Low-dose oral anticoagulation in patients with mechanical heart valve prostheses: final report from the early self-management anticoagulation trial II

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Aims
In mechanical heart valve recipients, low-dose international normalized ratio (INR) self-management of oral anticoagulants can reduce the risk of developing thrombo-embolic events and improve long-term survival compared with INR control by a general practitioner. Here, we present data on the safety of low-dose INR self-management.

Methods and results
In a prospective, randomized multi-centre trial, 1346 patients with a target INR range of 2.5–4.5 and 1327 patients with a target INR range of 1.8–2.8 for aortic valve recipients and an INR range of 2.5–3.5 for mitral or double valve recipients were followed up for 24 months. The incidence of thrombo-embolic events that required hospital admission was 0.37 and 0.19% per patient year (P = 0.79). No thrombo-embolic events occurred in the subgroups of patients with mitral or double valve replacement. The incidence of bleeding events that required hospital admission was 1.52 and 1.42%, respectively (P = 0.69). In the majority of patients with bleeding events, INR values were ≤3.0. Mortality rate did not differ between the study groups.

Conclusion
Data demonstrate that low-dose INR self-management does not increase the risk of thrombo-embolic events compared with conventional dose INR self-management. Even in patients with low INR target range, the risk of bleeding events is still higher than the risk of thrombo-embolism.

KEYWORDS
Oral anticoagulation; INR self-management; Heart valve prostheses; Thrombo-embolism; Bleeding

Introduction
Patients who undergo mechanical heart valve replacement require life-long oral anticoagulants. The Early Self-controlled Anticoagulation Trial (ESCAT) I demonstrated that self-management of oral anticoagulants improves the percentage of international normalized ratio (INR) values within the target range, reduces thrombo-embolic events, and improves long-term survival compared with the management of oral anticoagulants by a general practitioner.1,2 The ESCAT II study is a large prospective interventional trial that evaluates the effects of low-dose INR self-management on oral anticoagulants-related complications in patients with mechanical heart valve prostheses compared with conventional dose INR self-management. In a recently published interim analysis of the ESCAT II study, we found that the INR target range can be reduced from 2.5–4.5 to 1.8–2.8 in patients with aortic valve replacement and to 2.5–3.5 in patients with mitral valve or double valve replacement, without increasing the risk of thrombo-embolic events.3 In line with our findings, a target INR range of 2.0–3.0 for aortic heart valve prostheses for patients without additional risk factors and a target INR range of 2.5–3.5 for mitral heart valve prostheses have recently been recommended.4 Our interim
analysis of the ESCAT II study also demonstrated that the percentage of clinically relevant bleeding events was approximately three- to four-fold higher than the percentage of clinically relevant thrombo-embolic events. The relatively high number of bleeding events compared with the number of thrombo-embolic events in our study is in line with the results of an earlier investigation, demonstrating that a minimum risk of death was attained at 2.3 INR for patients with mechanical heart valve prostheses. With an increase of 1 unit of INR >2.5, the risk of death from cerebral bleeding, as well as from other causes, was approximately doubled. The ESCAT II study has now been terminated. Here, we provide final data on thrombo-embolism and hemorrhage of the ESCAT II study and present a detailed evaluation of major thrombo-embolic and bleeding complications.

Methods

Patients

In total, 2673 patients were included in the ESCAT II study. Mechanical aortic valve replacement was performed in 2164 patients, mitral valve replacement in 392 patients, tricuspid valve replacement in three patients, aortic plus mitral heart valve replacement in 113 patients, and a mitral plus tricuspid valve replacement in one patient. Exclusion criteria were: a contraindication to phenprocoumon (e.g. allergy), known ulcerous disease with bleeding tendency, hypo- or hypercoagulability (medical history), and an age of <18 years. All patients gave written informed consent to the study procedures. The study protocol was approved by the Ethics Committee of each of the six participating centres.

