

# Improvement of Oral Anticoagulation Therapy by INR Self-Management

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Thromboembolic complications after valve replacement are significantly reduced if the INR is increased from 1.0 to 2.0. Hemorrhagic events increase exponentially with more intensive oral anticoagulation. In INR (patient) self-testing (PST), patients self-check their INR after being appropriately educated and supplied with a coagulometer. Patients contact their home physician if the actual INR tends to run outside an individually defined target INR corridor for correction. For patient self-management (PSM), subjects are trained to self-test their INR and to adjust the anticoagulant dose according to their anticoagulation state. The median difference between self-tested and laboratory-tested INRs was <5.0%, indicating no significant differences between the two methods. PSM resulted in a significantly more stable oral anticoagulation therapy (OAT), which was the strongest predictor for a low complication rate

Adverse events of oral anticoagulation therapy (OAT) are due to OAT-related bleedings and/or thromboembolic (TE) complications, despite the use of such treatment. For patients with cardiac replacement devices, a broad variation in the frequency of these adverse events has been reported. However, this variance may be due to insufficient versus sufficient follow up techniques (1), to varying methods of data analysis (1,2), or to differences in the quality of OAT management (3).

after valve replacement surgery. Lower rates of thromboembolism (0.9 versus 3.6% per patient-year; pt-yr) and bleeding (4.5 versus 10.9% per pt-yr) ( $p < 0.001$ ) were seen in PSM subjects than with conventional INR management. A switch from conventional to PSM resulted in a 30% reduction in complication rates in the German Experience with Low Intensity Anticoagulation (GELIA) study. After appropriate education and provision with a handy coagulometer, the vast majority of patients after valve replacement can self-check INRs and adjust the anticoagulant dosage accordingly. PSM results in a significantly more stable oral anticoagulation treatment and consequently in lower incidences of thromboembolic and bleeding events.

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## Intensity versus stability of OAT

There is evidence that TE decreases rapidly if the INR is increased from 1.0 to 2.0, but only moderately if anticoagulation is further intensified (INR higher than 2.0) (4). Bleeding complications increase exponentially with more intensive OAT (4,5).

It is well recognized that lower INR targets - for example, 2.5-3.0 instead of 3.0-3.5 - result in a decrease in the overall complication rates (thromboembolic plus bleeding complications), whilst an increase in INR raises complication rates in the vast majority of patients (6-11). An accepted explanation for this is that the intensity of OAT in patients appointed to higher INR targets was inappropriately chosen, with a consequently unfavorable risk-to-benefit ratio (12). However, another explanation might be that whilst a more intensive anticoagulation results in broader variations of consecutive INR measurements, a lower intensity therapy results in a more stable anticoagulation (3).

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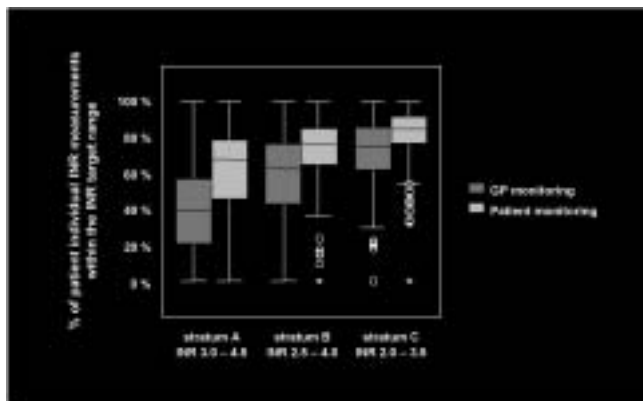


Figure 1: Stability of oral anticoagulation therapy in the GELIA study. The box and whisker plot gives the percentage of patients individual INR measurement within the INR target range. For all three strata, patient self-monitoring (PSM) resulted in a significant more stable anticoagulation than monitoring by the home physician/general practitioner (GP).

### Patient self-testing and self-monitoring

INR self-testing, referred to as patient self-testing (PST), was initially introduced to avoid inappropriate over- and undercoagulation in patients with mechanical heart valve prostheses (13). PST describes a situation where patients check their INR themselves and contact their physician if the actual INR is (near) outside the recommended target INR range. More recently, patients have been trained not only to control their INR but also to adjust the anticoagulation dosage accordingly - this is termed patient self-management (PSM) (14).

