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Effect of computer-aided management on the quality of treatment in anticoagulated patients: a prospective, randomized, multicenter trial of APROAT (*Automated PRogram for Oral Anticoagulant Treatment*)

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Background and Objectives. We carried out a prospective, randomized trial to test whether a computer-based decision support system to initiate and maintain oral anticoagulant (OA) treatment can improve the laboratory quality of therapy.

Design and Methods. Two separate sets of patients on oral anticoagulants, in five Italian anticoagulant clinics, were studied: 335 patients in the first three months of treatment (stabilization phase), 916 patients (775 patient-years) beyond the third month of treatment (maintenance phase). Patients were randomized to a computerized system, which included algorithms able to suggest OA dosing and to schedule appointments (computer-aided dosing) or to an arm in which OA were prescribed by the same teams of expert physicians without such algorithms (control group). Primary outcomes were: A) the percentage of patients reaching a stable state of anticoagulation during each of the first three months of treatment; B) the percentage of time individuals spent within the aimed therapeutic range (maintenance phase).

Results. Patients in the computer-aided dosing group achieved a stable state significantly faster ($p<0.01$) and they spent more time within the therapeutic range during maintenance ($p<0.001$) than controls. The favorable effect of computer-aided dosing was mainly due to a reduction of the time spent below the therapeutic range and was associated with an increase of mean INR value, of anticoagulant drug dosage, and with a reduction of the number of appointments per patient (all changes significant: $p<0.001$).

Interpretation and Conclusions. The computer decision-aided support improves the laboratory quality of anticoagulant treatment, both during long-term maintenance and in the early, highly unstable phase of treatment, and it also significantly reduces the number of scheduled laboratory controls.

Key words: oral anticoagulant therapy, computer-aided management, treatment quality

The number of patients receiving oral anticoagulant drugs (OA) has been constantly increasing during the last ten years, due to both more extensive indications for common diseases, such as atrial fibrillation, and safer treatment deriving from the use of the ISI-INR system for laboratory controls. As a consequence of the relatively narrow therapeutic window of OA and the very large individual difference in sensitivity to these drugs, satisfactory management of long-term oral anticoagulant treatment (OAT) still remains a difficult task.[1,2] Relevant help could stem from the use of computers. Mathematical models, usually derived by the regression analysis of prothrombin times or Thrombotest values against time following the loading dose of anticoagulant (mainly warfarin), able to predict the maintenance dose, had already been elaborated more than 20 years ago, particularly in the UK.[3-7] Notwithstanding the promising results obtained in a few pilot studies, these models were not widely applied until very recently, following the diffusion of informatics in medicine and the lowering of costs of personal

computers. The use of a computer has been shown to have a favorable impact in this field, as in many other fields of medical practice,[8] by the availability of specialized databases, direct link with laboratory testing, printing of personalized prescriptions, and scheduling the appointments for follow-up. In the last decade, a few specific software programs have also been developed for the management of OAT, implementing algorithms useful for supporting the therapeutic decision of physicians in charge. The first favorable experiences on dedicated software was obtained in 1977 by the Dutch Thrombosis Service;[9,10] however this software needed an expensive mainframe calculator and was developed for only one OA drug (phenprocumon). More recently, several other computer programs have been proposed to support dosing decisions, almost exclusively for warfarin,[11] using sophisticated algorithms based on complex pharmacokinetic and pharmacodynamic considerations. Some of them have been evaluated in the clinical context, mainly with good results,[12-17] but on small numbers of patients.

A software program (*PARMA = Program for Archive, Refertation, and Monitoring of Anticoagulated patients*) was developed in Italy in 1985.[18] It has been progressively modified as a tool to help the management of anticoagulated patients. It is now widely used by anticoagulant clinics in Italy on the basis of good results observed in local experiences.[19-21] A formal trial on this software was planned by the *Italian Federation of Anticoagulant Clinics* (FCSA) to compare the effects on the laboratory quality of treatment obtained with a computer-aided dosing of OA with those of experienced medical staff in some of the federated anticoagulant clinics.

Design and Methods

Aims

The main objective of this study was to assess the impact on the quality of OAT of using computer-aided dosing of OA (which includes an algorithm able to suggest the doses of OA and to schedule the follow-up appointments) *versus* the same computer program in which no algorithm helping drug prescription was present. Patients starting treatment, who are usually unstable, and patients on long-term therapy, who are usually in a stable condition, were considered separately. In the long-term therapy group the primary end-point was the percentage of time spent by the single patient in the scheduled therapeutic range. Some other parameters, such as the number of appointments per patient, the dosage of anticoagulant drug, the average value of INRs, were also taken as secondary end-points. In the starting treatment group, (i.e., during the first three months of OAT), the main end-point was the time required to achieve a *stable condition*, i.e., three consecutive INR values within the scheduled therapeutic range obtained at least one week from each other. The average time spent within the therapeutic range limits was also considered as a secondary end point.

Subgroup analyses were performed in both groups, based on the administered drug (acenocoumarol or warfarin), and on the target anticoagulation level (high or low, see below).

