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# Impact of a Pharmacotherapeutic Programme on Control and Safety of Long-Term Anticoagulation Treatment

## A Controlled Follow-Up Study in Spain

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## Abstract

**Background:** In patients undergoing oral anticoagulation treatment, correct control of the international normalized ratio (INR) is necessary. This study sought to assess the effectiveness of a pharmacotherapeutic follow-up programme (PTP) on achieving an optimal INR range, reducing the need for rescue medications and for monitoring the development of possible adverse events associated with poor oral anticoagulation therapy control (haemorrhagic events and thromboembolic disease).

**Objective:** The aim of this study was to evaluate the effectiveness of a PTP targeted at the anticoagulated patient to ensure proper self-control of anticoagulation.

**Methods:** This was a prospective, controlled, multicentre cohort study conducted at four primary care centres in Galicia (northwest Spain), covering a group of patients receiving anticoagulation treatment exposed to pharmacotherapeutic follow-up by a primary care pharmacist (n = 272), and a concurrent control group (n = 460). The intervention consisted of a patient health-education programme plus activities involving collaboration with the physician. The educational intervention exposure period was 12 months (starting from February 2006 and finishing in February 2007), during which time a minimum of one INR determination per month was performed. To assess the quality of haematological control, the British Committee for

Standards in Haematology criteria were used, namely (i) 50% or more determinations per patient within a range of 0.5 units above or below the target INR; and (ii) 80% or more determinations per patient within a range of 0.75 units above or below the target INR. As an indicator of correct control of coagulation, we also assessed the occurrence of oral anticoagulation therapy-related adverse events, such as active bleeding, haematomas (jointly referred to as haemorrhagic events) and thromboembolic events. Depending on the type of response variable, negative binomial regression or Cox proportional risks models were fitted.

**Results:** Compared with the control group, the PTP managed to improve correct INR ranges by (i) 25% (relative risk [RR] = 0.75; 95% CI 0.69, 0.82) in terms of the number of patients who had their determinations within ±0.5 units of the target range; and (ii) 26% (RR = 0.74; 95% CI 0.67, 0.81) in terms of the number of patients who had their determinations within ±0.75 units of the target range. Patients belonging to the intervention group registered a 75% reduction in bleeding (hazard ratio [HR] = 0.25; 95% CI 0.18, 0.36). For every 3.27 patients exposed to the PTP, one event would be prevented (number needed to treat = 3.27; 95% CI 2.73, 4.07).

**Conclusions:** Including patients receiving oral anticoagulant treatment in a PTP enhances INR control, efficacy and safety of treatment, and efficiency of primary healthcare services.

## Background

In recent years, there has been a sharp rise in the number of patients needing oral anticoagulation treatment.[1-3] Oral anticoagulants call for special control, however, as they are drugs with an extremely narrow therapeutic margin.[4-7] Moreover, they are associated with an elevated risk of thrombotic events[8,9] and/or appearance of haematomas and active bleeding (jointly referred to as haemorrhagic events), particularly at a digestive and intracranial level.[3,10] To make these medications safer it is essential that regular monitoring be carried out, by determination of the international normalized ratio (INR) and also by correct self-testing on the part of the patient. This, in turn, calls for proper communication between patients and health staff,[11-13] otherwise INR values may stray outside the appropriate range and therefore increase the risk of events linked to suboptimal or superoptimal anticoagulation.[14-17]

A number of studies have evaluated the role played by health education in oral anticoagulation therapy at a hospital[18-21] and primary care level.[22-28] The current trend is to monitor oral anticoagulation therapy at a primary care level.[29] This is due to the need for an integrated approach to and control of such anticoagulated patients as part of overall improvement in healthcare quality. According to some authors, anticoagulated patients ought to be attended on a coordinated basis by a team that includes at least one pharmacist. Indeed, a pharmacist is fundamental to this kind of team;[18-22,28,30] however, most of the primary care studies undertaken have either been descriptive or presented their results as a comparison between physicians and pharmacists.[31-33] Moreover, we were unable to identify a study that focused on a pharmacotherapeutic follow-up programme (PTP) that included collaboration activities with the patient's physician and compared it with that of routine care.