Individual adjustment of the intensity of oral antico-

agulation therapy and maintenance of low INR targets has attracted both patients and physicians since the early 1990s, when coagulometers which had good analytical performance and could be conveniently handled first became available (15). In a prospective study with 231 simultaneous INR measurements, a high accuracy of INR self-testing was demonstrated, with a median difference between parallel controls of single measurements of only 4.5% (16).

### Stability of OAT by INR self-management (PSM)

Based on information from the German Experience with Low Intensity Anticoagulation (GELIA) database (17), there is strong evidence that INR self-monitoring results in a significantly higher percentage of INRs within the target INR range, and thus a more 'stable' OAT than in patients monitored by general practitioners (18).

A more detailed analysis revealed that PSM resulted in a higher percentage of individual INR measurements within the INR target range, irrespective of the intensity of OAT (Fig. 1). There was a close correlation between the intended target INR ranges (INR 3.0-4.5 versus INR 2.5-4.0 versus INR 2.0-3.5) and the percentage of individual INR measurements inside the target range. In fact, in patients with an intended INR range of 3.0-4.5 (stratum A), the 'median' percentage of INR measurements within that range was only 41% (CI: 0.21-0.57), compared with 0.63% (CI: 0.43-0.75) for the INR range 2.5-4.0 and 0.75% (CI: 0.64-0.85) for INR range 2.0-3.5.

It may be concluded from these results - which were

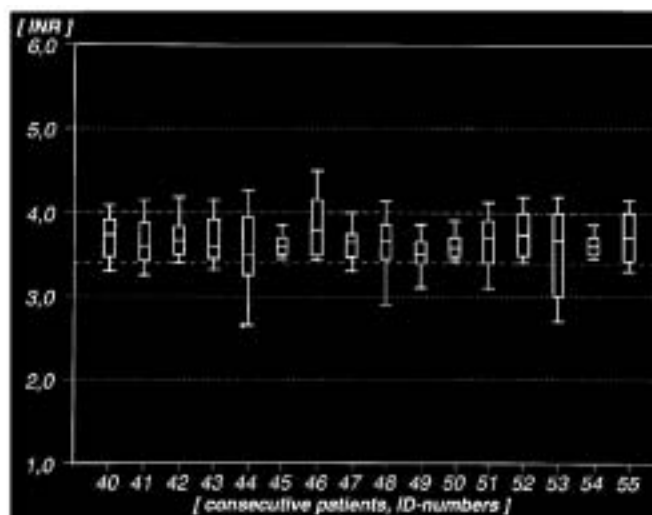
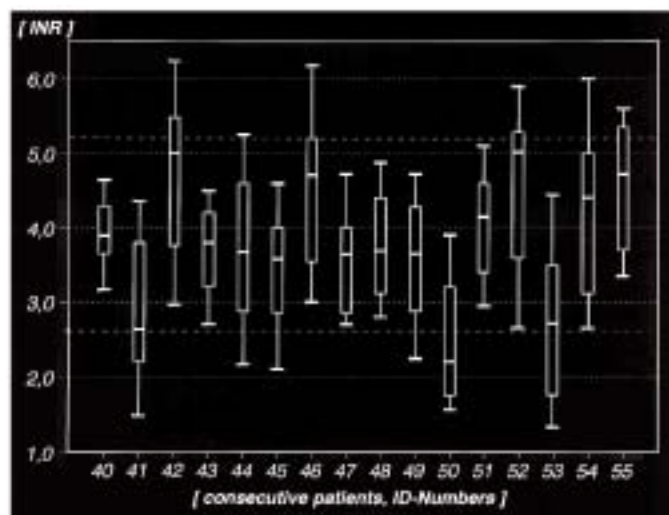


Figure 2: Stability of oral anticoagulation therapy in randomly selected patients treated by oral anticoagulation monitoring by their home physician (left side) and having patient self-monitoring (right side). PSM results in a significant more stable anticoagulation.