Design

Patients were randomized into two arms.

1. Group C (computer-aided dosing): patients assigned to this group were monitored with the use of the algorithms of the PARMA program. The final decision about the prescription and the schedule of follow-up appointments was left to the experienced physician of the anticoagulant clinic, who was free to accept or to modify the computer suggestions.

2. Group M (manual): in this group the computer was used only to file and analyze patient's data, but the algorithms for suggesting OA dosage and for scheduling the follow-up appointments were not active (not installed). Therefore, the physician of the anticoagulant clinic had to decide the drug dosage and to schedule the next follow-up with only the help of the on-screen database.

Centers

Five anticoagulant clinics, all federated with the FCSA (*Italian Federation of Anticoagulation Clinics*), participated in the study. Each anticoagulation clinic follows-up more than 1,000 patients and has a staff of physicians who had a structured training and at least five years of experience in this field.

Patient selection

Enrollment of patients started in December 1996 and ended in December 1997. All patients gave informed consent to participate in the study. Patients were enrolled independently of their age, sex, indication for OAT, targeted therapeutic range and expected duration of treatment. To reach a statistically significant sample size, each Center randomized between 80 and 100 patients for each of the two groups during the enrollment period.

The two following categories of patients were considered eligible for the study:

1. Group 1: patients starting OAT (stabilization phase). Each patient was enrolled before his or her second control appointment, and was followed-up

for at least three months. These patients were consecutively recruited, from among those eligible and who accepted to participate, starting from January 1997. The total number of patients in this group was 335.

2. Group 2: patients on long-term OAT (maintenance phase), who had been taking OAT for more than 3 months before enrollment. These patients were randomized in the last two weeks of 1996, and were followed-up for one whole year (1997). Ninety-five out of the 335 patients enrolled in group 1, with clinical indications for a long-term OAT, were also included in group 2 after the conclusion of the first three months of treatment, and monitored for one year. The total number of patients in this group was 916 (for a total of 775 patient-years).

To increase the comparability of results among the anticoagulation clinics, the use of only two separate therapeutic ranges was suggested:

- *Low Intensity* = INR 2.0 to 3.0; target value 2.5. Patients with deep venous thrombosis/pulmonary embolism, atrial fibrillation, heart valve disease, biological valve prosthesis.
- *High Intensity* = INR 3.0 to 4.5 ; target value 3.5. Patients with a mechanical heart valve prosthesis, coronary or other arterial disease.

The great majority of patients were set within these two categories, but a minority of patients had personalized therapeutic intervals set by the physician in charge. A cut-off point of 2.8 for the target INR was retrospectively considered more appropriate to discriminate clearly between high and low treatment intensity, and it was applied in the subsequent stratification.

Laboratory methods

Prothrombin time (PT) tests, expressed as INR, were performed in all Centers using the same reagent/instrument combination, namely, human recombinant thromboplastin (Recombiplastin™, Instrumentation Laboratory, Milan, Italy), and a MLA1800 Coagulometer™ (IL, Milan, Italy). All the participating centers performed regular external quality control exercises, as programmed by the FCSA (mandatory condition to be included in the Federation). The results were good for all Centers at every exercise.

Software

The PARMA system (release 3.2) mainly consists of a dedicated database, including a single file for each patient, protected for different access levels and customized by some specialized features to help the practice of oral anticoagulant treatment. Essential records of patients' demographic, clinical and follow-up data are available for easy on-screen consultation. At the end of the routine procedure, a personalized prescription sheet is printed for each patient, containing the INR result, the daily dose of anticoagulant drug and the date of the next follow-up. The program also includes a system of data processing meant to assess the laboratory quality of OAT automatically, as well as several statistical facilities.

An algorithm automatically proposing the dosage of OA for each of the two oral anti-coagulant drugs on the market in Italy (acenocoumarol or sodium warfarin) is included. This algorithm was derived from a series of logical tests, allowing screening of those patients in whom a confirmation of previous dosage was indicated. For relatively unstable or out-of-range patients, mathematical models, mimicking the habits of expert medical teams, were used to define an algorithm which is able to suggest an appropriate change of OA dosage. A feature capable of automatically suggesting the (first) maintenance dose following the priming dose was also developed and included in the PARMA program, based upon the individual biological response to the drug loading dose (see *Appendix* for more details).

Statistics

Data from all the participating Centers were sent to the co-ordinating Center in Parma, where all calculations and analyses were performed. The demographic and baseline clinical characteristics of the patients in the two groups considered were compared by means of parametric (Student's t-test) or non-parametric (chi-squared) tests, as appropriate (STATISTICA for Windows, Ver. 4.5, Statsoft Inc., 1993). The quality of treatment was evaluated by means of the percentage of time (days) spent by each patient within the therapeutic range, measured by the *step method* proposed by Rosendaal *et al.*[22] The results, expressed as patient days spent within or outside (i.e., over plus under) the therapeutic range for both experimental groups (computer versus manual), were plotted in a two by two contingency table and the difference was analyzed by the chi-squared test.

