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A randomised control trial of patient self-management of oral anticoagulation compared with patient self-testing

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Summary

Several studies suggest that patient self-management (PSM) may improve the quality of oral anticoagulation therapy as measured by time spent within the international normalised ratio (INR) target range. We performed a prospective randomised control trial to determine whether the improvement in quality of treatment afforded by PSM is greater than that achieved by patient self-testing (PST) alone. A total of 104 of 800 eligible patients aged 22–88 years (median = 59·8), attending our hospital anticoagulant clinic and receiving long-term warfarin for >8 months agreed to participate. Patients were randomised to PSM ($n = 55$) or PST ($n = 49$). Both groups measured their INR using the CoaguChek S every 2 weeks or more frequently if required, for a period of 6 months. Seventy-seven of 104 (74%) patients completed the study (PSM = 41 and PST = 36). The 'drop out' rates for both groups were similar. There was no significant difference between the percentage time in target therapeutic range for PSM (69·9%) and PST (71·8%). Both groups combined showed a significant improvement over the previous 6 months (71·0% vs. 62·5%; $P = 0·04$). Changes in time within the therapeutic range in individual patients (+5·86) also showed a significant difference. The quality of warfarin control in both PST and PSM may be superior to that achieved by conventional management in a specialised hospital anticoagulation clinic.

Keywords: anticoagulation, warfarin, international normalised ratio.

Oral anticoagulation therapy (OAT) is widely used for the prevention and treatment of thrombosis. Most of the estimated 950 000 people in the UK currently receiving OAT (Rose, 1996) take warfarin, a vitamin K antagonist with a half-life of 36–42 h. An ageing population and newer indications for long-term anticoagulation, particularly atrial fibrillation (Petersen *et al*, 1999), but also primary prevention of ischaemic heart disease (MacCallum *et al*, 2000) and long-term prevention of recurrent venous thromboembolism (Ridker *et al*, 2003) are responsible for the number of patients receiving warfarin increasing by approximately 10% per year. This increasing workload has placed considerable strain on hospital anticoagulation clinics, and this combined with patients wanting more autonomy and control over their condition, has led to growing interest in patient self-testing (PST) and patient self-management (PSM).

Several studies suggest that the quality of OAT afforded by PSM is as good as or better than that achieved by conventional management (Hasenkam *et al*, 1997; Sawicki, 1999; Sidhu & O'Kane; 2001; Beyth *et al*, 2000; Korfer & Kortke, 2001; Gadisseur *et al*, 2003; Menendez-Jandula *et al*, 2005). However, in most of these studies, the existing quality of OAT was poor, and differences in testing frequency and international normalised ratio (INR) measurement preclude direct comparisons of OAT quality. Furthermore, the testing intervals in PSM patients and the control groups were different, which makes direct comparison of time in therapeutic range difficult.

Two recent publications compared the OAT quality achieved by PSM against that of dedicated anticoagulation clinics in Spain and the Netherlands (Menendez-Jandula *et al*, 2005; Gadisseur *et al*, 2003). Only one of these studies compared PSM with PST (Gadisseur *et al*, 2003) and in both studies, the patients received acenocoumarol or phenoprocoumon rather than warfarin. These anticoagulants have different half-lives to warfarin, and this was found to be the major predicting factor of OAT quality. These data are not

directly applicable to the management of oral anticoagulation in the UK, where the predominant oral anticoagulant used is warfarin, and majority of patients are managed in dedicated hospital anticoagulation clinics.

We report the data from a prospective randomised controlled trial, in which the quality of warfarin control achieved by PSM was compared with that of PST against the background of existing care in a specialised hospital anticoagulation clinic. We also assessed patient compliance with a self-management programme.

Patients and methods

All patients attending the anticoagulant clinic at University College Hospital over the age of 18 years, receiving long-term anticoagulation treatment for a period of at least 8 months were eligible for this study. We excluded the patients with a history of poor compliance, those with dexterity or sight problems that would prevent successful self-testing (unless a willing and able caregiver able to perform self-testing was available), those deemed to have intellectual impairment that would preclude self-management or who had known drug or alcohol dependency. Poor compliance was defined as: missing more than three clinic appointments in the 6 months prior to the study, poor treatment adherence or a history of altering their own warfarin dosage without medical consent.

Ethical approval was obtained from the Joint University College London/University College London Hospitals Committees on the Ethics of Human Research. Eight hundred patients who fulfilled the inclusion criteria were invited to participate in the study, and those who gave informed consent were randomised to self-testing or self-management. Both the self-testing patients and self-managing patients measured their INR using the same method (Roche CoaguChek S; Basel, Switzerland). Patients attended a nurse-led training course, which covered self-testing and self-management (Murray *et al*, 2004). Following a successful assessment of the patient's ability to self-test and understanding of self-management, the PSM group routinely tested their INR every 2 weeks for a period of 6 months. Dose changes were based on a treatment algorithm issued to each patient, which also included instructions on scheduling of next test and when to contact the clinic. Patients were asked to contact the clinic in the case of very low or high INR readings (INR < 1·5 or >5·0). Patients in the PST group were also asked to perform a capillary blood test once every 2 weeks for 6 months. They contacted the anticoagulation clinic staff with the INR result who advised of dose changes and their next test date using computer-assisted dosing (4S DAWN Clinical Software; Milnthorpe, Cumbria, UK). They were also asked to report any problems with bruising, bleeding or thrombosis.

All patients were asked to perform an internal quality control (QC) sample (*CoaguChek PT Control*) once a month. They were also asked to perform at least one external quality assessment (EQA) [UK National External Quality Assessment Scheme (NEQAS)] exercise during the study. In each exercise, two EQA plasma samples were distributed for prothrombin time (PT)/INR determination on the CoaguChek S. The plasma samples were reconstituted by the patient and tested in the usual manner as for capillary whole blood. The limits for results within consensus (i.e. target range for acceptable results) were defined as 15% above and below the median INR.

Patient compliance was assessed by calculating the frequency of testing, the frequency of QC testing, and any failure on the patient's part to communicate out of control results (<1·5 or >5·0) to the clinic.

Data analysis

Patients were asked to record their INR results together with the date of test, their warfarin dose, QC results and any changes in medication. Data were collated into an excel spreadsheet for analysis. Percentage time in therapeutic range was calculated using the method of linear interpolation, described by Rosendaal *et al* (1993). This analysis takes account of the time-interval between tests in estimating therapeutic quality, as 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. As the data showed non-normal distribution, the Wilcoxon signed-rank test was used to test for differences between median values for paired data, and the Mann–Whitney *U*-test was used for independent groups. A *P*-value of <0·05 was considered statistically significant. Two-way ANOVA was used test for interaction across groups.

Results

Of the 800 patients contacted, 104 (13%) agreed to participate in the study. Following randomisation, 55 were allocated to PSM and 49 to PST ($n = 49$). No significant differences were observed between baseline characteristics of the two groups (Table I). Seventy-seven (74%) patients completed the study (PSM = 41, PST = 36). The 'drop out' rates for both groups were compared with difficulty in obtaining an adequate capillary sample being the most common reason given for failing to complete the study (Table II). Patients were asked to perform an INR measurement every 2 weeks (i.e. 13 tests during the study); however, if their warfarin dose was changed, additional tests would be required. The mean number of tests performed was 15·2 and 13·9 for the PSM and PST groups respectively (range 9–23 PSM and 8–27 PST), indicating excellent compliance.

Overall, no statistically significant difference in the percentage time in therapeutic range was found between PST and PSM (Table III). When we examined the patients' historical data of their regular clinic visits, we found no statistically significant differences between the percentage time in therapeutic range for the previous 6 months and that obtained by the self-testing or self-managing patients. However, when combined, the self-

Table I. Patient demographics.

