

OPTIMAL ORAL ANTICOAGULANT THERAPY IN PATIENTS WITH MECHANICAL HEART VALVES

S.C. CANNEGIETER, M.D., F.R. ROSENDAAL, M.D., A.R. WINTZEN, M.D., F.J.M. VAN DER MEER, M.D., J.P. VANDENBROUCKE, M.D., AND E. BRIËT, M.D.

Abstract Background. The optimal intensity of oral anticoagulant therapy for patients with mechanical heart valves (i.e., the level at which thromboembolic complications are effectively prevented without excessive bleeding) is not known. We attempted to determine the optimal intensity by calculating the incidence of both complications at different levels of anticoagulation.

Methods. Data were collected on all patients with mechanical heart valves who have been seen at four regional Dutch anticoagulation clinics since 1985. The primary outcome events were episodes of thromboembolism or major bleeding. The intensity-specific incidence of each type of event was calculated as the number of events that occurred at a certain intensity of anticoagulation (expressed in terms of the international normalized ratio [INR]) divided by the number of patient-years during

which the INR was at this level in the total patient population.

Results. A total of 1608 patients were followed during 6475 patient-years. Cerebral embolism occurred in 43 patients (0.68 per 100 patient-years) and peripheral embolism in 2 (0.03 per 100 patient-years). Intracranial and spinal bleeding occurred in 36 patients (0.57 per 100 patient-years) and major extracranial bleeding in 128 (2.1 per 100 patient-years). The optimal intensity of anticoagulation, at which the incidence of both complications was lowest, was achieved when the INR was between 2.5 and 4.9.

Conclusions. The intensity of anticoagulant therapy for patients with prosthetic heart valves is optimal when the INR is between 2.5 and 4.9. To achieve this level of anticoagulation, a target INR of 3.0 to 4.0 is recommended. (N Engl J Med 1995;333:11-7.)

PATIENTS with mechanical heart-valve prostheses receive lifelong, high-intensity oral anticoagulant therapy to prevent thromboembolic complications, but this treatment is associated with an increased risk of bleeding.¹ The risks of thromboembolism and bleeding depend on the intensity of anticoagulation. The optimal intensity — that is, the level at which thromboembolic complications are effectively prevented without excessive bleeding — is not known. A number of trials have been conducted in which different levels of anticoagulation were compared, some in combination with antiplatelet therapy.²⁻⁴ These studies, in which only two levels were compared and which did not take into account discrepancies between achieved levels and target intensities, do not offer comprehensive information about the optimal intensity of anticoagulation; therefore, a direct relation between the intensity of anticoagulation and the frequency of adverse events cannot be determined from their results.

We developed a method to determine the optimal intensity of anticoagulation,⁵ which extends methods developed by others for slightly different purposes,^{6,7} and used it to study the dose–effect relation between the intensity of anticoagulation and the benefits and risks of the treatment. On the basis of the medical records of 1608 patients with mechanical prostheses, we calculated the incidence of both thromboembolic and bleeding complications at different achieved levels of anticoagulation. The optimal intensity was defined as

the level at which the incidence of both thromboembolism and bleeding was lowest.

METHODS

Oral Anticoagulation

In the Netherlands, treatment with coumarin derivatives (phenprocoumon or acenocoumarol) is monitored by regional anticoagulation clinics.⁸ All patients with mechanical prosthetic heart valves receive anticoagulant treatment through these clinics, which they visit regularly every one to six weeks. At each visit, a short history is taken and patients are asked about thromboembolic or bleeding complications, other diseases, and hospital admissions. Samples of antecubital venous blood are obtained, prothrombin times are measured, and the results are expressed in terms of the international normalized ratio (INR). The daily dose of the anticoagulant agent for the upcoming period and the length of this period are determined by physicians; the target range for the prothrombin time is an INR of 3.6 to 4.8.

Patients

Four anticoagulation clinics that use the same computer-assisted system to determine dosage⁹ participated in this study: those in Leiden, The Hague, Enschede, and Oost-Gelderland. Beginning on January 1, 1985, all patients with mechanical prosthetic valves who were treated in the clinics in Leiden and The Hague, which were using the system at that time, were included in the study. The anticoagulation clinics at Enschede and Oost-Gelderland later introduced computerized registration. Their patients were therefore included from the date their records were computerized, which varied between January 1, 1985, and May 1, 1987. Patients who later underwent heart-valve replacement were included as of the date of discharge (at least 30 days after surgery). Follow-up ended when a patient died or moved to a different region, when the anticoagulation was stopped permanently for any reason, or at the end of the study after six years of follow-up at each site. Patients who were seen at the anticoagulation clinics for less than one month and who were not residents of the region were excluded.

