# European Concerted Action on Anticoagulation (ECAA): Studies on Computer-Assisted Anticoagulant Dosage

Leon POLLER

FRCPath, Honorary Professor, Co-ordinator, European Concerted Action on Anticoagulation, Central Facility, Manchester University, Manchester, UK

Turk J Haematol 2002;19(2):179-184

It is a great honour to be invited to contribute to this issue dedicated to my long-standing friend and colleague, Professor Orhan Ulutin who has made distinguished contributions to the haematology literature. We have shared an interest in research into causal factors of thrombosis and its prevention, for almost 50 years.

## INTRODUCTION

The European Concerted Action on Anticoagulation has been concerned with both clinical and laboratory aspects of oral anticoagulation in 16 European states. Many relevant reports have been published in recent years.

The worldwide increase in the scale of oral anticoagulant treatment in recent years has followed publication of clinical reports demonstrating their value in a widening spectrum of disorders[1]. A 10% increase per annum is estimated for EU countries[2]. Increased benefit/risk ratio resulting from lower dose oral anticoagulant administration combined with implementation of the WHO INR system of prothrombin time standardisation of laboratory control has played a part in this development.

One possible way of preserving present clinical standards in the face of the increased demand is by computerisation of anticoagulant dosage. Good results from computer dosage programs have been claimed but lacked confirmation by randomised studies[3-5]. The ECAA therefore launched a multicentre randomised study to evaluate the procedure.

A small randomised study from Manchester had previously demonstrated that three earlier, UK computerised dosage programs were almost as good in achieving INR targets as the experienced medical staff of a specialist centre[6]. The ECAA computerised dosage study was the first attempt at a multicentre randomised evaluation of the safety and effectiveness of computerised anticoagulant dosage. The advantages of multicentre evaluation are not only in providing larger patient entry but also in giving a more dependable compa-

**ECAA Steering Group:** L Poller (UK); AMHP van den Besselaar (NL); J Jesperson (DK); FJM van der Meer (NL); C Shiach (UK); A Tripodi (I).

rison between computer and traditional medical staff dosage because standards of the latter vary considerably from centre to centre. An individual centre's comparison with a computerised dose program if it is better or worse than average may not therefore be representative.

The results were from five centres comprising two in the UK and three in other EU countries. Participant centres had to have a sufficient patient-entry to guarantee adequate recruitment of subjects in the six months of the study. The five centres selected for the DAWN AC anticoagulant therapy management system (4S Information Systems, Milnthorpe, Cumbria, UK) program which is the subject of this report were the Royal Infirmary, Manchester, UK; St. Bartholomew's Hospital, London, UK; the Aker Sykehus Hospital, Oslo, Norway; Centralsygehuset, Esbjerg, Denmark; and Centro Hospitalar, V.N. Gaia, Portugal.

The computer program was used in parallel with the traditional (manual) method of dosing by the experienced medical staff at each centre.

## PATIENTS

Two groups of patients at different stages of anticoagulant administration were studied.

### Stabilisation Patients

These consisted of patients discharged from hospital within 6 weeks from the start of anticoagulation. They are considered to be most challenging subjects for control of anticoagulant dosage and as many patients as possible were to be recruited for this group.

### Stabilised Patients

The second group consisted of patients already stabilised on long-term anticoagulant therapy. Nearly all had received a minimum of 22 weeks anticoagulation.

All sequential patients were randomly allocated to either traditional medical staff (manual) dosage or computerised dosage. In the stabilisation group, each new patient was given an appointment for first attendance within one week following discharge form hospital. Following counselling on the aims and objectives of long-term anticoagulation, they were to be informed of the study design before being invited to take part and giving their consent. They were assured that the computerised dosage would be monitored by medical staff who would continue to be responsible for their treatment.

Patients randomised to the traditional (manual) medical staff dosage were to be reviewed in the normal way at each centre by the doctor who normally supervised the dosage.

