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**CLINICAL RESEARCH** **Meta-Analysis**

# The Optimal Intensity of Vitamin K Antagonists in Patients With Mechanical Heart Valves

## A Meta-Analysis

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**OBJECTIVES** The purpose 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 international normalized ratio [INR] of 3.0 or lower) or high-intensity VKA therapy (mean target INR above 3.0).

**RESULTS** Thirty-five eligible studies were identified, including in total 23,145 patients, who were studied for 108,792 patient-years. For patients with an aortic valve, high intensity resulted in a lower incidence of thromboembolic events (risk ratio [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 compared with low-intensity VKA therapy for both aortic and mitral valve prostheses (RR = 0.94 [$p = 0.0067$] and 0.84 [$p < 0.0001$]), respectively.

**CONCLUSIONS** This meta-analysis shows that both aortic and mitral valves will benefit from a treatment strategy with a target INR higher than 3.0. (J Am Coll Cardiol 2003;42:2042–8) © 2003 by the American College of Cardiology Foundation

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 relationship between preventing thromboembolism and introducing bleeding complications is represented by a U-shaped relationship between the intensity of VKA and the risk of thromboembolic and bleeding events. Therefore, the optimal VKA intensity defined as the intensity at which the incidence of both thromboembolic as well as bleeding complications is lowest, is a delicate equilibrium. The first American College of Chest Physicians guidelines published in 1986 recommended an international normalized ratio (INR) between 3.0 and 4.5, regardless of the position of the valve (1,2). In 1995 Cannegieter et al. (3) described, on the basis of a discrepancy between targeted and achieved INR, the relationship 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 and 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 (4). 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 (5), depending on the position and type of the valve. However, these latest guidelines are based on only a few studies. Thus, the range of optimal intensity of VKA is an ongoing matter of debate, moreover because 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

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**Abbreviations and Acronyms**
CI = confidence interval
INR = international normalized ratio
RR = risk ratio
VKA = vitamin K antagonists

formulate 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 the 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 that met the following criteria were included: 1) the 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 analyzed according to the guidelines for reporting morbidity and mortality after cardiac valvular operations of Edmunds et al. (6). 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 analyzed studies with aortic and mitral valve prostheses. These studies were subdivided into low- 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 and prothrombin time ratios were converted to INR, using the international sensitivity index 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 were calculated. In case the number of events was 0, 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. Because 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. The 95% 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 value of $p < 0.05$ (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 as follows: 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 (7–32). Four studies only reported on aortic valve prostheses (33–36), and five other

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**Table 1.** Overview of Studies Used for the Analysis of Mechanical Aortic Valves

