The Belgian Improvement Study on Oral Anticoagulation Therapy: a randomized clinical trial

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\textbf{Aims} In Belgium, general practitioners (GPs) mainly manage oral anticoagulation therapy. To improve the quality of oral anticoagulation management by GPs and to compare different models and interventions, a randomized clinical trial was performed.

\textbf{Methods and results} Stratified randomization divided 66 GP-practices into four groups. A 6-month retrospective analysis assessed the baseline quality. In the prospective study, each group received education on oral anticoagulation, anticoagulation files, and patient information booklets (groups A, B, C, and D). Group B additionally received feedback every 2 months on their anticoagulation performance; group C determined the international normalized ratio (INR) with a CoaguChek device in the doctor’s office or at the patient’s home; and group D received Dawn AC computer assisted advice for adapting oral anticoagulation. For the different groups, the time spent in target INR range (Rosendaal’s method) and adverse events related to anticoagulation were determined and compared with the same quality indicators at baseline. There was a significant increase in per cent of time within 0.5 INR from target, from 49.5% at baseline to 60% after implementing the different interventions. However, neither the per cent in target range nor the event rates differed among the four groups.

\textbf{Conclusion} The interventions significantly improved the quality of management of oral anticoagulation by Belgian GPs, mainly as a result of an education and support programme.

\textbf{Keywords} Oral anticoagulation; General practitioner; Quality improvement; Randomized clinical trial

\textbf{Introduction} The past years have seen an increase in interest in the management of oral anticoagulation. Principally, this has been driven by the increasing numbers of patients receiving oral anticoagulation as a result of trials demonstrating the effectiveness of this treatment in preventing strokes in patients with atrial fibrillation (AF).\textsuperscript{1,2} However, the risk of therapy with oral anticoagulants is high because deviation from the therapeutic range is an important cause of treatment failure, including both thromboembolism and haemorrhage.\textsuperscript{3–5} According to the British guidelines on oral anticoagulation, at least 50% of the results of the patient population should not differ >0.5 international normalized ratio (INR)-units from target and 80% not >0.75 INR-units.\textsuperscript{6} The quality of anticoagulation depends, in part, on the model of care.\textsuperscript{7} In The Netherlands, anticoagulation clinics follow-up the therapy.\textsuperscript{8} With this model of care, patients are in target range 63.5% of the time.\textsuperscript{9} The USA and the UK have a mixed system, the anticoagulant dosing being prescribed either by the anticoagulation clinic or by the general practitioners (GPs).\textsuperscript{7,10,11} In Germany, France, and Belgium, GPs mainly manage oral anticoagulation.\textsuperscript{12–14} Studies in these countries showed per cent of time in range of, respectively, 33 and 64%, 69%, 58 and 49.5%.\textsuperscript{12–16} Appropriate education and supportive tools could achieve an adequate quality of anticoagulation.\textsuperscript{17} The aim of this clinical trial was to improve the quality of anticoagulation management by GPs by comparing the effect of several interventions.

\textbf{Methods} The past years have seen an increase in interest in the management of oral anticoagulation. Principally, this has been driven by the increasing numbers of patients receiving oral anticoagulation as a result of trials demonstrating the effectiveness of this treatment in preventing strokes in patients with atrial fibrillation (AF).\textsuperscript{1,2} However, the risk of therapy with oral anticoagulants is high because deviation from the therapeutic range is an important cause of treatment failure, including both thromboembolism and haemorrhage.\textsuperscript{3–5} According to the British guidelines on oral anticoagulation, at least 50% of the results of the patient population should not differ >0.5 international normalized ratio (INR)-units from target and 80% not >0.75 INR-units.\textsuperscript{6} The quality of anticoagulation depends, in part, on the model of care.\textsuperscript{7} In The Netherlands, anticoagulation clinics follow-up the therapy.\textsuperscript{8} With this model of care, patients are in target range 63.5% of the time.\textsuperscript{9} The USA and the UK have a mixed system, the anticoagulant dosing being prescribed either by the anticoagulation clinic or by the general practitioners (GPs).\textsuperscript{7,10,11} In Germany, France, and Belgium, GPs mainly manage oral anticoagulation.\textsuperscript{12–14} Studies in these countries showed per cent of time in range of, respectively, 33 and 64%, 69%, 58 and 49.5%.\textsuperscript{12–16} Appropriate education and supportive tools could achieve an adequate quality of anticoagulation.\textsuperscript{17} The aim of this clinical trial was to improve the quality of anticoagulation management by GPs by comparing the effect of several interventions.

