

International Normalized Ratio Self-Management After Mechanical Heart Valve Replacement: Is an Early Start Advantageous?

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Background. Severe thromboembolic and hemorrhagic complications after mechanical heart valve replacement essentially depend on the intensity of oral anticoagulation and the fluctuation of individual international normalized ratio (INR) values.

Methods. After heart valve replacement with Medtronic Hall, St. Jude Medical, and CarboMedics implants, patients were randomly divided into two groups, one controlling INR values at home, the other being monitored by family practitioners.

Results. Almost 80% of the INR values recorded by patients at home were within the stipulated therapeutic range, INR 2.5 to 4.5, compared with just 62% of INR

values recorded by family practitioners. The overall complication rate (hemorrhages and thromboembolic events) of the self-management group was significantly ($p < 0.05$) decreased compared with the conventional group.

Conclusions. Through INR self-management, an improvement in the quality of ongoing oral anticoagulation could be shown. Starting this form of therapeutic control early after mechanical heart valve replacement appears to effect a further reduction in anticoagulant-induced complications.

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Although numerous mechanical and biologic heart valves are now available after more than 30 years of continual improvement in this field, none of them fulfills all of the demands we make of an ideal replacement for a destroyed human heart valve [1]. Biologic implants show a lower thrombogenicity and therefore require no long-term anticoagulation. Because of their structural degeneration, however, their use is restricted to elderly patients. During an 11-year follow-up it was possible to show that biologic heart valve replacements involve a 40% higher explantation rate than mechanical heart valve replacements [2]. Despite progress made in the field of mechanical heart valves, thromboembolism is still a frequent complication after heart valve replacement. The risk of thromboembolism is reduced through treatment with oral anticoagulants, and yet with the newer valves it is still 1.5% in aortic position and 3% in mitral position [3, 4]. Hemorrhage rates vary in degree depending on the quality of the anticoagulation, ranging from 4.2% to 15.4% per patient-year [3, 5–9].

Thromboembolism and anticoagulant-induced hemorrhage thus continue to account for 75% of all complications after mechanical heart valve replacement [3]. These complications occur most frequently during the first 6 months after operation. The risk then becomes low where it remains constant for years [8–10].

Risk levels in conjunction with ongoing anticoagulation therapy are considerably higher in cases in which international normalized ratio (INR) values fluctuate strongly. When anticoagulant-induced complications occur, as many as 60% of the coagulation values controlled are not within the therapeutic range [11, 12].

Valid studies to find an appropriate anticoagulation intensity, ie, an intensity that results in the lowest possible morbidity (thromboembolic and hemorrhagic complications), are not available to date. Current recommended therapies are therefore largely empirically based. The previously available studies also omit inclusion of INR self-management and its goal of improved therapy compliance (oral anticoagulation) as the basis for stable anticoagulation intensity. This study investigates the extent to which INR self-management after mechanical heart valve replacement affects improved anticoagulation stability. It also examines the extent to which freshly operated on patients who are trained in INR self-management just 6 to 11 days after operation are able to effect a potential reduction in morbidity (thromboembolic and hemorrhagic complications).

Patients and Methods

Our so-called ESCAT study (Early Self-Controlled Anticoagulation Trial) was monocentric, randomized, and prospective. It began on February 1, 1994, and closed in October 1997, in line with the randomization, having included 1,200 patients.

Of these 1,200 patients, data from the first 600 to

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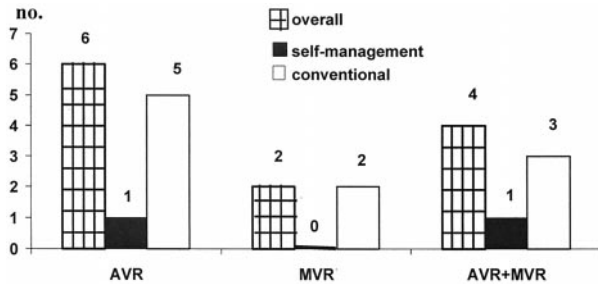


Fig 1. Early mortality according to valve position and study group. (AVR = aortic valve replacement; MVR = mitral valve replacement.)

undergo a complete 2-year follow-up and survive were evaluated. We excluded from our analysis patients who died within the perioperative phase or immediate postoperative phase (n = 37, Figs 1 and 2) or who dropped out of the follow-up (n = 90, Figs 3 and 4). We define perioperative as during the operation and immediately postoperative as within 30 days of operation. None of the deaths was directly related to our investigation.