The time needed to achieve a stable state in the group of patients starting treatment was calculated considering the number of days elapsed from the day of the second appointment to the first day of the period in which a stable condition was achieved. This condition was considered to have been reached when three consecutive values of INR within the aimed range limits were obtained at

least one week apart from each other, following the method proposed by Peterson *et al.*[23] The percentage of patients achieving this stable condition during the first, second and third month was the parameter finally used. Differences due to computer-aided dosing were analyzed by a non-parametric (chi squared) test.

Results

Checking the effects of randomization

Patients studied in the two main groups, i.e., computer-aided and manual, were not significantly different for age, gender, anticoagulant drug, clinical diagnosis, indication for and duration of OAT, and target INR (Table 1).

A total of 1,358 patients were recruited (Table 1). During the induction phase, 145 patients were randomized to the computer group (C) and 190 to the manual (M) one; 458 patients were randomized during the maintenance phase in each of these groups, and they were followed-up for an equal period of time (387.1 patient-years in group C, and 387.4 in group M).

Effect of computer-aided dosing on outcomes

Induction phase. In the first phase of treatment, patients in group C reached a stable state significantly earlier (39% in the first month) than patients in group M (27%; $p<0.01$). Seventy-three percent of patients in group C *versus* 57% of patients in group M achieved a stabilized state within the first two months ($p<0.05$, Figure 1). Moreover, during the three months follow-up, patients in group C spent more time within the therapeutic range than patients in group M (Table 2), with highly significant differences for the figures considering all the three-month period ($p<0.001$, last row in the table). Similar differences ($p<0.001$, last column) were also present during the first two months, when these periods were examined separately, while during the third month the difference between group C and group M was not significant. Several patients randomized in the induction phase study (46 out of 145 in group C, and 49 out of 190 in group M) were followed for one year. Patients in group C continued to spend more time within the

Table 1. Baseline and follow-up data of patients.

Characteristic	A - Induction phase Computer	Manual	Total	B - Maintenance phase Computer	Manual	Total
Demographics						
All patients, n (male%)	145 (57%)	190 (57%)	345 (57%)	458 (54 %)	458 (54 %)	916 (54 %)
Age, mean (SD)	67.9 (14.2)	68.8 (12.3)	67.8 (13.1)	66.9 (13.1)	66.7 (12.5)	66.8 (12.7)
(Patients, n/Center)						
Center A	71	77	148	101	99	200
Center B	28	23	51	103	98	201
Center C	18	25	43	99	102	201
Center D	27	51	78	71	71	142
Center E	3	14	17	84	88	172
Indications (%):						
Venous thromboembolism	41	41	41	14	13	14
Non-ischemic heart disease(*)	39	36	37	26	32	28
Arterial disease	16	19	18	30	27	29
Heart-valve prosthesis				21	19	20
Other diagnosis	4	4	4	9	9	9
Follow-up						
TOTAL (Patient years)	31.3	40.0	71.3	387.1	387.6	774.7
Drug						
Warfarin (Patient years)	18.4	26.1	44.5	258.3	260.7	519.0
Acenocoumarol (Patient years)	12.9	13.9	26.8	128.8	126.9	255.7
INR Target						
Low (Patient years)	31.3	40.0	71.3	246.7	249.9	496.6
High (Patient years)	–	–	–	140.4	137.7	278.1

**Most of patients in this group had non-valvular atrial fibrillation.*

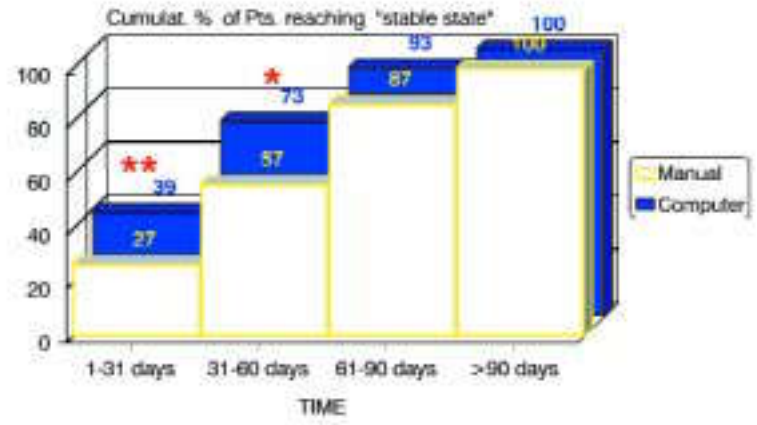

Figure 1. Cumulative percentages of patients reaching a *stable state* (= at least 3 INR values within therapeutic range at a week from each other) during each of the first three months of OAT. Significant differences in favor of the computer-dosing group for the first (p<0.01) and the first plus second month (*p<0.05).**

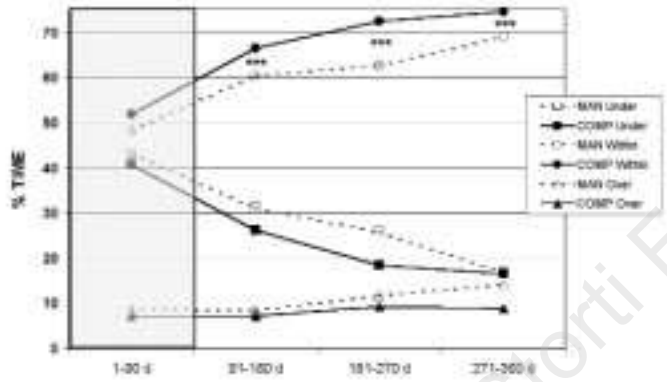

Figure 2. Time spent in the three degrees of anticoagulation by patients followed from the start of treatment for one year (total number 95). The differences in favor of the COM (Computer aided dosing) group versus the control (MANual) group persisted at a high level of statistical significance (*p<0.001) for all the follow-up time.**

therapeutic range, than patients in group M, throughout this maintenance phase, as shown in Figure 2. A significant difference (p<0.001) was indeed recorded at the statistical analysis in each single quarter.

Maintenance phase. In the maintenance phase, in which an overall number of 15,249 follow-ups were considered (7,487 in group C, and 7,762 in group M) during a total of 775 patient-years (387.1 for group C, and 387.6 for group M), the computer-aided dosing with the algorithms included in the PARMA system proved to be effective, as shown in Table 3, in which the overall values for all the period are recorded. Patients in group C spent significantly more time within the therapeutic range than patients in group M (71.2% versus 68.2%). There was also a significant difference in the percentage of time spent within the therapeutic range for each of the drug groups (warfarin: C = 72.5% vs. M = 70.5%; acenocoumarol: C = 68.7% vs. M = 63.5%), as well as for INR target groups (high: C = 70.6% vs. M = 68.2%; low: C = 71.6% vs. M = 68.3%) as shown in Table 3. All these differences were highly significant (p<0.001) at the statistical analysis. The advantage for group C was mainly due to a reduction of the time spent below the therapeutic range in all patients, as well as in the subgroups examined.

The longer period of time spent within the therapeutic range by the patients in group C (p<0.001) was also confirmed in a separate analysis of single quarters (from the 1st to the 4th) during the one-year of follow-up, as referred to the total number of patients (columns furthest right in Tables 4 and 5). Table 4 also shows that the time spent within the therapeutic range by patients treated with either warfarin or acenocoumarol was significantly longer for patients in group C. A similar pattern for subgroups is shown in Table 5, in which the two different INR target groups were separately examined.

Some of the secondary outcomes of the study are shown in Table 6. The improvement in treatment quality obtained by the algorithms included

Table 2. Induction phase % of time spent in/out of range.§ Single months, drugs.

Period (pts/yr)	Warfarin (n = 44.5 pts/yr)			Acenocoumarol (n= 26.8 pts/yr)			Total [both drugs] (n= 71.3 pts/yr)		
	C	p*	M	C	p*	M	C	p*	M
1st Month (n= 25.3)									
Under^	45.8		43.0	38.7		43.8	43.0		43.2
Within^	46.5	ns	45.4	48.9	°°°	41.1	47.4	°°°	44.0
Over^	7.7		11.6	12.4		15.1	9.6		12.8
2nd Month (n= 24.2)									
Under^	43.9		47.2	41.3		51.6	42.8		48.7
Within^	51.5	°°	47.3	50.5	°°°	41.3	51.1	°°°	45.2
Over^	4.6		5.5	8.2		7.1	6.1		6.1
3rd Month (n= 21.8)									
Under^	33.9		35.2	38.7		40.1	36.0		37.0
Within^	60.2	ns	57.7	54.7	ns	54.2	57.8	ns	56.4
Over^	5.9		7.1	6.6		5.7	6.2		6.6
Total (All months) (n= 71.3)									
Under^	41.6		42.2	39.6		45.3	40.8		43.3
Within^	52.2	°°°	49.6	51.4	°°°	45.3	51.9	°°°	48.1
Over^	6.2		8.2	9.0		9.4	7.3		8.6

*C: computer; M: manual. ^% time spent/range; *χ^2 statistics, 2×2 contingency tables (within range versus under+over; Computer versus Manual). Statistical significance for the difference Computer versus Manual: ns = p >0.05; °p < 0.05; °°p < 0.01; °°°p < 0.001. §Data for statistical computing were entered as absolute time spent by patients in the single quality classes but, in order to simplify data exposition, only the percentages (of patient time) are reported in the table (see Design and Methods for details).*

Table 3. Maintenance phase: % of time spent in/out of range.§ Total (one year) results.

