Journal club

EINSTEIN-CHOICE trial – rationale for the extended anticoagulation in secondary prevention

Anticoagulant treatment is effective in preventing recurrence after venous thrombo-embolism. The management of deep vein thrombosis as well as pulmonary embolism is divided in an initial acute treatment, a long-term treatment, and an extended treatment. Usually, patients were treated with anticoagulants for three to 12 months after acute venous thromboembolism [1]. According to the literature, after termination of anticoagulation the observed cumulative incidence rate of recurrence was 5.2% after one month, 10.1% after six months, 12.9% after one year, and finally, 30.4% after 10 years [2, 3]. Multiple risk factors have been identified to predict the individual risk of recurrence and to decide which patient would profit from extended anticoagulant therapy [1, 3, 4].

In the past years, several concepts of modified anticoagulation treatment to prevent recurrence with reduced bleeding risk have been evaluated. First, vitamin K antagonists have been tested in a reduced dosage [5]. In a clinical study published in 2003, a total of 738 patients haven been randomized and divided into groups of either an INR between 2.0 and 3.0 or 1.5 and 1.9 after initial anticoagulation for three to four months. The results showed similar bleeding rates (4.9% in the low-intensity vs. 3.7% in the conventional therapy group) with a higher recurrence and rate of death in the low-intensity group (1.9% in the conventional low-itensity therapy group vs. 0.7% recurrence of venous thromboembolism in the conventional group). Subsequently, the authors concluded that a dose-reduction of vitamin K antagonists cannot be recommended in prolonged anticoagulation after venous thromboembolism.

Another concept tested in two studies published in 2012 is continuation of treatment with 100 mg of aspirin after an initial anticoagulation for three to 12 months with vitamin K antagonists or new anticoagulants [6, 7]. But the ASPIRE and WARFASA trials showed only moderate reduction in recurrence of venous thromboembolism. Aspirin was tested as a possible alternative to placebo in the WARFASA trial, in which patients with unprovoked venous thromboembolism who had completed six to 18 months of oral anticoagulation were randomized to either take aspirin 100 mg or placebo for two years. The results showed lower recurrence rates in the aspirin group with 6.6% vs. 11.2% per year in the placebo group (hazard ratio 0.58; 95% CI, 0.36–0.93; p = 0.02), resulting in an overall recurrence risk reduction for thromboembolic events of about 40%, while haemorrhagic complications were similar in both groups. Those results could not be confirmed in the ASPIRE trial, which was published the same year with about twice the participants and an observation time of four years. In this study, no significant reduction of recurrence rates could be found for patients treated with aspirin compared to placebo (recurrence rate of 6.5% in the placebo group vs. 4.8% in the aspirin group per year, hazard ratio with aspirin 0.74, CI 0.52 to 1.05; p = 0.09).

Finally, the concept of dose reduction was tested again using the factor X antagonist apixaban [8]. The Amplify-Extension, a randomized double-blind study, published in 2013, tested 2.5 mg or 5 mg apixaban twice daily for a total administration time of 12 months. All patients had completed six to 12 months of initial anticoagulation before study randomization. Both apixaban doses showed a significant relative risk reduction of recurring venous thromboembolism with recurrence rates of 3.8% in the 2.5 mg, 4.2% in the 5 mg, and 11.6% in the placebo group, as well as hazard ratios of 0.33 for apixaban 2.5 mg vs. placebo (95% CI 0.22–0.48) and 0.36 for the apixaban 5 mg vs. placebo comparison (95% CI 0.25–0.53). Non-major bleeding was found in 3.0% of patients in the 2.5 mg apixaban group, in 4.2% of the 5 mg apixaban group, and 2.3% in the placebo group. The results showed a benefit to extended treatment with apixaban for 12 months and the feasibility of a dose reduction in the prolonged period of anticoagulation.

The EINSTEIN-CHOICE study compared these two concepts of secondary prevention after venous thromboembolism [9]. Aim of the double-blind phase 3 study was to evaluate the recurrence rates as well as the safety endpoint of rivaroxaban in doses of 20 mg and 10 mg versus Aspirin 100 mg in the extended treatment of venous thromboembolism. A total of 3,365 patients with deep vein thrombosis or pulmonary embolism were randomized after an initial anticoagulation with vitamin K agonists or new oral anticoagulants for six to 12 months and assigned in a 1:1:1 ratio to either receive 20 mg of rivaroxaban, 10 mg of rivaroxaban or 100 mg of aspirin for a total of 12 months. The recurrence rate for thromboembolism was 1.5% in the 20 mg and 1.2% in the 10 mg group compared to 4.4% in the aspirin group. Both rivaroxaban groups showed a significant superiority in regards to the recurrence rate of thromboembolism with a hazard-ratio for the 20 mg rivaroxaban group vs. aspirin of 0.34 (95% confidence interval [CI] 0.20–0.59) and 0.26 in

the 10 mg group vs. aspirin (CI 0.14–0.47), p<0.001 for both groups. Major bleeding occurred in 0.5 % in the 20 mg rivaroxaban group, 0.4 % in the 10 mg rivaroxaban group, and 0.3 % in the aspirin group. The authors concluded that both dosages of rivaroxaban showed a reduction of the relative risk for recurrence of thromboembolism of about 70 % compared to aspirin, while the rates for major and non-major bleeding events were similar for all groups. Furthermore, patients with an unprovoked thromboembolism showed a higher recurrence rate especially in the aspirin group with recurrence rates of 3.6 % after provoked and 5.6 % after an unprovoked event, while both rivaroxaban groups reduced the relative risk by 70 % in both provoked and unprovoked deep vein thrombosis.

Exclusion criteria of this study were an indication for therapeutic-dosed anticoagulants or for antiplatelet therapy as well as a calculated creatinine clearance of <30 mL/min. Therefore, the study results cannot be applied to these patient groups.

The findings correspond to the recommendations of current guidelines, in which especially patients with an unprovoked deep vein thrombosis of the proximal leg or pulmonary embolism with a low risk of bleeding should be treated with an extended anticoagulation after evaluation of the risk-benefit ratio [1]. A good example to simplify the evaluation of extended treatment was made by the German alliance against thrombosis, in which risk factors are integrated in an ample scheme, divided in different severity levels and subsequently assigned to recommendations for the duration of extended treatment [10].

In conclusion, according to the current literature and guidelines, there are different therapeutic concepts for extended anticoagulation after venous thromboembolism. In some patients, decision to terminate anticoagulation is clear, e. g. in patients with lower limb thrombosis or thrombosis with a serious trigger factor. In other patients, risk of recurrence is very high and anticoagulation should be continued in full dose. In the remaining patients, evaluation of extended treatment should be an individual decision, depending on their medical history, bleeding risk, and patient's preference. In patients with moderate risk of recurrence, rivaroxaban and apixaban can be used in reduced doses for extended treatment according to the results of the EINSTEIN CHOICE and Amplify Extension study. Aspirin is not sufficient to prevent venous embolism.

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