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Patient self-testing is a reliable and acceptable alternative to laboratory INR monitoring

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Summary

An ageing population and the continuing expansion of clinical indications for coumadin therapy have increased pressure on hospital anticoagulant clinics. One solution is patient self-testing (PST) of the international normalized ratio (INR) using capillary blood samples on point-of-care coagulation monitors at home. We conducted a prospective study to determine whether patients can achieve accurate INR values through PST, using the CoaguChek S (Roche Diagnostics, Lewes, UK). The main outcome measurements were: comparability of INR values obtained by PST and the hospital laboratory, patient acceptability as assessed by a questionnaire and anticoagulant control. Eighty-four patients [53 men, 31 women; median age 59 years (range 26–83)], receiving long-term oral anticoagulation (warfarin), were recruited from our Anticoagulation Clinic. Patients were randomized to weekly self-testing or continuing 4-weekly hospital laboratory monitoring of INR. Comparison of INRs ($n = 234$) showed no significant differences between the CoaguChek (median INR 3·02) and laboratory testing (median INR 3·07). There was excellent correlation between the two methods ($r = 0{\cdot}95$), with 85% of CoaguChek results within 0·5 INR units of the laboratory method. On four occasions, differences of >1 unit INR were obtained, but in each case the patient's anticoagulation was unstable (INR >4·5 by both methods) and the differences in INR would not have altered patient management. 87% of patients found self-testing straightforward, 87% were confident in the result they obtained and 77% preferred self-testing. We conclude that PST is a reliable alternative to hospital clinic attendance and is acceptable to the majority of suitably trained patients.

Keywords: anticoagulation, international normalized ratio.

It is likely that approximately 950 000 people in the UK currently receive oral anticoagulant therapy (OAT), with this number estimated to increase at approximately 10% /year (Rose, 1996). Warfarin is the most widely used oral anticoagulant in the UK and has a half-life of 36–42 h. The increased usage of warfarin is largely related to implementation of long-term anticoagulation in an ageing population for atrial fibrillation (Petersen *et al*, 1989). Newer indications include primary prevention of ischaemic heart disease (MacCallum *et al*, 2000) and long-term prevention of recurrent venous thromboembolism (Ridker *et al*, 2003). Consequently, several models of patient care, involving various degrees of decentralization, have been suggested to manage the increased workload arising from the increased demand. One solution is patient self-testing (PST), i.e. the measurement of the prothrombin time (PT) expressed as an international normalized ratio (INR) by the patients themselves using capillary blood samples on small point of care (POC) coagulation monitors. Such monitors need to be accurate over the full therapeutic range of the INR, between 2·0–4·5, and require an acceptable independent evaluation (Fitzmaurice & Machin, 2001). A number of studies have proved comparability between POC testing and conventional laboratory techniques based on POC testing by healthcare professionals (Bachour *et al*, 2001; Vacas *et al*, 2001; Havrda *et al*, 2002; Shiach *et al*, 2002; Loebstein *et al*, 2003; Jackson *et al*, 2004), whereas

others have questioned the reliability of POC test INR results (Poller *et al*, 2003; Vacas *et al*, 2003). Of note, INR results obtained by technically skilled healthcare professionals using POC testing devices have been reported to be more reliable than those achieved by non-technical trained individuals (Delaney *et al*, 1999). There is a paucity of data on the comparison of INR results obtained by PST with laboratory INRs. White *et al* (1989) reported, in a study on 26 patients and based on results during the first 8 weeks of OAT, comparison of INRs obtained by self-testing using a Coumatrack monitor (Du Pont, Wilmington, DE, USA) with those from hospital laboratories. However, comparisons between PST INR and laboratory INR were not performed on the same sample, limiting conclusions from this study. There are no published evaluation studies on the reliability of PST within the setting of a routine anticoagulant clinic in the UK.

We report data from a prospective trial, commissioned by the Medicines and Healthcare Products Regulatory Agency (MHRA) and approved by the British Committee for Standards in Haematology (BCSH) Haemostasis and Thrombosis Task Force, to investigate the accuracy and acceptability of PST in a trained and motivated group of patients.

