Safety management in mechanical heart valve replacement and oral anticoagulant therapy

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Chapter 8

A Randomized Crossover Comparison between Oral Anticoagulation Self-Management and Management by the Thrombosis Service in the Netherlands

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Submitted
8.1 ABSTRACT

**Background** The development of portable prothrombin time monitoring devices allows the determination of the prothrombin time (expressed as INR) from capillary whole blood and thus facilitates self-monitoring of anticoagulation and self-adjustment of the coumarin dose, potentially associated with improved control of anticoagulation and more convenience for patients. This study compared self-management of oral anticoagulant therapy with conventional management by a specialized Thrombosis Service in a randomized crossover study.

**Methods** 48 educated patients were randomized to perform self-management or to be managed by the Thrombosis Service for a period of three months. After this period the alternative strategy was followed in each patient. INRs were collected on weekly basis in both periods. The accuracy of the regulation of anticoagulation was defined as the number of INR determinations within the therapeutic range and the total time (by means of linear interpolation) of "adequate" anticoagulation (in the target range) compared to the results of the management by the Thrombosis Service.

**Results** During self-management patients were 57.7% of the time in the target range, as compared to 51.7% in the Thrombosis Service management period (p=0.067). Patient were 85.9% and 80.1% of the time (=83.2% and 77.4% of the INR values) within a range of ± 0.5 INR units from the target range during self-management and Thrombosis Service management, respectively (p=0.027). Serious under- or over-anticoagulation (INR<1.5 or >5.0) occurred during 3.5% of the self-management period and during 5.3% of the anticoagulation clinic management period (p=0.07).

**Conclusion** Self-management of oral anticoagulant therapy is safe and results in control of anticoagulation that is equivalent to management by the Thrombosis Service. Self-management of anticoagulation may be considered an effective strategy to improve long-term treatment with anticoagulant agents.
8.2 INTRODUCTION

Oral anticoagulants have been in use for years for the prevention of thromboembolic events in various clinical circumstances like prosthetic heart valves, atrial fibrillation, but also in the treatment and prevention of (recurrent) deep-vein thrombosis and pulmonary embolism. The required minimal therapeutic anticoagulation level depends on the origin of the thromboembolic process and different target ranges have been recommended for various clinical states\(^1\). The risks of side effects in terms of thromboembolic or hemorrhagic complications are closely related to the intensity of anticoagulation and correlate to the length of time patients spend outside the individual established therapeutic interval\(^2\). Retrospective and prospective studies have shown an exponential increase in thromboembolic events in patients with heart valve prostheses or atrial fibrillation as the INR drops below a level of 1.5\(^{1,3-6}\). In addition, there is also an exponential increased risk of bleeding above the level of 5.0\(^{1,4}\). Due to many intrinsic and extrinsic factors that influence the intensity of anticoagulant therapy, and the high risk of thromboembolic or hemorrhagic complications, patients are restricted to frequent routine PT control and dose-adjustments by experienced physicians to achieve and maintain a stable therapeutic level.

The formation of specialized anticoagulant clinics was a welcome development that could improve the management of oral anticoagulant therapy by maintaining a more effective therapeutic anticoagulation level and thereby reducing the bleeding and thromboembolic events\(^1,7,8,9\). Despite the well-organized Thrombosis Services, the management of anticoagulant therapy is still labour intensive for both patient and health care system. Besides, the frequent venous access and patient’s visits to the laboratory can also affect the patient’s compliance with the therapy. Therefore, the need for simpler, cheaper and more convenient strategies still challenged thought.

The development of portable monitoring devices allows the determination of the prothrombin time (expressed as INR) from capillary whole blood. Previous studies have indicated the benefit of portable whole blood PT time monitoring systems for patient self-management of oral anticoagulant therapy\(^{10-15}\). The anticipated advantages of patient self-management include improved convenience for the patients and better compliance. In addition, self-testing allows for more frequent control\(^{16}\). Although these studies indicate the feasibility of patient self-management, no cross-over studies have been executed, which could exclude influence of life-style, medication, education or other external factors on the quality of anticoagulation therapy in comparing the patient self-management with the anticoagulation-clinic guided management.

This study investigated the safety and efficacy of self-management of oral anticoagulant therapy by patients and to assess whether this self-management results in an equally well or even improved regulation of oral anticoagulation. To compare patient self-management with
conventional management, the typical situation of well-organized Thrombosis Services in the Netherlands sets the stage for an optimal reference standard.

