Will Direct Oral Anticoagulants Have a Chance in Prosthetic Valves?

Mahmoud Abdelnabi,[1] Abdallah Almaghraby[2] and Yehia Saleh[2,3]

1. Cardiology and Angiology Unit, Department of Clinical and Experimental Internal Medicine, Medical Research Institute, University of Alexandria, Egypt;
2. Department of Cardiology, Faculty of Medicine, University of Alexandria, Egypt; 3. Michigan State University, East Lansing, MI, US

Abstract

Although there are abundant data highlighting the safety and efficacy of direct oral anticoagulants, to date, recent guidelines have limited their use to stroke prevention in patients with non-valvular AF, as well as in the prevention and treatment of venous thromboembolism and pulmonary embolism. Encouraging data about the off-label use of direct oral anticoagulants have been shown in several other indications, such as intracardiac thrombi, left ventricular thrombi and left atrial appendage, but a large sector of patients are still not addressed, such as valvular and prosthetic patients.

Keywords

Prosthetic valves, direct oral anticoagulants, vitamin K antagonist, left ventricular thrombi, rivaroxaban

Vitamin K antagonist (VKA) oral anticoagulants have been ruling the field of anticoagulation for cardiovascular indications for years now. Recently, this dominance has been threatened by the introduction of direct oral anticoagulants (DOACs), with abundant data highlighting their safety and efficacy. To date, recent guidelines have limited the use of DOACs to stroke prevention in patients with non-valvular AF and in the prevention and treatment of venous thromboembolism and pulmonary embolism.

Although DOACs represent a major advance in oral anticoagulation, there are several limitations for their use, such as prosthetic valves, mitral stenosis and left ventricular thrombi. Given that patients with moderate-to-severe mitral stenosis have been excluded from all pivotal trials, the American College of Cardiology and the European Society of Cardiology currently recommend using warfarin over DOACs in AF patients with moderate-to-severe mitral stenosis.[1,2] However, recently, in a large retrospective analysis comparing DOACs with warfarin in mitral stenosis, Kim et al. concluded that DOACs showed a lower incidence of thromboembolic events and intracranial haemorrhage in comparison with warfarin.[3] Based on the previous promising results, a prospective clinical trial for the evaluation of the superiority of DOACs in moderate-to-severe mitral stenosis is required. However, the geographical distribution of rheumatic heart disease has always been a hindering factor in conducting a large prospective study.

Regarding left ventricular thrombi, due to a lack of prospective clinical trials, warfarin is the only approved medication so far. Nonetheless, several case reports and case series showed the efficacy of DOACs in left ventricular thrombi.[4,5] In addition, several prospective trials are examining the use of different DOACs in patients with left ventricular thrombi.

Regarding prosthetic valves, the European Society of Cardiology recommends lifelong oral anticoagulation using VKA in mechanical valve patients. Moreover, low-dose aspirin (75–100 mg/day) in addition to VKA should be considered after thromboembolism, despite an adequate international normalised ratio. For patients with bioprosthesis, oral anticoagulation using a VKA should be considered for the first 3 months after surgical implantation of a mitral or tricuspid bioprosthesis. However, after surgical implantation of an aortic bioprosthesis, low-dose aspirin (75–100 mg/day) should only be considered for the first 3 months.[6] Hence, to date, there is no place in the guidelines for DOACs in prosthetic valves.

Several trials were conducted to evaluate the efficacy and safety of DOACs in prosthetic valves, such as the Randomised, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN), which was prematurely terminated due to safety concerns. The RE-ALIGN study concluded that in patients with mechanical mitral or aortic valves, dabigatran was not only less effective than warfarin for thromboembolic prevention, but was also associated with an increased risk of bleeding; therefore, it should not be used in mechanical valve patients.[7] Possible explanations for the increase in thromboembolic complications with dabigatran included inadequate plasma levels of the drug and dabigatran's mechanism of action, which differs from warfarin.[7]

Despite the unfavourable outcomes of the RE-ALIGN study, several retrospective analyses and prospective studies were conducted to evaluate the safety and efficacy of different DOACs in prosthetic valves, such as the Dabigatran Versus Warfarin After Bioprosthesis

Valve Replacement for the Management of Atrial Fibrillation Postoperatively (DAWA) study, which aimed to evaluate the efficacy and safety of dabigatran in patients with bioprosthetic mitral and/or aortic valve replacement and AF. Due to inconclusive results and low enrolment rates, the study was terminated.[8]

Duraes et al. conducted a pilot study to evaluate the effect of the use of rivaroxaban for anticoagulation in seven patients with unstable international normalised ratios at least 3 months following isolated mechanical mitral valve replacement, and concluded that the use of rivaroxaban for 90 days in mechanical mitral valve prosthesis was not associated with thromboembolic or bleeding events. Hence, rivaroxaban use in mechanical prostheses may be feasible, efficacious and safe. However, larger-scale randomised controlled clinical trials are required to evaluate this possibility before it is adopted as an alternative to warfarin in this patient population.[9]

Transcatheter aortic valve replacement (TAVR) has recently been approved for low-risk patients with severe aortic stenosis, thus the number of TAVR procedures within the next decade is expected to rise significantly. Currently, for TAVR patients, the European Society of Cardiology recommends dual antiplatelet therapy for the first 3–6 months, followed by lifelong single antiplatelet therapy for patients who do not require oral anticoagulation for other reasons. Nonetheless, single antiplatelet therapy may be considered after TAVR in the case of high bleeding risk.[6] However, in a retrospective study, several patients who underwent a successful TAVR were noted to have reduced leaflet motion on CT. Interestingly, after therapeutic anticoagulation, the reduced aortic valve leaflet motion was resolved; hence, it was presumed that valve thrombosis was contributing to the pathogenesis.[10]

Consecutively, several trials investigated DOACs in patients undergoing TAVR. The Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet Strategy After Transcatheter Aortic Valve Replacement to Optimise Clinical Outcomes (GALILEO) assessed whether a rivaroxaban-based regimen is superior in reducing death or first antithrombotic events compared with an antiplatelet-based regimen in patients undergoing a successful TAVI procedure. It was halted, because data showed that rivaroxaban was associated with greater risks of all-cause mortality, thromboembolic events and bleeding in patients who had undergone TAVR.[11]

To further investigate the role of anticoagulation in TAVR patients, the Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis (ATLANTIS) is an on-going clinical trial to test the superiority of an apixaban-based strategy versus dual antiplatelet therapy strategy in patients who have undergone a successful TAVI procedure to reduce the risk of post-TAVI thromboembolic and bleeding complications.[12]

To date, the limited evidence about the safety and efficacy of DOACs in prosthetic valve patients make it difficult to define solid recommendations for their use in this population. Currently, the available data demonstrated that DOACs use (specifically dabigatran) in mechanical valve patients is neither safe nor effective. Also, prospective and retrospective data analyses of DOACs use in patients with bioprosthetic valves are contradictory.

Further research is required to justify whether the use of DOACs for thromboembolic prevention in prosthetic valves is safe and efficient. The question still stands, will DOACs have a chance in prosthetic valves or will warfarin, with all its drawbacks, always be the only available option? ∎

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