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Drug Assessment Report
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Rivaroxaban

(▼Xarelto®) for atrial fibrillation
Is it good to lose control?

Abstract

- Rivaroxaban is an oral anticoagulant that does not require monitoring of prothrombin time (INR) and lacks an antidote.
- It has shown comparable efficacy and safety profiles with warfarin in one trial but anticoagulation with the latter was deficient.
- When anticoagulation control was adequate, no differences in the incidence of stroke or systemic embolism were found, and there were fewer cases of bleeding under warfarin.
- There are no direct comparisons with other new oral anticoagulants.
- Until more evidence on safety is available and given its high cost, it should only be used when adequate anticoagulation is impossible with vitamin K antagonists.

Indications[1]
Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

Mechanism of action[1]
It blocks Factor Xa at a central point in the coagulation cascade, where the extrinsic and intrinsic pathways meet, helping to modulate thrombin generation.[1,2] Preventing thrombin generation helps inhibit clot formation.

Posology and form of administration[1]
The recommended maximum dose is 20 mg once daily. It should be taken with food. It requires dose adjustment in cases of renal impairment (see "Use in special situations").

Clínical efficacy
This indication is supported by evidence from a double-blind clinical trial, the ROCKET-AF[3-5] carried out in 14,264 patients with non-valvular atrial fibrillation and CHADS2 score ≥ 2 in which a comparison was made between rivaroxaban 20 mg daily (15 mg daily in cases of Cr CL between 30 and 49 mL/min) and warfarin at doses adjusted to the INR. The protocol established that the majority of the patients (90%) should have suffered from previous thromboembolism or have presented three or more risk factors thus bearing high risk.[5] This study was designed as a non-inferiority trial. The efficacy primary endpoint was stroke or systemic embolism. No significant differences were found (HR= 0.88; 95%CI 0.74-1.03), thus fulfilling non-inferiority criteria. The safety primary endpoints were severe bleeding and non-severe but clinically relevant bleeding. Like with efficacy, no significant differences found (HR= 1.04; 0.96-1.11).

It is worth mentioning the poor INR control in patients under warfarin. The average period in which patients complied with therapeutic range (TRT) was only 55%. In those centres with better TRT, the incidence of bleeding was statistically higher in patients under rivaroxaban than with warfarin.

Safety
Adverse reactions[1]
Frequent (1/100 to <1/10): bleeding, anaemia, dizziness, headache, syncope, tachycardia, hypotension, pruritus, rash, ecchymosis, pain in the extremities, fever, peripheral oedema, decreased general strength and energy, increased levels of transaminases.
Less frequent (1/1000 to <1/100): thrombocitopenia, allergic reactions, dry mouth, renal impairment, localised oedema, increase in bilirrubin, alcaline phosphatase, LDH, lipase, amylase, and GGT; oozing of blood or fluid from the surgical wound in patients undergoing surgery.
Rare (1/10000 to <1/1000): jaundice, increase in conjugated bilirrubin.
Unknown frequency: pseudoaneurism after surgery, renal impairment.

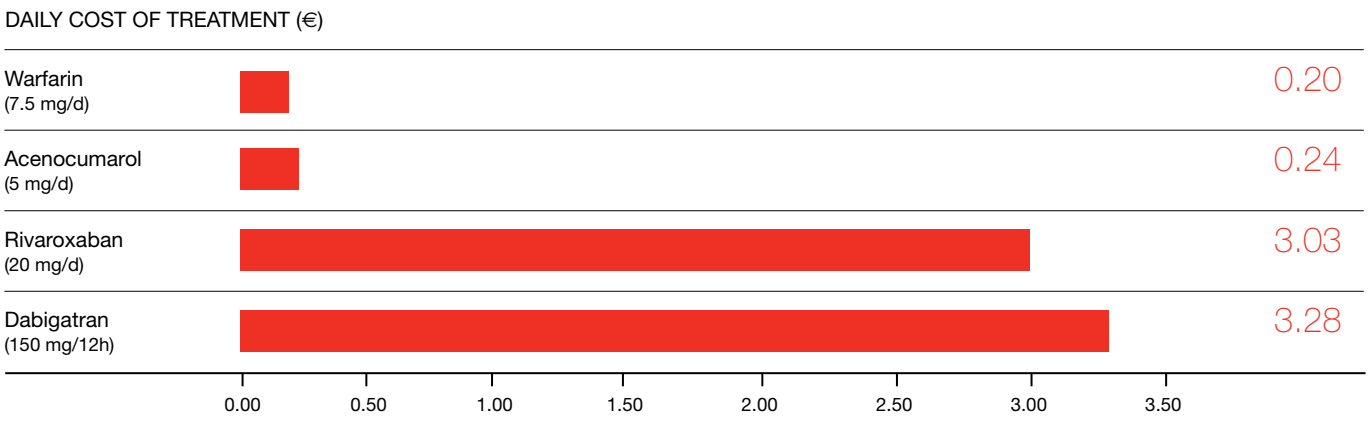
Only when vitamin K antagonists fail, and with some doubt

Contraindications[1]
Hypersensitivity to the main active substance or any of the excipients.
Clinically significant active bleeding.
Any injury or condition with significant risk of severe bleeding.[9]
Concurrent treatment with any anticoagulant, except for changes in treatment or when administering heparin to maintain a venous catheter.
Liver disease associated with coagulopathy and a clinically relevant risk of bleeding, including cirrhotic patients with Child Pugh B and C.

