Management of antithrombotic therapy in venous and arterial thromboembolism

Vink, R.

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Chapter 3

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

Roel Vink, MD*; Roderik A. Kraaijenhagen, MD†; Barbara A. Hutten, PhD‡; Renée B.A. van den Brink, MD†; Bas A. de Mol, MD§; Harry R. Büller, MD*; Marcel Levi, MD*.
From the Departments of Vascular Medicine*, Cardiology †, Clinical Epidemiology & Biostatistics‡ and Cardiopulmonary Surgery§, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

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Abstract

Objective: The objective of this study was to compare two different intensities of vitamin K antagonists (VKA) among patients with mechanical heart valves using meta-analytic techniques.

Background: Patients with mechanical heart valves are at increased risk for valve thrombosis and systemic embolism, which can be reduced by VKA. The range of optimal intensity of VKA is still a matter of debate. Methods: A computerized search in the Pubmed database was made for relevant articles. A meta-analysis was performed of all eligible studies with data on the incidences of thromboembolic and bleeding complications in patients with mechanical heart valve prostheses during different intensities of VKA therapy. The studies were classified into low intensity VKA therapy (mean target INR of 3.0 or lower) or high intensity VKA therapy (mean target INR above 3.0).

Results: 35 eligible studies were identified including in total 23145 patients, that were studied for 108792 patient-years. For patients with an aortic valve, high intensity results in a lower incidence of thromboembolic events (RR=0.73, p<0.0001), however the incidence of bleeding was increased (RR=1.23, p<0.0001). In the mitral valve group, the incidence rate for thromboembolism was lower in the high intensity group (RR=0.74, p<0.0001), without a significantly increased bleeding incidence (RR=1.08, p=0.0524). The total number of thromboembolic and bleeding events was decreased in the high intensity group as compared to low intensity VKA therapy for both aortic and mitral valve prostheses (RR=0.94 (p=0.0067) and 0.84 (p<0.0001)), respectively.

Conclusion: This meta-analysis shows that both aortic and mitral valves will benefit from a treatment strategy with a target INR higher than 3.0.
INTRODUCTION

Patients with mechanical heart valves are at increased risk for valve thrombosis and systemic embolism, predominantly stroke. The incidence rates of these serious complications can be reduced by vitamin K antagonist (VKA) therapy and life-long anticoagulation is recommended in patients with mechanical heart valves. However, life-long anticoagulant therapy is associated with a risk of severe and sometimes fatal bleeding. The relation between preventing thromboembolism and introducing bleeding complications is represented by an U-shaped relation between the intensity of VKA and the risk of thromboembolic - and bleeding events. The optimal VKA intensity, therefore, defined as the intensity at which the incidence of both thromboembolic as well as bleeding complications is lowest, is a delicate equilibrium. The first ACCP guidelines published in 1986 recommended an INR between 3.0 and 4.5, regardless of the position of the valve

In 1995 Cannegieter et al. described, based on a discrepancy between targeted and achieved INR, the relation between the effectiveness of anticoagulation and the actually achieved intensities. The study showed that the optimal intensity of anticoagulation, resulting in the fewest adverse events, lies between INR levels of 2.5 to 4.9. The incidence of the events rises sharply above or below this range. As a target range, they recommended an INR of 3.0 to 4.0 for both aortic and mitral valves, although it was shown that the risk of thromboembolic complications appears to vary with the position of the valve. Patients with a prosthesis in the mitral position have a significantly higher risk of thromboembolic complications than those with an aortic valve prosthesis. Based on this discrepancy, more recently, a minor discrimination in anticoagulation intensity was recommended between aortic and mitral valves and the target range was lowered to 2.0 and 3.5, depending on the position and type of the valve. These latest guidelines, however, are based on only a few studies. Thus, the range of optimal intensity of VKA is an ongoing matter of debate, moreover since it is difficult to assess the individual risk of thromboembolism and bleeding in an individual patient. To obtain reliable estimates on the adverse events and to make guidelines for daily clinical practice we performed an extended analysis of all published studies with data on the incidence of thromboembolic and bleeding events in patients with a mechanical heart valve in either the aortic or the mitral position during different intensities of VKA therapy.
METHODS