Study design

1311 St. Jude Medical heart valves (St Jude Medical GmbH, Nuremberg, Germany), 1260 Medtronic Hall heart valves (Medtronic Hall, Medtronic GmbH, Dusseldorf, Germany), and 102 other heart valves from different manufacturers were implanted (38 Carbomedics heart valves, 35 ATS heart valves, eight Advantage heart valves, eight On-x heart valves, four Pyroline heart valves, three Ultrackor heart valves, two Mosaic heart valves, two Omni Carbon heart valves, and two Tissuemed heart valves). The conventional dose (CON) group (n = 1346) had a target INR range of 2.5–4.5. The low-dose (LOW) group (n = 1327) had a target range of 1.8–2.8 for aortic valve recipients and 2.5–3.5 for mitral or double valve recipients. Study duration was from October 1998 to March 2006. The follow-up period was 24 months for each patient. The concept of INR self-management at our clinics is described in detail elsewhere. Briefly, all study participants joined a training course for INR self-management. Each patient had to learn to determine the INR values and to correct the dose of anticoagulants autonomously. The participants of the ESCAT II study had to check their INR values once a week during the first study year and once a fortnight during the second study year. The results had to be submitted to the study centre every month. All patients had to visit their study centre for a cardiologic check-up every 6 months. Patients were asked to report any complication to the study centre immediately. Moreover, the patients were asked during their follow-up visits whether any complication had occurred within the last 6 months. All reports of grade III complications were sent from the emergency hospital to the study centre and were double-checked by a cardiologist of the centre. Finally, the study centre in Bad Oeynhausen contacted each local study centre regularly in order to get information about the number of bleeding and thrombo-embolism events. Only grade III complications were used for data analysis, as previously described. Briefly, grade III thrombo-embolism was defined as heart valve prosthesis thrombosis or severe thrombo-embolism requiring inpatient treatment or causing long-term impairment (including transient ischaemic attacks). Grade III bleeding was defined as severe bleeding, requiring transfusion, surgical or endoscopic intervention, and inpatient care or causing long-term impairment. Moreover, each death and its cause was documented during follow-up.

Statistics

Statistical evaluations were performed with the program SPSS, version 11 (Chicago, IL, USA). For comparative evaluations, $t^2$ test and Student’s $t$-test (normally distributed data) were used. Normal distribution of the data was tested using the Kolmogorov-Smirnov test. Categorical variables were reported using the number (n) and percentage of observations. Continuous variables were expressed as mean (SD) and median and interquartile range (IQR) when appropriate. For comparative analyses of baseline characteristics, we used Fisher’s exact test, the unpaired t-test, and the Mann–Whitney U-test when appropriate. Kaplan–Meier analyses were used to calculate freedom from grade III complications and survival rates. Differences in complication and survival rates between study groups were tested with the log-rank test. We used univariable and multivariable Cox proportional hazard analysis to examine the associations of different parameters, such as study group, age, left ventricular ejection fraction (LVEF), atrial fibrillation, diabetes mellitus and hypertension with freedom from thrombo-embolism or haemorrhage. $P$-value of <0.05 was considered statistically significant.

Results

Baseline characteristics of the two study groups are given in Table 1. The study groups did not differ with regard to age, sex, and several biochemical and clinical parameters. It was noteworthy that a significant percentage of patients in both study groups were hypertensive and required treatment with antihypertensive drugs.

A total of 532 patients (19.9%) terminated the study prematurely. Reasons were: patient could not manage the device/no confidence in the device (n = 102), had more confidence in her/his physician (n = 92), measurements were stopped because of illness (n = 74), non-compliance of patients (n = 162), non-interest in INR self-management (n = 19), missed or incomplete instruction for INR self-management (n = 45), device not paid by health insurance (n = 5), and too high travel costs to the place of re-examination (n = 7). Some even terminated with no comment (n = 26). The percentage of study dropouts in the low-dose INR and the conventional dose INR did not differ significantly (data not shown). Patients dropped out after a median study period of 7 months (IQR, 1–18 months). Until the patients dropped out, all INR values and complication data of these patients were considered for statistical analysis.