	Number or median (range)	
	PSM group	PST group
Male	33	30
Female	22	19
Age (years)	59·0 (30–85)	60·9 (22–88)
Indications for anticoagulation		
Atrial fibrillation	23	19
Replacement heart valve	13	11
Venous thromboembolic	9	11
Cardiovascular prophylaxis	5	3
Cerebrovascular prophylaxis	5	5
INR target range		
2·0–3·0	40	37
3·0–4·0	15	12

INR, international normalised ratio; PSM, patient self-management; PST, patient self-testing.

Table II. Reasons for patients not completing the study.

Reason for withdrawal	PSM group (%)	PST group (%)
Moved away from area	1 (1·8)	0 (0·0)
Illness (did not complete training)	1 (1·8)	2 (4·1)
Non-compliance*	1 (1·8)	2 (4·1)
Warfarin stopped	1 (1·8)	1 (2·0)
Target range changed mid-study	0 (0·0)	1 (2·0)
Caregiver problems	0 (0·0)	1 (2·0)
Nervous about self-management	5 (9·1)	0 (0·0)
Difficulties with fingerprick testing	5 (9·1)	6 (12·2)

*These patients failed to attend clinic and/or self-test on a regular basis.
PSM, patient self-management; PST, patient self-testing.

managing and self-testing patients spent more time within the therapeutic range during the study than during the previous 6-month study period 71·0% (95% CI, 64·7–76·4) vs. 62·5% (95% CI, 56·1–74·0; $P = 0·04$). No evidence was found for interaction between groups and treatments (two-way ANOVA; $P = 0·86$). When we studied differences for percentage time in therapeutic range for individual patients, we found no statistically significant differences between self-testing or self-managing patients and their results from the previous 6 months [PST + 5·24% (95% CI, −2·44–12·91); PSM 6·41 (−1·84–14·67)], but a significant improvement was observed when the two groups were combined [+5·86 (95% CI, 0·32–11·41)].

The target INR value had no significant effect upon time in range with broadly similar levels of oral anticoagulant control seen in both groups: time in therapeutic range; PSM 71·9% (95% CI, 63·1–78·3) vs. PST 71·8 % (95% CI, 65·4–78·1) for patients with a target INR of 2·5; PSM 63·3% (95% CI, 54·9–71·7) vs. PST 71·9 (95% CI, 62·4–81·3) for patients with a target range of 3·5. The mean daily warfarin dose (1–16 mg) had no significant effect on the percentage time in range with similar values for patients taking <5 mg and >5 mg [69·2% (95% CI, 61·4–77·0) vs. 69·4% (95% CI, 62·3–76·5)] respectively.

The percentage time spent outside of the control limits (below 1·5 and above 5·0) is shown in Table IV. Intentional low INR values because of the warfarin dose reduction or discontinuation prior to elective surgery, dental treatment, etc. were not included in these figures. The percentage time outside control limits in the self-testing patients was approximately half of that observed in the previous 6 months (1·06% vs. 1·96%), whereas only a modest improvement was seen in the self-managing patients. However, of 25 tests outside control limits in the PSM group, 10 were due to poor compliance in just three patients. On more than one occasion, these three patients failed to report out of control results to the clinic and consequently the necessary dose changes were not made. When the data were reanalysed excluding these patients' results, values similar to those in the PST group were observed, i.e. 1·34% (95% CI, 0·29–2·39) time in out of control limits.

Table III. Percentage time in range.

			Previous 6 months			
	Self-management	Self-testing	PSM group	PST group	PSM and PST combined	PSM and PST during previous 6 months
Number of patients	41	36	41	36	77	77
% Time in therapeutic range (95% CI)	69·9 (60·8–76·7)	71·8 (64·9–80·1)	62·1 (52·8–74·7)	63·3 (52·5–80·6)	71·0 (64·7–76·4)	62·5 (56·1–74·0)
Interquartile range	23·1	22·1	37·7	39·5	22·5	35·0
% TIR self-testing *versus* self-management groups†	$P = 0·46$		$P = 0·67$			
% TIR *versus previous* 6 months*	$P = 0·11$	$P = 0·10$			$P = 0·04$	

% TIR are shown for self-testing patients, self-managing patients during the study period. % TIR obtained by routine anticoagulation clinic management during the previous 6-month period are shown for comparison.
CI, confidence interval; NS, not significant; TIR, time in range; PSM, patient self-management; PST, patient self-testing.
*Wilcoxon signed-rank test.
†Mann–Whitney *U*-test.

