https://doi.org/10.38109/2225-1685-2017-4-114-120

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DABIGATRAN ETEXILATE IN ELDERLY PATIENTS WITH ATRIAL FIBRILLATION: WHAT'S NEW?

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SUMMARY

The article discusses stroke prevention in elderly patients with atrial fibrillation. The principles of choosing anticoagulant therapy in this group of patients are discussed. The importance of the safety profile of the selected anticoagulant is emphasized considering the high prevalence of comorbidities in elderly patients. The efficacy and profile of dabigatran etexilate demonstrated in randomized clinical trials and in real clinical practice is analyzed in detail. Based on the data discussed, the authors are coming to conclusion that dabigatran can be considered the preferred anticoagulant for long-term treatment in elderly patients with atrial fibrillation.

Key words: *dabigatran etexilate, anticoagulant, NOAC, stroke, elderly patients, atrial fibrillation.*

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For citation: Tkacheva O.N., Vorobyeva N.M. Dabigatran etexilate in elderly patients with atrial fibrillation: what's new? Eurasian heart journal. 2017, November 25; 4:118-120 [in Russian].

Atrial fibrillation (AF) is the most common heart rhythm disorder in the elderly, with its incidence growing with age. As it has been shown in the Framingham study [1], if the risk of developing AF in individuals aged 50-59 years is assumed to be 1.0, then with an increase in age by one decade only (60-69 years) it goes as high as almost 5-fold [relative risk (RR) 4.98; 95% confidence interval (CI) 3.49-7.10], and in those in the nineties, almost – 9-fold (RR 9.33, 95% CI 6.68-13.0). AF is associated with a significant increase in the risk of thromboembolic complications, the most dangerous among which is cardioembolic stroke. In patients with AF, age is a significant risk factor for cardioembolic stroke. Thus, according to the Framingham study [2], the frequency of cardioembolic stroke with AF increases with age and comprises 6.7% in persons aged 50-59 years and 36.2% in those at the age of 80-89. Consequently, elderly patients more often need the administration of anticoagulants.

However, older age is associated not only with increased stroke risk, but also with that of bleeding, the main side effect of anticoagulant therapy. The greatest danger, especially in the elderly, is represented by hemorrhagic stroke or intracranial bleeding, which often result in death or persistent disability. Taking this into account, for long-term treatment of the elderly AF patients it is important to choose an anticoagulant which, on the one hand, would effectively prevent thromboembolic complications and on the other, would be the safest in terms of development of any bleeding and hemorrhagic stroke in particular. Therefore, administration anticoagulants to the elderly individuals should be individualized and based on careful assessment of the risk / benefit ratio.

Dabigatran etexilate is an oral direct anticoagulant, a reversible selective thrombin inhibitor. After oral administration dabigatran etexilate is rapidly absorbed in the gastrointestinal tract and, by hydrolysis in the liver and plasma, is transformed into dabigatran, which is an active substance. Dabigatran exerts an inhibitory effect on free and fibrin-associated clotting of thrombin, as well as on thrombin-induced platelet aggregation. Experimental studies showed a direct correlation between plasma concentration of dabigatran and anticoagulant activity. After oral intake, the anticoagulant effect develops rapidly and reaches its maximum on average after 3 hours. The drug is excreted unchanged mainly through the kidneys (80-85%). Its half-life is 12 to 14 hours; therefore, dabigatran should be taken twice daily. Dabigatran prolongs the activated partial thromboplastin time (APTT), so in emergencies APTT value may help to monitor its anticoagulant effect with the help of APTT.