8.3 MATERIAL AND METHODS

8.3.1 Study population

In total, 51 patients were included in the study. 12 patients were already recruited for the pilot phase as described in the previous chapter. An additional 39 were selected over the next year. The patients were selected based on their physicians' (not investigators') assessment of their understanding of anticoagulation therapy.

Inclusion criteria were:
- indication for chronic oral anticoagulant treatment
- oral anticoagulation therapy for at least three months before inclusion
- minimal age of 18 years

Exclusion criteria are (relative) contraindications for oral anticoagulant agents.

The study protocol was approved by the Institutional Review Board of the Academic Medical Center of the University of Amsterdam. All patients gave oral and written informed consent to participate in the study.

8.3.2 Patient education

All eligible patients underwent a structured educational program to be able to carry out anticoagulation self-management. This educational program was adapted from previously published educational programs. The patients were educated by the author in two sessions of about four hours.

In the first session a small group of patients (4-6 per group) received structured and interactive teaching on the function of the anticoagulation system, the principles of anticoagulant therapy and monitoring of anticoagulant therapy. Instructions on self-measurement of the INR by means of a capillary finger stick and utilization of an automated device was given using a video presentation and a live demonstration. Patients then were given the opportunity to measure their own INR (at least once or as many times as they wished) in the presence of an instructor. In the ten-days interval between the first and the second session, patients had the opportunity to self-measure their INR in their own environment and to report their experience in the second session. Furthermore, this second session was devoted to teaching and practicing how to device a proper oral anticoagulant dosing scheme. For teaching purposes, a standard dose-adaptation normogram was used, but
patients were encouraged to adjust and tailor this normogram according their individual experience. After concluding the educational program the patients had about a 4-6 weeks training period to demonstrate their ability to perform self-measurement of the INR and to adjust their coumarin dose. A 24-hours helpdesk was instituted to answer any question or to assist with any problem that might arise.

8.3.3 Measurement of INR

Venous blood (9 vol) was collected in 3.2% sodium citrate (1 vol) and plasma was obtained by centrifugation at 1,800 x g for 20 min. The prothrombin time (PT) was measured in plasma using Tromborel-S reagent (Dade Behring, Leusden, the Netherlands, ISI value 1.19) on an Elektra 1600 coagulometer (MLA, Pleasantville, NY). PT values were expressed in INR according to international convention. The portable instrument used was the CoaguChek® monitor (Roche Diagnostics, Almere, the Netherlands), described previously \(^{(17,18)}\). In brief, a drop of capillary whole blood is collected by finger stick (using Softclix®) and dropped onto a test carrier that has been inserted into the monitor. The blood is drawn to the ‘reaction zone’ by capillary forces. The reaction zone of the test carrier contains rabbit brain thromboplastin (International Sensitivity Index (ISI) value = 1.0). Blood contact with the thromboplastin triggers the coagulation cascade. The system determines the INR based on the thromboplastin-induced clotting time in about two minutes. Each production lot of CoaguChek® test strip is calibrated against HepatoQuick by the manufacturer. The corresponding code-chip stores the calibration data of the used thromboplastin in the strips. A quality control to evaluate the performance of every single CoaguChek is made by the investigator at the start of the use of the equipment using the standardized CoaguChek PT control plasma.

8.3.4 Study design

Fifty-one patients on chronic anticoagulant therapy with oral agents were educated and trained to perform self-management of anticoagulation. After the training period the patients were randomized to

1. Three months anticoagulation treatment managed by their own Thrombosis Service: The Thrombosis Service would perform a standard venous blood test every week and establish a dosis scheme for the next week.

2. Three months self-management of anticoagulation. The patients were requested to measure the INR once weekly at home, using the CoaguChek. Based on the INR they had to make dose-adjustments without consultation.

After three months the alternative management strategy was employed.
8.3.5 Statistics

All data are presented as mean ± SD. The accuracy of the regulation of anticoagulation using the CoaguChek®, was assessed by evaluating the number of INR values within the therapeutic range and by measuring the proportion of time of adequate anticoagulation (in the therapeutic target range) by the self management group compared to the results of the management by the thrombosis Service. The proportion of time in the target range is computed by means of linear interpolation (Rosendaal). For comparisons of groups the independent sample t-test was used.