| Author (Ref.) | Valve Type | Pt-Yrs | VT* | TE* | VT+TE* | Hemor* | All* | Age | % Male |
|---|---|---|---|---|---|---|---|---|---|
| High-intensity aortic valve | | | | | | | | | |
| Aris et al. 1996 (7) | MS | 12,929 | 0.08 | 8.74 | 8.82 | 8.97 | 17.79 | 53 | 52 |
| Nitter-Hauge et al. 1996 (8) | MH | 7,611 | 0.53 | 18.00 | 18.53 | ns | ns | 56 | 69 |
| Milano et al. 1992 (9) | SO | 1,650 | 0.61 | 12.12 | 12.73 | 9.09 | 21.82 | 48 | 78 |
| Peter et al. 1993 (10) | OC | 269 | 1.86 | 7.43 | 7.43 | 11.15 | 18.59 | 61 | 67 |
| Obadia et al. 1997 (33) | MH | 884 | 0.57 | 5.66 | 5.66 | 30.54 | 36.20 | 63 | 82 |
| Podesser et al. 1998 (11) | ED | 1,978 | ns | ns | 8.59 | 16.68 | 25.28 | 55 | 64 |
| Debetaz et al. 1997 (12) | SJ | 1,750 | 1.71 | 20.00 | 21.71 | 33.14 | 54.86 | 58 | 32 |
| Aagaard et al. 1995 (13) | CM | 647 | 0.77 | 3.09 | 3.09 | 7.73 | 10.82 | 57 | 61 |
| Sethia et al. 1986 (14) | BS | 1,121 | ns | 3.57 | 3.57 | 1.78 | 5.35 | 50 | ns |
| Total | | 28,839 | 0.87 | 9.83 | 10.01 | 14.89 | 23.84 | 56 | 58 |
| Low-intensity aortic valve | | | | | | | | | |
| Kim et al. 1994 (15) | MH/MS | 1,045 | ns | 8.61 | 8.61 | ns | ns | 55 | 52 |
| Torregrosa et al. 1999 (16) | OC | 970 | 0.52 | 1.03 | 1.03 | 10.31 | 11.34 | 54 | 75 |
| Borman et al. 1998 (17) | SO | 1,593 | 0.63 | 11.30 | 11.93 | 12.55 | 24.48 | 58 | 60 |
| Akins et al. 1996 (18) | MH | 765 | 0.65 | 13.07 | 13.07 | 16.99 | 30.07 | 57 | 76 |
| Goldsmith et al. 1999 (19) | SO | 505 | 0.99 | 27.72 | 27.72 | 23.76 | 51.49 | 58 | 56 |
| Bortolotti et al. 2001 (20) | SO | 1,703 | 0.59 | 13.51 | 14.09 | 13.51 | 27.60 | 60 | 72 |
| Smith et al. 1993 (21) | SJ | 1,640 | 0.30 | 6.10 | 6.10 | 9.76 | 15.85 | 54 | 72 |
| Dalrymple-Hay et al. 2000 (22) | CM | 2,495 | 0.40 | 16.43 | 16.83 | 16.43 | 33.27 | 63 | 68 |
| Ismeno et al. 2001 (34) | SJ | 512 | 0.98 | 3.91 | 3.91 | 1.95 | 5.86 | 64 | 34 |
| Nistal et al. 1996 (23) | CM | 522 | 0.96 | 30.65 | 30.65 | 19.16 | 49.81 | 54 | 74 |
| Baudet et al. 1995 (24) | SJ | 6,419 | 2.49 | 8.41 | 10.91 | 9.50 | 20.41 | 57 | 69 |
| Khan et al. 2001 (25) | SJ | 3,881 | 3.09 | 24.99 | 28.09 | 20.10 | 48.18 | 65 | 51 |
| Thevenet et al. 1995 (26) | OC | 760 | 0.66 | 1.32 | 1.32 | 6.58 | 7.89 | 58 | 57 |
| Nakano et al. 1994 (27) | SJ | 1,919 | 0.52 | 13.03 | 13.55 | 1.04 | 14.59 | 48 | 67 |
| Fiane et al. 1998 (28) | CM | 3,176 | 0.31 | 8.82 | 9.13 | 6.93 | 16.06 | 62 | 57 |
| Lund et al. 1990 (35) | SJ | 296 | 1.69 | 13.51 | 13.51 | ns | ns | 60 | 53 |
| Zellner et al. 1999 (29) | SJ | 2,376 | 2.95 | 20.20 | 23.15 | 26.94 | 50.08 | 55 | 70 |
| Olesen et al. 1991 (36) | LK | 2,301 | 0.87 | 13.47 | 15.21 | 6.52 | 21.73 | 53 | 73 |
| Otaki et al. 1993 (30) | OC | 166 | 3.01 | 3.01 | 3.01 | 3.01 | 3.01 | 49 | 47 |
| Damle et al. 1987 (32) | OS | 454 | 1.10 | 22.03 | 22.03 | ns | ns | 51 | 70 |
| Arom et al. 1987 (31) | SJ | 1,095 | 0.46 | 13.70 | 13.70 | ns | ns | ns | ns |
| Total | | 34,593 | 1.16 | 13.09 | 13.69 | 12.06 | 25.39 | 57 | 64 |

*Expressed as number of events per 1,000 patient-years.

Age = mean age at valve implantation; All = all thromboembolic and bleeding events; BS = Björk-Shiley; CM = Carbomedics; ED = Edwards Duromedics; Hemor = hemorrhage; LK = Lillehei-Kaster; MH = Medtronic Hall; MS = Monostrut; ns = not specified; OC = Omnicarbon; OS = Omniscience; Pt-yrs = patient-years; SJ = St. Jude; SO = Sorin; TE = thromboembolism; VT = valve thrombosis; VT+TE = all valve thrombosis or thromboembolism.

reports concerned mitral valve prostheses only (37–41). 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 9,808 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 1 and 2, the results of the separate studies are given, divided in four subgroups, namely, patients with prosthetic aortic valves or prosthetic mitral valves with either high- or low-intensity VKA therapy.