Patients and methods

Ethical approval was granted by the Joint University College London (UCL)/UCL Hospital (UCLH) Committees on the Ethics of Human Research and patients gave informed consent. Eighty-four patients were recruited from the UCLH Haematology Department Anticoagulant Clinic between September 2002 and April 2003.

Eligibility

All patients over the age of 18 years, attending the clinic, who had received long-term oral anticoagulation for at least 8 months and with a previous record of good compliance, were identified. Approximately 800 patients were contacted by letter; 84 of these volunteered for the study and, following written consent, were prospectively randomly allocated to the intervention (PST) or control group (continuing with laboratory testing with no specific education or training).

Protocol

Self-testing patients were trained by a single nurse practitioner in the use of a POC coagulometer (CoaguChek S; Roche Diagnostics) (Sawicki, 1999). Patients attended two training sessions at least 1 week apart, which covered theoretical aspects of oral anticoagulation and POC INR monitoring. Following a satisfactory assessment of their ability to self-test, they proceeded to the trial (Murray *et al*, 2004). These patients tested themselves at home once a week and recorded the result for a 6-month period. The results obtained by self-testing were not used for management of anticoagulation during the study. Anticoagulant control was based on a laboratory test performed every 4 weeks. Self-test and laboratory INR tests used for comparability studies were collected within 1 h of each other. The control group simply attended the anticoagulant clinic every 4 weeks or more frequently, if clinically indicated. The purpose of the control group was to control for possible biases because of selection and the effect of increased patient training. Dosage adjustments were performed for both groups of patients by the anticoagulant clinic staff using the laboratory INR and computer-assisted dosing (Dawn Clinical Software, Milnthorpe, Cumbria, UK). The PST group performed internal quality control (QC) tests (CoaguChek PT Control; Roche Diagnostics) every week and an external quality assessment using a lyophilized plasma preparation provided by the UK National External Quality Assessment Scheme (UK NEQAS), once during the study (Murray *et al*, 2003). Patients in the self-testing group were asked to complete a patient acceptability questionnaire after 3–4 months. The questionnaire sought individual patient's views on six aspects of using the CoaguChek S: ease of use, frequency of repeated tests, difficulty of getting an adequate sample, ease of the use of QC materials, confidence in the result and preference for home testing *versus* hospital testing.

Prothrombin time/INR measurement

Venous blood was collected into one-tenth volume 0·105 mol/l citrate (Vacutainer®; Becton Dickinson, Franklin Lakes, NJ, USA) using 19 or 21 gauge needles and minimal stasis and plasma was obtained by centrifugation at 2000 ***g*** for 10 min. To measure the INR, a recombinant human thromboplastin reagent (Innovin; Dade Behring, Marburg, Germany) was used on a CA-1500 coagulometer (Sysmex, Kobe, Japan). The geometric mean was determined using blood from 20 healthy normal volunteers and the thromboplastin-specific international sensitivity index provided by the manufacturer was verified using frozen INR verification plasmas (Precision Biologic, Dartmouth, Canada).

Assessment of anticoagulant control. The different testing frequencies used for PST, laboratory control and laboratory results in the previous 6 months made direct comparison of the time spent in the therapeutic range difficult, but this remained an important issue. Routine clinical practice recommends the use of a target INR-value rather than a target range (Haemostasis and Thrombosis Task Force of the BCSH, 1998). For the purposes of this exercise, the target INR | 0·5 INR units was used as an acceptable therapeutic range. Time in range was determined using the TIME IN RANGE CALCULATOR software (4S Dawn Clinical Software) using the method of Rosendaal *et al* (1993).

Statistics. Statistical analysis was performed using ANALYSE-IT™ software (Analyse-It Software, Leeds, UK). Mean INR values were compared using a paired *t*-test, with statistical

significance defined as $P < 0{\cdot}05$. For the regression analysis, outliers were rejected where they were outside the 95% confidence interval. Bland and Altman plots were used to illustrate the degree of agreement or divergence between the two methods, as the numerical value increased. Fisher's exact test was used to test the significance of the difference between the observed time in therapeutic range between patient groups.

