SCIENTIFIC EDITORIAL

Lessons from the RE-ALIGN trial

Les enseignements de l’étude RE-ALIGN

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Patients operated for mechanical heart valve replacement have a low rate of reinter-
vention but suffer valve-related events due to thromboembolism and bleeding caused by
anticoagulant therapy. New oral anticoagulants (NOACs) are easier to use than vitamin K
antagonists and offer a good compromise between efficacy and safety in large trials on
venous thromboembolism and non-valvular atrial fibrillation [1–5]. NOACs were therefore
also promising in patients with mechanical heart valves. However, the presentation of the
results of the Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics
of Oral Dabigatran Etxilale in Patients after Heart Valve Replacement (RE-ALIGN) at the
annual congress of the European Society of Cardiology in September 2013, followed by
their publication, was disappointing [6].

The RE-ALIGN trial was a phase II trial in which the main endpoint was to validate a
dose algorithm to obtain a trough level of dabigatran > 50 ng/mL. Thromboembolic events
and bleeding, which are the usual clinical endpoints in studies on anticoagulant therapy
for prosthetic heart valves, were secondary endpoints. The majority of patients (88%) had
single aortic valve prosthesis, but only 29% were classified as at low risk for thromboem-
bolism. Patients were randomized according to a 2:1 ratio to dabigatran or warfarin, either
during the first week following valve replacement, or at least 3 months after surgery.

Dabigatran doses in the RE-ALIGN trial were far higher than in atrial fibrillation or venous
thromboembolism. The starting dose was between 150 and 300 mg twice daily according to
creatinine clearance and was readjusted according to actual dabigatran plasma level.
The lowest dose in the RE-ALIGN trial corresponded to the highest dose in the Randomized
Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial [3]. It was used in only 15% of
patients as a starting dose and 11% after readjustment. Thus, 89% of patients in the
RE-ALIGN trial received a higher dose of dabigatran than in other indications.

Abbreviations: INR, international normalized ratio; NOAC, new oral anticoagulant drug; RE-ALIGN, Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etxilale in Patients after Heart Valve Replacement; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy.

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During follow-up of the 168 patients allocated to dabigatran, 5% suffered strokes, 2% transient ischaemic attacks, 2% myocardial infarctions and 3% asymptomatic prosthetic thrombosis. On the other hand, the only thromboembolic events in the 84 patients treated with warfarin were transient ischaemic attacks, with a rate of 2%. Major bleeding was observed in 4% of patients in the dabigatran group and 2% in the warfarin group. The trial was not powered on the basis of clinical events and this explains why the differences between allocated treatment groups did not reach statistical significance. Although the primary endpoint was not in question, these findings were sufficient to bring about the premature termination of the trial and to add an explicit contraindication of dabigatran in patients with prosthetic heart valves.

The excess of severe bleeding in the dabigatran group was mainly related to postoperative pericardial bleeding. This may have been favoured by a too early introduction of dabigatran after valve replacement. However, there is no explanation for the excess of stroke, which was observed throughout follow-up and not clustered to the early postoperative period, which is known to be at higher risk for thromboembolism. The conjunction of excess thromboembolism and bleeding makes it unlikely that the use of higher doses of dabigatran would improve the risk-benefit ratio of anticoagulant therapy.

The results of the RE-ALIGN trial provide further proof that the safety and efficacy of new drugs cannot be extrapolated from trials conducted in other contexts. The fact that the risk-benefit ratio of dabigatran was lower in the RE-ALIGN trial may be due to particularities of thrombosis on mechanical valve prosthesis. The artificial components of the prosthesis activate the contact pathway of secondary haemostasis. In addition, flow velocity is higher in valve prostheses, in particular in the aortic position, than in venous thrombosis or in atrial fibrillation. Vitamin K antagonists inhibit four factors of secondary haemostasis and may ensure a more complete blockade of the contact pathway than a drug acting on a single factor. This is also an illustration of the limitations of animal models, which suggested that dabigatran was effective in preventing prosthetic thrombosis in mechanical heart valves.