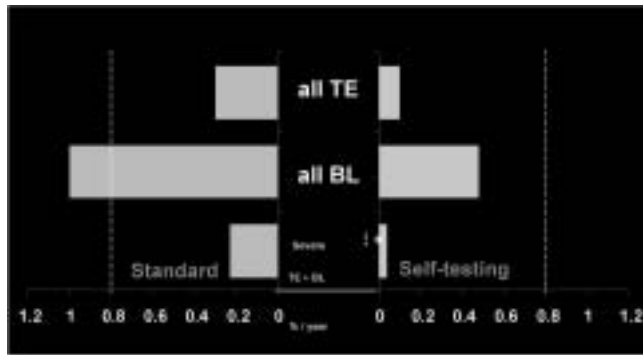


Figure 3: Number of all thromboembolic (TE) and bleeding events (BL) as well as patients with severe TE plus BL in a randomized study comparing standard oral anticoagulation management and patient self-management.

derived from the largest oral anticoagulation database currently available for patients with mechanical heart valve prostheses - that the more stable the OAT, the lower the intensity of anticoagulation (target INR range). Consequently, patients should be allocated to the lowest individual possible INR range and be advised to keep meticulously within this target. For more details regarding the GELIA study, reference may be made to the study protocol (17).

### Improvement of OAT by PSM

In an early pilot study, PSM and standard monitoring by general practitioners (GP) were compared in a randomized manner (16,19). This study initiated a variety of activities, but was never followed by a large prospective randomized multicenter study, as the majority of patients refused to be enrolled in the non-self-testing arm.

In the pilot study, 150 consecutive patients with St. Jude Medical aortic or mitral valve replacements were allocated randomly to either PSM every third day ( $n = 75$ ) or to a standard OAT management by the GP, without specific control intervals ( $n = 75$ ). All 150 patients underwent standardized training in the self-management of oral anticoagulation using the Coagu-Chek system (Boehringer Mannheim, Germany), and were monitored during this education period to a target therapeutic range of 3.5-4.0. They were then asked to keep within this range during the entire follow up period. The therapeutic corridor was defined as INR 3.0-4.5.

Thrombotic, thromboembolic and hemorrhagic complications were recorded by the patients themselves, using special documentation cards. In addition, all patients underwent an outpatient evaluation every three months.

Among the group with standard anticoagulation



Figure 4: Comparison of severe adverse events (thromboembolic and bleeding complications) for patient self-management and monitoring of oral anticoagulation therapy by general practitioners, taking patients as their own controls. For more details, refer to the text.

management, 2,166 INR tests were documented during follow up. The mean interval between two tests was  $18.9 \pm 7.7$  days. Among the INR measurements, 23.3% were within the target therapeutic range, and 1,273 (58.8%) were within the target INR corridor. The incidences of bleeding complications of any severity and thromboembolic complications were 10.9% and 3.6% per year, respectively.

Patients with PSM had 9,982 INR tests documented during the same follow up period. The average interval between two tests was  $3.9 \pm 0.3$  days, and the mean INR was  $3.7 \pm 0.3$  (range: 2.6 to 4.6). Among all INR measurements 4,372 (43.2%) were within the target INR range and 92.4% ( $n = 9,226$ ) were within the target INR corridor. All documented INR measurements of 16 randomly selected patients (according to consecutive identification numbers for both strata) of both the PSM group and the conventionally managed group are detailed in Figure 2.

Bleeding complications (4.49% per year) and thromboembolic complications (0.9% per year) were significantly ( $p < 0.001$ ) lower in patients with PSM (Fig. 3).

Further evidence for the improvement of OAT by PSM was provided by the GELIA study (3): a total of 355 patients with initial GP monitoring of their OAT switched during the follow up period to PSM, and were used as their own controls (Fig. 4). During GP monitoring, an average of 1.5 INR measurements was performed each month (median interval between consecutive INR measurements, 21.4 days). By comparison, the same patients made 3.3 INR measurements per month when performing PSM (median interval 9.1 days between consecutive measurements). During PSM, the incidence of severe events decreased by 29.8%, to a mean of 3.28 events (CI: 2.1-4.2) per year.

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