Results

Eighty-four patients were randomized to the study; 44 to the self-testing group and 40 to the control group. Patient demographics, target INR values and indications for anticoagulation were similar for both groups (Table I), although it was notable that the median age of the control and self-testing groups (58·4 and 57·9 years, respectively) was lower than that of the anticoagulant clinic population as a whole (65·7 years). Four patients experienced difficulty performing self-testing and did not proceed onto the study following training. One further patient, randomized to the self-testing group, did not attend training. Therefore, of the 44 patients randomized to the self-testing group, 39 commenced self-testing, whereas all patients randomized to the control group entered the study. Nine self-testing patients and one from the control group failed to complete the study (Table II). There were no significant differences between self-testing and laboratory INRs (234 paired measurements in 31 self-testing patients), (Table III). Excellent correlation was obtained between the methods ($r = 0{\cdot}95$; Fig 1) and no trend was observed with increasing INR-value (Fig 2). Overall, 85% of the results was within 0·5 INR units of each other. On four occasions, differences of >1 unit INR were obtained, but in each case the INR was above the desired therapeutic range (INR >4·5 by both methods) and the differences in INR would not have altered patient management.

Table I. Patient characteristics.

	Self testing group	Control Group
Male	29	24
Female	15	16
Mean age (years)	57·9	58·4
Age range (years)	26–83	31–75
Indications for anticoagulation		
Atrial fibrillation	11	12
Replacement heart valve	16	9
Venous thromboembolism	10	14
Cardiovascular prophylaxis	5	3
Cerebrovascular prophylaxis	2	2
Target ranges		
2·0–3·0	26	19
3·0–4·0	9	11
1·5–2·0	1	0
1·5–2·5	0	1
2·0–2·5	0	2
2·5–3·5	7	4
3·0–3·5	1	3

Table II. Reasons for patients not completing the study.

Reason for withdrawal	Self-test group	Control group
Poor compliance*	2	1
Serious illness (pretraining)	1	NA
Failed to attend training	1	NA
Visual problems	1	NA
Unable to obtain sample	1	NA
Poor dexterity	4	NA
Warfarin discontinued	1	0
Moved to another area	2	0
Patient died	1	0
Total withdrawals	14	1

NA, not applicable.

*The patients failed to attend the clinic and/or self-test on a regular basis.

Table III. Self-testing international normalized ratio (INR) *versus* laboratory INR ($n = 234$).

	CoaguChek INR	Laboratory INR
Mean	3·02	3·07
Standard deviation (SD)	0·99	0·95
Minimum	1·20	1·25
Maximum	6·90	6·86

Self-testing INR *versus* laboratory INR: paired *t*-test results were non-significant.

No significant difference between percentage time in therapeutic range in the self-testing and control groups was observed using Fisher's exact test (Table IV), irrespective of whether the laboratory or CoaguChek methods were studied. Ten minor bleeding/bruising events were reported, with five from each group. Overanticoagulation was thought to be a contributory factor in five of these events (three in the self-testing group and two in the control group).

Questionnaires were returned by all 31 patients who were still self-testing after 3 months (one of these failed to complete the study, because of the moving from the area). Majority of the patients (84%) initially found it difficult to obtain an adequate sample, but most of them subsequently found self-testing very easy (55%) or quite easy (32%). Only one patient found the CoaguChek S difficult to use, but most patients found that they occasionally had to repeat tests and some still experienced difficulty in obtaining an adequate sample (16%). Most patients (87%) were confident in the result that they obtained and, of those who expressed a preference, most (77%) preferred self-testing rather than attending the hospital anticoagulant clinic. None of the patients experienced difficulty using the internal QC procedure. The self-testing patients who completed the study were conscientious in performing and recording their weekly tests, with compliance of >98%. On