**High- versus 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 3, expressed as number of events per 1,000 patient-years. With high-intensity VKA therapy (mean target INR above 3.0), the incidence of valve thrombosis was 0.87 per 1,000 patient-years and the incidence of embolism was 9.83 per 1,000 patient-years compared with 1.16 events per 1,000 patient-years and 13.09 per 1,000 patient-years for the low-intensity group (mean target INR below 3.0), with risk ratios (RR) of 0.75, 95% CI 0.50 to 1.13 and 0.75, 95% CI 0.70 to 0.81, respectively. The total number of thromboembolic events (a combination of valve thrombosis and embolism together) was 10.01 per 1,000 patient-years for the high-intensity group and 13.69 per 1,000 patient-years for the low-intensity group (RR = 0.73, 95% CI 0.68 to 0.78). There was an increase in the incidence of bleeding events in the high-intensity group compared with low-intensity VKA therapy (14.89 vs. 12.06 per 1,000 patient-years; RR = 1.23, 95% CI 1.16 to 1.31). The total number of events, that is, all thromboembolic and bleeding events, in the high-intensity group was 23.84 per 1,000 patient-years; in the low-intensity group 25.39 events per 1,000 patient-years. This is a decrease of events with a significant RR of 0.94 (95% CI 0.88 to 0.99).

**High- versus 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 4. Patients who received high-intensity VKA therapy had a lower risk for valve thrombosis and systemic emboli-

**Table 2.** Overview of Studies Used for the Analysis of Mechanical Mitral Valves

| Author (Ref.) | Valve Type | Pt-Yrs | VT* | TE* | VT+TE* | Hemor* | All* | Age | % Male |
|---|---|---|---|---|---|---|---|---|---|
| High-intensity mitral valve | | | | | | | | | |
| Aris et al. 1996 (7) | MS | 11,549 | 0.35 | 17.14 | 17.49 | 10.39 | 27.88 | 53 | 52 |
| Nitter-Hauge et al. 1996 (8) | MH | 1,632 | 1.84 | 19.00 | 20.83 | ns | ns | 56 | 69 |
| Milano et al. 1992 (9) | SO | 963 | 1.04 | 12.46 | 13.50 | 9.35 | 22.85 | 48 | 33 |
| Remadi et al. 2001 (37) | SJ | 4,877 | 2.05 | 6.97 | 9.02 | 9.84 | 18.86 | 60 | 46 |
| Dalrymple-Hay et al. 2000 (22) | CM | 1,096 | 0.46 | 14.60 | 14.60 | 22.81 | 37.41 | 65 | 44 |
| Jegaden et al. 1994 (38) | SJ | 1,334 | ns | ns | 20.99 | 9.00 | 29.99 | 55 | ns |
| Goldsmith et al. 1999 (19) | SO | 316 | 1.58 | 9.49 | 9.49 | 22.15 | 31.65 | 61 | 56 |
| Borman et al. 1998 (17) | SO | 1,120 | 5.36 | 21.43 | 26.79 | 6.25 | 33.04 | 58 | 60 |
| Peter et al. 1993 (10) | OC | 117 | 4.27 | 17.09 | 17.09 | 8.55 | 25.64 | 61 | 67 |
| Debetaz et al. 1997 (12) | SJ | 1,000 | 0.50 | 29.00 | 29.00 | 34.00 | 63.00 | 57 | 44 |
| Podesser et al. 1998 (11) | ED | 1,286 | ns | ns | 11.66 | 10.89 | 22.55 | 53 | 50 |
| Thevenet et al. 1995 (26) | OC | 444 | 2.25 | 9.01 | 11.26 | 11.26 | 22.52 | 58 | 57 |
| Aagaard et al. 1995 (13) | CM | 333 | 3.00 | 18.02 | 21.02 | 12.01 | 33.03 | 54 | 38 |
| Sethia et al. 1986 (14) | BS | 1,788 | ns | 16.78 | 16.78 | 1.68 | 18.46 | 50 | ns |
| Total | | 27,855 | 2.06 | 15.91 | 17.11 | 12.94 | 29.76 | 56 | 51 |
| Low-intensity mitral valve | | | | | | | | | |
| Kim et al. 1994 (15) | MH/MS | 708 | ns | 18.36 | 18.36 | ns | ns | 55 | 52 |
| Hayashi et al. 1994 (39) | SJ | 845 | ns | 15.38 | 15.38 | ns | ns | 49 | 41 |
| Torregrosa et al. 1999 (16) | OC | 1,210 | 2.48 | 6.61 | 9.09 | 7.44 | 16.53 | 54 | 35 |
| Akins et al. 1996 (18) | MH | 481 | 2.08 | 20.79 | 22.87 | 18.71 | 41.58 | 62 | 27 |
| Bortolotti et al. 2001 (20) | SO | 1,021 | 2.94 | 18.61 | 21.55 | 10.77 | 32.32 | 58 | 37 |
| Camilleri et al. 2001 (40) | SO/SJ | 396 | 7.58 | 12.63 | 20.20 | 10.10 | 30.30 | 58 | 49 |
| Nistal et al. 1996 (23) | CM | 431 | 4.64 | 37.12 | 41.76 | 27.84 | 69.61 | 55 | 34 |
| Baudet et al. 1995 (24) | SJ | 1,580 | 4.43 | 17.72 | 22.15 | 8.86 | 31.01 | 53 | 46 |
| Khan et al. 2001 (25) | SJ | 2,662 | 2.25 | 28.93 | 31.18 | 19.16 | 50.34 | 65 | 51 |
| Nakano et al. 1994 (27) | SJ | 3,318 | 0.90 | 15.97 | 16.88 | 1.81 | 18.69 | 48 | 39 |
| Fiane et al. 1998 (28) | CM | 677 | 4.43 | 10.34 | 14.77 | 2.95 | 17.73 | 62 | 57 |
| Zellner et al. 1999 (29) | SJ | 1,868 | 0.54 | 33.73 | 34.26 | 15.52 | 49.79 | 52 | 38 |
| Damle et al. 1987 (32) | OS | 547 | 1.83 | 21.94 | 23.77 | ns | ns | 51 | 35 |
| Arom et al. 1987 (31) | SJ | 778 | 3.86 | 25.71 | 29.56 | ns | ns | ns | ns |
| Fiore et al. 1998 (41) | MH/SJ | 789 | 5.07 | 32.95 | 38.02 | 17.74 | 55.77 | 60 | 38 |
| Otaki et al. 1993 (30) | OC | 194 | 5.15 | 5.15 | 10.31 | 2.58 | 10.31 | 49 | 47 |
| Total | | 17,505 | 3.44 | 20.12 | 23.13 | 11.96 | 35.33 | 55 | 42 |