The 600 remaining patients (394 men [66%], 206 women [34%]) had a mean age of 62.5 years, with a standard deviation of 10.2 years. An aortic valve replacement had been performed in 447 patients (74.5%), a mitral valve replacement in 111 patients (18.5%), and a multiple valve replacement in 42 patients (7%). This distribution of four aortic to each mitral valve replacement reflects the normal distribution in Germany at the current time, as reported by the German Society for Thoracic and Cardiovascular Surgery. Permanent postoperative atrial fibrillation was present in 153 of these patients (25.5%). Food and Drug Administration–approved implants were selected in varying distributions, including Medtronic Hall (Medtronic Hall, Medtronic GmbH, Dusseldorf, Germany), St. Jude Medical (St. Jude Medical GmbH, Nürnberg, Germany), and CarboMedics (Sulzer Carbo-medics GmbH, Hamburg, Germany) valves.

In accordance with the study protocol, 295 patients were included in the so-called conventional group (group A) and 305 patients in the INR self-management group (group B). The patients in group B were trained in INR self-management 6 to 11 days after operation. After successful training, each of them received a coagulation monitor, initially Biotrack from the Ciba Coming com-

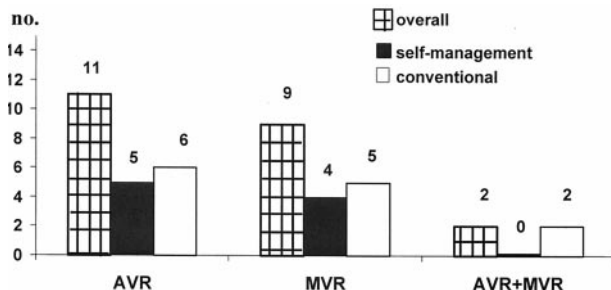


Fig 2. Late mortality according to valve position and study group. (Abbreviations as in Figure 1.)

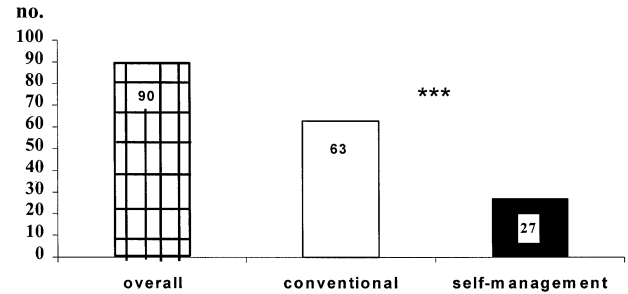


Fig 3. Distribution of study drop-outs. ***p ≤ 0.001.

pany, later to be renamed CoaguChek plus from the Roche Diagnostics company (Roche Diagnostics GmbH, Mannheim, Germany). Randomization was conducted in accordance with the Masters Random list. The two groups were comparable with regard to age, rhythm, valve distribution, and risk factors (Fig 5). Every month the study center received by post the INR values recorded in group A by family practitioners and the INR values recorded in group B by the patients themselves. Within the framework of the study, patients were also asked to record any complications (thromboembolism, hemorrhage) themselves, these records then being double-checked by the study center. All patients were required to visit the study center as outpatients for a cardiologic check-up every 6 months, including coagulation controls. Each patient therefore underwent four outpatient controls during the 2-year follow-up. All patients had been checked with the ultrasound system Sonos 2500/5500 from Hewlett-Packard (Agilent Technologies, Böblingen, Germany).