Target INR (pts/yr)	Warfarin (n = 519.0 pts/yr)			Acenocoumarol (n= 255.7 pts/yr)			Total [both drugs] (n= 774.7 pts/yr)		
	C	p*	M	C	p*	M	C	p*	M
High (≥2.8 INR) (n = 278.1)									
Under^	19.4		21.6	28.5		31.8	22.7		25.5
Within^	73.9	°°°	72.8	64.6	°°°	61.0	70.6	°°°	68.2
Over^	6.7		5.6	6.9		7.2	6.7		6.3
Low (<2.8 INR) (n = 496.6)									
Under^	16.6		18.1	17.8		21.5	17.0		19.1
Within^	71.7	°°°	69.5	71.3	°°°	65.3	71.6	°°°	68.3
Over^	11.7		12.4	10.9		13.2	11.4		12.6
All Targets (n = 774.7)									
Under^	17.5		19.3	22.0		25.8	19.0		21.4
Within^	72.5	°°°	70.5	68.7	°°°	63.5	71.2	°°°	68.2
Over^	10.0		10.2	9.3		10.7	9.8		10.4

*C: computer; M: manual. ^% time spent/range; *χ^2 statistics, 2×2 contingency tables (within range versus under+over; COMPUTER versus MANUAL). Statistical significance for the difference Computer versus Manual: ns = p > 0.05; °p < 0.05; °°p < 0.01; °°°p < 0.001. §Data for statistical computing were entered as absolute time spent by patients in the single quality classes but, in order to simplify data exposition, only the percentages (of patient time) are reported in the table (see Design and Methods for details).*

in the PARMA system during the maintenance phase caused a significant reduction of the follow-ups needed per patient-year, in both the INR target subgroups (high: C = 18.4 versus M = 19.4; low: C = 15.6 vs. M = 16.3; p<.001), and with both the anticoagulant drugs (p<0.001). The longer time spent by patients of the high INR target subgroup in the therapeutic range with the computer-aided dosing was also associated with significantly larger amounts of drug prescribed, both of warfarin (C = 33.3 mg/week vs. M = 31.3 mg/week; p <.001), and acenocoumarol (C = 19.2 mg/week vs. M = 17.8 mg/week; p<0.01). Surprisingly, there was no significant difference between the doses prescribed in the low INR range subgroups.). Finally, there was an excellent agreement between the algorithm suggestions and the physicians' final decisions (in more than 80% of occurrences the experienced physician accepted the computer suggestions).

Discussion

Previous studies had already proved the possibility of predicting short term warfarin requirements from the correlation with the initial response to a loading dose, by using different algorithms and measuring their precision through different parameters.[4,6,7,11]

The results obtained in the present study prove that in the phase of stabilization patients in the computer-aided dosing group reached a stable state significantly faster than patients in whom OA dosage was decided by experienced physicians without the help of the computer algorithms. Similar results were obtained in a recent international collaborative study (ECAA study, 1998-24), in which a different software (and presumably, different algorithms) was used in the stabilization phase. In the ECAA study, however, patients in the control group were followed-up without any help by the computer (i.e. without the availability of on-

Table 4. Maintenance phase: % of time spent in/out of Range.§ Single Quarters of theYear, DRUGS.

Period (pts/yr)	Warfarin (n = 519.0 pts/yr)			Acenocoumarol (n= 254.7 pts/yr)			Total [both drugs] (n= 774.7 pts/yr)		
	C	p*	M	C	p*	M	C	p*	M
1st Quart.(n=179.9)									
Under	24.6		26.9	24.5		28.3	24.5		27.4
Within	69.2	°°°	67.3	67.1	°°°	61.2	68.6	°°°	65.4
Over	6.2		5.8	8.4		10.5	6.9		7.2
2nd Quart. (n=228.1)									
Under	18.1		19.1	22.4		29.4	19.5		22.5
Within	72.7	°°	71.4	69.5	°°°	62.1	71.7	°°°	68.0
Over	9.2		9.5	8.1		8.5	8.8		9.5
3rd Quart. (n=200.6)									
Under	12.3		14.1	20.2		23.5	15.1		17.4
Within	73.7	°°°	70.8	69.5	°°°	65.2	72.2	°°°	69.0
Over	14.0		15.1	10.3		11.3	12.7		13.6
4th Quart. (n=166.1)									
Under	15.0		17.0	21.2		21.1	17.2		18.4
Within	74.4	°°°	72.4	67.5	°	65.8	72.0	°°°	70.2
Over	10.6		10.6	11.3		13.1	10.8		11.4

*C: computer; M: manual. ^% time spent/range; *χ^2 statistics, 2×2 contingency tables (within range versus under+over; Computer versus Manual). Statistical significance for the difference Computer versus Manual: ns = p >0.05; °p < 0.05; °°p < 0.01; °°°p < 0.001. § Data for statistical computing were entered as absolute time spent by patients in the single quality classes but, in order to simplify data exposition, only the percentages (of patient time) are reported in the table (see Design and Methods for details).*

Table 5. Maintenence phase: % of time spent in/out of range.§ Single Quarters of the Year, INR TARGETS.