Contraindications
Hypersensitivity to the active substance.
Allergy to the excipients (contains E110 colorant).
Severe renal impairment (CrCL < 30 mL/min), liver impairment or disease.
Active bleeding, organic lesion at risk of bleeding or alterations in coagulation.
Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole and tacrolimus.

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.



Warnings and precautions[1]

Risk of bleeding

In clinical trials, a higher incidence of mucosal bleeding (epistaxis, gums, gastrointestinal, genital and urinary mucosae) and anaemia were observed in patients under rivaroxaban compared to those under treatment with vitamin K antagonists (VKA). Therefore, in addition to adequate clinical follow-ups haemoglobin and hematocrit monitoring could prove useful.

In patients at high risk of bleeding (renal or liver impairment, drug interactions, coagulation disorders, active ulcer-related gastrointestinal disease, recent gastrointestinal ulcer, vascular retinopathy, intramedular or intracraneal vascular anomalies) careful vigilance should be implemented for any sign of bleeding complications. Any reduction in haemoglobin or blood pressure requires a search for bleeding.

Patients with valvular protheses

There is no evidence about rivaroxaban efficacy in these patients. It is not recommended.

Use in special situations[1]

Pregnancy and lactation: contraindicated. **Renal impairment:** no dose adjustments are necessary in patients with mild renal impairment (CrCL 50-80 mL/min). In cases of moderate (CrCL, 30-49 mL/min) or severe (CrCL 15-29 mL/min) renal impairment, the recommended dose is 15 mg daily, with precaution in severe cases. Its use is not recommended in cases of CrCL < 15 mL/min. Employ with caution in patients with renal impairment and treatment with potent CYP3A4 inhibitors (for example clarithromycin, telithromycin). Liver impairment Contraindicated in patients with cirrhosis (Child Pugh B and C). **Children:** No information. It is not recommended in patients under 18 years. **Elderly:** no dose adjustments required.

Interactions[1]

This drug is not recommended in patients under treatment with systemic antifungal azoles, (for instance, ketoconazole, itraconazole, voriconazole, and posaconazole) or HIV protease inhibitors (for example, ritonavir). As potential CYP3A4 and P-gp inhibitors they may increase serum concentrations and the risk of bleeding. It is expected that fluconazole has a lower interaction and can be administered concomitantly, but with precaution.

Precaution is also advised in patients treated with drugs that affect blood coagulation, such as NSAIDs, antiplatelet drugs, and other antithrombotic agents. Consider prophylaxis with PPIs in patients with increased risk of gastrointestinal ulcers.

Potent CYP3A4 inductors (like rifampicin, phenytoin, carbamazepine, phenobarbital or St Johns wort) can reduce serum levels.

Concurrent use of dronedarone should be avoided given the limited clinical information.

Place in therapeutics

Oral anticoagulants are the most frequent drugs used in the prevention of stroke and systemic embolism in patients with atrial fibrillation. Their indication is based on risk assessment, and the most common tool employed for evaluation is the CHADS[2] score.

Treament with VKA maintaining an INR between 2 and 3 has proven effective but requires careful monitoring. Rivaroxaban is a new anticoagulant which obviates this need, but it has not proven more advantageous. In fact, it has shown to produce more bleeding in centres where INR control under VKA was good. The absence of coagulation control in patients under rivaroxaban makes it impossible to know whether anticoagulation is effective and/or the patient's compliance is adequate. The lack of any available antidote makes its management even more difficult.

Factors such as rivaroxaban showing no superiority in efficacy vs VKAs, uncertainty on safety issues, lack of knowledge of long-term safety, impossibility of guaranteeing adequate anticoagulation, absence of antidote and the costly price, limit the use of this drug to represent an option for those patients where adequate control of VKA is not possible.

There is no evidence on the effects of rivaroxaban compared to other anticoagulants. The cost of rivaroxaban is slightly lower than dabigatran.

Presentations

XARELTO® (Bayer) 15 mg 28 tablets (84.80 €), 20 mg 28 tablets (84.80 €)

References and a full report

Available at: www.dtb.navarra.es

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