Complication Definitions

Thromboembolism

- Grade I Questionable events (eg, dizziness) not requiring medical treatment.
- Grade II Complaints presumably connected with the ongoing anticoagulation, requiring outpatient treatment and causing no lasting impediments.

- I = difficulties with device
- II = travel cost too high
- III = illness/psychological difficulties
- IV = lack of support from family physician
- V = illness or death in family
- VI = lack of interest
- VII = preference for family physician
- VIII = reasons not given

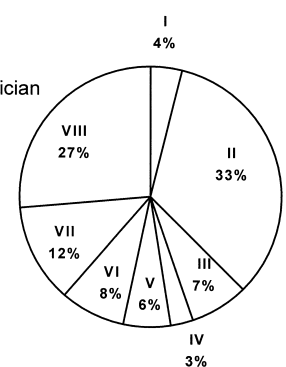


Fig 4. Reasons for study drop-outs.

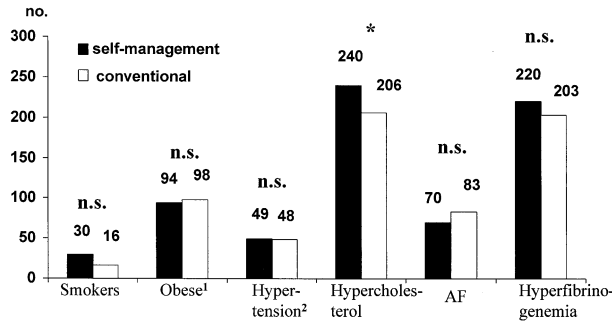


Fig 5. Distribution of risk factors between the two groups. ¹ Men, body weight 15% higher than normal; women, body weight 10% higher than normal. ² Blood pressure greater than 150/60 mm Hg. (AF = atrial fibrillation; n.s. = not significant.) *p ≤ 0.05.

Grade III Prosthetic thrombosis, severe thromboembolism requiring inpatient treatment and causing long-term impediments (including transient ischemic attacks).

Bleeding

- Grade I Mild bleeding (eg, of the gums) not requiring medical treatment.
- Grade II Hemorrhage leading to outpatient medical care, not requiring surgical or endoscopic intervention.
- Grade III Severe hemorrhage, requiring transfusion, surgical or endoscopic intervention and inpatient care. Long-term impediments.

Statistics

The statistical calculations were performed using SPSS 7.5 (SPSS GmbH Software, Munich, Germany) and represent our descriptive evaluations as of November 28, 1998. All results refer to the number of patients included and not the number of documented coagulation controls as this would distort the results considerably, the number of results submitted varying considerably from patient to patient. Variable independence was tested using Fisher's exact test.

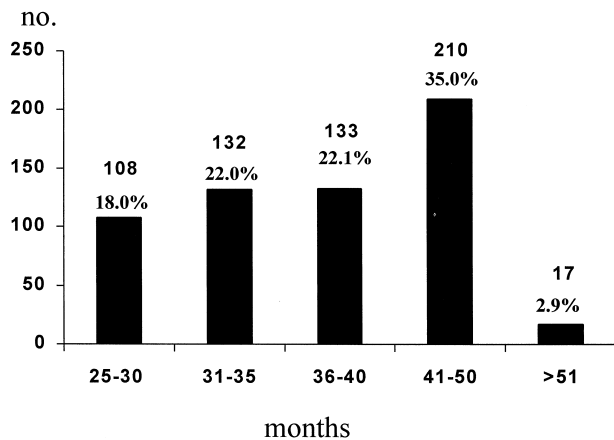


Fig 6. ESCAT-1 observation period for 600 patients.

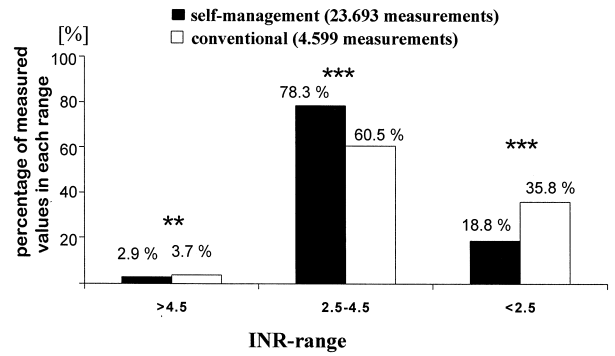


Fig 7. Percentages within the therapeutic international normalized ratio (INR) range. (**p ≤ 0.01; ***p ≤ 0.001.)