8.4 RESULTS

Three of the 51 patients included in the study dropped out. One during the education period due to a difficulty in performing the finger stick (visual impairment). One because of a car accident, which made it impossible to continue the self-management and one because of an unexpected operation during the study period. These three were not included in the final analysis. The relevant demographic and medical characteristics of the remaining 48 patients are presented in table 1.

The mean difference of all measured INRs from the target value was 10.1% (±20.3) during the three months period of self-management as compared with 11.9% (±22.0) in the period managed by the thrombosis service. This difference was not significant.

The mean percentage of INR values that patients were in the predefined target range was 55.3% for the self-management period and 49.7% for the Thrombosis Service period. Outside the range, in both periods about two-third of the values were under the target range and one-third above. Patients were for 82.8% and 77.4% of the INR values within a range of ±0.5 from the therapeutic target range during self-management and Thrombosis Service management, respectively (figure 1). The mean percentage of time that patients were in the predefined target range was 57.7% for the self-management period and 51.7% for the Thrombosis Service period (p=0.067).

The number of patients that was more than 50% of the time in the therapeutic target range was 30 (62.5%) in the self-management period versus 26 (54.2%) in the thrombosis service period. The number of patients that was more than 75% of the time in the therapeutic target range was 13 (27.1%) during self-management versus 6 (12.5%) in the thrombosis service period (p<0.05, odds ratio 2.47, 95% confidence interval 1.01-6.69) (figure 2).

Of the 48 patients 27 had a better control of anticoagulation (defined as the period of time in the therapeutic target range) during self-management than during anticoagulation clinic-guided management (odds ratio 4.64, 95% confidence interval 2.1-10.2). In 3 of 49 patients there was no difference and in 17 of 49 patients the anticoagulation clinic management
resulted in a better control of anticoagulation than self-management. The order of management modality in the study did not affect any of these parameters. Serious under- or over-anticoagulation (INR<1.5 or >5.0) occurred during 3.5% of the self-management period and during 5.3% of the anticoagulation clinic management period. In the anticoagulation clinic-management group three minor bleedings occurred (one joint bleeding after minor trauma at an INR of 7.5, one calf muscle bleeding at an INR of 4.2, and one episode of recurrent nose bleeding at an INR of 6.5), whereas in the self-management period one minor nose bleeding (INR 2.4) occurred. In the anticoagulation clinic-management period there was one episode of clinically suspected recurrent deep-vein thrombosis (though not confirmed by objective testing) at an INR of 1.4 and one patient with a prosthetic aortic valve, who suffered from a transient ischemic attack (TIA). During self-management there were no symptoms and signs of thrombotic complications. The differences in clinical outcome are not statistically significant.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=48)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Range</td>
<td>22-71</td>
<td></td>
</tr>
<tr>
<td>- Mean age</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Male</td>
<td>29</td>
<td>60%</td>
</tr>
<tr>
<td>- Female</td>
<td>19</td>
<td>40%</td>
</tr>
<tr>
<td><strong>Type of anticoagulation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Acenocoumarol</td>
<td>30</td>
<td>63%</td>
</tr>
<tr>
<td>- Phenprocoumon</td>
<td>18</td>
<td>37%</td>
</tr>
<tr>
<td><strong>Reason for anticoagulation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mechanical heart valve</td>
<td>23</td>
<td>48%</td>
</tr>
<tr>
<td>- Chronic atrial fibrillation</td>
<td>10</td>
<td>21%</td>
</tr>
<tr>
<td>- Venous thromboembolism</td>
<td>15</td>
<td>31%</td>
</tr>
<tr>
<td><strong>Target range</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 2.0 - 3.0</td>
<td>2</td>
<td>4%</td>
</tr>
<tr>
<td>- 2.5 - 3.5</td>
<td>15</td>
<td>31%</td>
</tr>
<tr>
<td>- 3.0 - 4.0</td>
<td>25</td>
<td>52%</td>
</tr>
<tr>
<td>- 3.5 - 4.5</td>
<td>6</td>
<td>13%</td>
</tr>
</tbody>
</table>
Chapter 8

Figure 1: Cumulative proportion of total measurements per INR unit outside the target range for the self-management group and the conventional care group.