The overall aim of this study was to evaluate the effectiveness of a PTP targeted at the anticoagulated patient to ensure proper self-control of anticoagulation. As specific objectives, we

considered testing the influence of PTP on achieving an optimal INR range, reducing the need for rescue medications and for monitoring the development of possible adverse events associated with poor control of oral anticoagulation therapy (haemorrhages and thromboembolic disease).

## Methods

This study was conducted at four primary care centres in Galicia (northwest Spain), which serve a population of approximately 45 000, mostly from rural districts. The study period was the 12-month period starting from February 2006 and finishing in February 2007.

### Study Design

This was a prospective, controlled, multicentre, cohort study covering a group that was exposed to follow-up by a primary care pharmacist and a concurrent control group that was not.

Anticoagulated patients at one of the primary care centres all underwent a PTP (the intervention group). Anticoagulated patients at the remaining three centres did not undergo a PTP (the control group). In both the intervention and control groups, a minimum of one INR determination per month was performed on each subject. In all instances, blood specimens were extracted for INR determination purposes, and oral anticoagulant dosage guidelines handed out to patients at the primary care centre.

### Patients

All patients at the designated primary care centres who fulfilled the inclusion criteria were included in the study population. These criteria required patients to (i) be undergoing oral anticoagulation therapy; (ii) have had their anticoagulant dosage adjusted and their original dosage guideline set by the haematology department of the referral hospital; and (iii) have had their blood specimens extracted for INR determination and the ensuing results handed to them at the primary care centre. The following were excluded: (i) any patient who refused oral anticoagulation therapy follow-up by a primary care pharmacist (oral anticoagulation therapy monitoring had to be performed by the haematology department of the referral hospital); (ii) any patient having one or more hospital admissions exceeding 3 months during the follow-up period; and (iii) any patient who had refused to be included in a PTP.

### Pharmacotherapeutic Follow-up Programme

In the pharmacotherapeutic follow-up group, each patient who met the inclusion criteria was given the INR results by the resident primary care pharmacist, who explained the new dosage and performed an individualized patient follow-up. This PTP consisted of a series of activities, some targeting the patient and others aimed at improving pharmacist-physician collaboration.

Patient-targeted activities mostly comprised health-education activities. They were designed to ensure that patients attained the greatest degree of autonomy possible, and understood and developed a self-management attitude, fully aware not only of the dangers posed by variations in the therapeutic range but also of how to act in risk situations. To this end, the primary care pharmacist informed patients, both verbally and in writing, as to the necessity of their treatment, correct dosage and administration, and any adverse reactions; the importance of therapeutic compliance; what to do in the event of omission or oversight; the risks of self-medication; the importance of reporting any change in treatment; and the contraindication of intramuscular injections and certain medications (such as aspirin [acetylsalicylic acid] and anti-inflammatories).

In addition, this programme included activities involving collaboration with the physician, such as (i) choosing treatment for concomitant diseases, in order to decide on a medication that would either not interact with the anticoagulants or, alternatively, not provoke a clinically significant interaction; (ii) bringing forward INR control, in cases of a medication that might interact with the oral anticoagulation therapy being introduced into the patient's pharmacotherapy where no safer treatment was available; (iii) choosing the most patient-friendly oral anticoagulation therapy

dosage forms so as to avoid pills being prescribed in fractions that might entail or lead to error (e.g. pills pre-grooved in quarters that then have to be cut into eighths); and (iv) preventing the combination of more than two different weekly dosages.

### Control Group

We selected a control group that had the same characteristics as the intervention group (rural setting, the time taken to arrive at a reference hospital was similar to that in the intervention group, commencement of primary care oral anticoagulation therapy on the same date, similar haematology protocols, etc.). This group underwent standard oral anticoagulation therapy-related care routinely administered in Galicia.[34,35]

Where the INR result was not within the appropriate range for the patient's condition, it fell to the haematology department at the referral hospital to modify the dosage and to the general practitioner (GP) to inform the patient of the new dosage to be followed. Indeed, the GP was confined to only informing the patient of the new dosage to be taken, rather than making the dose modification themselves.

Where the INR result was within the appropriate range for the patient's condition, he/she was informed of this by a member of staff who was neither a primary care pharmacist nor a physician. These results were handed out, without the patients receiving any supplementary information or being included in any special follow-up programmes. As a consequence, therapeutic compliance was not reinforced; possible complications arising from an under- or overdose in the event of involuntary noncompliance were not foreseen; concomitant diseases, whether newly appearing or resulting from exacerbation of an existing disease, were not recorded; and interactions of any new medications that came to form part of the patient's treatment went unreported.