Selection of articles
A computerized search in Pubmed database over the period January 1965 to June 2002 was performed to retrieve studies with data on the incidences of thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. The key words used were: heart valve prosthesis, mechanical heart valve, anticoagulants, coumarin, warfarin, thromboembolism and hemorrhage. Subsequently, a manual search of the reference lists from the retrieved articles was done to identify additional articles. Only studies which met the following criteria were included: 1) possibility to differentiate between aortic valve prosthesis and mitral valve prosthesis, 2) specification of the target INR or prothrombin time of VKA-therapy, 3) no change in the target INR or prothrombin time ratio during follow up, 4) thromboembolic and bleeding events classified according to Edmunds et al 6 or otherwise adequately classified and 5) mean age of the patients older than 18 years. Studies were excluded when: 1) the number of patients lost to follow up was larger than 5%, 2) the study included bioprostheses or caged-ball valves, 3) the patients received antiplatelet therapy alone or antiplatelet therapy in combination with VKA and 4) the cohort was the same as reported in another included study.

Data extraction
All potentially eligible articles were evaluated independently by two reviewers. Data on the position and type of the prosthetic valve, target INR or prothrombin time ratio, number of patients and patient-years were extracted from each study. The outcome events of interest included valve thrombosis, systemic embolism and bleeding. A data form was used to collect this information. Disagreements were resolved by consensus.

Outcome events
The events were analysed according to the guidelines for reporting morbidity and mortality after cardiac valvular operations of Edmunds et al. Briefly, thromboembolic events included all neurologic and peripheral embolic events. A neurologic event includes any new, temporary or permanent focal or global neurologic deficit. A peripheral embolic event is an operative, autopsy proven or clinically documented embolus that produces symptoms from complete or partial obstruction of a peripheral artery. Valve thrombosis is any thrombus, in the absence of infection, that occludes (part of) the transvalvular blood flow and/or that interferes with the function of the valve. Valve thrombosis may be documented by operation, autopsy or clinical investigation (e.g. echocardiography, angiocardiography or magnetic resonance imaging). A bleeding
event is defined as any episode of major internal or external bleeding that causes death, hospitalization, permanent injury or requires transfusion.

Subgroups
We separately analysed studies with aortic and mitral valve prostheses. These studies were subdivided into low intensity VKA therapy or high intensity VKA therapy. Low intensity VKA therapy was defined as a mean target INR of 3.0 or lower. High intensity was defined as a mean target INR above 3.0. The results of the thrombotest (TT) and prothrombin time ratios were converted to International Normalized Ratios (INR), using the ISI of the prothrombin time assays as reported by the authors or requested from them.

Statistical analysis
For each outcome event and per study separately, an annual incidence (number of outcome events divided by the number of patient-years) and its standard error was calculated. In case the number of events was zero, a statistical correction for the standard error was made by adding a fictive number of 0.5 events to the number of events and to the number of patient-years. The significant Chi-square test for each outcome result may implicate heterogeneity between the studies. Therefore we did not use the fixed effect method, but the random effect method. Since study size would have small effect in a random effect model, the calculated incidences were averaged by adding the yearly incidence rates of all studies divided by the number of studies. Ninety-five percent confidence intervals (CI) of rate ratios were calculated with the assumption of a Poisson distribution. Statistical significance between the incidences of two groups was calculated using the Wald test. A p-value less then 0.05 (two-sided) was considered to be statistically significant.