Figure 2: Proportion (%) of patients who are for the percentage of time in the target range for the self-management group and the conventional care group.
Oral anticoagulation with coumarins is an effective therapeutic modality for treatment and prevention of arterial and venous thromboembolism. However, the substantial inter- and intra-individual variation in the biological effect of coumarin renders many patients outside the therapeutic target range over a considerable period of time. This is cumbersome for several reasons. Firstly, clinical studies show that under- and over-coagulation enhance the risk of adverse clinical outcomes, i.e. thromboembolism or bleeding, respectively. For example, a 0.9-2.5% annual incidence of major bleeding in patients on coumarin for various indications has been demonstrated and the risk of bleeding increases several-fold in patients with higher INRs. Hence, the variability in the intensity of anticoagulation necessitates frequent laboratory control and dose-adjustment, which forms a second drawback of oral anticoagulation. Previous studies have shown that anticoagulation management by a specialized anticoagulation clinic results in a superior control of anticoagulation as compared with control in general practice, however, in certain areas this may even amplify the practical problem of relatively frequent checks. Self-management of anticoagulation may overcome the need for frequent visits to an anticoagulation clinic and may still be associated with an optimal control of anticoagulation. Self management may achieve maximal individualization, frequent control when necessary, and improved compliance, which are all factors that have been shown to improve the number of occasions that patients are in the therapeutic range of anticoagulation. In the present study we demonstrate that self-management of oral anticoagulation results in an identical control of anticoagulation that is at least as good and potentially superior to control by a well-organized anticoagulation service in a randomized crossover trial. Patients appeared to be well able to measure their INR and to devise appropriate dosing schemes for their anticoagulant agents. There was a slight benefit in the control of anticoagulation during the self-management period in comparison with the period that anticoagulation was managed by the anticoagulation clinic.

Previous studies have also shown the feasibility of self-management of oral anticoagulation and a number of retrospective cohort studies have indicated that self-management of anticoagulant treatment was equivalent or superior to conventional care. In multicenter prospective randomized trials from Germany and the US it was demonstrated that control of anticoagulation was better in patients that managed their anticoagulation themselves as compared to patients who had their anticoagulation managed by a general practitioner. The present report is the first to indicate that self-management is at least as effective as management of anticoagulation by specialized anticoagulation centers.

In this study the adequacy of anticoagulant control was established in terms of being in the target range. In fact, the incidence of bleeding or thrombotic episodes would provide a potentially more relevant outcome assessment. However, the sample size, study period and
study design did not permit to establish a statistical significant difference in these parameters, though there was a trend in favor of self-management. Nevertheless, clinical studies invariably show that there is a clear relationship between adequate control of anticoagulation and a lower incidence of bleeding and thrombotic complications in patients on oral anticoagulants. Hence, the equivalent control of anticoagulation between anticoagulant clinic-guided therapy and self-management of oral anticoagulation, as demonstrated in our study, may potentially be extrapolated to a beneficial effect of this management strategy on clinical outcome. Although we did not specifically select eligible patients for our study, a certain degree of patient selection cannot be excluded. Indeed, relatively young patients or patients with a busy working or social life might be overrepresented in our study group. Strictly spoken, we can only limit our conclusions on the safety and efficacy of self-measurement of INR and self-dosing or coumarins to the type of patients included in our study. However, similar to others, we have encountered that all patients who are able to lead an independent and self-sufficient life, are in principle capable of self-management of anticoagulation, regardless of the level of education and social status. Interestingly, a similar experience has been gathered for self-control and self-management of insulin-dependent diabetes mellitus\textsuperscript{(19,20)}. In our practice, limiting factors for performing self-measurement of the INR with the CoaguChek\textsuperscript{®} device were mainly physical factors, such as visual impairment or tremor.

Despite the ability of patients to perform self-management of oral anticoagulation, adequate support remains necessary. Follow-up, repeat education, counsel in case of sustained dysregulation of anticoagulation, or advice on interruption of therapy in case of bleeding or the need to undergo an invasive procedure are -amongst others- issues that need to be taken care of. In the organization of such support the anticoagulation clinics may play a major role. Nevertheless, self-management of anticoagulation may be a cost-effective approach, as was shown in a previous analysis.

In conclusion, this study showed that self-management of oral anticoagulant therapy is safe and as effective as management by a specialized anticoagulation clinic. In addition, self-management was well accepted and appreciated by the participating patients. Self-management of anticoagulation may be considered as a novel, patient-friendly, and effective strategy to improve long-term treatment with anticoagulant agents.
8.6 REFERENCES