*Expressed as number of events per 1,000 patient-years.
Abbreviations as in Table 1.

zation than those receiving low-dose VKA, with a RR of 0.60 (95% CI 0.47 to 0.76) and 0.79 (95% CI 0.74 to 0.84), respectively. The occurrence of bleeding complications did not differ with the use of high-dose VKA compared with low-dose VKA (12.94 vs. 11.96 events per 1,000 patient-years; RR = 1.08, 95% CI 1.00 to 1.16, p = 0.0524). The total number of events (thromboembolic and bleeding events) was 29.76 per 1,000 patient-years in the high-intensity VKA group and 35.33 per 1,000 patient-years in the low-intensity VKA group (RR 0.84, 95% CI 0.79 to 0.89).

**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 RRs are shown in Table 5. Treatment with high-intensity therapy significantly increased bleeding events in patients with a prosthetic aortic valve compared with patients with a mitral valve (RR = 1.15, 95% CI 1.06 to 1.25). No difference in bleeding complications was observed between patients with aortic and mitral valves treated with low-intensity VKA (RR = 1.01, 95% CI 0.94 to 1.07). The

**Table 3.** Incidence Rates of Thromboembolic and Hemorrhagic Complications in Patients With Mechanical Aortic Valve, According to Vitamin K Antagonist Intensity

| | Events/1,000 Pt-Yrs | | | | |
|---|---|---|---|---|---|
| | Aortic Valve High | Aortic Valve Low | Risk Ratio | 95% CI | p Value |
| VT | 0.87 | 1.16 | 0.75 | 0.50–1.13 | 0.1260 |
| TE | 9.83 | 13.09 | 0.75 | 0.70–0.81 | <0.0001 |
| VT+TE | 10.01 | 13.69 | 0.73 | 0.68–0.78 | <0.0001 |
| Hemor | 14.89 | 12.06 | 1.23 | 1.16–1.31 | <0.0001 |
| All | 23.84 | 25.39 | 0.94 | 0.88–0.99 | 0.0067 |

CI = confidence interval; other abbreviations as in Table 1.