Therefore, patients with mechanical prostheses will continue to be treated for the foreseeable future with warfarin. All efforts that have been made to reduce complications of vitamin K antagonists should therefore be pursued, in particular management using anticoagulant clinics and INR self-monitoring. Unstable international normalized ratios (INRs) are associated with a higher rate of complications and with an increase in long-term all-cause mortality in patients with mechanical heart valve prostheses [7]. Self-monitoring of INR not only improves the quality of life of patients under vitamin K antagonists, but also decreases the risk of thromboembolism and bleeding, as shown by a meta-analysis of randomized trials [8].

The results of the RE-ALIGN trial cannot be extrapolated to other direct anticoagulant drugs, in particular anti-Xa drugs such as rivaroxaban, apixaban and edoxaban. However, no specific trials seem to be planned for the use of other NOACs in patients with mechanical heart valve prosthesis.

It can be expected that the current absence of indication of NOACs for mechanical prosthesis will be an incentive to continue, or even strengthen, the trend towards favouring implantations of bioprostheses at the expense of mechanical valves. In the report of the European Association for Cardio-Thoracic Surgery, the percentage of mechanical prostheses implanted decreased steadily during the 2000s and represented only one in four aortic valve replacements in 2006 to 2008 [9]. In the United States Society of Thoracic Surgeons’ database, the percentage of mechanical aortic valve replacement decreased from 50% in 1997 to 20% in 2006 [10].

At the present time, it is clear that any NOAC should not be used in patients with a mechanical valve prosthesis [11]. The situation is less clear with bioprostheses. Bioprostheses do not require anticoagulant therapy by themselves and this is their main advantage. However, certain patients with bioprosthesis may require long-term anticoagulant therapy when there are other indications, in particular atrial fibrillation [11]. This is of particular importance given the contemporary epidemiology of heart valve disease, which is characterized by a marked increase in prevalence after the age of 65–70 years [12]. This age also corresponds to an increased prevalence of atrial fibrillation and to the age after which bioprostheses are favoured. In these cases, thrombogenicity is due to atrial fibrillation and not to the prosthesis. However, patients with bioprostheses were not included in any trial evaluating NOACs in atrial fibrillation. The immediate consequence of the RE-ALIGN trial was the decision from the European Medicines Agency’s Committee for Medicinal Products for Human to add the following contraindication: "Pradaxa® is now contraindicated in patients with prosthetic heart valves requiring anticoagulant treatment". This statement is not restricted to mechanical prostheses. The prescription of NOACs is an off-label use at present and should be discouraged in patients with bioprosthesis. This issue highlights the need for specific trials testing the efficacy and safety of NOACs in patients with bioprostheses and atrial fibrillation.

Finally, the findings of the RE-ALIGN trial will have limited consequences in the fast-moving field of oral anticoagulant therapy, since patients with mechanical heart valve prosthesis only account for a small number of all prescriptions of anticoagulant therapy compared with atrial fibrillation and venous thrombosis. The drug company should be acknowledged to have taken the risk of testing a new drug in this specific and risky indication. Unfortunately, randomized trials have always been scarce in the field of heart valve prosthesis, although the RE-ALIGN trial highlights their importance. We should not reproduce the experience of low-molecular weight heparins, which are widely used in patients with mechanical prosthesis, but are still off-label because of the lack of appropriate controlled trials. The RE-ALIGN trial is a timely warning against inappropriate extrapolations on indications for NOACs and off-label prescriptions. Inappropriate use of NOACs has already been reported in patients with mechanical prosthesis and may cause serious harm to the patient [13]. Beyond the immediate disappointment following a "negative" trial, the findings of the RE-ALIGN trial should be a strong incentive to perform specific randomized trials testing the safety and
efficacy of presently available and ongoing NOACs, at least in patients with atrial fibrillation and bioprosthesis or valve repair.

Disclosure of interest

Dr Iung has received consultant fees from Abbott, Boehringer Ingelheim, Valtech, and speaker's fees from Edwards Lifesciences. Dr Vahanian is a member of the Advisory Board for Abbott and Valtech and has received speaker's fees from Edwards Lifesciences and Siemens.

References