Period (pts/yr)	Warfarin (n = 519.0 pts/yr)			Acenocoumarol (n= 254.7 pts/yr)			Total [both drugs] (n= 774.7 pts/yr)		
	C	p*	M	C	p*	M	C	p*	M
1st Quart. (n=179.9)									
Under	21.1		24.1	29.6		32.1	24.5		27.4
Within	70.5	°°°	66.4	65.7	°°	64.1	68.6	°°°	65.4
Over	8.4		9.7	4.6		3.8	6.9		7.2
2nd Quart. (n= 228.1)									
Under	19.0		21.1	20.6		25.6	19.8		22.5
Within	71.0	°°°	68.3	72.9	°°°	68.6	72.7	°°°	68.4
Over	10.0		10.6	6.5		5.8	7.5		9.1
3rd Quart. (n=200.6)									
Under	13.3		15.4	18.4		20.7	15.1		17.2
Within	72.0	°°°	68.4	72.7	°°°	70.0	72.2	°°°	69.0
Over	14.7		16.2	8.9		9.3	12.7		13.8
4th Quart. (n=166.1)									
Under	14.4		15.4	21.7		23.1	17.2		18.4
Within	72.9	°°°	70.0	70.5	ns	70.5	72.0	°°°	70.2
Over	12.7		14.6	7.8		6.4	10.8		11.4

*C: computer; M: manual. ^% time spent/range; *χ^2 statistics, 2×2 contingency tables (within range versus under+over; Computer versus Manual). Statistical significance for the difference Computer versus Manual: ns = p >0.05; °p < 0.05; °°p < 0.01; °°°p < 0.001. § Data for statistical computing were entered as absolute time spent by patients in the single quality classes but, in order to simplify data exposition, only the percentages (of patient time) are reported in the table (see Methods for details).*

Table 6. Maintenance phase: secondary end-points.* Results for total period (one year).

Drugs	Parameter (mean ± SD)	High INR target (≥ 2.8)			Low INR target (< 2.8)		
		Computer	p	Manual	Computer	p	Manual
Warfarin							
	Appointments/patient	18.4±4.82	°°°	19.4±7.42	15.6±4.71	°°°	16.3±4.76
	INR	3.10±0.93	°°°	2.90±0.69	2.50±0.76	ns	2.51±0.75
	mg/week	33.3±15.7	°°°	31.3±12.8	29.7±12.9	ns	29.7±14.4
	(Nr. of appointments)	(1,982)		(1,995)	(3,192)		(3,318)
Acenocoumarol							
	Appointments/patient	19.1±9.82	ns	19.6±5.04	16.1±4.63	°°°	18.4±4.82
	INR	3.03±1.05	ns	2.99±0.99	2.51±0.85	ns	2.59±0.81
	mg/week	19.2±9.82	°°	17.8 ±10.4	14.7±6.70	ns	14.8±6.81
	(Nr. of appointments)	(1,207)		(1,262)	(1,106)		(1,187)
TOTAL (All Drugs)							
	Appointments/patient	18.6±8.74	°°°	19.5±7.42	15.7±4.69	°°°	16.8±4.95
	INR	3.07±1.01	°°°	2.95±0.84	2.51±0.82	ns	2.55±0.76
	mg/week	–		–	–		–
	(Nr. of appointments)	(3,189)		(3,257)	(4,288)		(4,505)

**Statistical significance, Student's test", for Computer versus Manual: ns = p > 0.05; °p < 0.05; °°p < 0.01; °°°p < 0.001.*

screen records of the patient). At variance with the ECAA Study, in our study all the facilities offered by the computer were exactly the same for group C and group M patients, the only difference being the unavailability of the algorithm suggesting dosage in group M. Moreover, if compared to the results of this study, in the ECAA study the performance of the physicians without the help of the computer were extremely variable, *center-dependent* and, in some centers, quite poor. In our study, in the first two months of treatment significantly more patients in group C were within the therapeutic range if compared with patients in group M (Table 2). This difference was also present during the maintenance phase in the subgroup of patients starting treatment (95 out of 328) and followed-up for one whole year (Figure 1). This rapid and persistent stabilization of OAT obtained by the use of computer in the early, unstable phase of treatment when both hemorrhagic and thromboembolic complications are more frequent,[25-28] is of interest from a clinical point of view. In a recent, large Italian study (ISCOAT[29]), major hemorrhagic events were significantly more frequent during the first three months than in the following period of treatment, with a relative risk of 1.75 (C.I. 12.7 to 33.5). This was also proven true for thrombotic complications (RR = 20.6, C. I. = 12.7 to 33.5) by the same group.[30] Even though the present study cannot demonstrate an improved clinical quality of treatment (i.e., a decrease in bleeding and/or thrombotic complications), it is reasonable to assume that the better control of anticoagulation could decrease the incidence of adverse events.

A smaller difference between group C and group M during the third month of treatment (Table 2) was to be expected, since most patients had probably achieved a stable state by that time. However, in the subgroup followed for a whole year (as well as in the overall results of the maintenance group), there was again a significant difference between the two groups, probably due to the ability of the maintenance algorithm to reduce the variance of individual responses (Figure 1).