### Follow-up

At the start of follow-up, the following details were recorded for each patient in both the intervention and control groups: demographic data, indication for oral anticoagulation, pharmacological treatment, target INR range, and anticoagulant and required dosage. Variables such as weight, height, tobacco habit and alcohol consumption were also collected.

At each haematological control visit (minimum of one per month), the INR was determined. Standard laboratory measurement methods were used whereby a specimen was obtained by venipuncture or, alternatively, a specimen of capillary blood was obtained using portable coagulometers for monitoring prothrombin time. Both methods have been validated and the respective INRs are mutually equivalent.[36]

Losses to follow-up were defined as resolution of the disease process for which oral anticoagulation had been prescribed (pulmonary thromboembolism, deep vein thrombosis and/or atrial fibrillation), and death.

### Definition of Variables

To assess the quality of haematological control, the British Committee for Standards in Haematology (BCSH) criteria were used,[37] with the following two variables thus being created for each subject: (i) 50% or more determinations lying within a range of ±0.5 units of the target INR; and (ii) 80% or more determinations lying within a range of ±0.75 units of the target INR.

As an indicator of correct control of coagulation, we also assessed the occurrence of oral anticoagulation therapy-related adverse events, such as active bleeding, haematomas (jointly referred to as haemorrhagic events) and thromboembolic events. While the need to prescribe rescue medications, such as low-molecular weight heparin (LMWH) and/or vitamin K, was used as an indicator of good clinical patient-management, a further variable, namely the number of consultations required to achieve the correct INR value, was defined as an indicator of clinical disease management.

### Statistical Analysis

The sample size was determined by the number of anticoagulated patients who received pharmaceutical care at the primary care centres studied.

We performed a descriptive analysis of the qualitative variables, by means of the number and percentage of the quantitative variables based on quartiles, and the variables of time to appearance of haemorrhagic event estimated using Kaplan-Meier curves.

The hypothesis test was performed by fitting one of the following three types of models according to the type of response variable: (i) where the response variable was dichotomous (e.g. 50% of determinations for any given patient within ±0.5 units of the target range), we applied Cox regression models, which, unlike logistic regression, enable relative risks (RRs) to be estimated; (ii) where the dependent variable was a count variable, such as number of consultations required to control the INR, a negative binomial regression model was used, which, unlike Poisson regression, enables standard errors to be corrected for the overdispersion parameter; or (iii) in the case of response variables for which there could be more than one event across the follow-up period, we used Cox's proportional risks regression models for multiple events.[38] This approach deems every observation for every individual an independent unit of analysis, albeit dependent on explanatory variables. Under such conditions there is no guarantee of the efficiency of the estimates. Consequently, standard errors were robustly estimated by grouping jackknife estimates.[39,40]

To assess whether the results of the models would change if only time to appearance of the first event was taken into account, a complementary analysis was conducted by censuring all subjects at the time of the first event, and applying Cox proportional risks regression models.

To construct all the models, we first performed a bivariate analysis (using the Chi-squared test for comparison of proportions, and the Mann-Whitney U-test for comparison of medians). We then constructed a multivariate model that included all independent variables that had displayed a statistical significance of <0.2 in the bivariate analysis. Independent variables with a higher level of statistical significance were successively eliminated from this model, provided that the coefficients of the principal exposure variables changed by no more than 10%.[41,42] An intent-to-treat analysis was conducted, in which all the p-values considered were two-tailed and $p < 0.05$ was deemed to be significant.

The number needed to treat (NNT) at 1-year of follow up, and 95% CIs for haemorrhagic events were also calculated.

Statistical analyses of the data were performed using the SPSS v15.0 for Windows and R v2.11.0 for Windows software programmes. The results were expressed as hazard ratios (HRs) with their 95% CIs, or risk ratios (RR) with their 95% CIs, depending on the model.

The study was formally authorized by the Primary Care Authority Research Committee corresponding to the area in question.

## Results

At the outset, there were 754 study subjects (279 in the intervention group and 475 in the control group). Of these, 7 in the intervention group and 15 in the control group were excluded because of hospitalization of over 3 months during follow-up. Across the study, 32 patients in the intervention group and 20 in the control group were lost to follow-up. Overall, a total of 732 patients were studied, 272 in the intervention and 460 in the control group.