\textbf{Population} All 255 GPs, for whom the clinical laboratory of the Medical Centre for GPs in Tessenderlo determines the INRs on venous blood, were invited to participate. A total of 96 GPs (38%), regrouped in 66 GP-practices, of which 44 were single-handed, participated in the study.

\textbf{Design} In a first retrospective part of the study, the time in range and the number of adverse events related to anticoagulation for these 66 practices were determined over a 6-month period. In the second 6 months, the GPs received education and the practices were
randomized into four groups (Figure 1). The same laboratory determined the INR-values for groups A, B, and D. The GPs provided additional patient-related information. The ethics committee of the University Hospital Leuven approved the study. All participating GPs signed an informed consent.

Randomization

One could imagine differences in performance according to the experience of the GP with oral anticoagulation and the type of practice (single-handed GP or group practice). Therefore, to avoid imbalances, the 66 GP-practices were divided into four different groups using a stratified block randomization. Six different strata of GP-practices were defined depending on the number of anticoagulated patients (<5 patients, 6–14 patients, ≥15 patients) and the type of practice (single-handed GP or group practice). These six strata (numbered containers with cards) were divided blindly over the four intervention groups by a university staff member as follows: out of the first container a card was drawn and placed in box A, the next card in box B, C, D, A, B, etc. The same procedure was followed for the other five boxes.

Interventions

Basic intervention

Each group received basic intervention respecting Grol’s multifaceted approach as explained subsequently. All GPs followed the same interactive training. A summary of the guidelines was printed on the cover of a folder containing the anticoagulation files. The British guidelines on oral anticoagulation were used as reference. The GPs also received information booklets on anticoagulation for their patients. A website was created with guidelines, study design, and general information. Every 2 months, a newsletter informed the GPs on the study progress and requested them to send the anticoagulation files for control.

Feedback

Every 2 months, the GPs of group B received feedback on the performance of the practice when compared with the entire group B and to the criteria proposed by the guidelines.

CoaguChek® device

Before starting the study, the GPs were trained in using the CoaguChek device to determine the INR on the spot using capillary blood. Every 3 months, the clinical laboratory performed an electronic quality control on the device.

Dawn AC® computer assisted advice

The GP took blood and sent this to the laboratory for INR determination. The pathologist introduced the INR in the Dawn AC computer programme that generated a recommended dosing scheme and the time to next visit. The pathologist reviewed the computer-generated advice and faxed it the same afternoon to the GP. GPs were free to follow this advice, as each therapeutic decision remained their responsibility.

Outcome

The primary outcome measure was the quality of anticoagulation management, defined as the proportion of time that INR-values were within target range. These were defined as within 0.5 INR-units and 0.75 INR-units from the chosen target INR of 2.5 or 3.5. Secondary outcome measures were the number of thromboembolic complications and the number of haemorrhages defined according to The European Atrial Fibrillation Trial Study Group.

Patients

Only patients treated with oral anticoagulation for at least 28 days were included (steady state). Patients who discontinued the anticoagulation therapy for a surgical procedure during the study were excluded from analysis.

Data collection

Patient data were prospectively collected using anticoagulation files systematically completed by the GPs. These files were collected and supervised every 2 months by the medical study co-ordinator. If a haemorrhagic or thrombo-embolic event was reported, confirmatory documents (hospital, radiological, etc.) were claimed. The INRs of patients of group C were systematically noted by the GPs on these files; those of groups A, B, and D were collected from the laboratory.