RESULTS

Studies
The literature search identified 141 potentially eligible articles. Of these 141 articles, 35 could be included in the analysis. Reasons for exclusion were: inability to differentiate between aortic and mitral valves (23 studies), intensity of oral anticoagulant therapy was not specified (27 studies), the use of antiplatelet therapy (14 studies), the events or patient-years were not specified (18 studies), the cohort was the same as another included study (8 studies), lost to follow up not specified or exceeding 5% (6 studies), or other reasons (10 studies). The list of excluded articles will appear in the online appendix for this article (www.cardiosource.com/JACC.html).
Not all of the outcome events were reported in all of the studies. Of the 35 studies, 26 were eligible for analysis of both aortic and mitral valve prostheses. Four studies only reported on aortic valve prostheses and five other reports concerned mitral valve prostheses only. The 35 studies included 23,145 patients with a total of 108,792 patient-years. For the aortic valve prostheses group 13,337 patients were followed for 63,432 patient-years and 9808 patients in the mitral valve prostheses group were followed for 45,360 patient-years. In the high intensity VKA group, the highest observed upper limit of the INR was 4.8.

In Tables I and II the results of the separate studies are given, divided in 4 subgroups, i.e. patients with prosthetic aortic valves or prosthetic mitral valves with either high or low intensity VKA therapy.

**High vs. low intensity VKA therapy in patients with aortic valve prostheses**
The incidence rates of valve thrombosis, thromboembolism and bleeding for high and low intensity VKA therapy in patients with an aortic valve prosthesis are shown in Table III, expressed as number of events per 1000 patient-years. With high intensity VKA therapy (mean target INR above 3.0), the incidence of valve thrombosis was 0.87 per 1000 patient-years and the incidence of embolism was 9.83 per 1000 patient-years as compared with 1.16 events per 1000 patient-years and 13.09 per 1000 patient-years for the low intensity group (mean target INR below 3.0), with risk ratios of 0.75, 95% CI 0.50-1.13 and 0.75, 95% CI 0.70-0.81, respectively. The total number of thromboembolic events (a combination of valve thrombosis and embolism together) was 10.01 per 1000 patient-years for the high intensity group and 13.69 per 1000 patient-years for the low intensity group (risk ratio = 0.73, 95% CI 0.68-0.78). There was an increase in the incidence of bleeding events in the high intensity group as compared with low intensity VKA therapy (14.89 versus 12.06 per 1000 patient-years; risk ratio = 1.23, 95% CI 1.16-1.31). The total number of events, i.e. all thromboembolic and bleeding events, in the high intensity group was 23.84 per 1000 patient-years; in the low intensity group 25.39 events per 1000 patient years. This is a decrease of events with a significant risk ratio of 0.94 (95% CI 0.88-0.99).
### Table I. Overview of studies used for the analysis of mechanical aortic valves

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**Legend to Tables I and II**

- * expressed as number of events per 1000 patient-years
- VT = valve thrombosis
- TE = thromboembolism
- VT+TE = all valve thrombosis and thromboembolism
- Hemor = hemorrhage
- CI = confidence interval
- All = all thromboembolic and bleeding events
- Ptsys = patient-years
- ns = not specified
- age = mean age at valve implantation

**Valve types**

- MH = Medtronic Hall
- SJ = St Jude
- CM = Carmedics
- SO = Sorin
- OC = Omnicarbon
- OS = Ommiscience
- BS = Björk-Shiley
- MS = Monostrut
- CK = Lillehei-Kaster
- ED = Edwards Duromedics
Table II. Overview of studies used for the analysis of mechanical mitral valves

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<td>11.96</td>
<td>35.33</td>
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**High vs. low intensity VKA therapy in patients with mitral valve prostheses**

The results of the analysis in the group of patients with a prosthetic mitral valve are listed in Table IV. Patients who received high VKA therapy had a lower risk for valve thrombosis and systemic embolisation than those receiving low dose VKA, with a risk ratio of 0.60 (95% CI 0.47-0.76) and 0.79 (95% CI 0.74-0.84), respectively. The occurrence of bleeding complications did not differ with the use high dose VKA as
compared to low dose (12.94 versus 11.96 events per 1000 patient-years; risk ratio = 1.08, 95% CI 1.00-1.16, p-value= 0.0524). The total number of events (thromboembolic and bleeding events) was 29.76 per 1000 patient-years in the high intensity group and 35.33 per 1000 patient-years in the low intensity VKA group (risk ratio 0.84, 95% CI 0.79-0.89).

**Table III.** Incidence rates of thromboembolic and hemorrhagic complications in patients with mechanical aortic valve, according to VKA intensity

<table>
<thead>
<tr>
<th>Aortic valve high</th>
<th>Aortic valve low</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
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<tr>
<td>VT events/1000 ptyrs</td>
<td>0.87</td>
<td>1.16</td>
<td>0.75</td>
<td>0.50-1.13</td>
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<td>TE events/1000 ptyrs</td>
<td>9.83</td>
<td>13.09</td>
<td>0.75</td>
<td>0.70-0.81</td>
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<td>VT+TE events/1000 ptyrs</td>
<td>10.01</td>
<td>13.69</td>
<td>0.73</td>
<td>0.68-0.78</td>
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<tr>
<td>hemorrh events/1000 ptyrs</td>
<td>14.89</td>
<td>12.06</td>
<td>1.23</td>
<td>1.16-1.31</td>
</tr>
<tr>
<td>all events/1000 ptyrs</td>
<td>23.84</td>
<td>25.39</td>
<td>0.94</td>
<td>0.88-0.99</td>
</tr>
</tbody>
</table>

**Table IV.** Incidence rates of thromboembolic and hemorrhagic complications in patients with mechanical mitral valve, according to VKA intensity

<table>
<thead>
<tr>
<th>Mitral valve high</th>
<th>Mitral valve low</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
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<td>VT events/1000 ptyrs</td>
<td>2.06</td>
<td>3.44</td>
<td>0.60</td>
<td>0.47-0.76</td>
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<tr>
<td>TE events/1000 ptyrs</td>
<td>15.91</td>
<td>20.12</td>
<td>0.79</td>
<td>0.74-0.84</td>
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<tr>
<td>VT+TE events/1000 ptyrs</td>
<td>17.11</td>
<td>23.13</td>
<td>0.74</td>
<td>0.70-0.78</td>
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<tr>
<td>hemorrh events/1000 ptyrs</td>
<td>12.94</td>
<td>11.96</td>
<td>1.08</td>
<td>1.00-1.16</td>
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<tr>
<td>all events/1000 ptyrs</td>
<td>29.76</td>
<td>35.33</td>
<td>0.84</td>
<td>0.79-0.89</td>
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</table>

**Legend to Tables III and IV**

VT = valve thrombosis; TE = thromboembolism; VT+TE = all valve thrombosis and thromboembolism; Hemor = hemorrhage; CI = confidence interval; All = all thromboembolic and bleeding events

**Aortic versus mitral valve prostheses**

The number of valve thrombosis and thromboembolic events is significantly lower in the aortic valve group compared with the mitral valve group for both low and high intensity VKA therapy. The risk ratios are shown in Table V. Treatment with high intensity therapy
give rise to a significant increase in bleeding events in patients with a prosthetic aortic valve as compared to patients with a mitral valve (risk ratio = 1.15, 95% CI 1.06-1.25). No difference in bleeding complications was observed between patients with aortic and mitral valves treated with low intensity VKA (risk ratio = 1.01, 95% CI 0.94-1.07). The total number of events (thromboembolism and bleeding) for both high and low intensity treatment was lower in the aortic valve group than for patients in the mitral valve group (risk ratios 0.80, 95% CI 0.75-0.85 and 0.72, 95% CI 0.68-0.76).

Table V. Risk ratios of thromboembolic and hemorrhagic events for patients with a mechanical aortic valve as compared to mechanical mitral valve

<table>
<thead>
<tr>
<th>Event</th>
<th>Risk Ratio</th>
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<th>p-value</th>
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<td>TE</td>
<td>0.62</td>
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<td>&lt; 0.0001</td>
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<tr>
<td>TE+VT</td>
<td>0.59</td>
<td>0.54-0.63</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Hemor</td>
<td>1.15</td>
<td>1.06-1.25</td>
<td>0.0014</td>
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<tr>
<td>All</td>
<td>0.80</td>
<td>0.75-0.85</td>
<td>&lt; 0.0001</td>
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</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>VT</td>
<td>0.34</td>
<td>0.29-0.39</td>
<td>&lt; 0.0001</td>
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<tr>
<td>TE</td>
<td>0.65</td>
<td>0.62-0.68</td>
<td>&lt; 0.0001</td>
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<tr>
<td>TE+VT</td>
<td>0.59</td>
<td>0.57-0.62</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Hemor</td>
<td>1.01</td>
<td>0.94-1.07</td>
<td>0.8026</td>
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<tr>
<td>All</td>
<td>0.72</td>
<td>0.68-0.76</td>
<td>&lt; 0.0001</td>
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</table>

Legend to Table V
VT = valve thrombosis; TE = thromboembolism; VT+TE = all valve thrombosis and thromboembolism
Hemor = hemorrhage; CI = confidence interval; All = all thromboembolic and bleeding events; Ptyrs = patient-years

**DISCUSSION**

Anticoagulant therapy with vitamin K antagonists for patients with a mechanical heart valve has been the subject of intense debate. Since 1992, the target range of the INR has been lowered from INR values between 3.0 and 4.5 to less intensive values, that is, between 2.0 and 3.5. Furthermore, since aortic valve prosthesis are considered less thrombogenic than prostheses in the mitral position, a target INR at the lower side of this range is advised for aortic valves, whereas a target INR at the upper side of this range is suggested for mitral valves. Nevertheless, the present literature review shows that patients with a mechanical heart valve in the aortic as well as in the mitral position...
will benefit from high intensity VKA treatment. The number of thromboembolic events is lowest for both the aortic and the mitral valve group with the strategy of this high target INR. The total number of thromboembolic and bleeding events, the most important parameter for the efficacy of treatment, is significantly decreased when patients are treated with high intensity VKA therapy as compared to low intensity therapy.

Although the decrease in thromboembolic events is similar for both aortic and mitral valves (risk ratio = 0.73 and 0.74), it was shown that in patients with a mechanical aortic valve treated with high intensity VKA therapy significantly more bleeding episodes occurred as compared to those treated with low intensity VKA. A nonsignificant trend toward a higher frequency of bleeding events with high intensity VKA was observed in the mitral valve group of our study. Therefore, since the strong correlation between the intensity of VKA and the risk of bleeding events is a well-established fact, this high intensity strategy is relatively more effective for mitral valve prostheses than for aortic valve prostheses (risk ratios for total number of events 0.84 and 0.94, respectively).

Patients with a mechanical heart valve in the aortic position have an increased risk for bleeding complications as compared to patients with a mechanical mitral valve. This risk is significantly increased at high levels of VKA therapy. The number of bleeding events is 14.89 per 1000 patient-years in the aortic valve group versus 12.94 events per 1000 patient-years in the mitral valve group (risk ratio 1.15, 95% CI 1.06-1.25). A possible mechanism for this observation is that the two patient groups have a different bleeding risk profile. Hypertension and atherosclerosis may result in a slightly increased bleeding risk. These cardiovascular risk factors are frequent among patients with aortic stenosis, which is the main indication for aortic valve replacement. Another possibility may be that patients with an aortic prosthesis are in a general better condition and may lead a more active life, thereby somewhat increasing the risk of bleeding.

The incidence of valve thrombosis and thromboembolism is higher in patients with mitral valve prostheses than with aortic valve prostheses for both low and high intensity VKA therapy. This is presumably due to different bloodflow properties over the mitral valve as compared to the aortic valve and the relatively increased incidence of atrial fibrillation in patients with mitral valve heart disease.

There are a few limitations of the present study. First, most reports used for this analysis are based on an intention to treat INR range, and therefore information on the actually achieved intensity of VKA treatment and the compliance of therapy was lacking. The time spent in the therapeutic range is approximately 50-70% in well designed cohorts and it is unlikely that the achieved INR range in our study-population will exceed this percentage. Since most of the adverse events occur in the period of under- or overcoagulation, it is plausible to assume that the risk for embolism and bleeding will
Chapter 3

decrease with a more stable level of anticoagulation. In addition, a major effect of anticoagulation control on the long-term survival was shown in a recent study, demonstrating that a high variability in INR was the strongest independent predictor of reduced survival. In this report, there was a 32% difference in survival at 15 years between patients with low and high variability in anticoagulation control. This observation emphasises the importance of adequate management of anticoagulation. Several developments in therapeutic quality control have improved the safety and efficacy of VKA therapy. Monitoring of VKA therapy by a specialized anticoagulation clinic reduces the bleeding and thromboembolic event rates. More recently, home testing of the intensity of anticoagulation by means of a portable coagulometer that performs an INR on a single drop of capillary blood has become available. INR home testing appears to be a safe and efficient anticoagulation control method which results in a higher percentage of target range values compared to the conventional laboratory-based testing regimen.

A second limitation may be that most of the included studies were cohort series, without a control group. These cohort studies, however, allow for the estimate of the absolute risk of bleeding and thrombosis. This pooled analysis of 35 studies, with in total more than 23,000 patients who were followed for more than 100,000 patient-years, indeed yielded sufficient power to detect significant differences in favour of high intensity VKA therapy. To minimize the risk for bias, we only selected studies wherein all the adverse events were classified according to an international accepted scoring system.

Another limitation is that some studies used older valve types. However, most valve types used in the analysis are still being used for insertion nowadays.

Total mortality would be an important outcome in this analysis. Unfortunately, from the majority of the studies used for the analysis, no data on mortality could be retrieved to be able to estimate a reliable mortality rate.

Our recommendations are based on data derived from patients with a mean age at valve implantation of 55 years. Since there is a trend towards valve replacements in older age groups and the fact that older patients have an increased bleeding risk, it's uncertain whether this group of patients will benefit from high intensity VKA therapy. However, in our analysis we were not able to identify age-associated risks, since most of the studies only report on age as a baseline characteristic.

The role of antiplatelet therapy in patient with mechanical heart valves remains controversial. Two recent randomised trials evaluated the effects of adding aspirin to VKA treatment. Turpie et al. showed that aspirin (100mg/d) in combination with VKA (INR 3.0-4.5) was associated with fewer thromboembolic events than VKA alone, although the rate of major bleeding was increased. Messchengieser et al. demonstrated in their trial that aspirin (100mg/d) in combination with VKA (INR 2.5-3.5) was as effective as VKA (INR 3.5-4.5) alone. The results from these studies cannot be
considered as sufficient evidence for recommending combination therapy. In exceptional cases of patients with thromboembolic complications despite adequate VKA therapy, the addition of antiplatelet therapy can be considered for the prevention of thromboembolic events.

In conclusion, this analysis shows that both patients with aortic and mitral valve will benefit from high intensity VKA therapy, with a target INR above 3.0. For daily practice, we recommend an INR between 3.0 and 4.5. Since aortic valve prosthesis are considered less thrombogenic than prosthesis in the mitral position, a target INR at the lower side of this range is advised for aortic valves, whereas a target INR at the upper side of this range is suggested for mitral valves. However, a prospective study that address both the intensity of VKA and the position of the mechanical heart valve are definitely needed before the discussion can be resolved.

This project is supported by a grant of the Netherlands Heart Foundation, grant 2000.068.

REFERENCE LIST


APPENDIX

List of excluded articles:

- Inability to differentiate between aortic and mitral valves 1-23
- Intensity of oral anticoagulant therapy was not specified 24-50
- The events or patient-years were not specified 51-68
- The use of antiplatelet therapy 69-82
- The cohort was the same as another included study 83-90
- Lost to follow up not specified or exceeding 5% 91-96
- Other reasons 97-106

REFERENCE LIST


53