In total, the 2673 patients accrued 4294 patient-years of observation. During the investigation period, the LOW and the CON groups submitted a total of 69 190 and 70 938 INR values to the study centre, respectively. In patients with aortic valve replacement, mean INR values were 2.40 (SD, 0.50) in the LOW group and 2.80 (0.59) in the CON group ($P<0.001$). In patients with mitral and double valve replacement, mean INR values were 2.90 (0.60) in the LOW group and 3.10 (0.67) in the CON group ($P<0.001$). The mean phenprocoumon doses in the CON group and in the LOW...
group were 16.8 (6.9) and 15.9 (6.3) mg/week, respectively (P < 0.001).

Approximately 77% of the INR values measured in the LOW group and ~75% of the INR values measured in the CON group were within the group-specific target range. We also evaluated the time spent within target range during the first, second, third, and fourth half-years. There were no significant time effects, neither in the CON group nor in the LOW group (data not shown). Moreover, the results did not differ between the aortic position and the mitral or double valve position (data not shown). In the LOW group, 7% of the INR values were below and 16% above the target range. The corresponding values for the CON group were 23 and 2%, respectively.

During the entire study period, 75 major complications that needed hospital admission occurred in 70 patients. Of these 75 complications, 12 were thrombo-embolic events and 63 were bleeding events. Sixty-seven complications occurred in 2164 patients with aortic valve replacement and eight complications (only bleeding events) occurred in 392 patients with mitral valve replacement. The incidence of thrombo-embolic and bleeding events per patient-year did not differ significantly between the study groups. In detail, thrombo-embolic events occurred in seven patients of the CON group and in five patients of the LOW group. Incidence per patient-year was 0.37 and 0.19% in the CON and LOW groups, respectively (Table 2). Out of the 12 patients with thrombo-embolic events, prolonged reversible ischaemic neurological deficits occurred in three patients, transient ischaemic attacks in eight patients, and valve prosthesis thrombosis in one patient. Concomitant diagnoses were hypertension in eight patients, atrial fibrillation in five patients, and reduced LVEF (30–50%) in four patients. Four patients had fibrinogen concentrations of >360 mg/dL (range: 516–747 mg/dL). Only two patients (without atrial fibrillation) took aspirin (100 mg/day).

Thirty-three bleeding events occurred in the CON group and 30 bleeding events in the LOW group. Incidence of bleeding per patient-year was 1.52 and 1.42% in the CON and LOW groups, respectively (Table 2).

Figure 1 illustrates the individual courses of the INR values in those patients who developed a major thrombo-embolic event. Data are given for the last 8 weeks before the event occurred. Mean values ranged between 2.08 (SD,
The principle finding of this large randomized, prospective interventional trial is that in patients with INR self-management the incidence of grade III thrombo-embolic events was low, even when the target INR range was only 1.8–2.8 for patients with aortic valve replacement. In the subgroup of patients with mitral or double valve replacement (19% of the study population), no major thrombo-embolic events occurred with a target INR range of 2.5–3.5.

Several medical associations have published guidelines on oral anticoagulants for patients with mechanical heart valve prosthesis. The European Society of Cardiology has recommended an INR of 3.0–3.5 for second-generation valves in the mitral position, whereas an INR of 2.5–3.0 was considered sufficient for second-generation valves in the aortic position. The American College of Cardiology and the American Heart Association guidelines of 2006 recommend an INR of 2.0–3.0 for aortic valve replacement with bileaflet mechanical or Medtronic Hall prostheses in patients with no risk factors. If a patient has risk factors, oral anticoagulants are indicated to achieve an INR of 2.5–3.5. After aortic valve replacement with other mechanical valves, or after mitral valve replacement, an INR of 2.5–3.5 is also recommended.

The quality of oral anticoagulation determines both thrombo-embolic and bleeding complications. A high percentage of INR values within the target range can significantly reduce the incidence of thrombo-embolic events. In the subgroup of patients with mitral or double valve replacement, both the CON group and the LOW group had mean INR values close to the recommended INR level of 3.0. In addition, both groups had a high percentage of INR values within their target range. Our data demonstrate that the recommended INR target level of 3.0 in combination with INR self-management is indeed able to guarantee a very low risk of thrombo-embolic events in patients with mitral or double valve replacement.