Statistical analysis

A power analysis was performed to evaluate the feasibility of the study. Different scenarios indicated that at least 40 GPs (assuming on average 10 patients on oral anticoagulation per GP) were needed to obtain 80% power to detect a difference in the time in range among the four groups (anticipated times in range 40, 50, 50, and 80%, respectively). INR results were registered and INR-person-time was calculated as the time a patient stayed within a pre-determined INR-interval according to Rosendaal’s algorithm, assuming a linear increase or decrease between two consecutive INR determinations. A linear mixed model with group as a fixed and GP as a random effect was used to compare the patient-specific per cent INR in range and the number of tests per patient per month (log-transformed). Bonferroni corrections were used to correct for multiple testing whenever pairwise comparisons among the four groups were performed. For the comparison of the retro- and prospective parts of the study, a patient was also added as a random effect (the same patient could be involved in both parts of the study).
study). A random-effects logistic regression (patient as random effect) has been used to compare dichotomized outcomes among the four groups. For these outcomes, a GEE analysis has been performed to compare the retro- and prospective parts of the study. The per cent INR values <2 and the per cent INR values >5 are dichotomized as ‘at least one INR value <2’ vs. ‘no INR value <2’ and ‘at least one INR value >5’ vs. ‘no INR value >5’, respectively. The per cent changes in therapy (changes in dosage) have been dichotomized as ‘at least one change in dosage’ vs. ‘no change in dosage’. Cox regression was used to analyse the relation between event rate and different covariates. GP has been added as a random effect (‘frailty’) when enough events were available. For all analyses the alpha-level was set at 5%. All analyses were performed with the statistical package SAS (version 8.2), using the procedure PROC MIXED for the linear mixed model, PROC NLMIXED for the random-effects logistic regressions, and PROC GENMOD for the GEE analysis. The frailty model has been fitted using coxph function in Splus 2000.

For a subgroup of patients in group D, the relations between the average deviation in date of blood sampling, the average deviation in dosage, and the per cent of time in target have been explored using Spearman correlations.

Results

Patients

Out of 936 patients on oral anticoagulation, 834 patients (455 men and 379 women) were included in the study. A total of 91 patients who underwent a surgical intervention with an interruption of the anticoagulation during the study period were excluded from the analysis. Patients were only included after a starting-up period of at least 28 days (leading to exclusion of another 11 patients). The mean age was 70.2 years (±11.9). Patients were anticoagulated with a target INR of 2.5 because of AF (51.5%), to prevent arterial thromboembolism (15%), for deep venous thrombosis (8%), or for pulmonary embolism (9%). Patients were anticoagulated with a target INR of 3.5 because of a mechanical prosthetic heart valve (16%) or for the antiphospholipid syndrome (0.5%). In total, 85% were anticoagulated using phenprocoumon, 9% using acenocoumarol, and 6% using warfarin. The risk factors for stroke and the occurrence of thrombo-embolic complications or bleedings were as follows: 423 patients had hypertension, 121 diabetes mellitus, 205 a prior stroke or transient ischaemic attack, 132 peripheral vascular disease, 227 congestive heart failure, 129 a previous myocardial infarction, 262 a valve disease, 43 a history of malignancy, and 129 patients were smokers.

Proportion of time that INR-values were in range

INR values

The median follow-up was 4.8 months (Q1–Q3: 3–5.5). The median number of anticoagulant patients per practice was 12 (Q1–Q3: 6.5–15). 6303 INR-values were obtained with a median number of tests per patient per month of 1.5 (Q1–Q3: 1.2–2.1). A total number of 104365 therapy days were observed. There was no significant difference among the four groups in number of tests per patient per month, per cent of patients with treatment changes or per cent of patients with at least one INR <2 (Table 1). A significantly difference in per cent of patients with a least one INR >5 was between the intervention groups (P = 0.009). A significant decrease in per cent of patients with an INR >5 was
found after the implementation of the interventions ($P = 0.019$).

**Per cent of time in range**
The 6 months retrospective analysis showed that the patients of the practices assigned to groups A, B, C, and D were 55, 49, 46, and 44% of time within 0.5 INR-units from target, respectively. There was no significant difference among the four groups in the per cent within 0.5 INR-units from target ($P = 0.50$) or within 0.75 INR-units from target ($P = 0.70$).

After implementation of the different interventions, group A was 63% of time within 0.5 INR-units from target, group B 60%, group C 57%, and group D 55% (Table 1). There was no significant difference among the four groups in the per cent within the 0.5 target range ($P = 0.13$) or within the 0.75 target range ($P = 0.12$). For both target ranges, the per cent of time in range was significantly higher during the interventions than at baseline ($P < 0.0001$, Table 1). *Figures 2 and 3* present the change per GP-practice from baseline, for the two target ranges, respectively, for each intervention. There is no evidence that the increases from baseline are different between the intervention groups ($P = 0.8$ for the 0.5 target range, $P = 0.9$ for the 0.75 target range).

**Poor compliance of the GPs to the computer generated advice in group D**
The lack of improved performance with computer-generated advice was unexpected (compared with the suspected scenario in the power-analysis). A possible reason could be the ignorance of the computer advice by the GPs. In an attempt to verify this hypothesis, a subanalysis was performed of 764 observations from 129 patients of group D, for whom the data were most complete. Per patient, the average deviation in date of blood sample and the average deviation in dosage have been calculated. The
median for the date deviations equals 7.5 days (IQR = 6.4 days), and the median for the dosage deviations equals 7.1% (IQR = 16.5%). There was a significant negative correlation between the average deviation in days from proposed management and the per cent in target (spearman $-0.285$, $P = 0.001$). There also was a significant negative correlation between the average deviation from proposed dosage and the per cent in target (spearman $-0.217$, $P = 0.015$).

Event rates
The overall incidence of minor bleeding was 12.2 per 100 patient-years (Table 2). The overall incidence of major bleeding was 4.9 per 100 patient-years (three were fatal). The incidence of thrombo-embolic events was 5.94 per 100 patient-years (14 were fatal). Testing for the presence of an event (irrespective the type of event), no significant difference was found in event rate among the four groups ($P = 0.07$).

There was no significant relation between the event rate and hypertension, diabetes mellitus, prior stroke or transient ischaemic attack, congestive heart failure, myocardial infarction, valve disease, smoking habit, peripheral vascular disease, or a history of malignancy. There was a significant positive relation between the age and the frequency of an event ($P = 0.0003$); an increase in risk of 4.5% per supplementary year was found (hazard ratio = 1.045; 95% CI, 1.02–1.07).

Discussion
The clinical purpose of oral anticoagulation is to prevent thrombo-embolic events with minimal bleeding complications. As there is a negative correlation between the adherence to target and the risk for complications, the quality of oral anticoagulation management can be expressed as time within target. This study wanted to improve the quality of oral anticoagulation management.
by the GPs by comparing the effect of different interventions. Implementation of different interventions resulted in a significant increase in per cent of time within 0.5 INR-units and 0.75 INR-units from target. However, there was no significant difference among the four intervention groups. The basic intervention increased the per cent in target range by eight. Patients with a target INR of 2.5 were significantly more in range than patients with a target INR of 3.5. There was no significant difference in event rate among the four groups. Apart from group C, one clinical laboratory performed all INR analyses. In the CoaguChek group, control venous sampling was omitted, in view of previous validation studies of this device and to prevent confusion for the GPs.22,23 A check for a possible inclusion bias of participating GPs (participation rate of 38%) showed no significant difference in distribution \( P = 0.7 \) of the INRs between patients from participating and patients from non-participating GPs, all determined by the same laboratory. It is, however, difficult in this type of studies to exclude a ‘study effect’ as an important contributor to this improved quality.28 Knowing that physician and patient education is important for improving quality, we were, however, surprised that point-of-care testing or computerized dosing support did not give a significant benefit in comparison to multifaceted education and feedback, although a tendency to a higher increase in per cent in target range for the group with the CoaguChek and the group with the computer assisted monitoring was found. Combining these two interventions may lead to a higher per cent in range. Fitzmaurice et al.29 combined the use of the CoaguChek and computer assisted monitoring in a nurse-led anticoagulation clinic in general practice; these authors found a time in range of 69%. In our study, the per cent in range for both interventions separately was 57 and 55%, respectively.