Table I gives a breakdown of the main characteristics of patients in the intervention and control groups. Distribution by sex, age, weight, tobacco habit and indications for anticoagulation proved similar in both groups. There were differences, however, in body mass index (BMI) and alcohol consumption. The most common indication for anticoagulation was atrial fibrillation (84.6% in the intervention group vs 80.9% in the control group; $p = 0.122$). Insofar as acenocoumarol dosage forms were concerned, 86% of patients in the intervention group versus 95% in the control group were receiving treatment with acenocoumarol 4 mg ($p < 0.01$).

Among the reasons for stopping treatment, there were 8 patients (2.9%) who died in the intervention group and 11 (2.4%) in the control group ($p = 0.40$). The disease disappeared in 2 patients in the intervention group (0.7%) and 3 (0.7%) in the control group ($p = 0.61$). No statistically significant differences were observed between the two

**Table I.** Clinical and demographic characteristics of patients requiring oral anticoagulation treatment

| Variables | Intervention [n (%)] (n = 272) | Control [n (%)] (n = 460) | p-Value |
|---|---|---|---|
| Sex | | | |
| male | 142 (52.2) | 213 (46.3) | 0.071[a] |
| female | 130 (47.8) | 247 (53.7) | |
| Age [y] | 74 (69, 80)[b] | 74.5 (68, 80)[b] | 0.506[c] |
| Weight [kg] | 70 (65, 78)[b] | 72 (62, 81)[b] | 0.210[c] |
| Height [cm] | 164 (156, 170)[b] | 158.5 (152, 166)[b] | <0.01[c] |
| Body mass index | 26.6 (24.8, 27.8)[b] | 28 (25.87, 30.47)[b] | <0.01[c] |
| Tobacco habit | | | |
| smoker | 15 (5.5) | 25 (6.0) | 0.472[a] |
| non-smoker | 257 (94.5) | 394 (94.0) | |
| Alcohol consumption | | | |
| consumer | 176 (64.7) | 230 (54.9) | <0.01[a] |
| non-consumer | 96 (35.3) | 189 (45.1) | |
| Indication for oral anticoagulation therapy | | | |
| atrial fibrillation | 230 (84.6) | 372 (80.9) | 0.122[a] |
| deep vein thrombosis | 10 (3.7) | 23 (5.0) | 0.261[a] |
| pulmonary thromboembolism | 8 (2.9) | 16 (3.5) | 0.436[a] |
| biological valvular prosthesis | 9 (3.3) | 8 (1.7) | 0.134[a] |
| mechanical valvular prosthesis | 23 (8.5) | 32 (7.0) | 0.273[a] |
| other indications[d] | 41 (15.1) | 48 (10.4) | 0.042[a] |
| Oral anticoagulation therapy dosage forms | | | |
| acenocoumarol 1 mg | 11 (5.5) | 9 (4.5) | 0.077[a] |
| acenocoumarol 4 mg | 234 (86) | 437 (95) | <0.01[a] |
| warfarin 1 mg | 24 (8.8) | 11 (2.4) | <0.01[a] |
| warfarin 3 mg | 0 (0) | 1 (0.2) | 0.628[a] |
| warfarin 5 mg | 2 (0.7) | 2 (0.4) | 0.475[a] |

a Chi-squared.

b Median (25th percentile, 75th percentile).

c Mann-Whitney U-test.

d Other indications included antiphospholipid syndrome, acute cerebrovascular accident, stroke, transitory ischaemic attack, hypertrophic myocardiopathy, aortic valvulopathy (without valve replacement), mitral stenosis, heterozygotic factor V Leiden mutation, ascending aorta aneurysm and acute myocardial infarction.

groups in terms of these reasons for stopping treatment. Significant differences were nevertheless observed in terms of appearance of contraindications as a reason for stopping oral anticoagulation therapy, i.e. such contraindications appeared in 12 patients (4.4%) in the intervention versus 6 (1.3%) [p = 0.01] in the control group.

Table II shows the effect had by the PTP on the different response variables. The intervention group was observed to improve by 25% (RR = 0.75; 95% CI 0.69, 0.82) in terms of the number of patients who had their determinations within ±0.5 units of the target range, and by 26% (RR = 0.74; 95% CI 0.67, 0.81) in terms of the number of patients who had their determinations within ±0.75 units of the target range.