The potential of dabigatran in AF was studied in a randomized clinical study RE-LY [3] involving 18 113 patients (mean age, 72 years; 64% men). The majority (n=10 855, 59.9%) of the study participants were below 75 years of age. The age group of 75 to 79 years included 4 231 patients (23.4%), 80 to 84 years, 2 305

(12.7%) patients, and 722 (4.0%) of the patients were above 85 years of age. About 6,000 patients had a high risk of stroke (3-6 on the CHADS2 scale) and several concomitant diseases, such as arterial hypertension (92% of patients), chronic heart failure (48%), coronary heart disease including myocardial infarction (31%), and diabetes mellitus (45%). Two fixed doses of dabigatran (110 and 150 mg twice daily) were compared with individually titrated doses of warfarin (target values of the international standardized ratio (INR) 2.0 to 3.0). Dabigatran 150 mg twice daily was more effective than warfarin and reduced the risk of stroke and systemic embolism by 34% (RR 0.66, 95% CI 0.53-0.82, p <0.001) with comparable risk of major bleedings. At dose of 110 mg twice a day dabigatran did not demonstrate any advantages in the prevention of stroke (RR 0.91, 95% CI 0.74-1.11, p=0.34) with a lower risk of major bleeding. Both doses of dabigatran were effective independently of the patient's age.

The results of the age-dependent subanalysis published in 2017 [4] demonstrated that the benefits of dabigatran over warfarin for stroke prevention persisted in all age subgroups (RR in the range from 0.63 to 0.70 for dabigatran 150 mg twice daily and from 0, 52 to 1.08 for dabigatran 110 mg twice daily). The risk of intracranial hemorrhage was also lower in those taking dabigatran, regardless of their age and dose of the drug.

According to the prescribing information for the drug, it is indicated at a dose 110 mg for: 1) patients ≥80 years of age; 2) increased risk of bleeding (e.g. >3 points on the HAS-BLED scale); 3) continuous treatment with verapamil. In the remaining cases, dabigatran is recommended at a dose of 150 mg. Based on this, Lip G.Y.H. et al. [6] performed a post-hoc analysis of RE-LY study data, with the purpose to evaluate efficacy and safety of dabigatran dosed in strict compliance with the prescribing information, as compared to warfarin. This analysis showed that among 6 015 and 6 076 patients who received dabigatran 110 and 150 mg respectively, only in 1780 and 4296 patients the dose of the drug was in accordance with the prescribing information. Patients with excessive or insufficient dosing of dabigatran were excluded from the analysis, leaving 6 004 patients in the dabigatran group. Compared to warfarin (n=6 022), treatment with dabigatran at doses consistent with the prescribing information was associated with a 26% reduction in the risk of stroke and systemic embolism (RR 0.74, 95% CI 0.60-0.91), a 78% reduction in hemorrhagic stroke (RR 0.22, 95% CI 0.11-0.44), a 14% reduction in overall mortality (RR 0.86, 95% CI 0.75-0.98), and a 20% reduction in cardiovascular mortality (HR 0.80, 95% CI 0.68-0.95). Treatment with dabigatran was also associated with a lower incidence of large (RR 0.85, 95% CI 0.73-0.98), life-threatening (RR 0.72, 95% CI 0.58-0.91), intracranial (RR 0, 28, 95% CI 0.17-0.45) and any (HR 0.86, 95% CI 0.81-0.92) bleeding, while the risk of gastrointestinal bleeding was comparable to that for warfarin (RR 1.23; 95% CI 0.96-1.59). The results indicate that dosing of dabigatran in accordance with the prescribing information helps to increase its efficacy and safety, compared to warfarin.

It should be noted that, based on the results of the RE-LY study, experts from the European Heart Society [7] propose to consider a reduced dose of dabigatran (110 mg) in patients aged 75 to 79 years, leaving this option to the discretion of the treating physician.

Currently, dabigatran has the largest evidence base obtained in the real-world studies among all new oral anticoagulants (NOACs) for the treatment of elderly patients with AF. As early as in 2014, the results of a large-scale observational cohort study in the United States [8] were published with more than 130,000 participants aged ≥65 years with AF who were eligible for free Medicare insurance. Of the more than 300,000 people enrolled in the Medicare system and meeting the eligibility criteria, 2 cohorts were formed, with 67,207 patients in each (the warfarin and dabigatran groups). Two dabigatran doses were used, 75 and 150 mg twice daily (110 mg dose in the US has not been registered). The vast majority of the patients received dabigatran at a dose of 150 mg, and 75 mg dose was prescribed mainly in renal dysfunction.