In the group of patients randomised to the computer system, INR values were entered into the computer program. The computer then suggested the dose of oral anticoagulant and the time-interval to the next visit. All advice on dosage and time interval between visits from the computer was reviewed by an experienced doctor. If either was considered to be harmful, confirmation of this opinion from a second medical person was to be sought. In case of over-anticoagulation, suspension of treatment for a variable number of days according to the result was advised. A maximum upper limit of 6 weeks for the time-interval between visits was chosen. At each visit, the following were recorded in the computer dose group: The INR, the suggested dose, the recommended time-interval between visits, any alteration to the computer-generated advice and any clinical events. The following data was provided: The percentage of time within the target therapeutic interval, numbers of INR below the target range (under-anticoagulated) and above the upper limit (over-anticoagulated)[7].

## INR THERAPEUTIC RANGES

The INR targets for the individual patients were decided at each centre.

## ANALYSIS

The endpoint for all groups and sub groups was the percentage of time within target INR range according to the Rosendaal method[7]. This analysis takes account of the time-interval between tests in estimating therapeutic success since the simple percentage of the number of tests within the target INR range may be misleading as more frequent tests are performed in unstable patients. Two types of percentage time in range have been calculated. The first is for the whole patient group. The percentage time in range for each patient has also been calculated and the average of patients' results within a group used to test for significance using the unpaired Student's t-test.

## RESULTS

Two hundred and eighty five sequential patients were randomised into the study at the five centres by the ECAA on Anticoagulation[8]. Two hundred and fifty four remained after exclusions (122 in the computer dosage group and 132 received manual dosage).

All centres used warfarin. Nicoumalone (sinthrome) was given to 42% of patients at one of the centres.

Because of the initial delays caused by the reluctance of medical staff to trust the computer recommendations, the majority of patients (79%) in the first 3 weeks in the computer dose group received mainly manual dosage. After this period, 89% of the dosage in this group was according to computer recommendations. Therefore for genuine comparison, the first 3 weeks results were deleted for both groups and the first 6 weeks' control in the two groups has been taken as the weeks 4 to 9 of treatment, and the second period of 12 weeks' duration relates to the subsequent treatment weeks 10 to 21. The third comparison of the two groups relates to results from week 22 onwards. Week 22 onwards was chosen because it was observed that most of the patients in the stabilised group had been on warfarin for this period of 22 weeks.

In Table 1, the overall results for all patients from all five centres for all INR ranges are given. Results after exclusion of the first 3 weeks are subdivided as explained into the first period of 6 weeks, the second period of 12 weeks and the third period from 22 weeks. This is because there was necessarily some variable delay of entry into the computer-dosage program.

In the stabilisation period the number of INR tests performed was slightly less in the computer group. The percentage of time in range was nevertheless higher throughout. The dosage interval was similar, but the percentage of dosage changes was lower with the computer.

In the smaller group of stabilised patients, the number of INR estimations was again marginally less with the computer dosage. Time within target INR range was higher and there were less dosage changes. The incidence of INR above and below the target levels was similar as were the mean INRs.

Table 2 and Figure 1 give the percentage of INR results below and above the target ranges for the respective INR intervals and for all ranges combined in both stabilisation and stable patients.

For the combined results of patients in the stabilisation and stabilised groups, the benefit from computer dosage in achieving the target INR was highly significant (p= 0.004). When the two clinical groups were tested separately, the stabilised patients fared significantly better with computer dosage (p= 0.02) but the benefit in the stabilisation group did not quite achieve statistical significance (p= 0.06).

The results from this multicentre randomised study on computerised oral anticoagulant dosage are therefore encouraging. If the success in achieving target INR with computerised dosage had merely been equal to that of experienced medical staff at the same five experienced centres, it could be argued that this would have been a sufficient case for the computer program. This is because similar standards of treatment achieved in these specialist centres could be made available by the computer program to other hospitals and community clinics with varying degrees of expertise and experience. This is important since nurses, laboratory technicians and pharmacists in addition to medical staff, are now increasingly involved in anticoagulant dosage.

In practice the results were more favourable, showing a highly significant overall benefit in the combined clinical groups at the five centres in achieving the target INR assessed by percentage of the time within target INR range[7].

The smaller number of INRs above and below the therapeutic range which are an additional measure of safety also tended to be less overall with the computer program.

The present results with an advanced computer dosage system thus are even better than the earlier pilot study from Manchester[6]. This is despite the fact that the earlier study was performed "blind" whereas this was not feasible in the present multicentre study. Therefore the medical staff performing the manual dosage in this study were aware of the competitive challenge and they were in direct competition with the computer and this may have influenced their decisions.

