Bridging anticoagulant therapy early after mechanical heart valve surgery: systematic review with meta-analysis.

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Population, Intervention(s), exposure(s), outcomes:

Patients submitted to mechanical prosthesis implantation need anticoagulation in order to prevent prosthesis thrombosis [1]. Risk of prosthesis thrombosis is higher in the first days after surgery than later [2, 3] as it has been shown by transesophageal echocardiography [4]. The best moment to start anticoagulation remains a matter of debate. Some authors prefer to start unfractioned heparin or low molecular weight heparin during the first 48 hours after surgery [5]. Others prefer to start oral anticoagulation without bridging anticoagulant therapy [6]. Our purpose is to perform a systematic review of the literature evaluating patients with or without bridging anticoagulant therapy and its types, and their bleeding rates, thromboembolic rates and death.

Review question:
How does bridging anticoagulant therapy impact on early thromboembolic and bleeding risk compared to warfarin alone without bridging therapy?

Searches:
According to the PRISMA statement [7] for systematic reviews, and according to specific guidelines for non-randomized studies [8], a literature search in PubMed, Web of Knowledge, LILACS, SCOPUS, Cochrane and EMBASE will be performed. There will be language restrictions. Studies published in English, Spanish or Portuguese before 01 August 2014 will be sought. The searches will be re-run just before the final analyses and further studies retrieved for inclusion. The following terms will be used: "Early Anticoagulation", "Early anticoagulants", "bridging anticoagulant", “early
antiplatelet", "valve replacement", "heart valve surgery", "cardiac surgery", "prosthetic Valve Surgery", "Anticoagulants"[Mesh], "Heart Valve Prosthesis Implantation"[Mesh], "Heart Valve Prosthesis"[Mesh]. Besides textual and MeSH terms, hand search of each paper references and also "related citations", a search tool available in PubMed [9], were used to increase sensitivity of the search. Inclusion criteria were: papers evaluating unfractioned heparin (UH), low molecular weight heparin (LMWH), or oral anticoagulation (OA) during the first week after mechanical heart valve implantation with or without antiplatelet, presenting outcomes of bleeding, thromboembolic events or death during hospital stay; papers in English, Spanish or Portuguese with at least 10 patients >18 years old, all study designs. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened independently by two review authors to identify studies that potentially meet the inclusion criteria outlined above. The full text of these potentially eligible studies will be retrieved and independently assessed for eligibility by two review team members (GB and LGP). Any disagreement between them over the eligibility of particular studies will be resolved through discussion with a third reviewer (MRS).

**Data extraction:**
A standardized, pre-piloted form will be used to extract data from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and participant demographics and baseline characteristics; details of the anticoagulation and antiplatelet used and control conditions; study methodology; recruitment and
study completion rates; outcomes (thromboembolic and hemorrhagic events and death) and times of measurement; indicators of acceptability to users; suggested mechanisms of intervention action; information for assessment of the risk of bias. Two review authors (GB and LGP) will extract data independently, discrepancies will be identified and resolved through discussion (with a third MRS author where necessary). Missing data will be requested from study authors. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses [10] will be used to evaluate study quality.

**Strategy for data synthesis:**

We will provide a narrative synthesis of the findings from the included studies, structured around the type of intervention (bridging anticoagulation or not), target population characteristics, type of outcome and intervention content. We will provide summaries of intervention effects for each study by calculating rates (percentages with confidence intervals) in each group or arm (with and without bridging). These rates will be indirectly compared by Comprehensive Meta-analysis software by one group meta-analysis with subgroup comparisons. If available, direct comparisons will be done. We anticipate that there will be limited scope for meta-analysis because of the range of different outcomes measured across the small number of existing trials. However, where studies have used the same type of intervention and comparator, with the same outcome measure, we will pool the results using a random-effects meta-analysis, with risk ratios for binary outcomes, and calculate 95% confidence intervals and two sided P values for each outcome. Heterogeneity between the
studies in effect measures will be assessed using both the $\chi^2$ test and the $I^2$ statistic. We will consider an $I^2$ value greater than 50% indicative of substantial heterogeneity. We will conduct sensitivity analyses based on study quality. We will use stratified meta-analyses to explore heterogeneity in effect estimates according to: study quality; study populations; the logistics of intervention provision; and antiplatelet use. We will also assess evidence of publication bias.

Pooling of results will be done only if we judge studies are comparable by patient characteristics. One group meta-analysis from Comprehensive Meta-Analysis (CMA®) software will be used to evaluate pooled rates (by random effects model) of embolic and hemorrhagic events and death with difference between subgroups tested. Subgroup analysis and sensitivity analysis will be performed if possible.

References:


