

INR Self-Management Permits Lower Anticoagulation Levels After Mechanical Heart Valve Replacement

H. Koertke, MD; K. Minami, MD; D. Boethig, MD; Th. Breyman, MD; D. Seifert, MD; O. Wagner; N. Atmacha, MD; A. Krian, MD; J. Ennker, MD; U. Taborski, MD; W.P. Klövekorn, MD; R. Moosdorf, MD; W. Saggau, MD; R. Koerfer, MD

Background—The Early Self Controlled Anticoagulation Trial (ESCAT I) showed that anticoagulation self-management after mechanical heart valve replacement decreased complication rates by maintaining INR levels closer to the target range than International Normalized Ratio (INR) home doctor management. The therapeutic range for the INR in that study was between 2.5 and 4.5 for all positions of prosthetic valves. ESCAT II should find out whether lowering the target range for INR self-management would further reduce complication rates.

Methods—ESCAT II is a prospective controlled randomized (valves: St. Jude Medical Standard or Medtronic Hall, treatment: conventional/low-dose) multicenter study with 3 300 patients. We present interim results of 1 818 patients. 908 were categorized as having a low-dose target range, which was INR 1.8 to 2.8 for prostheses in aortic position and 2.5 to 3.5 for prostheses in mitral position or in combined valve replacement. The control group (conventional group) with 910 patients aimed at an INR of 2.5 to 4.5 for all valve positions.

Results—In the conventional group, 74% of INR values measured were within the therapeutic range. In the low-dose group, 72% of the values were within that range. The linearized thromboembolism rate (% per patient year) was 0.21% for both groups. The bleeding complication rate was 0.56% in the low-dose regimen group versus 0.91% in the conventional group.

Conclusions—Early onset INR self-management under oral anticoagulation after mechanical heart valve replacement enables patients to keep within a lower and smaller INR target range. The reduced anticoagulation level resulted in fewer grade III bleeding complications without increasing thromboembolic event rates. (*Circulation*. 2003;108[suppl II]:II-75-II-78.)

Key Words: anticoagulation ■ heart valve replacement ■ INR self-management ■ low-dose anticoagulation

Despite more than 30 years of continuous improvement in the field of mechanical and biological heart valves, the ideal heart valve prosthesis remains to be developed.¹ Current biological implants do not require long-term anticoagulation, but they are not durable enough. During an 11-year follow-up, it was possible to show that biological heart valve prostheses have a 40% higher explantation rate than mechanical prostheses.² Mechanical heart valve prostheses still bear the risk of thromboembolism. Treatment with oral anticoagulants under International Normalized Ratio (INR) self-management can reduce thromboembolism to 1.5% per patient year (ppy).³ Reported bleeding rates vary with the quality of anticoagulation, ranging from 4.2% to 15.4% ppy.⁴⁻⁹

Bleeding complications that occurred in the Early Self-Controlled Anticoagulation Trial (ESCAT I) study³ were

almost evenly distributed between the group, which was managed by the family doctor (3.0% ppy) and the group with INR self-management (3.8% ppy). Nevertheless, in that study, the self-management group had 80% of their measured INR values within the therapeutic range in comparison with only 65% in those controlled by their family doctors.

Thromboembolism and bleeding under anticoagulants thus continue to account for 75% of all complications following mechanical heart valve replacement.³ These complications occur most frequently during the first 6 months after surgery. Later on, the risk decreases and remains constant for years.⁸⁻¹⁰

Anticoagulation-related risk is higher when long-term INR variance is higher. When bleeding or thromboembolism occurs, as many as 60% of the INR values were observed not to lie within the therapeutic range.¹¹

From the Heart and Diabetes Center North Rhine-Westphalia Bad Oeynhausen, Germany, Clinic of the Ruhr University of Bochum, Bochum, Germany (H.K., K.M., D.B., T.B., D.S., O.W., K.); Evangelisches und Johanniter Klinikum, Duisburg, Germany (N.A., A.K.); Heart Center Lahr, Lahr, Germany (J.E.); Kerckhoff-Klinik, Bad Nauheim, Germany (U.T., W.P.K.); Heart Center Marburg, Clinic of the Philipps-University Marburg, Marburg, Germany (R.M.); and the Klinikum Ludwigshafen, Clinic for Heart Surgery, Ludwigshafen, Germany (W.S.), Clinic of the Ruhr University of Bochum, Bochum, Germany

Correspondence to Heinrich Koertke, MD, Herz- und Diabeteszentrum NRW, Georgstrasse 11, 32545 Bad Oeynhausen, Germany. Phone: +49 5731 97-2319, Fax: +49 5731 97-1871, E-mail: hkoertke@hdz-nrw.de

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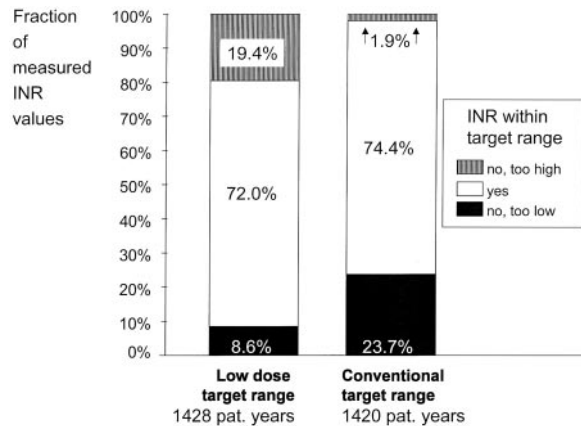


Figure 1. Cumulative INR frequencies as sent to the study center. The mean and standard deviation signs show that most of the observed bleeding events occurred at INR values that lie within the commonly recommended range of 2.5 to 4.5. There are no significant differences in mean INR values between patients with complications and patients with an uneventful course.

The common prescription policy for patients with mechanical valve replacement declares a therapeutic range from INR 2.5 to 4.5. This large range includes a zone of higher risk for bleedings (Figure 1), beginning from INR >3.5. ESCAT I has shown that INR self-management reduces the INR oscillations. After we observed that self control led to a more exact control of the INR level, we tried to eliminate this high risk zone. Thus, ESCAT II was designed to assess the effects of low-dose self-controlled anticoagulation therapy.

This paper gives interim results of ESCAT II and asks whether a narrowed target INR range is able to further reduce complication rates in patients with mechanical heart valve prostheses.

Patients and Methods

ESCAT II is a prospective controlled randomized multicenter study with 3300 patients. The six participating institutions are listed in the title of this paper. It began in October 1998 after the consent of the Ethics Committee of the Ruhr University of Bochum, and now includes 1 818 patients. The present analysis is a planned interim analysis.

All patients gave their written consent to participation in the study. Randomization concerning valve type and anticoagulation group was carried out in accordance with the Masters Random List. The nontranslucent randomization envelopes were opened immediately before valve implantation. The study protocol includes the transmission of all measured INR values to the study center, a medical examination in the valve-implanting hospital every 6 months, terminating 2 years after valve implantation.

According to the study protocol, 910 patients were included in the conventional group with the INR target range 2.5 to 4.5. A further 908 patients formed the INR low-dose group (for aortic valve recipients the INR target range was 1.8 to 2.8, for mitral/ double valve patients 2.5 to 3.5). All patients in the study performed INR self-management. Training began 6 to 11 days after surgery. Every patient who passed the INR self-management examination received a coagulation monitor (CoaguCheck S, Roche Diagnostics, Mannheim, Germany). Both groups were very comparable with regard to age, rhythm, valve distribution and risk factors such as age, weight, body mass index, gender atrial fibrillation, hypertension, and hypercholesterolemia. Every month the study center received the INR values recorded by the patients themselves. Patients were asked to report any complication (thromboembolism, bleeding) immediately.

Such reports were double-checked by the study center. All patients were asked to visit the study center for a cardiologic check-up every 6 months, including coagulation controls and transthoracic echocardiography (Sonos 5500, Philips, Eindhoven, Netherlands).

Twenty eight patients (1.0%, 12 low-dose, 16 conventional) who died within 30 days of surgery were excluded from our analysis. Late death was observed in 21 low-dose and in 14 conventionally treated patients. None of the deaths in this period were related to our study.

The remainder of the 1 818 patients had a mean age of 59.7 ± 10.1 years. Of these patients, 1459 (80%) underwent aortic valve replacement, 271 (15%) underwent mitral valve replacement, and 86 (5%) underwent double valve replacement. This distribution is similar to the usual distribution in Germany at the current time.¹² Permanent postoperative atrial fibrillation was present in 436 of these patients (24%). Medtronic Hall tilting disc and St. Jude Medical bileaflet valves (prostheses authorized by the Federal Drug Administration) were randomized in equal quantities.

Complication Definitions

Thromboembolism (TE)

Grade I—questionable events (eg, dizziness), not requiring medical treatment;

Grade II—complaints presumably related to ongoing anticoagulation, requiring outpatient treatment and causing no permanent impairment;

Grade III—heart valve prosthesis thrombosis, severe thromboembolism requiring inpatient treatment or causing long term impairment (including transient ischemic attacks).

Bleeding (BL)

Grade I—mild bleeding (eg, of the gums), not requiring medical treatment;

Grade II—bleeding leading to outpatient medical care, not requiring surgical or endoscopic intervention;

Grade III—severe bleeding, requiring transfusion, surgical or endoscopic intervention, inpatient care or causing long-term impairment.

Karnofsky,¹³ modified according to Koertke/ Koerfer.

Statistics

The statistical calculations were performed using SPSS for Windows Version 10.01. Parameters were compared with chi-square or Fisher's exact test, as appropriate. Kaplan-Meier survival plots were compared by log-rank test.

Results

The total observation time for our patients was 2 848 patient years (conventional group=1 420 patient years, low-dose group=1 428 patient years, average 1.3 years). Follow-up completeness reached 94.5%.

INR values (usually determined weekly) were submitted to our study center. The reported INR distribution in relation to the group's recommended range is shown in Figure 2: The low-dose patients with a reduced and narrowed INR target range were indeed able to keep 72% of their values within the allowed range. The broader target range of the conventional group (INR 2.5 to 4.5) was reached in 74.4% of all measurements.

Only a few values were found outside the target range in either group. In the conventional group, 23.7% of the values exceeded the permitted range and 1.9% dropped below it. In the low-dose regimen, 8.6% of the values fell below the therapeutic range and 19.4% exceeded it. Although fewer patients with the conventional target range exceed the recommended upper limit, more complications occurred. The

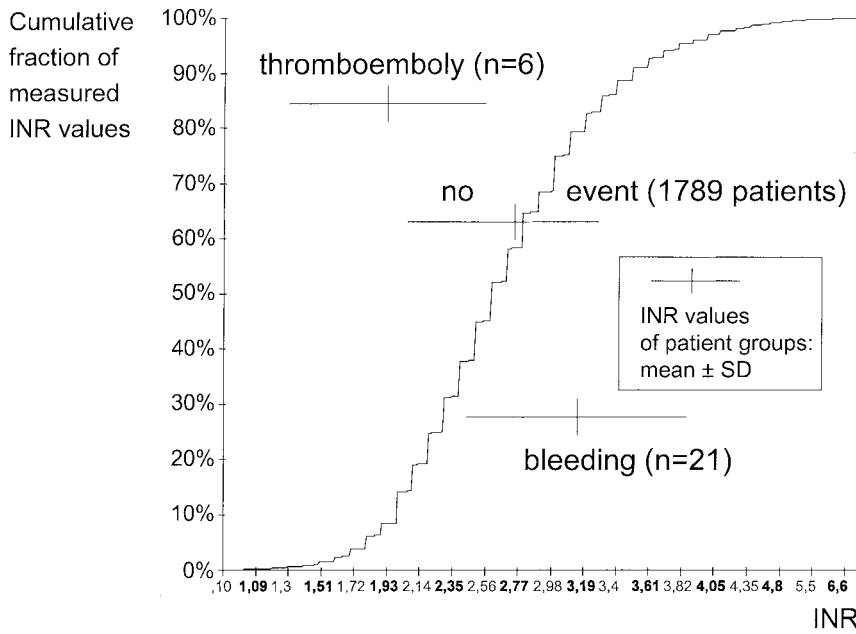


Figure 2. INR values of aortic valve replacement patients. Self-controlling patients are able to keep large percentages of their INR values within the desired ranges, even if the range is narrower than usual, as in the low-dose group. Although the thromboembolism rate is equal in both groups (0.21% yearly, three patients in each group), the bleeding frequency is much lower in the low-dose group (0.56% yearly, eight patients) than in the group with the conventional target range.

risk of thromboembolic events did not increase despite the low and narrow therapeutic range of the low-dose regimen.

Therefore, in the entire observation period, there were 27 grade III complications (bleeding and thromboembolic events). Table 1 shows that bleeding complications occurred 13 times in the conventional-dose group compared with 8 times in the low-dose group. Thus, the relative bleeding risk in the conventional group was 1.6 times more than that in the low-dose regimen group. In each group, three thromboembolic episodes occurred. It should be mentioned that all complications were observed among the patients with aortic valve replacement only. This is because of the distribution of valve prosthesis in our patient population. Event occurrence over time was linear. This is illustrated in the Kaplan-Meier curves of both ESCAT II groups (Figure 3).

Discussion

Oral anticoagulation is well established in many fields of medicine for secondary prevention of cardiovascular thromboembolic accidents. It is important to control its therapeutic effect and to keep its possible risks at the

lowest possible level. Because there are different thromboplastins that cause different values of prothrombin time. The International Sensitivity index (ISI) and, thereafter, the INR¹⁴ have been developed as ways of measuring the level of oral anticoagulation.

Oral anticoagulation inherently bears the problem of bleeding disorders and, on the other hand, its diminished effect in the given clinical situation could lead to a thromboembolic episode. Scheduling the dose in an optimal way could lead to a diminished rate of complications.

One step toward this goal was improving the quality of INR management in the patients. This was addressed in ESCAT I³ and other studies^{15,17} with the introduction of INR self-management. The study showed that self-management yielded more accurate INR values, and that patients stuck to their INR reference range with higher accuracy than those who were controlled conventionally by their family doctors.

The second step toward this goal was to address the dose of the oral anticoagulant, reducing it to minimize the rate of bleeding. In the ESCAT I study, there was a significantly lower rate of thromboembolic complications in the group of

Number and Linearized Incidence (% per Observation Year) of Hemorrhagic and Thromboembolic Complications in 600 Consecutive Patients Included in the ESCAT I Studies and of the First 1 818 ESCAT II Patients

Complications (Grade III)	1 ESCAT I, gpc (1136 pat.y.)	2 conventional sc (1420 pat.y.)	3 low-dose sc (1428 pat.y.)	RR 2 vs. 3	RR 1 vs 3.
Overall	66 (5.8%)	16 (1.12%)	11 (0.87%)	1.3	6.7
Bleedings	34 (3.0%)	13 (0.91%)	8 (0.56%)	1.6	5.4
Thromboembolism	32 (2.8%)	3 (0.21%)	3 (0.21%)	1	13

Karnofsky (12), modified according to Koertke/Koerfer. gpc, general practitioners controlled; sc, self control; pat. y., patient years; RR, relative risk.

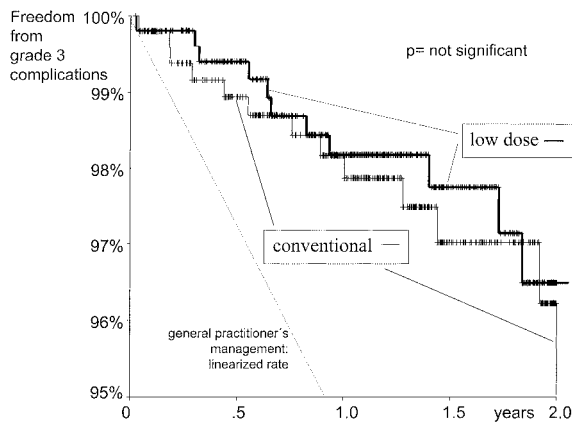


Figure 3. Kaplan-Meier plot showing freedom from grade III complications. Results of the low-dose group seem slightly advantageous when compared with the self-controlled conventional INR range group, but there is no statistical significance. ESCAT I results of the group with INR management by general practitioners (dotted line) are inferior: the yearly complication incidence is 5.8%.

patients who performed INR self-management. It therefore seemed worth initiating a therapeutic regimen with lower INR values under the cover of INR self-management. That was the aim of this study: to investigate whether INR self-management would permit a lower therapeutic range without endangering the patients by subjecting them to more thromboembolic episodes.

Our data showed that patients with INR self-management and low dose stuck to their therapeutic values (INR 1.8 to 2.8 in aortic valve replacement and 2.5 to 3.5 in mitral valve replacement) in 72% of their readings. The other group of patients (INR 2.5 to 4.5) had a nearly similar accuracy as 74% of values were within the therapeutic range. It should, however, be mentioned that those patients had a significantly wider therapeutic range. Interestingly, in the conventional group most failures to adhere to the indicated INR range were exhibited as falling short of the given range (23.7%), whereas in the low-dose regimen most failures were higher than it (19.4%). This phenomenon could be explained by the fear of the conventional group to reach or even exceed the upper INR limit permitted and of the low-dose regimen group to remain under the lowest INR limit permitted, thereby exaggerating their dose adjustment which ultimately led to the failure rates.

Regarding the complication rates, similar values were elicited for both study groups. From the data of our study, we can expect a reduction in thromboembolic episodes of 0.21% per patient year by narrowing and reducing the INR target range (low dose anticoagulation) under the guidance of INR self-management, still keeping the bleeding rate as low as 0.56% per patient year. This makes low-dose anticoagulation a very promising and ideal therapeutic regimen.

However, there are certain aspects that should be mentioned in this context. First, the relative bleeding risk in the group of patients with high INR therapeutic regimens was 1.6 times higher than in the group with low-dose regimens. Nevertheless, because of the limited number of patients (we report results on an interim analysis), results were not

statistically significant. Assuming similar complication rates for the rest of the study, reduction in bleeding complications can be expected to be statistically significant. Secondly, it should be stressed that it is of utmost importance never to mention the low-dose regimen without limiting it to those patients who perform INR self-management. It was shown in ESCAT I that patients who were managed by their family doctors had significantly more values outside their therapeutic range than those who practiced self-management.³ This also had been described by Stein.¹⁶ There are many communities in which INR self-management is not available and where negligence occurs concerning INR control at regular intervals. It would, therefore, be very dangerous to generalize the low-dose regimen without mentioning this limitation.

In conclusion, a low-dose INR therapeutic regimen combined with INR self-management is very promising. It can reduce the incidence of bleeding complications without increasing thromboembolic incidences. The enrollment of further patients in the study will give further insight into the significance of the results.

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