In comparison with warfarin, dabigatran therapy was associated with a 20% reduction in the risk of cardioembolic stroke, 66% reduction in in intracranial hemorrhage, and 14% reduction in death.

In 2016, the results of an independent observational study run by FDA (Food and Drug Administration) USA [9] became available, that were based on the data of the US National Medicare program. The study looked at effectiveness and safety of dabigatran and rivaroxaban in elderly AF patients. To date, this is the first real world study, in which two NOACs were compared. It included more than 118,000 AF patients ≥65 years of age without previous experience with vitamin K antagonists, who received full doses of NOACs (dabigatran 150 mg twice daily or rivaroxaban 20 mg once a day). Compared to rivaroxaban, dabigatran therapy reduced the risk of intracranial hemorrhage by 39% (RR 0.61, 95% CI 1.20-2.26), large extracranial hemorrhages by 32% (RR 0.68, 95% CI 1, 31-1.66), and massive gastrointestinal bleedings by 29% (RR 0.71, 95% CI 1.22-1.58). Overall mortality was also lower in the dabigatran group, being 22.2 vs. 24.7 per 1,000 patient-years in the rivaroxaban group (RR for rivaroxaban 1.15, 95% CI 1.00-1.32). The difference in the risk was statistically significant in patients aged 75 to 84 years and with a score on the scale CHADS2 >2. The data obtained allows to conclude on the better safety of dabigatran in a subgroup of AF patients at ≥65 years of age.

Also in 2016, the results of the analysis of the Medicare program, Part D [10], were published. In this program, the elderly AF patients were taking dabigatran at a dose of 150 or 75 mg twice daily (n=7,322 and n=1,818, respectively) or rivaroxaban 20 or 15 mg once a day (n=5,799 and n=2,568, respectively). The risk of cardioembolic stroke was virtually similar in the patients taking dabigatran 150 mg and rivaroxaban 20 mg (RR 1.05, 95% CI 0.97-1.13), as well as in those receiving dabigatran 75 mg and rivaroxaban 15 mg (RR 1, 05; 95% CI 0.94-1.18). Compared to dabigatran, 150 mg, rivaroxaban 20 mg was associated with a higher risk of other thromboembolic events (except for stroke) (RR 1.28, 95% CI 1.14-1.44), massive bleedings (RR 1.32; 95% CI 1.17-1.50) and death (RR 1.36, 95% CI 1.19-1.56). Similar results were obtained in the groups of patients taking dabigatran 75 mg and rivaroxaban 15 mg. Subgroup analysis has shown that the benefits of dabigatran in reducing the risk of death from any cause, massive or any bleeding are particularly obvious in the patients aged ≥75 years with chronic kidney disease or with more than 7 concomitant diseases. Thus, in the elderly patients, dabigatran and rivaroxaban showed similar efficacy in preventing cardioembolic stroke, but treatment with rivaroxaban was associated with a higher risk of death, massive bleeding, and thromboembolic events (other than stroke).

The results of these two real world studies indicate potentially more promising dabigatran positioning in the AF patients at ≥65 years of age. However, it should be borne in mind that in the absence of direct comparative studies between NOACs, the results of the real-world studies should be interpreted with caution, since they should be considered in the context of available evidence obtained in randomized controlled trials, with the most important issue being the reproducibility of the results obtained in randomized

trials in the real world clinical practice.