Results

In all patients recruited for the ESCAT study since it began in 1994, oral anticoagulation was monitored using INR values. As shown in Figure 6, the observation period ranged from 25 to 51 months (mean, 38.32 months). This corresponds to an overall observation period of 1,916 patient-years (conventional group, 943 patient-years; self-management group, 973 patient-years).

Accordingly, 18% of patients took part in the follow-up for 25 to 30 months, 22% for 31 to 35 months, 22% for 36 to 40 months, 35% for 41 to 50 months, and 3% of patients for more than 51 months.

In our study, an anticoagulation intensity of INR 2.5 to 4.5 was selected as generally acceptable, regardless of prosthesis distribution. During the entire investigation period, a total of 28,292 (23,693 self-management; 4,599 conventional) workable INR values were submitted to our study center. The intensity distribution is shown in Figure 7.

In group A, only 62% of recorded values were within the stipulated range during the entire observation period, compared with 79% in group B. Few INR values in either group were more than 4.5; the remaining values outside the stipulated range were less than 2.5, with group B achieving more favorable results than group A. This course of anticoagulation intensity was achieved by group B in just 4 weeks. Only 25 patients (8.3%) from group B gave back their coagulometers (CoaguChek plus), for varying reasons. This small group was discounted from the analysis.

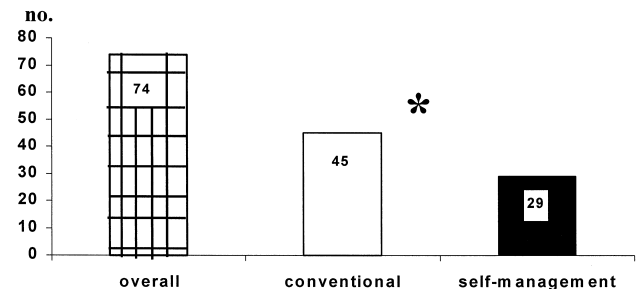


Fig 8. Grade III complications, with a significant difference (*p = 0.04) between the two groups.

Table 1. Number and Linearized Incidence (% per Observation Year) of Hemorrhagic and Thromboembolic Complications in 600 Consecutive Patients Included in the ESCAT Study

Complications Grade III	Conventional (943 Patient-Years)	Self-Management (973 Patient-Years)	p Value	OR
Overall	45 (4.7%)	29 (2.9%)	0.042	1.7
Hemorrhagic	25 (2.6%)	17 (1.7%)	NS	1.56
Thromboembolic	20 (2.1%)	12 (1.2%)	NS	1.75

NS = not significant; OR = odds ratio.

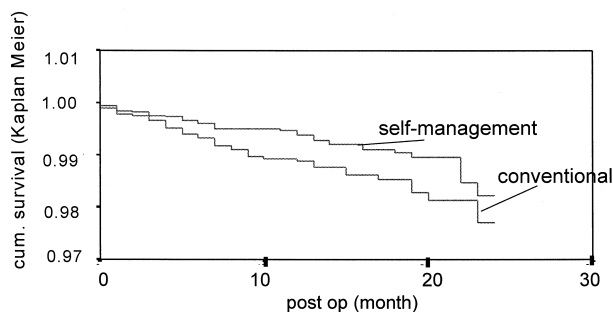


Fig 9. Freedom from grade III thromboembolic or hemorrhagic complications. (post op = postoperative; cum. = cumulative.)

Taken together for the entire observation period, grade III hemorrhagic and thromboembolic complications amounted to 74 events (Table 1). A statistically significant difference ($p = 0.04$) could be observed in favor of INR self-management (Fig 8). A high proportion of the complications in both therapeutic groups were hemorrhagic. The number of hemorrhagic complications was not significantly different between the two groups, the same as the number of thromboembolic complications.

