J.1 Anticoagulation and antiplatelet therapy

J.1.1 Research recommendation

What is the clinical and cost effectiveness of single or dual antiplatelet therapies or anticoagulants compared with placebo following transcatheter or surgical valve replacement (implantation) with biological prosthesis and following valve repair?

J.1.2 Why this is important

Biological surgical valve and transcatheter valve replacement/implantation

Cusp thrombosis is known to potentially occur occasionally in biological surgical valves and more often in transcatheter valves. It usually occurs in the first 3-6 months after valve replacement/implantation are in most cases it is subclinical at this stage, being identified on valve imaging by detecting thrombus on the affected valve cusp and reduced mobility of it. An immediate effect on valve function at the time of this diagnosis is rare and it manifests primarily through abrupt significant increase in transvalvular gradient and consequent decrease in calculated valve area, mainly in aortic valves. Commencement of anticoagulation at this stage has been found to result in gradual normalisation of valve function, as the thrombus resolves. Anticoagulation is only given as treatment in these rare cases of significant haemodynamic consequences of cusp thrombosis. However, there is concern that this cusp thrombosis even when undetected or subclinical may contribute to earlier degeneration of biological surgical and transcatheter valves. Consequently, it is thought that maybe preventive anticoagulation or dual antiplatelet therapy should be offered to prevent cusp thrombosis, to avoid early degeneration of the valve and premature need for redo intervention.

Valve repair

In the case of mitral valve repair, the rationale of offering an anticoagulant or dual antiplatelet drug early after the intervention would be to avoid the rarely occurring cerebrovascular or other arterial embolization of thrombus sometimes seen to form in the left atrium or suspected due to developed atrial fibrillation. This can be the result of reduction in mitral valve area as a result of mitral valve repair or mitral valve replacement with a biological surgical valve. As the experience with surgical mitral valve repair is larger, the phenomenon is recognised as rarely potential occurring in this case; however, it can also occur in patient having had transcatheter edge-to-edge mitral valve repair that decreases the mitral valve area further.

J.1.3 Rationale for research recommendation

Importance to ‘patients’ or the population	1. Potential increase of valve durability and delay of need for redo intervention on the valve in biological surgical valves and transcatheter valves replacement/implantation 2. Avoid thrombo-embolic complications following mitral valve repair (surgical or

	transcatheter) or replacement with a biological surgical valve
Relevance to NICE guidance	The comparison between antithrombotic treatment (anticoagulation or antiplatelets, or a combination) and placebo following biological surgical valve replacement, transcatheter implantation and valve repair interventions was considered in this guideline but none of the included randomised controlled trials covered this comparison. This meant that there was no included evidence to determine whether antithrombotic therapy is required following these types of valve interventions. Answering this question may provide stronger evidence on which to base recommendations about whether or not any antithrombotic therapy is required following these procedures.
Relevance to the NHS	Answer to this clinical question would allow standardisation of clinical practice in the NHS in this regard and potential reduction in cost if need for redo intervention is delayed.
National priorities	It is relevant to the NHS long term plan “action on prevention” priority.
Current evidence base	No randomised controlled trials have been performed comparing antithrombotic treatment (anticoagulation or antiplatelets, or a combination) and placebo following biological surgical valve replacement, transcatheter implantation and valve repair interventions, with all of them instead comparing between different types of antithrombotic treatment rather than comparing to placebo. As there is a lack of information regarding whether or not any form of antithrombotic therapy is required for all patients undergoing these procedures, randomised controlled trials covering a comparison of antithrombotic therapy with placebo is required to be able to make strong recommendations.
Equality considerations	None known.

J.1.4 Modified PICO table

Population	Inclusion Adults aged 18 years and over with repaired valves or biological prosthetic valves stratified by type of intervention: • transcatheter replacement • surgical replacement. • transcatheter repair • surgical repair Exclusion • Children (aged <18 years)

	• • Adults who have other indications for anticoagulant or dual antiplatelet treatment (e.g. have atrial fibrillation or a mechanical valve replacement or take dual antiplatelet therapy for an indication related to coronary disease)
Intervention	Oral anticoagulation therapy: • Vitamin K Antagonists (including: warfarin, acenocoumarol and phenindione) • Direct acting oral anticoagulants (DOACs) (including: dabigatran, rivaroxaban, apixaban and edoxaban) Oral antiplatelet therapy: • Single therapy (including aspirin, clopidogrel, ticagrelor and prasugrel) • Dual therapy (the combination of aspirin with either clopidogrel, ticagrelor or prasugrel). Combined oral anticoagulation and oral antiplatelet therapy
Comparator	Placebo Note that the focus of the question is to compare each specific type of antithrombotic therapy with a placebo group and comparisons between different types of antithrombotic treatment are not required. Separate comparisons are required for each of the specific antithrombotic groups to placebo, as follows: • Vitamin K antagonists vs. placebo • DOACs vs. placebo • Single antiplatelet therapy vs. placebo • Dual antiplatelet therapy vs. placebo Combined oral anticoagulation and oral antiplatelet therapy vs. placebo
Outcome	<u>Primary outcomes</u> All-cause mortality; Health-related quality of life; Major bleeding; Minor bleeding; Arterial thromboembolic events Primary outcomes should be reported at ≤12 months and >12 months. <u>Secondary outcomes</u> Hospital re-admission at 12 months; Withdrawal due to adverse events at 12 months; Thrombus on imaging at <12 months; Need for

	reintervention at medium term (6 months to 12 months) and long term (>12 months); Valve degeneration (mean transvalvular gradient) at ≥12 months.
Study design	Adequately powered randomised controlled trial
Timeframe	Long term
Additional information	None