The incidence of adverse events, i.e. haemorrhages (active bleeding or haematomas) and thromboembolic events, is shown in table III. Figure 1 depicts the Kaplan-Meier estimate of the cumulative incidence of haemorrhages. In the case of thromboembolic events, however, the fact that only nine patients in the control group and only one in the intervention group had had such

an event rendered analysis impossible. The control and intervention groups displayed statistically significant differences for both types of events. The Cox proportional risk regression model for multiple events showed that patients belonging to the intervention group had a 72% reduction in hazard of a haemorrhage (HR = 0.28; 95% CI 0.20, 0.40). A hazard analysis was also performed using the Cox proportional risk regression model for single events. Time to appearance of the first haemorrhagic event was calculated, and patients belonging to the intervention group were observed to have a 75% relative risk reduction of experiencing this first haemorrhagic episode (HR = 0.25; 95% CI 0.18, 0.36).

Moreover, the PTP managed to achieve an 8% reduction (odds ratio [OR] = 0.92; 95% CI 0.88, 0.96) in the number of medical consultations required to maintain individual patients' INR within the correct range. Similarly, there was a reduction in the number of times that the dose had to be adjusted (OR = 0.92; 95% CI 0.78, 1.08), i.e. in the form of an 8% reduction in the number of times needed to adjust the dose to prevent adverse drug effects, although this difference was not statistically significant (p = 0.34).

We likewise observed that the educational intervention achieved a 5-fold reduction (HR = 0.20; 95% CI 0.13, 0.32) in the need to use rescue medications, such as LMWH or vitamin K, for the treatment of persons who presented with an adverse effect (table III).

When we calculated the number of individuals who had to be included in a PTP to prevent a haemorrhagic event, we obtained an NNT of 3.27 (95% CI 2.73, 4.07) for 1-year of follow-up.

## Discussion

Our study indicates that the inclusion of oral anticoagulation therapy patients in an intensive PTP improves the number of patients with a correctly controlled INR by 25% and reduces the risk of having haemorrhagic events by around 4-fold. According to these data, the number of individuals who had to be included in an anticoagulated patient PTP to prevent a haemorrhagic event (NNT) was 3.27 (95% CI 2.73, 4.07) for 1-year of follow-up, a finding that suggests that these types of programmes may well be of great clinical and healthcare importance.

The magnitude, observed in our study, of the effect of applying a PTP to anticoagulated patients is clinically significant, not only for achieving correct control of the INR (RRs approximately 0.75) but also for preventing haemorrhagic events (NNT = 3.27). Purely in terms of the BCSH criteria,[37] the differences could be explained in part because there were 13% of INR determinations ±0.5 units outside the range in the control group versus only 0.7% in the intervention group. Comparison of these findings with those obtained in other studies is complex because the majority of studies[31,43] used other criteria, i.e. the American College of Chest Physician standards.[44]

It might be thought that the high clinical impact found in our study (NNT = 3.27) was caused by inadequate treatment of the control group

**Table II.** Effect of pharmacotherapeutic follow-up programme on quality of haematological control

| Dependent variable | Intervention [n (%)] | Control [n (%)] | Univariate effect measure [RR (95% CI)] | Multivariate effect measure[a] [RR (95% CI)] | p-Value |
|---|---|---|---|---|---|
| Patients with 50% or more INR determinations within a range of ±0.5 units of target INR[b] | 270 (99.3) | 400 (87.0) | 0.69 (0.64, 0.76) | 0.75 (0.69, 0.82) | <0.001 |
| Patients with 80% or more INR determinations within a range of ±0.75 units of target INR[b] | 270 (99.3) | 395 (85.9) | 0.67 (0.62, 0.74) | 0.74 (0.67, 0.81) | <0.001 |

a All models were assessed for possible confounding due to age, sex, height, weight, oral anticoagulation treatment dosage (mg/week), body mass index, tobacco habit, alcohol consumption, atrial fibrillation, deep vein thrombosis, pulmonary thromboembolism, presence of biological valvular prosthesis, presence of mechanical valvular prosthesis, and other factors.

b Analysis by Cox's proportional risk regression.