In line with the accumulated probability (Fig 9), more than 98% of patients in group B are still free of grade III anticoagulant-induced complications after an observation period of 24 months.

The therapeutic difference can be increased still further by taking into account the temporal sequence of grade III anticoagulant-induced complications (Fig 10). This figure clearly shows that anticoagulant-induced complications are at their highest in the first 11 months after the start of anticoagulation after heart valve replacement. In the further course they then decrease

considerably. Just starting INR self-management early was in itself sufficient to effect a convincing reduction in anticoagulant-induced complications, especially during the first year of therapy. After this period has elapsed, there is no longer a significant difference between the two forms of therapy.

Comment

This paper compares two different therapeutic approaches to determine the intensity of permanent oral anticoagulation. Permanent oral anticoagulation after mechanical heart valve replacement was indicated in both groups. The stipulated therapeutic range was selected as INR 2.5 to 4.5. International normalized ratio self-management led to a determination of values at weekly intervals. This in turn led to a highly significant improvement in the quality of the anticoagulation controls. Nearly 80% of the INR values submitted by the self-management group were within the ideal therapeutic range, compared with just 62% of values submitted by the practitioner-controlled group, a statistically significant difference of p less than 0.001. Our evaluation therefore shows an impressive increase in the quality of ongoing oral anticoagulation.

This improvement in the quality of ongoing anticoagulation was in itself sufficient to reduce the incidence of severe thromboembolic and hemorrhagic complications after mechanical heart valve replacement, with a statistical significance of $p = 0.04$. The considerable benefit to the patient was particularly noticeable in the first year of therapy, confirming indications for starting INR self-management early. Because of the relatively small

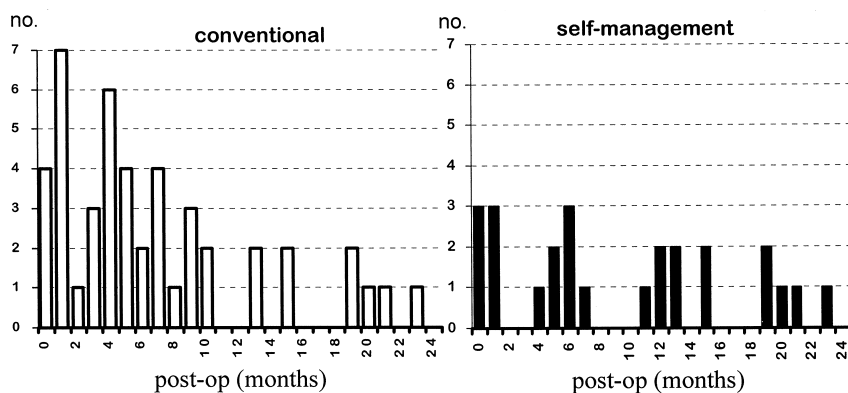


Fig 10. Course of grade III complications during 24 months postoperatively.

amount of emerging anticoagulation-related complications accorded grade III, we have not differentiated between thromboembolic and hemorrhagic events. A detailed and secure statement about this issue is anticipated with the final evaluation of the ESCAT I study.

Animal experiments and clinical trials have shown that thrombi can occur intraoperatively, during the implantation of a valve replacement. Reasons for this are valvular and mural endocardial lesions on the one hand, and the polyethylene terephthalate fiber (Dacron) ring (DuPont Company, Wilmington, DE), anchoring the valve replacement and sewn with it into the surrounding tissue, on the other. Thrombocytes marked with indium-III are able to show that thrombocytes can be deposited around the valve ring as early as the first 24 hours after operation [13, 14]. This is further confirmation of the advantages of starting INR self-management early after mechanical heart valve replacement.

The quality of the anticoagulation can be considerably increased through the introduction of INR self-management. Our results show that INR self-management should commence immediately after the onset of anticoagulation therapy.

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