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Drug Assessment Report
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Dabigatran

(▼Pradaxa®) in stroke prophylaxis in patients with atrial fibrillation

An option for anticoagulation when warfarin or acenocumarol fail

Abstract

- Dabigatran is an oral anticoagulant that does not require monitoring of prothrombin time (INR).
- In one open trial comparing warfarin, dabigatrin 150 mg/12h showed a lower incidence of stroke or embolic events, and a similar incidence of severe bleeding. Dabigatran 110 mg/12h showed a lower incidence of severe bleeding and no differencein the incidence of stroke or embolic events.
- In centres with adequate INR control there were no differences on the incidence of stroke, embolic events or severe bleeding vs warfarin.
- After commercialization there have been various alerts on the risk of bleeding and there are data on the possible increase in the incidence of myocardial infarctions.
- There are no available head-to-head comparisons with other new oral anticoagulants.

Indications[1]

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more of the following risk factors:

· previous stroke, transient ischaemic attack or systemic embolism;
· left ventricular ejection fraction < 40%;
· symptomatic heart failure ≥ New York Heart Association (NYHA) class 2;
· age ≥ 75 years;
· age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease or hypertension.

Mechanism of action[1]

This is a synthetic, non-peptide competitive, rapidly acting and reversible inhibitor of thrombin.

Posology and form of administration[1]

The habitual dose is 150 mg/12h with or without food. The dose should be reduced to 110 mg/12h in patients over 80 years and in those under concomitant therapy with verapamil. In patients between 75 and 80 years or with moderate renal failure, gastritis, esophagitis, gastrointestinal reflux or major risk of bleeding, the dose should be decided depending on the risk of thromboembolism or bleeding.

Clinical efficacy

The indication is based on the RE-LY[3] study that included 18,113 patients with atrial fibrillation (AF) and with at least one risk factor: severe valvular disease, recent stroke, risk of bleeding, CrCL <30 mL/min, active liver disease (including increase in liver transaminases >2 times the upper limit of normality) and pregnancy.

There were three treatment groups, namely dabigatran 110 mg/12h, dabigatran 150 mg/12h and warfarin at adjusted doses. The comparison between dabigatran and warfarin was not blinded. The median follow-up period of the trial was two years[3] and the primary endpoint was the incidence of stroke or any systemic embolic event.

Dabigatran was "non-inferior" to warfarin. The 150 mg dose was superior to warfarin, RAR= -1.1% (95%CI, -1.7% to -0.5%) after two years[3] (NNT=91). The benefits of dabigatran were only significant in those centres where patients treated with warfarin[4-6] presented a poorer INR control (TRT<66%).

There was a lower incidence of fatal bleeding in patients under dabigatran 100 and 150 mg compared to warfarin. With respect to warfarin, dabigatran 110 mg presented fewer severe bleeding while dabigatran 150 mg showed a similar risk. In comparison to warfarin, the risk of intracraneal bleeding was lower with dabigatran 110 and 150 mg compared to warfarin, while the risk of severe gastrointestinal bleeding was higher with dabigatran 150 mg.[3] In cases of adequate INR control (TRT>66%), there were no differences in the incidence of severe bleeding compared to warfarin with any of the two doses of dabigatran.[6]

Only when vitamin K antagonists fail, and with some doubt

Safety

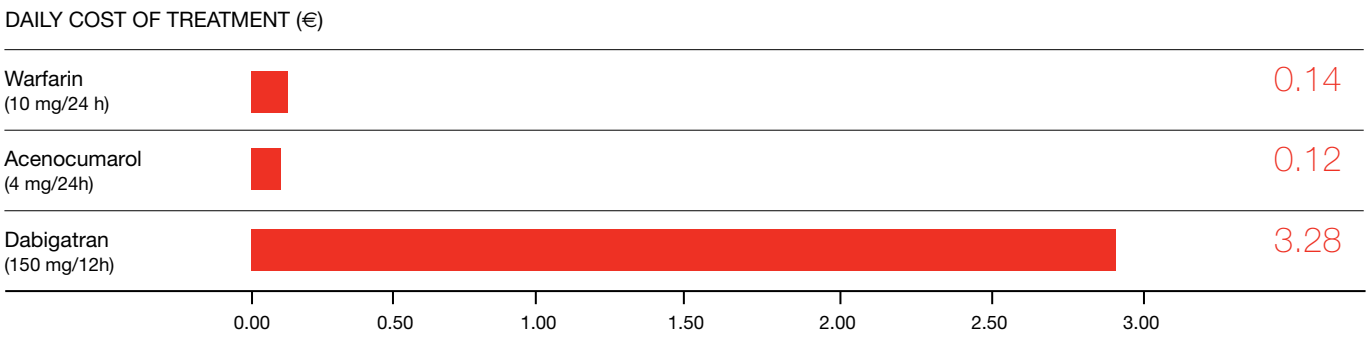
Adverse reactions[1]