Table 1. Results for all INR ranges, all sites

| | Stabilisation | | | | Stable | | | Both |
|---|---|---|---|---|---|---|---|---|
| Weeks | 4-9 | 10-21 | 22- | Total | -22 | 22- | Total | Total |
| Computer | | | | | | | | |
| Number of patients | 60 | 69 | 48 | 83 | 0 | 39 | 39 | 122 |
| Number of INRs | 191 | 248 | 174 | 619 | 0 | 314 | 314 | 933 |
| % time in range (Rosendall) | 60 | 71 | 72 | 68 | 0 | 72 | 72 | 70 |
| Mean of interval (days) | 13 | 17 | 20 | 17 | 0 | 20 | 20 | 18 |
| % of dose changes | 49 | 38 | 29 | 39 | 0 | 36 | 36 | 38 |
| % of dose interventions | 26 | 21 | 21 | 23 | 0 | 21 | 21 | 22 |
| % number of high INRs | 31 | 30 | 25 | 29 | 0 | 25 | 25 | 28 |
| % number of high INRs | 16 | 13 | 13 | 14 | 0 | 18 | 18 | 15 |
| Mean of INRs | 2.6 | 2.5 | 2.7 | 2.6 | 0.0 | 2.7 | 2.7 | 2.6 |
| Manual | | | | | | | | |
| Number of patients | 76 | 79 | 51 | 92 | 2 | 39 | 40 | 132 |
| Number of INRs | 220 | 246 | 212 | 693 | 5 | 382 | 387 | 1080 |
| % time in range (Rosendall) | 51 | 57 | 55 | 55 | 58 | 59 | 59 | 56 |
| Mean of interval (days) | 14 | 18 | 17 | 16 | 13 | 18 | 18 | 17 |
| % of dose changes | 60 | 57 | 52 | 57 | 0 | 47 | 46 | 53 |
| % of dose interventions | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| % number of low INRs | 37 | 37 | 33 | 36 | 60 | 27 | 27 | 33 |
| % number of high INRs | 12 | 17 | 19 | 16 | 0 | 20 | 19 | 17 |
| Mean of INRs | 2.5 | 2.7 | 2.5 | 2.6 | 2.6 | 2.7 | 2.7 | 2.6 |

Table 2. Percentage of INR results below and above target ranges

| | | % low INR | % high INR |
|---|---|---|---|
| Stabilisation patients | Computer (n= 92) | 29.1 | 13.2 |
| | Manual (n= 83) | 36.1 | 19.3 |
| Stable patients | Computer (n= 39) | 27.6 | 15.4 |
| | Manual (n= 40) | 32.9 | 17.2 |

In addition to the benefits in dose administration, the ECAA study concluded that computerised dosage has considerable potential for saving of medical, nursing and secretarial time. The additional administrative advantages of such a program would also be available and these include the possibility of large data banks of anticoagulant records, the provision of written dosage schedules, recording of concomitant treatments, clinical instructions regarding duration of therapy, clinic diaries as well as facilitating supportive documentation and letters.

The clinical benefit of this improved INR control from computerised dosage remains to be established. A clinical end-point study to be undertaken by the ECAA

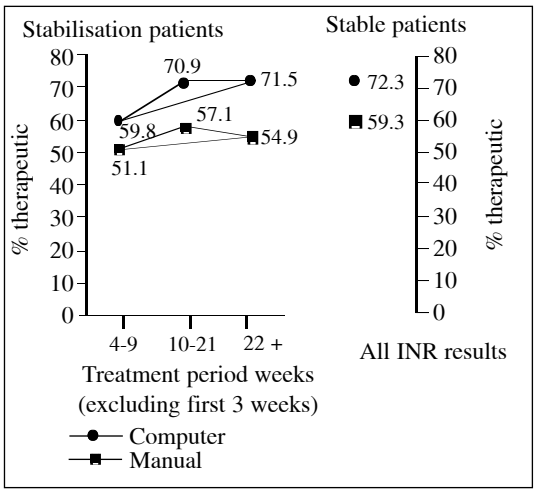


**Figure 1.** Percentage time in all INR ranges (Rosendaal).

over the next 4 years will attempt to resolve this and the resultant cost-effectiveness of computerised dosage. Forty centres will be involved in 16 EU countries and 4 associated states (see Figures 2 and 3), involving 16.000 patient-years. As the incidence of thrombotic and bleeding complications increases exponentially at INR less than 2.0 and over 4.0 respectively, it is possible that the clinical benefit could greatly exceed the percentage improvement in INR control. Two computer dosage programs will be included - DAWN AC and PARMA 4 in the new study with half of the centres and half of the participants allocated to each program.

