

More Indications Approved and Safety News for Dabigatran Etexilate

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For more than 50 years, the only oral anticoagulation therapy available was with vitamin K antagonists. The difficulties to monitor, the instability against other drugs or aliments and the risk of this therapy are well known and studied.

In the last years new families of oral anticoagulants were developed, known today as New Oral Anticoagulants (NOAC). The first one clinically studied was ximelagatran. Its hepatic toxicity stopped it for development. The next oral anticoagulants who accomplished important clinical studies were dabigatran, apixaban, rivaroxaban and edoxaban. From these, dabigatran is a direct thrombin inhibitor, while the other three are factor Xa inhibitors. However, all four NOAC are studied to date in similar clinical conditions.

In this paper we will show some clinical results and some adverse effects for the direct thrombin inhibitor of the group, dabigatran etexilate.

The main indications for which dabigatran was studied are prevention of stroke in non valvular atrial fibrillation and prevention and treatment of deep vein thrombosis and pulmonary embolism.

For preventing stroke in nonvalvular atrial fibrillation the Food and Drug Administration (FDA) approved it in October 2010 and the Eu-

ropean Medicine Agency did the same in August 2011. The main clinical study which granted these approvals was RE-LY (Randomized Evaluation of Long-term anticoagulation therapy), published in new England Journal of Medicine in 2009 (1). A second study on the subject followed – RELY-ABLE (Long Term Multi-center Extension of Dabigatran Treatment in Patients with Atrial Fibrillation) (2). Patients from RE-LY were followed between 2.3 and 4.7 years on dabigatran. Data showed that even over 6 years of long term therapy with dabigatran, advantages and safety from the RE-LY study are preserved.

But what were the main results of RE-LY?

Its main objective was to demonstrate that long term treatment with dabigatran was as effective and as secure as warfarin in preventing stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF). If so, the lack of the necessity of monitoring and the stability of the molecule against other concomitant administered drugs or against aliments would offer an important advantage over warfarin.

And this was demonstrated and even more (1). On 18 113 patients in 44 countries it was shown that the dose of 150 mg dabigatran etexilate twice a day (bid) was superior to warfarin in reducing both ischemic and hemorrhagic stroke in patients with non-valvular AF.

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Primary efficacy & safety outcomes	Dabigatran 150 mg twice daily following initial heparin treatment	Dose-adjusted warfarin following initial heparin treatment
Efficacy:		
VTE or VTE-related death	2.7%	2.4%
Safety:		
Major bleeding	1.0%	1.6%
Relative risk reduction vs. warfarin	40% relative risk reduction	-
Clinically relevant bleeding (including major bleeding)	4.4%	7.7%
Relative risk reduction vs. warfarin	44% relative risk reduction	-
Total bleeding	14.4%	20.4%
Relative risk reduction vs. warfarin	33% relative risk reduction	-

TABLE 1. RE-COVER and RE-COVER II - Pooled Analysis summary of results.

Primary efficacy & safety outcomes	Dabigatran 150 mg twice daily	Warfarin
Efficacy:		
Recurrent VTE & death	1.8% (26/1,430)	1.3% (18/1,426)
Absolute risk difference vs. warfarin	0.38% p=0.014	-
Safety:		
Major bleeding	0.9% (13/1,430)	1.8% (25/1,426)
Relative risk reduction in major bleeding vs. warfarin	48% relative risk reduction p=0.06	-
Major or clinically relevant bleeding	5.6% (80/1,430)	10.2% (145/1,426)
Relative risk reduction vs. warfarin	46% relative risk reduction p <0.001	-
Total bleeding	19.4% (277/1,430)	26.2% (373/1,426)
Relative risk reduction vs. warfarin	29% relative risk reduction p <0.001	-

TABLE 2. RE-MEDY - summary of results.

The relative risk reduction of stroke and systemic embolism was 35%. It showed a similar rate of major bleeding as warfarin, but intracranial bleeding was much more reduced (by 59%). The 110 mg dabigatran etexilate bid, given in old people and in those with higher risk of hemorrhage was as effective as warfarin in reducing stroke and systemic embolism, but bleeding of any kind was much more reduced than in warfarin, for instance by 33% for life

threatening bleeding and by 70% for intracranial bleeding.

Following these results, dabigatran etexilate was registered and used in more than 100 countries and the today experience in preventing the risk of embolism in atrial fibrillation is the largest between the new oral anticoagulants.

Another field in which therapy with dabigatran was developed is vein thrombosis. This was developed in a series of studies grouped in a program called RE-VOLUTION. This included four studies dedicated to the use of dabigatran after major orthopedic surgery (hip and knee replacement), two studies were dedicated to the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in general conditions and two to the prevention of DVT and PE.

The first four studies in the program were dedicated to the treatment of DVT and PE after major orthopedic surgery. The phase III studies included in this part of the program were: RE-NOVATE, RE-NOVATE II, RE-MODEL and RE-MOBILIZE. RE-NOVATE (3) and RE-NOVATE II (4) compared dabigatran once daily in different doses with enoxaparin after hip replacement. RE-MODEL studied the same after knee replacement (5) and RE-MOBILIZE did the same as the former, using as comparator the North American standard dose of enoxaparin (6). In all the studies the efficacy of dabigatran etexilate was as good as that of warfarin and the safety similar. The results of RE-NOVATE and RE-MODEL, published in 2007 lead the European Commission to grant the use of dabigatran etexilate in EU for prevention DVT and PE after hip or knee replacement even since 2008.

The next studies were dedicated to the general therapy and prevention of DVT and PE. RE-COVER (7) and RE-COVER II (8) were dedicated to the therapy itself, while RE-MEDY and RE-SONATE (9) were dedicated to the prevention of recurrent DVT and PE after surgery: RE-MEDY in comparison with warfarin, RE-SONATE in comparison with placebo.

All four studies were positive regarding efficacy and safety (Tables 1 and 2). Pooled analysis of RE-COVER and RE-COVER II showed that the efficacy was as good as of warfarin, while the safety was much better (10).

The results of these four trials determined FDA in April 2014 and the European Commission in June 2014 to approve dabigatran etexi-

late for the treatment and prevention of recurrence of DVT and PE

Together with the other NOAC (rivaroxaban, apixaban, maybe edoxaban - which will be commented in future issues of the Journal) dabigatran etexilate constitutes a milestone in the prevention of embolism either in non valvular atrial fibrillation or in deep vein thrombosis. However, there are a lot of things still to be studied and resolved.

First, it has to be studied atrial fibrillation in valvular heart disease. Second, it is to finalize the study of the suspected association between acute coronary syndromes and dabigatran. Data of some authors found this association nonsignificant (11), but an explanation of the possible linkage between dabigatran and myocardial infarction is not at all identified.

On the contrary, there are fields of research in which NOAC and, between them, dabigatran have to be studied: in the anticoagulation of valvular prosthesis, in valvular atrial fibrilla-

tion, in the therapy of ischemic stroke or of the transient ischemic attacks and even in the therapy of acute coronary syndromes. These objectives are as actual as were a few years before (12). One important step forward is the development of an antidote, aDABI-Fab, a Fab monoclonal antibody (13). The summary of the Phase I/II was presented at the AHA 2013 Congress. The product, named idarucizumab, is now in a Phase III study, RE-VERSE AD, which is actively enrolling patients.

All these data show that Dabigatran is an important achievement in efficient and secure long term oral anticoagulant therapy for a large category of patients.

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