More recently, the results of an observational cohort study based on data from the National Danish Registries [11] have been made available, in which patients with AF were assessed for efficacy and safety of reduced doses of dabigatran, rivaroxaban and apixaban, all compared to warfarin. A total of 55,644 patients who had not previously received oral anticoagulants and had indications for prescribing reduced doses of the NOACs were included in the study. Most patients (n=38,893) took warfarin (INR 2.0-3.0); dabigatran 110 mg twice daily was administered to 8,875 patients; rivaroxaban 15 mg once daily, to 3,476 patients, and apixaban 2.5 mg twice daily, to 4 400 patients. The average age of the study participants was 74 years, while the proportion of people aged ≥80 years of 36% (n=19,853), with just over half of them (n=10,176) above 85 years of age. The follow-up continued for an average of 2.3 years.

Compared to the warfarin group, in the patients ≥80 years of age the risk of stroke and systemic embolism was almost the same in the dabigatran group (RR 0.98, 95% CI 0.82-1.17) and somewhat lower in the rivaroxaban group (RR 0.71, 95% CI 0.52-0.95). In the apixaban group, a statistically insignificant trend towards increased risk was found (RR 1.15, 95% CI 0.94-1.41). The risk of any bleeding was slightly lower in dabigatran (RR 0.89, 95% CI 0.76-1.04) and apixaban (RR 0.78, 95% CI 0.63-0.96) groups and slightly higher under rivaroxaban (RR 1.13, 95% CI 0.91-1.40). The risk of death from any cause in the dabigatran group (RR 1.00, 95% CI 0.91-1.10) did not differ from that in the warfarin group, but was 54% and 67% higher in the apixaban (RR 1.54 95% CI 1.40-1.70) and rivaroxaban (RR 1.67, 95% CI 1.49-1.87) groups, respectively. Compared to warfarin, treatment with each NOAC was associated with a reduction in the risk of hemorrhagic stroke by 54% in the dabigatran group (RR 0.46, 95% CI 0.27-0.78), 18% in the apixaban group (RR 0.82, 95 % CI 0.46-1.45), and 46% in the rivaroxaban group (RR 0.54, 95% CI 0.23-1.29), with the greatest reduction in risk observed in those taking dabigatran. Thus, the results of this real-world study suggest that in patients with AF of age ≥80 years who received reduced doses of NOACs, dabigatran has the most optimal benefit / risk ratio. Even though these results were obtained in real clinical practice rather than in a randomized trial, they are of great value (especially given that no specially designed randomized clinical trials on the use of NOACs in the elderly patients have been conducted so far), since the study involved a significant number of patients older than 80 years (about 20 000, compared to 3,027 such patients in the RE-LY). To date, this is the largest clinical experience of using NOACs in people older than 80 years.

Thus, the efficacy and safety of dabigatran in the elderly patients with AF have been demonstrated both in the randomized RE-LY study and in several real-world studies. Both doses of the drug were studied – 110 and 150 mg. According to the results of RE-LY, the recommended dose of dabigatran is 150 mg 2 times a day, which is more effective in reducing the risk of cardioembolic stroke and systemic embolism than 110 mg twice daily, and has a safety profile confirmed in the real practice setting. The 110 mg dose of dabigatran 110 mg is absolutely indicated only at the age ≥80 years. In patients aged 75 to 79 years, the doctor is free to choose between the two doses of dabigatran.

In all of the studies reviewed above, a reduction in the risk of hemorrhagic stroke or intracranial bleeding, as well as overall and / or cardiovascular mortality was observed in patients taking dabigatran, compared to warfarin. Moreover, dabigatran is the only NOAC, whose administration is associated with a 15% reduction in cardiovascular mortality compared to warfarin, as demonstrated in the RE-LY study. In the study of the National Danish Registers, the overall mortality in the dabigatran group was similar to that in the warfarin group, but treatment with other NOACs (rivaroxaban and apixaban) was associated with a significant increase in mortality by 54-67%, as compared to warfarin. Given this, the choice of dabigatran as an anticoagulant for long-term treatment in the elderly AF patients (especially over 80 years) looks preferable.

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