Data Collection and Definitions of Events

The following information was extracted from the computerized files of the anticoagulation clinics: date of birth, sex, date of valve replacement, position and type of valves, all prothrombin-time measurements (expressed in terms of the INR) and their dates, data on all hospital admissions, and date of death for patients who died. Additional information about hospital admissions (such as discharge

From the Hemostasis and Thrombosis Research Center, Department of Hematology (S.C.C., F.R.R., F.J.M.M., E.B.), the Department of Clinical Epidemiology (F.R.R., J.P.V.), and the Department of Neurology (A.R.W.), University Hospital Leiden; and the Leiden Anticoagulation Clinic (F.J.M.M.) — both in Leiden, the Netherlands. Address reprint requests to Dr. Cannegieter at the Hemostasis and Thrombosis Research Center, Department of Hematology, Bldg. 1, C2-R, University Hospital Leiden, P.O. Box 9600, 2300 RC Leiden, the Netherlands.

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letters and autopsy reports) were collected from the hospitals or from general practitioners' archives.

The chief outcome variable was all thromboembolic and bleeding events — that is, cerebral infarction, peripheral embolism, valve thrombosis, intracranial and spinal bleeding, and major extracranial bleeding. Cerebral infarction was defined as neurologic deficit of sudden onset documented by a computed tomographic (CT) scan indicating the presence of infarction or the absence of hemorrhage or at autopsy. Peripheral embolic events were included in the category of acute peripheral ischemia, demonstrated by angiography, at operation, or at autopsy. Valve thrombosis was defined as impairment of the valve by the deposition of thrombus, demonstrated at operation or at autopsy. Intracranial and spinal bleeding was defined as a neurologic deficit of sudden or subacute onset, confirmed by CT scanning, surgery, or autopsy. Major extracranial bleeding was defined as an acute bleeding event that led to death or to admission to the hospital for treatment of the bleeding; bleeding that led to hospital admission for diagnostic procedures only was not considered major. Bleeding caused by trauma was also included. All strokes that could not be categorized as hemorrhagic or ischemic were designated "unclassified" strokes.

Since the aim of this study was to assess the optimal level of anticoagulation in otherwise healthy outpatients, we excluded all events that occurred during a period of endocarditis. We also excluded all complications that occurred during hospitalization for a different reason, since other diseases, interventions, and diagnostic procedures may affect the risk of complications far more than the intensity of the anticoagulant therapy. For the same reason, bleeding that occurred after surgery or after any other invasive procedure was also excluded from our analysis.

All complications were reviewed by an expert panel, whose members classified events according to these definitions. They also classified the outcome of the intracranial and spinal events as death, if the patient died as a direct consequence of the event, or as survival with or without neurologic deficit (as judged three weeks after the event); neurologic deficits were categorized according to whether patients were dependent or independent in performing activities of daily living. The panel was blinded to the intensity of anticoagulation at the time of the event.

When the outcome of interest was "all adverse events," follow-up ended at the first event. In the analysis of a particular event, follow-up ended at the time that the event of interest occurred; for example, if joint bleeding occurred, follow-up for cerebral embolism continued if this was the event of interest. As a result, the number of patient-years, used as the denominator in determining the different incidence rates, varied depending on the outcome of interest.

Assessment of the Intensity of Anticoagulant Therapy

The incidence rates of adverse events for specific levels of intensity of anticoagulation were calculated as the ratio of the number of events that took place when the prothrombin time was in a particular INR range to the number of patient-years during which the INR was at this level in the patient population. This method has been described in detail previously.⁵ Ninety-five percent confidence intervals for the incidence rates were calculated with the assumption of a Poisson distribution for the number of cases.¹⁰

Assessment of the Numerator

After an outcome event had been reviewed and classified by the expert panel, the INR at the time of the hospital admission was obtained from the hospital records. When the prothrombin time had not been measured or could not be retrieved, we used the most recent measurement at the anticoagulation clinic before the event, but only when the test had been performed less than eight days before the event. If this information was not available, the event was not included in this analysis.

Assessment of the Denominator

The total number of patient-years for all patients combined was subdivided according to INR intervals of 0.5. The number of patient-years in each INR category was estimated as follows. For each patient, the actual INR fluctuated between and around the target values and was measured at regular intervals. By assuming that the INR

changed in a linear fashion between measurements, it was possible to allocate a specific INR to each day. All days were then grouped according to INR ranges (in intervals of 0.5) and summed for all patients.⁵ With this approach, individual patients contributed person-time to periods of anticoagulation at different intensities, and the risks were estimated for the INR levels achieved, regardless of the target levels. When the length of time between two measurements exceeded eight weeks, no INR was allocated, since we felt we could not assume a linear change between two visits so far apart.

The influence of sex and age and position and type of valves was studied by further stratification of the INR-days. For each INR-day, the corresponding age was calculated. The patients were grouped in three age categories (younger than 50 years, 50 to 69 years, and 70 years or older). Intensity-specific incidence rates were calculated for these subgroups. For this analysis, the INR values for the days were grouped according to intervals of 1.0. To control for the effects of age, we performed a multivariate analysis with Poisson regression techniques.

RESULTS

Patients

At the start of the study, 795 patients who had already undergone valve replacement were enrolled. An additional 813 patients later entered the study: 767 who had a valve replacement after the study began and 46 who moved into the region. These 1608 patients were followed for a total of 6475 person-years (mean per patient, 4 years). Follow-up ended before the termination of the study for 254 patients who died and for 91 patients who moved to a different geographic region. Anticoagulant therapy was discontinued in 11 patients for various reasons, such as noncompliance. In three patients the mechanical prosthesis was replaced by a bio-prosthesis, so follow-up ended at the time of the valve replacement.

Of the 1608 patients, 879 were admitted to the hospital at least once during the follow-up period (a total of 2394 hospital admissions). Sufficient clinical information was available for 98 percent of these admissions.

The general characteristics of the 1608 patients included in the study are shown in Table 1.

Control of Anticoagulation

For all 1608 patients, 123,254 measurements of the prothrombin time were obtained during the follow-up period. The average time between two measurements was 2.7 weeks. With the method described above, we were able to estimate the number of patient-days per INR category. No INR value could be allocated to 139 patient-years of follow-up (2.1 percent of the total observation time), since the length of time between two consecutive measurements exceeded eight weeks. The distribution of the patient-time over the INR categories is summarized in Figure 1. The INR was within the target range of 3.6 to 4.8 for 61 percent of the total patient-time; for 31 percent of the time the INR was below 3.6; and for 8 percent the INR was above 4.8.

Outcome Events

The incidence rates of all adverse events are summarized in Table 2. Forty-five patients had a thromboembolic event (0.71 per 100 patient-years), all of which were cerebral (incidence, 0.68 per 100 patient-years)

Table 1. Characteristics of the Patients at the Beginning of Follow-up.

| CHARACTERISTIC | No. (%) |
|-----------------------------------|-------------|
| No. of patients | 1608 |
| No. of patient-years of follow-up | 6475 |
| Age (yr) | |
| <50 | 343 (21.3) |
| 50–69 | 995 (61.9) |
| ≥70 | 270 (16.8) |
| Sex | |
| Male | 879 (54.7) |
| Female | 729 (45.3) |
| Valve position | |
| Aortic | 961 (59.8) |
| Mitral | 485 (30.2) |
| Both | 158 (9.8) |
| Unknown | 4 (0.2) |
| Valve model* | |
| Caged ball or disk† | 53 (3.0) |
| Tilting disk‡ | 1354 (76.7) |
| Bileaflet§ | 347 (19.6) |
| Unknown | 12 (0.7) |

*A total of 158 patients had two valve prostheses.
 †Starr–Edwards in 46 and Cooley–Cutter in 7.
 ‡Bjork–Shiley in 1052, Sorin in 164, Medtronic–Hall in 137, and Lillehei–Kaster in 1.
 §St. Jude in 242, DuroMedics in 56, and CarboMedics in 49.

except for two cases of peripheral embolism (one in the kidney and one retinal; incidence, 0.03 per 100 patient-years). There were no cases of valve thrombosis that met our criteria. In 36 patients, central nervous system hemorrhage occurred (34 had intracranial hemorrhage, and 2 spinal; incidence, 0.57 per 100 patient-years). Major extracranial bleeding occurred in 128 patients (2.11 per 100 patient-years). These events were gastrointestinal (in 47 cases), genitourinary (12), or retroperitoneal (1); involved bleeding in the skin or muscles (33) or joints (5); were characterized by epistaxis (17); or were classified as “other” (13).

Seventy-two percent of all patients with a stroke died or had persistent neurologic impairment. The outcome of the hemorrhagic strokes was more severe than that of the ischemic strokes: 44 percent of the patients with an episode of intracranial bleeding died, whereas only 5 percent of the ischemic strokes were fatal. Also, 79 percent of the patients with ischemic strokes recovered without deficits or with a deficit allowing them to function independently, as compared with only 33 percent of the patients with hemorrhagic strokes.

The extracranial events were less severe than the other events; 124 of the 128 patients with extracranial bleeding recovered, and 4 died (incidence, 0.07 per 100 patient-years). Three of these four patients died of profuse gastrointestinal bleeding (one had colon cancer; in the other two there was no known underlying disease), and one died of bleeding from an ovarian tumor.

INR-Specific Incidence

Of the 79 patients with ischemic or hemorrhagic stroke, the prothrombin time was measured at the time of the event in 62. In seven additional cases, it had been measured at the anticoagulation clinic within eight days before the event. Thus, INR-specific incidence rates

could be calculated on the basis of data on 87 percent of the patients with stroke. In 111 of the 128 cases of extracranial bleeding, the INR was measured at the time of the event, and in 12 additional cases it had been measured less than eight days before at the anticoagulation clinic. Therefore, 96 percent of these events could be used for further analysis. The INR-specific incidence rates that were calculated from these data are presented in Figures 2 and 3.

The optimal intensity of oral anticoagulant therapy is that at which the incidence of both thromboembolic and bleeding complications is lowest. In Figures 2 and 3, this level can be found at INR values between 2.5 and 4.9. At these INR levels, the incidence of all adverse events (all episodes of bleeding and embolism and unclassified strokes) was only about 2 per 100 patient-years (95 percent confidence interval, 1.0 to 3.8). The incidence rose sharply when the INR fell below 2.5, ranging from 7.5 per 100 patient-years (95 percent confidence interval, 3.6 to 12.6) for an INR of 2.0 to 2.4 to 27 per 100 patient-years (95 percent confidence interval, 3.3 to 99) when the INR was in the very low range of 1.0 to 1.4 (a 13.5-fold increase from the lowest incidence). Once the INR rose to 5.0 or above, the incidence of adverse events again increased steeply: 4.8 per 100 patient-years (95 percent confidence interval, 2.6 to 7.7) for an INR of 5.0 to 5.5 and 75 per 100 patient-years (95 percent confidence interval, 54 to 101) when the INR was 6.5 or above (a 37.5-fold increase).

In 77 of the 164 bleeding events (47 percent), either trauma or some underlying disease was a contributing cause of the bleeding. This percentage did not differ substantially for the different INR categories. Thus, at higher INRs, the same percentage of bleeding episodes occurred without an apparent contributory cause as at lower INRs.

When the analysis was repeated for the events with the most unfavorable outcomes only (death or handicap

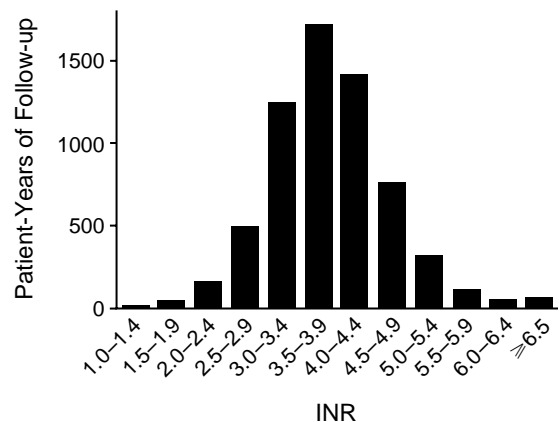


Figure 1. Distribution of Patient-Years of Follow-up among the INR Categories.

Follow-up totaled 6475 patient-years. A target INR of 3.6 to 4.8 was used. For 139 patient-years of follow-up, no INR value could be allocated, since the time between two consecutive measurements exceeded eight weeks.

resulting in dependency), the optimal intensity of anticoagulation remained the same — an INR of 2.5 to 4.9.

Differences among Subgroups

Overall Incidence

Women had a slightly higher risk of both thromboembolism and bleeding than men. The incidence of thromboembolism was 0.8 per 100 patient-years for women and 0.6 per 100 patient-years for men; the risk of bleeding was 3.1 per 100 patient-years for women and 2.4 per 100 patient-years for men.

The risk of thromboembolism was very low among patients younger than 50: only one patient in this age group had a thromboembolic event (incidence, 0.1 per 100 patient-years; 95 percent confidence interval, 0.0 to 0.5). Patients who were 50 or older had a much higher risk of thromboembolism than younger patients; the incidence of this complication was 0.8 per 100 patient-years (95 percent confidence interval, 0.5 to 1.1) among patients between 50 and 69 years of age and 1.1 per 100 patient-years (95 percent confidence interval, 0.6 to 1.8) among those 70 or older. The risk of bleeding did not vary much with age for those younger than 70 (under 50 years, 2.5 per 100 patient-years; 50 to 69 years, 2.8 per 100 patient-years). For patients 70 or older, the risk of bleeding was twice as high (5.6 per 100 patient-years).

The overall risk of thromboembolism was also influenced by the position of the valve. The incidence was 0.5 per 100 patient-years among patients with an aortic valve, 0.9 per 100 patient-years among patients with a mitral valve, and 1.2 per 100 patient-years among those with both an aortic and a mitral valve. As expected, the risk of bleeding did not depend on the position of the valve.

The overall incidence of thromboembolism was 0.5 per 100 patient-years for the bileaflet valves, 0.7 per 100 patient-years for the tilting-disk valves, and 2.5 per 100 patient-years for the caged-ball and caged-disk valves. The type of valve did not affect the risk of bleeding substantially.

To assess whether the differences among the subgroups were independent findings that could not be ex-

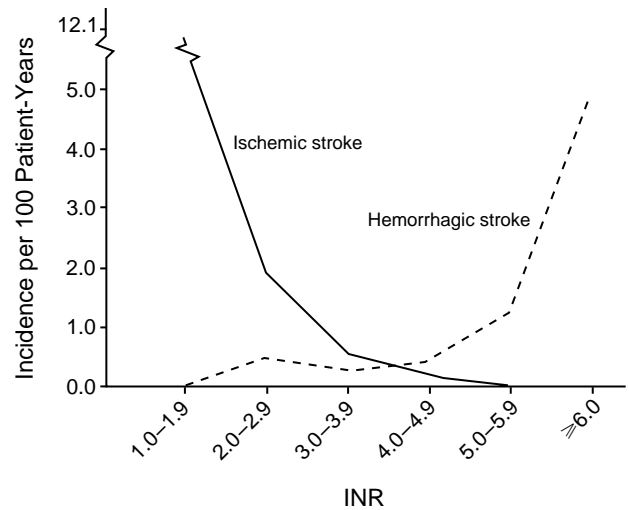


Figure 2. Incidence of Ischemic and Hemorrhagic Stroke According to INR Category.

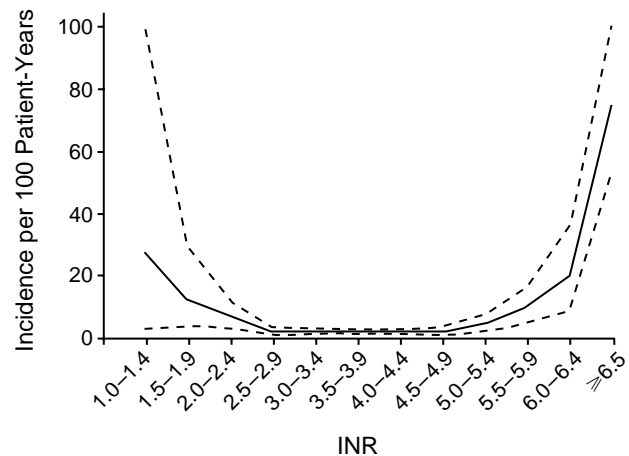


Figure 3. INR-Specific Incidence of All Adverse Events (All Episodes of Thromboembolism, All Major Bleeding Episodes, and Unclassified Stroke).

The dotted lines indicate the 95 percent confidence interval.

plained by a different age distribution for the various types and positions of valves, we performed a multivariate analysis with Poisson regression techniques. Since the rate ratios we found were equal in a univariate and a multivariate model, we concluded that the effects of age, the position of the valve, and the type of valve were independent.

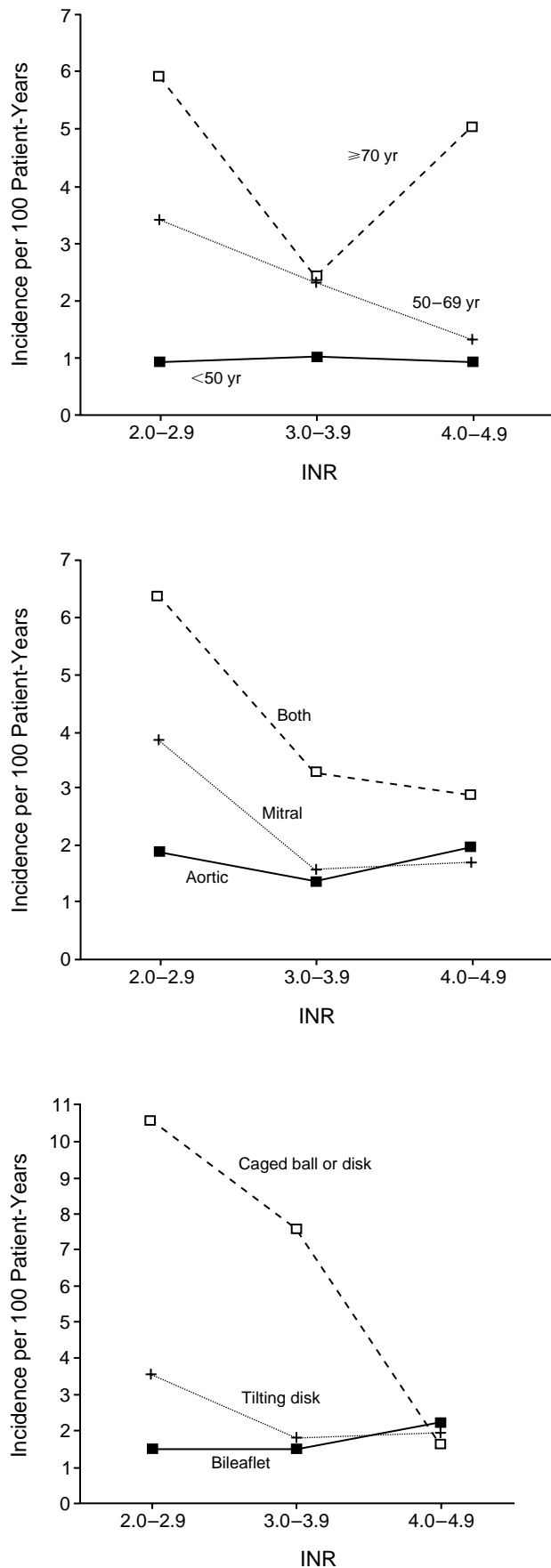
Optimal Intensity of Anticoagulation

To study the possibility that the optimal intensity of anticoagulation varied among these subgroups, we calculated the incidence of complications according to sex, age, the position of the valve, and the type of valve for INR values between 2.0 and 4.9. The optimal intensity was the same in both sexes. In the other three subgroups, a remarkably similar pattern was found: the lower the risk of a thromboembolic or bleeding episode was for a certain subgroup, the broader the optimal

Table 2. Adverse Events.

| EVENT | No. | INCIDENCE (PER 100 PATIENT-YEARS)* |
|----------------------------------|-----|------------------------------------|
| Thromboembolism | | |
| Cerebral infarction | 43 | 0.68 |
| Peripheral embolism | 2 | 0.03 |
| Valve thrombosis | 0 | 0 |
| Any thromboembolism | 45 | 0.71 |
| Fatal thromboembolism | 2 | 0.03 |
| Bleeding episode | | |
| Intracranial and spinal bleeding | 36 | 0.57 |
| Extracranial bleeding | 128 | 2.11 |
| Any bleeding | 164 | 2.68 |
| Fatal bleeding | 20 | 0.30 |
| Unclassified stroke | 14 | 0.23 |
| First events | 210 | 3.50 |

*Since follow-up ended when the event of interest occurred, the denominators differ for the various end points.



range for the INR (Fig. 4). For patients with a higher risk of thromboembolism (mitral valve position and older valve types), the optimal level was narrowed on the left side of the curve; in other words, the patients with these characteristics had a higher incidence of thromboembolism at lower intensities of anticoagulation. For patients with both an increased risk of thromboembolism and a higher risk of bleeding (those 70 or older), the optimal level was narrowed on both sides of the curve. However, confidence intervals for these intensity-specific incidence rates for particular subgroups overlapped considerably.

DISCUSSION

Although the need for oral anticoagulant therapy in patients with mechanical heart-valve prostheses is not in dispute, the optimal intensity of anticoagulation has been a matter of debate. The intensity of anticoagulation at which thromboembolism is effectively prevented without excessive bleeding is not known, even though anticoagulant agents are given as a lifelong therapy to a very large number of patients. It was not even possible to express the intensity in a standardized way until 1985, when the INR system was introduced.¹¹

The only studies in which an attempt has been made to determine the optimal intensity are randomized clinical trials in which two target levels have been compared.²⁻⁴ Recently, we developed a method that permits the direct assessment of the relation between the measured intensities of the anticoagulant therapy and its benefits and risks.⁵ With this method, the incidence of both thromboembolism and bleeding can be calculated at every level of anticoagulation. Application of this method to the records of more than 1600 patients with a total follow-up of more than 6000 patient-years showed that the optimal intensity is that which produces an INR between 2.5 and 4.9. In this range, the incidence of all adverse events was about 2 per 100 patient-years. This rate rose sharply both below and above this range — up to an incidence of 75 per 100 patient-years (95 percent confidence interval, 53 to 101) when the INR was 6.5 or above.

In order to achieve this INR in actual measurement of the prothrombin time, a target INR needs to be defined, and to do this the severity of both types of events must be taken into account. Since the outcome of the bleeding events in these patients was more severe than the outcome of the thromboembolic events, it might be argued that the optimal target level should be on the lower side of the optimal INR range, in order to avoid

Figure 4. Incidence of All Adverse Events at INRs within the INR Range of 2.0 to 4.9, According to Age, Valve Position, and Valve Type.

The top panel shows the incidence rates for three age groups: younger than 50 years, 50 to 69 years, and 70 years or older. The middle panel shows incidence according to valve position: aortic, mitral, or both aortic and mitral. The bottom panel shows the incidence according to valve type: bileaflet, tilting disk, or caged ball or disk.

bleeding. On the other hand, the risk of embolism rises sharply below an INR of 2.5 (Fig. 2). Furthermore, the actual INR achieved tends to be somewhat lower than the target level (Fig. 1); this implies that the lower limit of the target INR range should be well above 2.5. Therefore, we favor a target INR range of 3.0 to 4.0 for the total patient group.

We identified three characteristics in the patients that appeared to be associated with a lower risk of thromboembolism: an age younger than 50, a prosthetic valve in the aortic position, and a bileaflet valve. Patients who were 70 or older had an increased risk of bleeding. To study the possibility of modifying the optimal intensity according to these characteristics, we calculated the INR-specific incidence of events for each subgroup. As Figure 4 shows, a higher risk of thromboembolism narrows the optimal level on the left side of the curve, whereas a higher risk of bleeding narrows the optimal level on the right side of the curve. Since these findings are statistically not very stable because of the limited numbers of observations, they should be interpreted with caution.

In 1990, the British Society of Haematology recommended a target range of 3.0 to 4.5 for the INR, and in 1992 the American College of Chest Physicians recommended that the target range be 2.5 to 3.5.^{12,13} There seems to be a tendency to lower these recommended values, however, on the basis of the results of recent studies in which lower target ranges were used.^{2,14-17} Most of these studies were carried out in patients with valves in the aortic position and with bileaflet valves.¹⁴⁻¹⁶ Although such patients may have a lower risk of thromboembolism, our data do not support lowering the target INR range below 2.5 for these groups. On the contrary, they indicate that a target of 3.0 for the INR should be the minimum, especially for patients with a mitral valve or an older-model valve.

With regard to bleeding, three recently published studies also showed a clear relation between the intensity of anticoagulation and the frequency of hemorrhage.¹⁸⁻²⁰ In two of these studies, only prothrombin-time ratios were reported, a fact that prevents the assessment of the INR at which the risk of bleeding becomes unacceptable.

In other recent studies combination therapy with coumarin derivatives and antiplatelet agents has been studied.^{3,4} Turpie et al. reported a beneficial effect of adding aspirin to warfarin, with a target INR of 3.0 to 4.5 for the prothrombin time.³ However, the patients who received both drugs still had an incidence of major embolism that was more than twice as high as that in our patients (1.6 vs. 0.7 per 100 patient-years). The incidence of bleeding was also higher: 8.5 per 100 patient-years, as compared with 2.7 per 100 patient-years in our study. In our opinion, well-monitored anticoagulant treatment is preferable to combined therapy. When well-monitored anticoagulant treatment is not feasible, the addition of aspirin might be considered.

In conclusion, we found a clear relation between the intensity of oral anticoagulation with coumarin deriva-

tives in patients with mechanical heart-valve prostheses and the incidence of thromboembolism, on the one hand, and of bleeding, on the other. The optimal intensity of anticoagulation, producing the fewest events of both types, lies between measured INR values of 2.5 and 4.9. As a target range, we recommend an INR of 3.0 to 4.0.

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APPENDIX

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C.B.H.W. Lamers, J.W.H. Leer, A.E. Meinders, P.M. Rozing, C.C. Sterk, R.T.W.M. Thomeer, J. Thompson, B.J. Vermeer, R. Willemze, A.R. Wintzen, J. Zwartendijk, and A. Zwaveling; *Diaconessenhuis, Leiden*: A.A. de Rotte, J.D. Holtzer, R. Vink, H.J. Völker-Dieben, and S.A.G.J. Witteveen; *St. Elisabeth Ziekenhuis, Leiderdorp*: M. Bockhout, E.P. de Vries, A.R. Janssens, J.M.H. Moorrees, P.C.M. Rosekrans, T.L. See, W.J. van Amstel, C. van Rees, P.D.J. Vegt, E.M. Vroom, and R.J.W. Witteveen; *Sint Antoniusshove, Leidschendam*: J.A. Beker, M.G. Herben, H. Hollander, J.W.M. Loeff, A.M.M. Pennings, R.E. van der Flier, and P. Wigt; *Antonius Ziekenhuis, Nieuwegein*: C.A.P.L. Ascoop, J.M.P.G. Ernst, R.P.H.M. Hamerlijnck, H.A. van Swieten, and R.G.J.R.A. Vanderschueren; *St. Radboud Ziekenhuis, Nijmegen*: J.S. Bos, F.J.L. Davelaar, F.T.M. Huysmans, L.K. Laquet, W.A.J. van Daal, and J.J. Manni; *Academisch Ziekenhuis Dijkzigt, Rotterdam*: C.E. Bos, E. Bos, J.W. Deckers, and M.J.B.M. van den Brand; *Oogziekenhuis, Rotterdam*: D.A.E. Mertens; *Zuiderziekenhuis, Rotterdam*: X.H. Krauss and R. Slingerland; *Academisch Ziekenhuis, Utrecht*: J.J. Bredée, H. Lubsen, E.O. Robles de Medina, P.C. Scholten, and W.F. Treffers; *Academisch Ziekenhuis, Velp*: H.A. Rebel-de Vries and J.P. Staal; *Diaconessenhuis, Voorburg*: H. Bijlmer-Gorter, C.M.G.J.A. Marcoen, I.H. Oei, G. Slagboom, J.R. van der Mey, J.L. van Doorn, E.S. van Emmerik, H. Walinga, and J.G. de Wall; and *Streekziekenhuis Koningin Beatrix, Winterwijk*: J.P. de Jong, J.P. Klaassen, P. Sijbring, J.V.C. Stevens, R.A.H. Stukart, T.P.M. van Thiel, and A.A. Vafi.

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