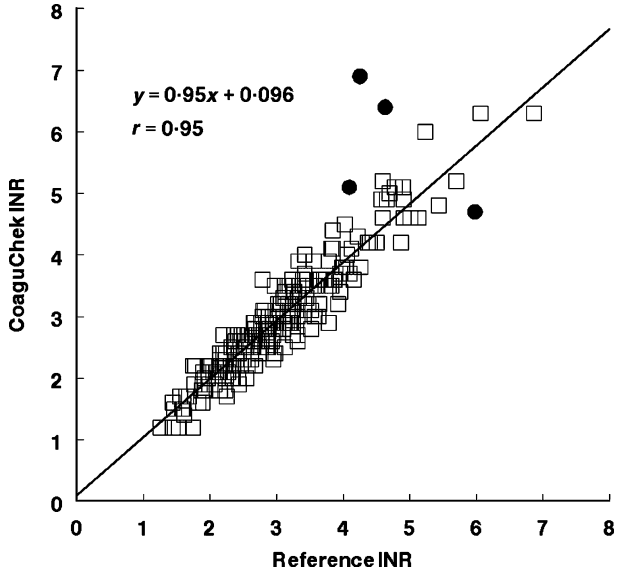

Fig 1. Self-testing international normalized ratio (INR) *versus* laboratory INR in self-testing patients. Four statistical outliers are shown.

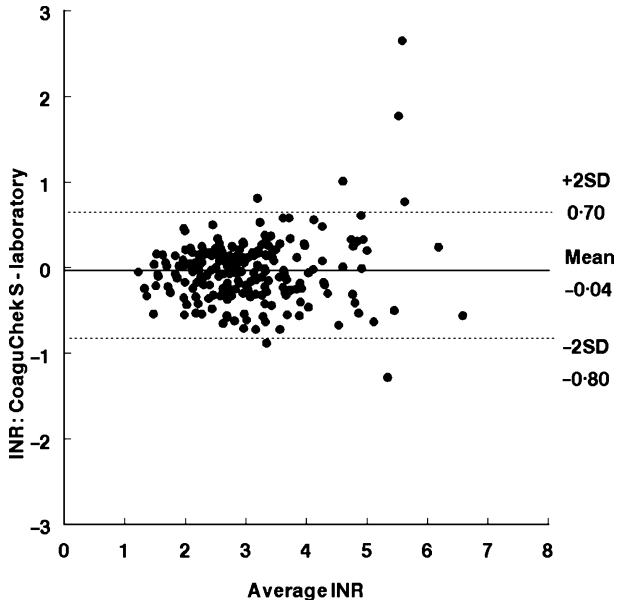

Fig 2. Bland and Altman diagram showing agreement between duplicate international normalized ratio (INR) results in self-testing patients.

the few occasions where weekly tests were not performed, this was generally the result of the patient experiencing difficulty with self-testing or disruption of their anticoagulant control because of hospitalization (two cases) or on one occasion, the loss of the CoaguChek S monitor.

Although 96·5% of internal QC results were within the manufacturer's stated range (2·2–4·7), this range was felt to be too wide and a poor level of imprecision was observed [percentage coefficient of variance (CV) = 15·9%]. During the course of the study, one instrument defect and one test-strip problem were encountered. On each occasion, both the patient's sample and the QC gave unexpected abnormal results and the problem, once identified, was easily corrected. However, on other occasions, abnormal QC values were obtained despite the patient's own result demonstrating adequate control of anticoagulation. No instrument or test-strip defects were demonstrated on these occasions. The NEQAS samples produced a narrower range of results (percentage CV 7·4% and 6·6% for two separate exercises).

Table IV. Percentage time in range: self-testing group *versus* control.

	Self-testing group		Control group (laboratory INR)
	CoaguChek INR	Laboratory INR	
Mean	61	66	64
Standard deviation (SD)	20	22	26
Minimum	24	23	7
Maximum	96	100	100

Fisher's exact test: control *versus* self-testing groups (laboratory testing), results were non-significant.
Control *versus* self-testing groups (CoaguChek; Roche Diagnostics), results were non-significant.