In patients considered during the maintenance phase, the improved results obtained by the computer prescription were demonstrated by the significantly higher percentage of time spent in the therapeutic range by patients of group C (Tables 3-5). These observations are in agreement with previous preliminary studies, both retrospective and prospective, carried out utilizing the PARMA system,[18-21] or other computer programs.[11-13,24] The larger number of patients followed up for a long time in the present study (775 patient-years, corresponding to 15,249 appointments) adds evidence to these findings. The larger percentage of patients within the therapeutic range was mainly due to a reduced number of patients below the lower limit of the range. The percentage of patients over the upper limit of the range (over-anticoagulated patients) was only marginally reduced by the use of the PARMA software (Tables 3-5). This finding suggests that the algorithms of the PARMA system counteract the well known prudence of physicians in charge, who tend to keep INR near to the lower limit of the therapeutic range, particularly in patients scheduled to higher ranges, so favoring under dosage, as already reported.[17] The better quality of treatment in group C was consistent throughout the whole year of follow-up, with only a few minor differences in the significance level, as can be seen by the quarter analyses (Table 4 and 5), probably due to the relatively lower numbers of patients in subgroups. The good quality of treatment obtained using the PARMA system is also confirmed by the significant reduction in the number of follow-ups per patient recorded in group C (Table 6), obviously linked to the significant increase of the stability within the therapeutic range. This finding was also reported by others,[31] but was not confirmed in the recent multicenter study of the ECAA.[24]

In conclusion, the prescription algorithms tested in this study were effective in improving the laboratory quality of OA treatment both in the stabilization and in the maintenance phases of patients followed by experienced physicians. Their use was associated with a reduction in the number of laboratory controls needed to maintain patients within the scheduled therapeutic ranges. A lower economic burden may be foreseen by implementating such dedicated software, particularly for clinics following a large number of patients. It is reasonable to assume that the better quality of treatment shown in this study will be reflected by a reduced prevalence of clinically relevant adverse events. This hypothesis should be tested in a large, specifically designed multicenter study.

Contributions and Acknowledgments

All listed authors contributed to the conception and design of the study. CM, MM, GP, VP, LR had the responsibility of data collection in their own Center. CM and AGD were responsible for statistical analysis and wrote the paper. AGD and MM were responsible for critical revision. All listed authors approved the final version of the manuscript to be submitted.

Order of authorship: CM was the principal investigator, the other authors were listed in alphabetic order. The last author AGD had a role as senior author in writing and revising the paper. The PARMA program was designed and developed with the fundamental and essential contribution of dr. Corrado Pattacini, Centro Malattie Emostatiche, Azienda Ospedaliera, Parma, Italy.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

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Potential implications for clinical practice

The use of computer-aided management of patients significantly improves the quality of their treatment with respect to the traditional method, even in a specialized anticoagulation clinic. This better quality of treatment is associated with a reduced number of laboratory controls required to maintain patients within their scheduled therapeutic range. These results could potentially: reduce the number of thrombotic and hemorrhagic complications: reduce costs of treatment: be associated with a better quality of the patient's life.

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Appendix

Induction period

Induction phase algorithm. In patients starting oral anticoagulants, the maintenance dosage (mg per week) suggestion was predicted by using an algorithm derived from a *bilogarithmic regression model*, based on the *individual* patient responses, i.e., the INR value at the 4th day after OAT *individual* induction dose.

A retrospective analysis of patient responses was performed, after *grouping* them on the base of total induction doses assumed in the first 3 days, and of the *drug* used: group A = 8-9 mg, group B = 10-12 mg, group C = 13-16 mg for acenocoumarol; and group A = 12.50-15 mg, group B = 16.25-20.00 mg, group C = 21.25-25 mg for warfarin. In each of these drug/dose groups, the first weekly maintenance dosage able to provide three following controls within therapeutic range was correlated, by a bilogathimc regression equation, with the INR value obtained after the loading dose (see an example of this correlation for group C of the two drugs, reported on Figure A-1). Slopes of

Table A-1. Criteria used in the logical model.

Exclusion Criteria

E1	Inadequate number of controls and/or recent interruption of treatment
E2/3	Relevant variations in anticoagulation level (E2) or in the drug dosage (E3) in the previous controls
E4	Presence of complications and/or drugs potentially interfering with OAT
E5	INR out of the therapeutic range >25 %
E6	Weekly dosage <5 or >30 mg for acenocoumarol and <7.5 or >55 mg for warfarin
E7	Control frequency <1 or >5 weeks
E8	INR variation of over 100 % or under -50 %
E9	INR out of the therapeutic range > 10 %
E10	Proposal of dosage variation >3.00 mg/week for acenocoumarol or >3.75 mg/week for warfarin

Confirmation Criteria

C1	Anticoagulation level stable in the last three controls
C2	Dosage stable (± 10%) in the last two controls
C3	Minor variations (<0.75/day) in the dosage in the last two controls
C4	INR within the therapeutic range, 10 % borderline levels excluded