The incidence of major bleeding is comparable with data from a meta-analysis of 33 studies.30 In that study, the incidence of major bleeding was 7.2 per 100 patient-years (95%, CI 7.19–7.24), being highest during the first 3 months of therapy, subsequently decreasing to 2.7 per 100 patient-years (95% CI, 2.71–2.77). In our study, only events after the first 28 days of therapy were included. The incidence of thrombotic events in our study is higher than reported in two available observational studies (ranging from 3.5 to 3.9 per 100 patient-years).5,29 By educating and supplying information on the risk of the anticoagulation therapy, the GPs became more conservative for higher INRs, demonstrated in a significant decrease of the per cent in patients with at least one INR >5. No change in the number of patients with at least one INR <2 was found.

Active education and information booklets improve the quality of GPs clinical handling.20 Our basic intervention was organized respecting Grol’s multifaceted approach of changing clinical practice by focusing on internal and external influences, namely, small group interactive learning, evidence based guidelines with attention for the specific needs of our GPs, team building with a newsletter, and patient oriented interventions. Several studies suggested that feedback with peer comparison improves the clinical practice of GPs.21,31 Sending a questionnaire to all the participating GPs, those who used the CoaguChek were most satisfied with the intervention and its surplus for their practice.32 A discrepancy was found between published and our results with the Dawn AC computer. Poller et al.24 using this program, reached 68% in range for the stabilization period and 70% for the stable period. A possible explanation could be that in our model the computer program was located centrally. In Poller’s study, the computer-generated dose was sent directly to the patients after validation of the protocol by a pathologist. The pathologist adapted 22% of the computer advices. In our setting, the computer protocol, validated by the biologist, was sent to the GPs. The GPs were free to follow the advice. Performing a subanalysis, we found a high non-compliance rate which could be explained by several factors: a lack of confidence in the computer program, GPs autonomy, limitation of the Dawn AC Computer program functioning only at a stable phase and not when the 1.5 > INR > 5, model of organization of the computer assisted advice, etc. The negative correlation between the deviations and the per cent in range indicates that this distrust in the computer program was misguided. If the GP did not follow the computer advice, this had to be communicated to the pathologist and introduced in the program to calculate the next computer advice. However, this elementary communication often was missing because it was considered too time-consuming. In this group, two GP-practices stopped their participation because it was too laborious. It may be preferable to give the GPs direct access to the computer program with a connection to his global patient file to make this model of care more efficient and time saving.

Our conclusions are limited to the studied model of care, namely, GPs organizing the oral anticoagulation management. Other strategies, all intended to reduce dosing and/or monitoring errors for oral anticoagulation, have been organized.33 Outpatient anticoagulation clinics provide

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<th>Table 2: Secondary outcome measures after different interventions</th>
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\( P \) is the value of test for differences between groups A, B, C, and D in prospective part of the study.

*Owing to lack of events, no frailty term has been added in the model.
services that typically include anticoagulation monitoring and follow-up, anticoagulant dose adjustment, and patient education. These clinics are usually run by pharmacists or nurses operating with physician back-up, and sometimes use specific dosing nomograms. Patient self-monitoring is another model of care where the patient performs point-of-care testing and also adjusts the oral anticoagulant therapy using a nomogram.

Conclusions
In conclusion, this study has shown that GPs should be formally trained and supported in the supervision of oral anticoagulation therapy. Multifaceted education has to be provided in the first place. A new model with the CoaguChek and direct access of the GPs to computer-assisted advice could provide a greater benefit. This needs to be tested.

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References