The rate of withdrawals was higher among patients under dabigatran than those with warfarin and dropouts due to adverse effects was greater with both doses of dabigatran in comparison to warfarin.[3]

Gastrointestinal adverse effects were more frequent in the groups under dabigatran (dyspepsia: 11.8% in dabigatran 110 mg; 11.13% with dabigatran 150 mg and 5.8% with warfarin). The annual rates of myocardial infarction were 0.74%, 0.72% and 0.53% for dabigatran 110 mg, dabigatran 150 mg and warfarin respectively, RR=1.38 (95%CI: 1.00-1.91) in the case of dabigatran 150 mg vs warfarin.[3] A meta-analysis concluded that dabigatran was associated with a 33% increase in the risk of myocardial infarction or acute coronary syndrome (OR=1.33; 95%CI, 1.03-1.71) vs different controls (warfarin, enoxaparin or placebo).[10]

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.



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.

Warnings and precautions[1]

Renal function must be evaluated (CrCL) whenever a decrease in renal function is suspected, and at least once a year in patients with mild renal impairment or patients over 75 years of age.

Precaution is advised in cases of increased risk of bleeding and concomitant use of antiplatelet agents, renal impairment, patients with previous myocardial infarction, heart valve protheses and patients with a body weight <50 kg.

Use in special situations[1]

Pregnancy: do not use unless absolutely necessary. **Lactation:** contraindicated. **Renal impairment:** contraindicated if CrCL < 30 mL/min and reduce doses in cases of moderate renal impairment (CrCL 30-50 ml/min) or high risk of bleeding. **Liver impairment:** not recommended in patients with increase in liver enzymes >2 the upper limit of normality. **Children:** not recommended in children under 18 years. **Elderly:** between 75 and 80 years with a high risk of bleeding or > 80 years, the dose should be reduced to 110 mg/12h; in those >75 years, the CrCL should be evaluated before initiating treatment and at least once a year.

Interactions[1]

The risk of bleeding increases with anticoagulants, antiplatelet drugs, NSAIDs, SSRIs, duloxetine or venlaxafine. Contraindicated with potent gp-P inhibitors: systemic ketoconazole, itraconazole, and tacrolimus.

Precaution and close monitoring: clinical follow-up of patients under treatment with amiodarone, verapamil, quinidine, and clarithromycin, especially patients with mild-moderate renal impairment.

Avoid the concomitant use of gp-P inducers (rifampicin, St. John's wort, carbamazepine, or phenytoin) or with dronedarone.

The EMA risk plan[1]

Includes the evaluation of the risk of bleeding in common conditions of use, gastrointestinal disorders, hypersensitivity, liver toxicity, myocardial infarction and pulmonary embolism.

Place in therapeutics

Oral anticoagulants are the most frequent drugs employed in the prevention of stroke and systemic embolism in patients with atrial fibrillation. Their indication is based on risk evaluation, the most frequently employed tool is the CHADS2 score. Treatment with vitamin K antagonists maintaining INR between 2 and 3 has proven effective, but requires careful monitoring. Dabigatran is a new anticoagulant that obviates the need for monitoring.

In the open RE-LY trial there was a lower incidence of embolism with dabigatran 150 mg/12h and a lower incidence of severe bleeding under dabigatran 110 mg/12h, although the benefits were only significant in those centres where patients presented poor INR control with warfarin (TRT <66%). Different alerts have been issued on the incidence of bleeding and there is still concern with regard to the increase in the risk of myocardial infarction. These data support the stance adopted by the Spanish Medicines Agency to restrict the use of dabigatran to patients with an inadequate INR control when treated with vitamin K antagonists. There is no evidence on the effects of dabigatran compared to other anticoagulants.

Presentations

Pradaxa® 110 mg 30 tablets (49.17 €), 110 mg 60 tablets (98.35 €) and 150 mg 60 tablets (98,35 €).

References and a full report

Available at: www.dtb.navarra.es

Servicio Navarro de Salud
Osasunbidea

INTERNATIONAL SOCIETY SDB OF DRUG BULLETINS

INFORMATION: **Servicio de Prestaciones Farmacéuticas** Plaza de la Paz s/n, 4ª planta 31002 Pamplona Teléfono 848429047 Fax 848429010 **NEW DRUGS ASSESSMENT COMMITTEE:** Iñaki Abad, Mª José Ariz, Ana Azparren, Mª Concepción Celaya, Juan Erviti, Javier Garjón, Javier Gorricho, Antonio López, Rodolfo Montoya, Mikel Moreno, Lourdes Muruzábal