The optimal intensity of vitamin K antagonists in patients with mechanical heart valves: a meta-analysis


CRD summary
This review compared the results of studies assessing low or high intensities of vitamin K antagonists (VKA) in patients with mechanical aortic and mitral heart valves. The authors concluded that high-intensity VKA was preferable. There were limitations to the quality of the review and the included studies, and the conclusions should therefore be treated with caution.

Authors' objectives
The aim was to compare the effects of two different intensities of vitamin K antagonists (VKA) in people with mechanical heart valves.

Searching
PubMed was searched from January 1965 to June 2002; the search terms were given. The reference lists of retrieved studies were also checked.

Study selection
Study designs of evaluations included in the review
No inclusion criteria were stated for study type. The included studies appeared to be cohort studies.

Specific interventions included in the review
Studies were eligible for inclusion if the target international normalised ratio (INR), or prothrombin time, were specified as part of a VKA regimen. In addition, there had to be no change in these criteria during follow-up. Studies of antiplatelet therapy alone or antiplatelet therapy in combination with VKA were excluded. Treatment in the included studies was classified as high intensity (mean target INR above 3.0) or low intensity (mean target INR 3.0 or lower).

Participants included in the review
The inclusion criteria stated that studies on adults (mean age over 18 years) with mechanical heart valves were sought, but only where it was possible to differentiate between those with aortic and mitral valve prosthesis. Studies where more than 5% of the participants were lost to follow-up, or where some participants had bioprostheses or caged ball valves, were excluded. The mean ages of the participants in the included studies ranged from 48 to 65 years.

Outcomes assessed in the review
The outcomes of interest were thromboembolic or bleeding events classified according to Edmunds, or which were otherwise adequately classified. Edmunds' classification included all neurological or peripheral embolic events. Neurological events were defined as any new temporary or permanent focal or global neurological deficit. Peripheral embolic events were defined as an operative, autopsy proven or clinically documented embolism producing symptoms from complete or partial obstruction of a peripheral artery. Valve thrombosis included any thrombus, in the absence of infection, that occluded or partially occluded blood flow through the valve. Bleeding events were defined as any major or minor internal or external bleeding that caused death, hospitalisation, permanent injury or required transfusion. Outcomes were given for valve thrombosis, any thrombosis, a composite of these, haemorrhage and total events.

How were decisions on the relevance of primary studies made?
Two reviewers independently evaluated potentially relevant papers for inclusion.

Assessment of study quality
The authors did not state that they assessed validity.

**Data extraction**
Two reviewers extracted the data independently, with any disagreements resolved by consensus. Where prothrombin times were used as treatment targets, these were converted to an INR. Treatment was classified as high-intensity VKA where the mean target INR was above 3.0, and low-intensity VKA where the mean target INR was 3.0 or lower. For each outcome in each study, the annual incidence rate (number of outcome events divided by number of patient-years) and standard error were calculated. Where no events occurred a nominal 0.5 was added in the calculations.

**Methods of synthesis**
How were the studies combined?
Average incidences for each event across studies were calculated by adding the yearly incidence rates of all studies and dividing by the number of studies. Risk ratios (RR) and 95% confidence intervals (CIs) were calculated assuming a Poisson distribution of the data. Statistically significant differences between incidences in different groups were investigated using a Wald test, with a P-value of less than 0.05 taken to be statistically significant.

How were differences between studies investigated?
Results for mitral valve prostheses were analysed separately to those for aortic prostheses. Other than this, the authors did not state a method for assessing differences between the studies.

**Results of the review**
Thirty-five studies (23,145 participants) were included in the review.

**Aortic valves.**

There were less valve thrombosis events in the high-intensity VKA group than in the low-intensity group: 0.87 versus 1.16 per 1,000 patient-years (RR 0.75, 95% CI: 0.50, 1.13, P=0.126). There were less thromboembolisms in the high-intensity group than in the low-intensity group: 9.83 versus 13.09 per 1,000 patient-years (RR 0.75, 95% CI: 0.70, 0.81, P<0.0001). The total number of thromboembolic events was less in the high-intensity group than in the low-intensity group: 10.01 versus 13.69 per 1,000 patient-years (RR 0.73, 95% CI: 0.68, 0.78, P<0.0001). There was an increase in bleeding events in the high-intensity group compared with the low-intensity group: 14.89 versus 12.06 per 1,000 patient-years (RR=1.23, 95% CI: 1.16, 1.31, P<0.0001).

When all embolic and haemorrhagic events were combined, there was a reduction in the total number of all events in the high-intensity group compared with the low-intensity group: 23.84 versus 25.39 per 1,000 patient-years (RR 0.94, 95% CI: 0.88, 0.99, P=0.0067).

**Mitral valves.**

Patients in the high-intensity VKA group had a lower risk of valve thrombosis and thromboembolism than those in the low-intensity group: 2.06 versus 3.44 per 1,000 patient-years for valve thrombosis (RR 0.60, 95% CI: 0.47, 0.76 P<0.0001), and 15.91 versus 20.12 per 1,000 patient-years for thromboembolism (RR 0.79, 95% CI: 0.74, 0.84, P<0.0001). Bleeding events did not differ significantly between high- and low-intensity VKA: 12.94 versus 11.96 per 1,000 patient-years (RR 1.08, 95% CI: 1.00, 1.16, P=0.0524). The total number of events was 29.76 per 1,000 patient-years in the high-intensity group and 35.33 per 1,000 patient-years in the low-intensity group (RR 0.84, 95% CI: 0.79, 0.89, P<0.001).

**Comparison between mitral and aortic prostheses.**

The number of valve thrombosis and thromboembolic events was significantly lower in the aortic valve group than in the mitral valve group for both high- and low-intensity VKA. For high-intensity VKA, patients with aortic prostheses were more likely to haemorrhage than those with mitral prostheses (RR 1.15, 95% CI: 1.06, 1.25). However, there was no difference in bleeding complications for low-intensity VKA (RR 1.01, 95% CI: 0.94, 1.07).
Authors’ conclusions
Patients with aortic or mitral valve prostheses will benefit from high-intensity VKA therapy, i.e. with a target INR of more than 3.

CRD commentary
The inclusion criteria for this review were only partially stated as there was no mention of what study designs were eligible for inclusion. The database search was limited to PubMed, thus it is possible that other studies were missed; this could affect the results of the review. The included studies appeared to be cohort, observational studies. Evidence from studies such as these is of a lower class than that from prospective clinical trials. In addition, the authors made indirect comparisons by comparing the results of studies using low-intensity VKA with the results of studies using high-intensity VKA (rather than summarising studies that directly compared the effects of high- versus low-intensity VKA treatment). Results from comparisons such as these are not as reliable as those from direct comparisons, as the characteristics of the studies may differ (i.e. the people in different studies may not be comparable for severity of disease, age etc.). Since there was little information on the participants in the studies (severity of disease, co-morbidities, cointerventions etc.), it may be difficult to generalise from the results. The authors also commented that the mean ages were low, thus it is not possible to tell whether the results would be applicable to older people. The conclusions should be treated with caution in view of the above comments.

Implications of the review for practice and research
Practice: The authors recommended a target INR of between 3.0 and 4.5 for daily practice. In particular, a target INR at the lower end of this range for aortic valves and one at the upper end for mitral valves.

Research: The authors stated that a prospective study is needed to assess the intensity of VKA treatment in relation to both aortic and mitral prosthetic valves.

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