In an INR range of 2.0–3.0 it is only recommended in patients after aortic valve replacement with bileaflet mechanical or Medtronic Hall prostheses with no risk factors, such as atrial fibrillation, left-ventricular dysfunction, previous thrombo-embolism, or hypercoagulable condition. In our patients with aortic valve replacement, the INR target range of 1.8–2.8 in the LOW group did not result in a
higher incidence of thrombo-embolic complications compared with the CON group with an INR target range of 2.5–4.5. In line with our results, an earlier randomized trial in patients with tissue heart valve replacement demonstrated that all major hemorrhagic complications occurred in the standard INR group (2.5–4.0) and none in the group with INR 2.0–2.25, indicating that a less intensive regimen is neither less effective nor less safe than standard anticoagulant therapy. The occurrence of thrombo-embolic events might be explained by several factors. First, in our study, the INR values were <1.5 and thus very low in some patients when the event occurred. Secondly, some patients had known risk factors such as atrial fibrillation, left-ventricular dysfunction, and high fibrinogen concentrations. In line with recent guidelines, an INR target range of <2.5 was probably too low for these patients. Thirdly, additional risk factors such as hypertension, diabetes, post-operative infection, and a history of cancer increase the risk of thrombo-embolic events, even when an INR target range of 2.5–3.5 is recommended. Finally, not all ischaemic neurological attacks are related to cardio-embolism. Embolic events are a well-known serious complication that is often observed in elderly. The aetiology is of multiple origins and is at least in part due to an increased risk of dehydration caused by age-related changes in kidney function, thirst perception, body water content, and homeostatic capacity.

There is a clear relation between anticoagulation intensity and the incidence of bleeding events. With an increasing duration of treatment, a cumulative increase in the risk of major haemorrhage is generally observed. The annual incidence of major haemorrhage (defined as intracranial haemorrhage or haemorrhage causing death or necessitating transfusion or hospitalization) has ranged between 1.2 and 7.0 episodes per 100 patients in different cohort studies, whereas in clinical trials with selected patients populations it has ranged between 0.5 and 4.2 per 100 patients. Minor bleeding episodes (those that have no costs or consequences) have an annual incidence of 2–24 episodes per 100 patients, depending on the target INR range. In our study, the incidence of major bleeding events was at the lower range of published data and was very similar in the CON and LOW groups. This might be explained by the fact that the mean INR values were relatively close together between the study groups. These results might be due to the fact that the training course for INR self-management was identical for all study participants and was performed before patients were randomized to the study groups. In general, data support earlier results that self-monitoring in a selected patient population is feasible and is able to influence and improve the quality of INR management.

Since the biological half-life of vitamin K-dependent clotting factors is 2–4 days, a recently measured INR value is a good predictor of the risk of developing a bleeding event in the near future. The majority of our patients had INR values of <3.0 within the last week before the bleeding event occurred. Most INR values were within the group-specific target range. Obviously, even the recommended INR target range of 2.0–3.0 is not safe for all patients on oral anticoagulant therapy. As mentioned before, an INR value which is >2.3 but <3.0 can already be life-threatening. There are several reasons why relatively low INR values can be associated with major bleeding events. First, vessel anomalies such as intracranial aneurysms might increase the risk of bleeding events in some patients. Secondly, hypertension, which was frequently present in both the CON and the LOW groups, can increase the risk of a bleeding complication if insufficient medical treatment leads to a rise in blood pressure. Thirdly, polymorphisms in the enzymes that are responsible for the metabolism of oral anticoagulants (cytochrome P450 CYP2C9) or function as drug target (vitamin K epoxide reductase) have been described. These polymorphisms might account for up to 50% of the inter-individual variability in INR values. Specific CYP2C9 variants are associated with a higher risk of bleeding events. Although the bleeding complications in the present trial with an INR time within the target range of 75% was ‘only’ 1.5%, this complication rate was several times higher than the rate of major thrombo-embolic complications. Consequently, there is a rationale for investigating in future studies whether or not INR self-management provides an opportunity to reduce further the INR target range and the risk of major haemorrhage without unacceptably increasing the risk of major thrombo-embolic events.

In summary, our data demonstrate that low-dose INR self-management does not increase the risk of thrombo-embolic events compared with conventional dose INR self-management. However, with the currently recommended target range, the risk of bleeding complications is still unsatisfactorily high.

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References

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