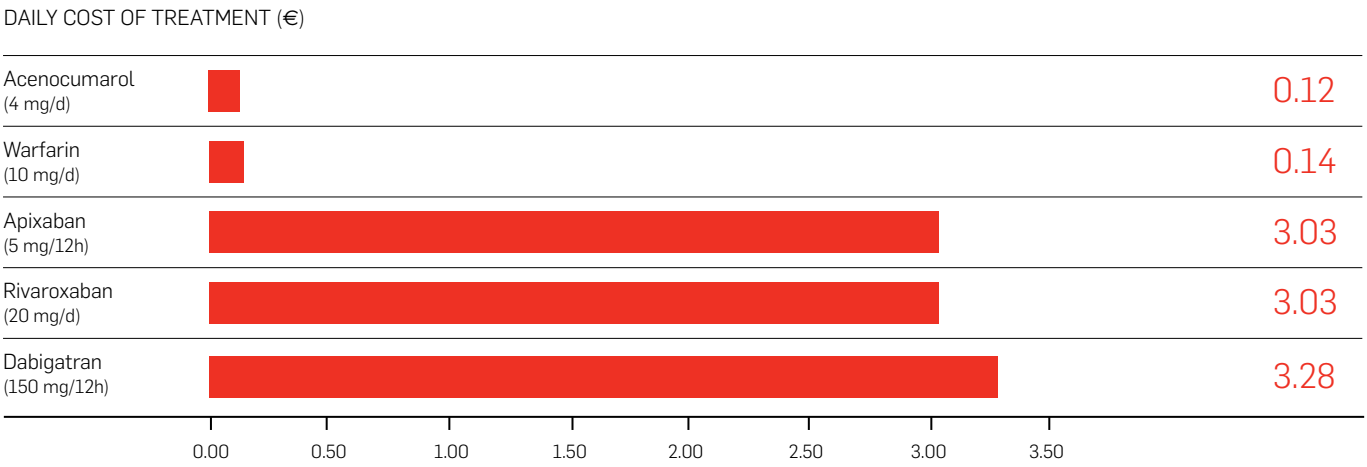
Precaution in clinical situations with increased risk of bleeding. Treatment should be discontinued in cases of severe bleeding.

Discontinue at least 48 hours before elective surgery or invasive procedures with a moderate or high risk of bleeding, at least 24 hours before if the risk is low.

CLASSIFICATION

4	IMPORTANT THERAPEUTIC INNOVATION
3	MODEST THERAPEUTIC INNOVATION
2	**SOME ADDED VALUE IN SPECIFIC SITUATIONS**
1	NO THERAPEUTIC INNOVATION
0	INSUFFICIENT EVIDENCE

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.



Use in special situations[1]

Pregnancy: not recommended. **Breastfeeding:** interrupt breastfeeding or discontinue treatment with apixaban. **Severe renal failure (CrCl = 15-29 mL/min):** reduce dose to 2.5 mg/12h. It is not recommended when CrCl<15 mL/min or dialysis. **Severe liver failure:** not recommended. Precaution in case of mild or moderate liver failure (Child Pugh A or B). **Elevated levels of liver enzymes (AST/APT> 2 x ULN) or bilirrubin ≥1.5xULN:** employ with precaution. **Children and adolescents <18 years:** no data available. **Elderly patients:** reduce doses to 2.5 mg/12h when at least two of the following characteristics are present: age ≥80 years, body weight ≤60 kg or serum creatinine ≥1.5 mg/dL (133 µmol/L).

Interactions[1]

Concomitant use with potent CYP3A4 and P-gp inhibitors are not recommended (azole-antimycotics or HIV protease inhibitors).

Precaution should be taken with concomitant use of potent CYP3A4 and P-gp inducers (rifampcin, phenytoin, carbamazepine, phenobarbital or St. John's wort) or with the use of NSAIDS (including acetylsalicylic acid).

Its use is not recommended with drugs associated with severe bleeding such as thromboytics, GPIIb/IIIa receptor antagonists, thienopyridines (clopidogrel), dipiridamol, dextran and sulfinpyrazone.

EMA Risk Management Plan[1]

Include the risk of bleeding and potential risk of liver damage.

Place in therapeutics

Atrial fibrillation confers patients with a risk of stroke and systemic embolism that is 5 times higher than that in the general population. In the prevention of stroke and embolism, oral anticoagulants are the elective choice. The indication for anticoagulation is based on an individual evaluation of risk of thromboembolism and bleeding. The $CHADS_2$ scale is a commonly employed tool to assess this risk. Currently anticoagulation is recommended in patients with a $CHADS_2$ score ≥2. However, in patients with a lower risk of thromboembolism ($CHADS_2$ <2), it is less certain that anticoagulation is an adequate treatment[17]. Treatment with vitamin K antagonists targeted at achieving INR levels between 2.0 and 3.0 has proven effective in these patients, but this strategy requires careful monitoring.

As in the cases of dabigatran and rivaroxaban, apixaban may not require this monitoring. However, this advantage has the inconvenience of making it impossible to both guarantee adequate anticoagulation control, and detect poor treatment adherence. On the other hand, although the probability of interactions is lower than in the case of vitamin K antagonists, it is not free of them.[17]

In patients with moderate risk, apixaban has reduced the incidence of stroke and systemic embolism and overall mortality, producing a lower incidence of severe bleeding, intracraneal and bleeding in other locations when compared to warfarin, whereas no differences were observed in gastrointestinal bleeding. However, this superiority in the bleeding profile has not been observed in the subgroup of patients with adequate INR control.[2]

The long-term safety profile of apixaban is unknown. It does not have an antidote, and there is no available method to monitor its anticoagulant activity, which could be necessary in cases of emergency.

The Spanish Medicines Agency has published a practical guide on the use of new oral anticoagulants in the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. It is recommended to initiate treatment with one of the new oral anticoagulants (dabigatran, rivaroxaban apixaban) if the patient comply with all the following criteria:[16]

· Presence of non-valvular atrial fibrillation with an indication for anticoagulation.

· Absence of general contraindications for anticoagulation

· Presence of at least one of he following clinical situations:

· Known hypersensitivity or specific contraindication to acenocumarol or warfarin. **2.** History of intracraneal bleeding (ICB). **3.** Ischemic stroke with high risk of ICB. **4.** Patients under therapy with vitamin K antagonists (VKA) that suffer severe arterial thromboembolic events despite adequate INR control. **5.** Patients under VKA with inadequate INR control despite good adherence to treatment. INR is considered inadequate when the percentage of the INR values within the therapeutic margin (2-3) is less than 60%. **6.** Impossible access to conventional INR monitoring.

Presentations

Eliquis® (Bristol-Myers Squibb/Pfizer EEIG) 5 mg 60 coated tablets (90.86 €)

References and full report

Available: http://www.bit.navarra.es

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