**INR** = international normalized ratio; **RR** = relative risk.

**Table III.** Effect of pharmacotherapeutic follow-up programme on clinical management

| Dependent variable | Intervention [n (%)] | Control [n (%)] | Univariate effect measure [HR (95% CI)] | Multivariate effect measure[a] [HR (95% CI)] | p-Value |
|---|---|---|---|---|---|
| Patients with haemorrhagic events[b] | 35 (12.9) | 200 (43.5) | 0.28 (0.20, 0.39) | 0.28 (0.20, 0.40) | <0.001 |
| Patients with thromboembolic disease events[b] | 1 (0.4) | 9 (1.9) | | | |
| Patients for whom rescue medication used[b] | 23 (8.5) | 151 (32.8) | 0.22 (0.14, 0.35) | 0.20 (0.13, 0.32) | <0.001 |

a All models were assessed for possible confounding due to age, sex, oral anticoagulation treatment dosage (mg/week), body mass index, tobacco habit, alcohol consumption, weekly dose, atrial fibrillation, deep vein thrombosis, pulmonary thromboembolism, presence of biological valvular prosthesis, presence of mechanical valvular prosthesis, and other factors.

b Analysis by Cox's proportional risk regression.

**HR** = hazard ratio.

(usual care). However, when the incidence of total haemorrhages in the control group (43% per year) is set against the incidence found in the control groups of other studies, it will be observed that the incidence in our patients was much lower than Jackson et al.[43] (36% in 3 months) and Chiquette et al.[31] (70 per 100 patient-years). Hence, the NNT that could be calculated from the data in the studies by Jackson et al.[43] and Chiquette et al.[31] are 4.8 in 3 months and 2.33 per year, respectively. Both figures are even lower than those reported in our study. This indicates that we are faced with a field of clinical activity where improvement could be achieved and where correct disease management could lead to advantages in settings as diverse and far apart as Spain (our study), Australia[43] and Texas (USA).[31]

Another factor that could have had a decisive impact on the effectiveness of this intervention is the PTP design. Our PTP entailed two types of activities, namely health-education activities for anticoagulated patients, and pharmacist-physician collaboration activities. Factors that differentiated the PTP from other possible programmes included the following: (i) the pharmacist's profile, in that she was a doctor of pharmacy and a specialist in hospital pharmacy practice who had undergone clinically-based residency training and who, prior to initiating the PTP, had received specific complementary training in haematology; (ii) coordination with hospital haematology department; (iii) coordination with the remaining members of the primary care team; (iv) allocation of a specific consulting room to anticoagulated patients where they could settle any doubts regarding their anticoagulant therapy or other treatments and report any therapy-related incidents (commencement of new treatment, appearance of haemorrhages, etc.) to the primary care pharmacist, who could be contacted at all times; and (v) designation of a single person, the primary care pharmacist, to act as the oral anticoagulation therapy reference point for the rest of the primary care and haematology team, a strategy that served to speed up both the process and the resolution of medical consultations (for further information on the activities involved in the PTP, and implications of both professionals and patients in the programme, please see Appendix I, Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A48).

Comparing our intervention to other studies is difficult because each study adapted its intervention to its own characteristics, i.e. environmental, health-delivery system, available resources and the intervention provider's educational background and communication abilities. Intervention intensity would seem to be crucial. It will be seen that in the two studies that had the greater effect (ours and Jackson et al.[43]), the interventions were also the more intensive ones. In the study by Jackson et al.,[43] patients received a home visit by the project pharmacist 4 days after discharge from hospital. In contrast, less intensive interventions, such as those based on telephone calls and mail,[22] achieved a lower effect magnitude.

A meta-analysis[45] of the effectiveness of pharmacist-led warfarin-therapy management has recently been published. This study provides effect measures stratified by study design (randomized vs

non-randomized controlled trials), comparison group (physician, nuclear) and quality of non-randomized studies. For bleeding variables, the effect observed was slightly greater in randomized controlled trials than in observational studies (RR = 0.51; 95% CI 0.28, 0.94 vs 0.71; 95% CI 0.52, 0.96). However, stratification by variables, such as coordination between physicians and pharmacists, type of intervention or intervention intensity indicators, is missing in this meta-analysis.