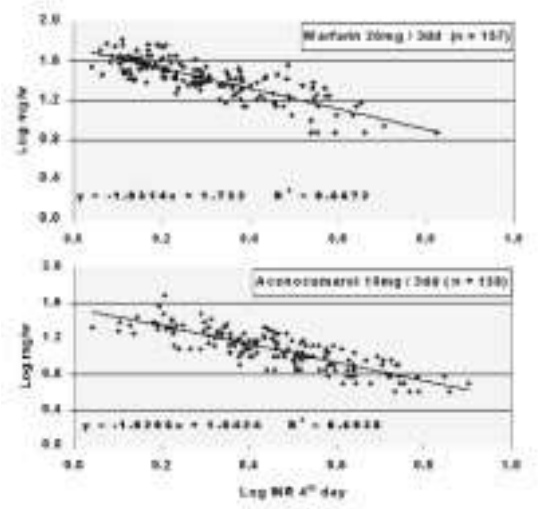

Figure A-1. Example of (bilogarithmic) regressions loading dose/INR values for two common dosages, separately for each of the two studied drugs. From the retrospective analysis of the files of Parma Hospital Thrombosis Service, used to develop the stabilization algorithm.

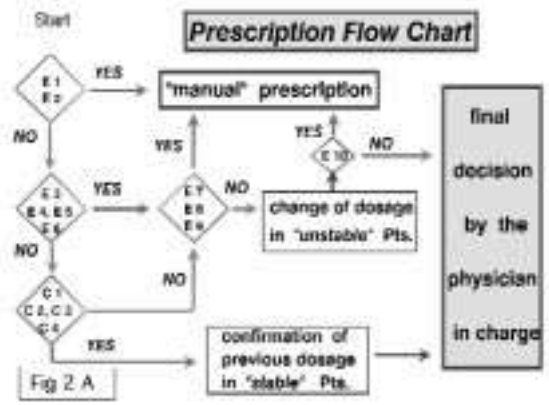

Figure A-2. Flow chart of algorithms active during the maintenance phase in PARMA software (see also Table A-1). From the retrospective analysis of the files of Parma Hospital Thrombosis Service, used for the maintenance algorithm.

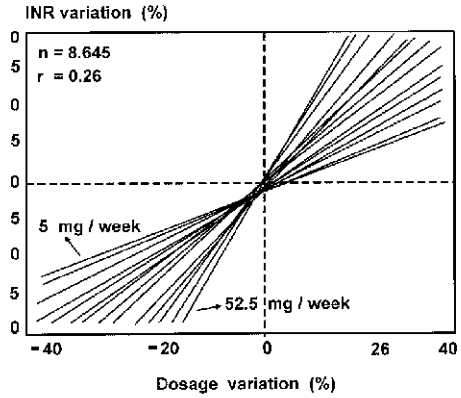

Figure A-3. The family of regression slopes for % variations of INR values (Y) on dose of warfarin (X), for a number of weekly dosages, from 5 to over 50 mg/week. Data derived from a retrospective analysis on the files of Parma Hospital Thrombosis Service were used by the algorithm suggesting a change of dose in relatively unstable patients during the maintenance phase.

these correlation families were considered by the algorithm in the formula to predict the maintenance dose in each patient, starting from 4th day INR value of same patient.

Phase 2: Maintenance period

Maintenance algorithms.

A) previous dosage confirmation or "manual" prescription/dose change (logical model), (see flow-chart on Figure A-2).

At the beginning of the procedure, the patient's last three controls are evaluated by a set of logical criteria derived from the rules usually applied by physicians working in the Parma Center during the prescription of dosage variations. These logical criteria are listed in Table A-1 (exclusion criteria and inclusion criteria).

If none of the exclusion criteria is present and all confirmation criteria are fulfilled, the patient is considered by the program as *stable* and the algorithm suggests the confirmation of the previous dosage. Otherwise, whenever one of the first set of exclusion criteria (E1, E2) is present, OAT must be manually prescribed (*no proposal* patients) There is a third possibility, i.e., when one or more of a second set of exclusion criteria (E3, E4, E5) are verified and/or one or more of the confirmation criteria (C1 to C4) are not present: in this case the patient is considered as *unstable* and he/she is evaluated with a third set of exclusion criteria (E, E8, E9). If all these three criteria are also absent, the algorithm gives a proposal of dosage variation or confirmation based on the mathematical model explained below. Otherwise, the physician should again directly prescribe OAT.

B) Proposal of variation or confirmation of previous dosage (mathematical model) (see flow-chart on Figure A-2).

It is applied to relatively unstable patients and it is based on a *three step* procedure.

The first step is the calculation of *INR target interval*, i.e., the middle value of patient therapeutic range ±10%.

The second step is represented by the calculation of the dosage modification (X) needed to induce an INR (Y) variation able to achieve a decoagulation value within the *INR target interval*. The dose is calculated on the base of an accurate retrospective analysis of more than 25,000 previous controls made during two years at the Parma Hospital Center (see an example of this work in Figure A-3).

The third step consists in the calculation of the *trend* in the anticoagulation level, i.e., a corrective factor which considers the direction of INR variation in the last two controls with regard to the ideal *INR target interval*.

A scheduling of the following appointment, included between 1 and 5 weeks, is also suggested; the visit being automatically anticipated if anticoagulation level is not stable or INR value is near to the border of therapeutic range.