EDITORIAL

Progress in the Prevention of Stroke

The Questions and Answers section presents the use of recently developed oral anticoagulants[1]. Because introduction of these drugs offers one of the most significant innovations in clinical practice in the past sixty years,[2] we would call attention to the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study[3] that compares the effectiveness of dabigatran, a new oral anticoagulant, with warfarin for patients with atrial fibrillation (AF).

Vitamin K antagonists, such as warfarin, protect against stroke in patients with AF. However, vitamin K antagonists can produce variable anticoagulant responses because of genetic polymorphisms, dietary vitamin K intake, and alterations of their metabolism. Coagulation monitoring and frequent dose adjustments are thus necessary to ensure proper therapeutic level of anticoagulation. This is troublesome for patients and physicians and expensive for the health system. The new oral anticoagulants produce a steady anticoagulant effect when given in fixed doses.

The RE-LY study included more than 18.000 AF patients that received either dabigatran (150 mg twice daily or 110 mg twice daily) without coagulation monitoring or warfarin (titrated dose given on an open-label basis). Dabigatran (150 mg twice daily) was found to be superior to well-controlled warfarin. According to the manufacturers, the renal dosing for dabigatran should be adjusted according to the creatinin clearance (CrCl) as follows: for CrCl 15-30, the dosage is 75 mg twice daily; for CrCl<15 or hemodialysis, the dosage is not defined. Ischemic and hemorrhagic stroke rates were lower in patients treated with dabigatran than in patients treated with warfarin. The rates of disabling or fatal stroke were also lower in the dabigatran-treated group.

Dabigatran was approved in Europe and the USA under the name "Pradaxa." In addition to recommended indications, dabigatran is a potential alternative to warfarin in patients requiring cardioversion.[4] Additional oral anticoagulant treatments (apixaban, rivaroxaban, edoxaban) for stroke prevention in patients with AF are on the horizon, and we expect that the price of this treatment will soon become affordable. One possible advantage is that these pharmacological innovations can be substituted for expensive electrophysiological atrial ablations that are not available to everyone.

The prevalence of atrial fibrillation (AF) is 10- to 20-fold higher in patients with end-stage renal failure than in the general population. Risk factors for development of AF in patients with severe renal impairment include degenerative valvular heart disease, accelerated vascular nervous system activation, and modulation of the renin-angiotensin system.[5] The clinical benefit of oral anticoagulation therapy for primary and secondary prevention of stroke is based on studies that exclude AF patients with severe renal impairment due to major bleeding episodes in anticoagulated hemodialysis. New oral anticoagulants probably should not be contraindicated in such patient population, but rather be considered on a patient-by-patient basis.[6]

Antithrombotic drug choices for stroke prevention of the patients with AF include addition of antiplatelet agents (aspirin, and aspirin plus clopidogrel) or anticoagulants (warfarin and new anticoagulants). The choice of therapy depends on the estimated risk of thromboembolic events in AF. According the CHA_2DS_2-Vasc. Score, the risk score (given in brackets) considers the following factors: left ventricular dysfunction (1), hypertension (1), age >75 (2), diabetes (1), prior stroke or TIA (2). A total score of 0 does not require therapy, a score of 1 requires ASA or anticoagulation, and a score of 2 or above requires anticoagulation for prevention of AF.

It is worth mentioning that the American Heart Association accepted a new definition for transient ischemic attacks (TIA).[7] Previous definition of TIA presumed a focal neurological deficit of vascular origin lasting less than 24 hours. The new definition is not based on a time limit; instead, it is based on the absence of brain injury, and is described as "a transient episode of neurological dysfunction caused by brain, spinal cord or retinal ischemia without acute infarction." A patient with transient symptoms but evidence of acute infarction on imaging studies (such as diffusion-weighted MRI) is now considered to have had a stroke.

Scripta Medica

References

1. Đokanović N, Stojaković N, Tomić N. Questions and answers. *Scripta Medica* 2011;42:46-52.
2. Galanis T, Thomson L, Palladino M, et al. New oral anticoagulants. *J Thromb Thrombosis* 2011:31:310-20.
3. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-51.
4. Nagarakanti R, Ezekowitz MD, Oldgren J, et al. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. *Circulation* 2011;123:131-6.
5. Mariunigh R, Lane DA, Lip GYH. Severe renal impairment and stroke prevention in atrial fibrillation. *JACC* 2011;57:1339-48.
6. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in atrial fibrillation patients: the Euro Heart Survey. *Chest* 2010;138:1093-10.
7. Albers GW. Stroke: more protection for patients with atrial fibrillation. *Lancet Neurol* 2010;9:2-4.