The cost benefit of any clinical gain will be assessed by a team of health economists from Birmingham University.

## ACKNOWLEDGEMENTS

Gratitude is expressed to the ECAA participant centres. The work was performed with the grant from the EC Commission, BioMed 1 PL93 1349.

## REFERENCES

1. Hirsh J, Dalen JE, Deykin D, Poller L, Bussey H. ACCP Consensus. Oral anticoagulants, mechanism of action, clinical effectiveness and optimal therapeutic range. Chest 1995;108:231-46.
2. Tripodi A, Chantarangkul V, Mannucci PM. Near patient testing devices to monitor oral anticoagulant therapy. Brit J Haemat 2001;113:847-52.
3. Wilson R, James AH. Computer assisted management of warfarin treatment. Brit Med J 1984; 289:422-4.
4. Ryan PJ, Gilbert M, Rose PE. Computer control of anticoagulant dose for therapeutic management. Brit Med J 1989;299:1207-9.
5. Weston Smith SG, Savidge GF. Computer control of anticoagulant dose. Brit Med J 1989;299:1529-30.
6. Poller L, Wright D, Rowlands M. Prospective comparative study of computer programs used for management of warfarin. J Clin Path 1993;46:299-303.
7. Rosendaal FR, Cannegieter SC, van der Meer FJM, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993;69:236-9.
8. Poller L, Shiach CR, MacCallum P, Johansen AM, Munster AM, Jespersen J, Magalhães A. European Concerted Action on Anticoagulation. Computerised anticoagulant dosage-a multicentre randomised study. The Lancet 1998;352:1505-9.

**Address for Correspondence:**

Leon POLLER, MD

Co-ordinator, European
Concerted Action on Anticoagulation
Central Facility, Manchester University
Manchester, UK

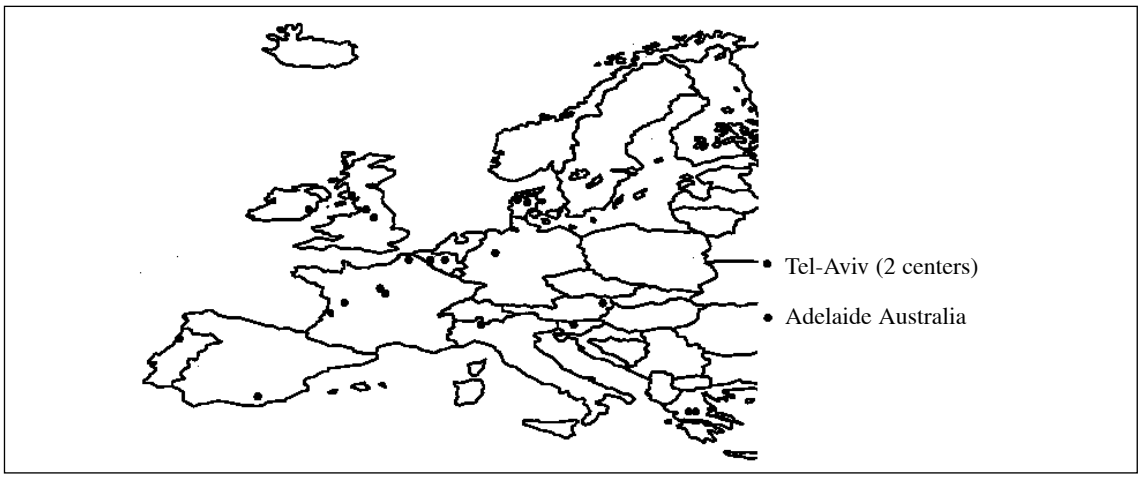


**Figure 2.** Dawn AC participants.


**Figure 3.** Parma participants.