Discussion

We have showed that suitably trained patients can obtain their INR by PST using the CoaguChek S, currently the most widely used handheld PT/INR monitor in the UK. The PST results showed excellent correlation with routine hospital laboratory monitoring of OAT ($r = 0·93$), with 85% of results within 0·5 INR units of each other. On the four occasions where differences of >1 unit INR were obtained, the INR was above the desired therapeutic range (INR >4·5 by both methods) and would not have altered patient management. The INR system is known to be unreliable above 4·5, limiting comparisons between different methods above this level (WHO Expert Committee on Biological Standardisation, 1983). Neither significant differences in anticoagulant control were observed between the self-testing and control groups during the study, nor between results obtained in individual patients during the study period and the previous 6 months. This is in contrast with the findings of White *et al* (1989) who reported that an improvement in OAT could be achieved through PST alone.

Another study evaluated the accuracy of home testing, but on a paediatric population ($n = 23$) with home testing performed by parents of children receiving OAT (Massicotte *et al*, 1995) using the Biotrack monitor (Ciba Corning Diagnostics, Medfield, MA, USA). In a recent study of patients receiving phenprocoumon (half-life 140 h) in the Netherlands, a comparison of PST with patient self-management *versus* specialized anticoagulant clinic management showed comparable levels of OAT control, as judged by mean time in range in

therapeutic range (Gadisseur *et al*, 2003). However, paired PST and laboratory INR results were not directly compared.

Although the number of patients who failed to complete the study was higher in the self-testing group than the control group (nine *versus* one), most patients found self-testing using the CoaguChek S straightforward and felt confident with the result they obtained (87%) and also expressed a preference for self-testing over attendance at the hospital anticoagulation clinic (77%).

It was generally felt that weekly QC testing was not cost-effective, as the manufacturer's stated range was too wide and poor level of imprecision was obtained. Furthermore, most out-of-range QC results were because of problems with the use and preparation of the QC reagent, rather than instrument/test-strip faults. Monthly testing, as recommended by the BCSH recommendations (Fitzmaurice & Machin, 2001), may be more appropriate with additional testing performed in the event of an unexpected INR result, following possible monitor damage and on starting a new box of test strips. As the NEQAS samples produced a narrower range of results, they were generally perceived to be of more value than the internal QC. Occasional paired PST and laboratory testing or comparison with a regularly quality controlled instrument in clinic may be a useful alternative for ensuring adequate quality assurance.

The present study only assessed one particular POC INR monitor. However, as patient demand for self-testing/self-management becomes more widespread, monitoring devices from other manufacturers should become more widely available. Test strips for POC INR monitors may now be prescribed on the Drug Tariff, subject to appropriate European Economic Community licensing (i.e. CE marking). However, it is recommended that before such instruments are introduced into clinical practice, they should have a satisfactory independent evaluation. The patient training on the use of such devices needs to follow nationally agreed guidelines and recommendations (Near Patient Testing Working Party. General Haematology Task Force of BCSH. Thrombosis and Haemostasis Task Force of BCSH, 1995; Fitzmaurice & Machin, 2001). The cost-effectiveness of self-testing has not yet been formally studied in the UK. In addition to instrument and test-strip costs, any economic assessment must include elements, such as transport, for the patient and clinic overheads, the potential for improved anticoagulant control with the reduced risk of thromboembolic or haemorrhagic complications, greater patient freedom and reduction in lost patient working time. The overall uptake for this trial was approximately 10% only. Some patients were apprehensive about entering a clinical trial, while others felt that allocation to the control group offered no advantages but required more frequent visits to clinic, but the low uptake suggests that the routine clinical utilization of such a self-testing programme may be limited to a minority of motivated patients receiving long-term oral anticoagulation.

We conclude that PST using the CoaguChek S offers a reliable alternative to laboratory determination of INR and is acceptable to the majority of suitably trained patients who previously attended a specialist anticoagulation clinic. Overall, these results are reassuring and should encourage implementation of a validated self-testing approach using a CoaguChek S system. This will potentially enable patients to progress to self-manage their own oral anticoagulant control using an agreed dosing algorithm. It is important that all self-testing patients remain registered with a clinician/nurse practitioner responsible for their oral anticoagulation regime in accordance with BCSH guidance (Fitzmaurice & Machin, 2001). Future MHRA studies will assess the efficacy of a patient self-management programme.

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Competing interests: none.

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