**Table 4.** Incidence Rates of Thromboembolic and Hemorrhagic Complications in Patients With Mechanical Mitral Valve, According to Vitamin K Antagonist Intensity

| | Events/1,000 Pt-Yrs | | | | |
|---|---|---|---|---|---|
| | Mitral Valve High | Mitral Valve Low | Risk Ratio | 95% CI | p Value |
| VT | 2.06 | 3.44 | 0.60 | 0.47–0.76 | <0.0001 |
| TE | 15.91 | 20.12 | 0.79 | 0.74–0.84 | <0.0001 |
| VT+TE | 17.11 | 23.13 | 0.74 | 0.70–0.78 | <0.0001 |
| Hemor | 12.94 | 11.96 | 1.08 | 1.00–1.16 | 0.0524 |
| All | 29.76 | 35.33 | 0.84 | 0.79–0.89 | <0.0001 |

Abbreviations as in Tables 1 and 3.

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 (RR 0.80, 95% CI 0.75 to 0.85, and RR 0.72, 95% CI 0.68 to 0.76, respectively).

## DISCUSSION

Anticoagulant therapy with VKA 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, because aortic valve prostheses 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 (5). 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 compared with low-intensity VKA therapy.

Although the decrease in thromboembolic events is similar for both aortic and mitral valves (RR = 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 compared with 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, because the strong correlation between the intensity of VKA and the risk of bleeding events is a well-established fact (3,42,43), this high-intensity strategy is relatively more effective for mitral valve prostheses than for aortic valve prostheses (RRs for total number of events 0.84 and 0.94, respectively).

**Table 5.** Risk Ratios of Thromboembolic and Hemorrhagic Events for Patients With a Mechanical Aortic Valve Compared With Mechanical Mitral Valve

| Aortic vs. Mitral Valve | Event | Risk Ratio Aortic vs. Mitral | 95% CI | p Value |
|---|---|---|---|---|
| High intensity | VT | 0.42 | 0.27–0.66 | <0.0001 |
| | TE | 0.62 | 0.56–0.68 | <0.0001 |
| | VT+TE | 0.59 | 0.54–0.63 | <0.0001 |
| | Hemor | 1.15 | 1.06–1.25 | 0.0014 |
| | All | 0.80 | 0.75–0.85 | <0.0001 |
| Low intensity | VT | 0.34 | 0.29–0.39 | <0.0001 |
| | TE | 0.65 | 0.62–0.68 | <0.0001 |
| | VT+TE | 0.59 | 0.57–0.62 | <0.0001 |
| | Hemor | 1.01 | 0.94–1.07 | 0.8026 |
| | All | 0.72 | 0.68–0.76 | <0.0001 |

Abbreviations as in Tables 1 and 3.

Patients with a mechanical heart valve in the aortic position have an increased risk for bleeding complications compared with 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 1,000 patient-years in the aortic valve group versus 12.94 events per 1,000 patient-years in the mitral valve group (RR 1.15, 95% CI 1.06 to 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 (44,45). 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 blood flow properties over the mitral valve compared with 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% to 70% in well-designed cohorts (46), and it is unlikely that the achieved

INR range in our study population will exceed this percentage. Because most of the adverse events occur in the period of under- or over-coagulation, it is plausible to assume that the risk for embolism and bleeding will 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 (47), 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 emphasizes 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 (48). 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. The INR home testing appears to be a safe and efficient anticoagulation control method which results in a higher percentage of target range values compared with the conventional laboratory-based testing regimen (49–51).

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 favor 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 internationally 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 allow estimation of a reliable mortality rate.

Our recommendations are based on data derived from patients with a mean age at valve implantation of 55 years. Because there is a trend towards valve replacements in older age groups and because older patients have an increased bleeding risk (3), it is 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, because 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 randomized trials evaluated the effects of adding aspirin to VKA treatment. Turpie et al. (52) showed that aspirin (100 mg/day) in combination with VKA (INR 3.0 to 4.5) was associated with fewer thromboembolic events than VKA alone, although the rate of major bleeding was increased. Meschengieser et al. (53) demonstrated in their trial that aspirin (100 mg/day) in combination with VKA (INR 2.5 to 3.5) was as effective as VKA (INR 3.5 to 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. Because aortic valve prostheses 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. However, a prospective study that addresses both the intensity of VKA and the position of the mechanical heart valve is definitely needed before the discussion can be resolved.

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## APPENDIX

For the list of excluded articles, please see the December 17, 2003, issue of *JACC* at www.cardiosource.com/jacc.html.