Insofar as better INR control and a reduction in hemorrhagic events are concerned, the findings of our study are coherent with a decrease in the number of medical visits needed to maintain each patient's INR within the desired range and, by extension, the number of INR determinations needed per patient.[46,47] The effect of these two variables, although statistically significant, is probably less relevant from a clinical point of view since the reductions found were in the order of 8%. Finally, the PTP was likewise associated with a reduction in the use of rescue medications.[14-17]

The principal limitation of our study was the lack of random distribution in the allocation to groups. To offset this, we controlled for possible variables (alcohol, tobacco and BMI) that were not balanced and could have been associated with worse anticoagulation control.[48-52] It will be seen that the results of both the raw and adjusted analyses are very similar. This indicates that, even though statistically significant intergroup differences are observed, the effect is not relevant compared with that of the primary care pharmacist. Adjustment could not be made for patient comorbidities, such as diabetes mellitus or arterial hypertension, or for other potential confounding variables, such as dietary habits, owing to a lack of records. While this amounts to a limitation on our study, we nevertheless feel that the effects found were not due to a failure to adjust for these variables. It is highly unlikely that the unmeasured variables in both groups would differ by a wide enough margin to account for an effect magnitude as great as that observed by us.

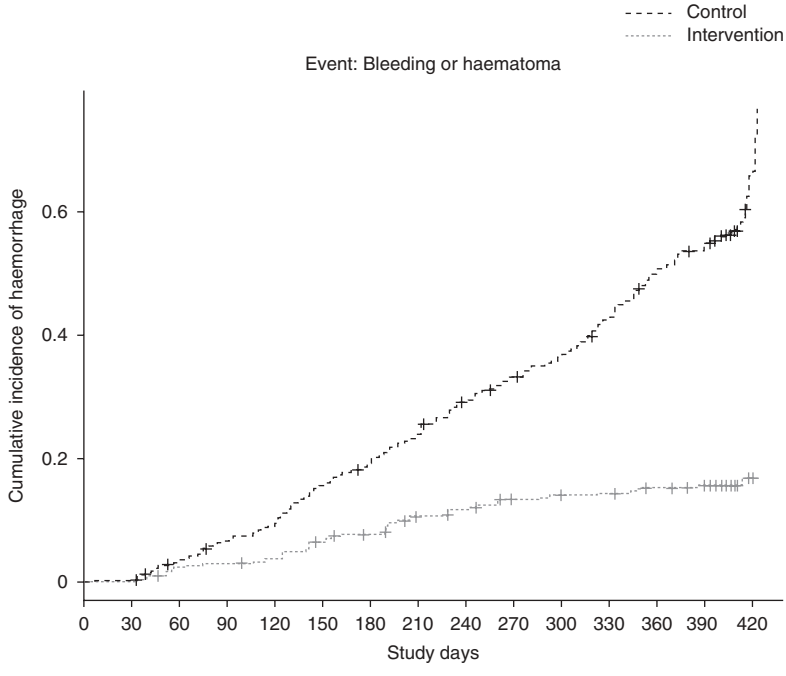


**Fig. 1.** Kaplan-Meier estimate of the cumulative incidence of haemorrhage in the control and intervention groups, taking into account that each patient could experience more than one event during the study period.

Moreover, some risk of selection bias or the presence of systemic characteristics might be thought to exist between the patients who were and those who were not exposed to the intervention. Nevertheless, the control and intervention samples comprised all patients at the designated primary care centres who were on oral anticoagulant treatment at the time. It should be stressed that we selected a control group that had the same characteristics as the intervention group (rural setting, the time taken to arrive at a reference hospital was practically identical to that in the intervention group, commencement of primary care oral anticoagulation therapy on the same date, similar haematology protocols, etc.). No different clinical characteristics were observed between the control and intervention groups, nor was any pre-selection made on the basis of such differences.

A further study limitation is the fact that we were unable to estimate the costs of the programme for the purpose of conducting a cost-effectiveness analysis as this would have called for a different type of study design.

## Conclusions

This study shows that the inclusion of patients with oral anticoagulant treatment in specific and intensive PTPs improves control of their INR, and thus increases the efficacy of treatment and considerably reduces the risk of appearance of adverse events associated with oral anticoagulation therapy control. With respect to the extrapolation of the results obtained, we feel that these types of programmes could be useful in other settings[43] and could even be implemented by other primary or specialized health professionals and therefore achieve better INR control in this increasingly large group of patients.

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