Table IV. Percentage time outside control limits (INR < 1·5 or >5·0).

			Previous 6 months	
	Self-management	Self-testing	PSM group	PST group
Number of patients in study	40	35	40	35
% Time outside control limits (95% CI)	2·21 (0·72–3·71)	1·06 (0·32–1·81)	2·56 (0·13–4·99)	1·96 (0·26–3·66)
PST *versus* PSM*	NS	NS		
% Outside limits versus previous 6 months*	NS	NS		

Data from two patients, whose warfarin was reduced or discontinued prior to elective surgery or dental treatment during the study, were excluded from this table.

CI, confidence interval; PSM, patient self-management; PST, patient self-testing.

*Mann–Whitney *U*-test.

Patients in the both groups were asked to test QC plasma once a month. If this had been followed by all patients, approximately 462 internal QC (IQC) tests would have been performed. In fact, only 294 IQC tests were performed, indicating a 59% compliance rate. The mean number of IQC tests for each group was 3·90 and 3·72 for the PSM and PST groups respectively, with a range of 0–9 QC tests over the 6 month period. Several different lots of CoaguChek PT Control were used during the study, and each had different target values. Overall, intra-lot imprecision was acceptable at 11·5%. Results for all four EQA samples tested were skewed to a greater or lesser extent by outlying high INR determinations, resulting in coefficients of variation of 7·8%, 16·1%, 16·4% and 43·3% with between 4·8% and 26·3% outwith consensus.

Discussion

This randomised control trial found no significant difference between the quality of OAT achieved through PSM and that obtained by self-testing patients managed by a specialised hospital anticoagulation clinic. Furthermore, self-testing and self-managing patients spent significantly more time within the target therapeutic range during the study than during the previous 6 months under routine anticoagulation clinic management. As with many other clinical trials, uptake was low, with only 13% of contacted patients enrolling to this study. A total of 104 patients were randomised to PSM or PST with 74% completing the study (PSM = 41, PST = 36), with similar 'drop out' rates for both groups. Testing in both groups performed using the Roche CoaguChek S, which has previously received satisfactory evaluations for both professional use (Bachour *et al*, 2001) and PST (Gardiner *et al*, 2005). There was no significant difference in testing frequency between the PST and PSM groups, indicating excellent compliance.

We have shown that, although the quality of OAT in self-managing patients was no better than in self-testing patients, but that when the two groups were combined, they showed a significant improvement over the quality of OAT achieved by conventional management in the previous 6-month period. This increase in time in therapeutic range is in agreement with other studies, in which PSM was compared with specialised anticoagulant clinic management, in which the initial quality of OAT was good (Sidhu & O'Kane, 2001; Gadisseur *et al*, 2003; Menendez-Jandula *et al*, 2005). This may be due to increased patient education and awareness as suggested by Gadisseur *et al* (2003), more frequent testing as suggested by Horstkotte *et al* (1998) or, more likely, a combination of the two.

As thrombotic and bleeding risks are known to increase exponentially at INRs <1·5 and >5·0, respectively, the incidence of INR values outside these control limits was recorded. The time outside control limits in the self-testing patients was approximately half that observed in the previous 6 months. A similar reduction in time outside control limits although expected, was not observed in the self-managing patients, and this was attributable to a small minority of patients (three of 25) showing poor compliance. This demonstrated the importance of careful documentation of both INR results and warfarin dose by self-managing patients and also highlighted the importance of reviewing anticoagulant control of the patients on a regular basis (Fitzmaurice & Machin, 2001). Those who demonstrate repeated poor compliance are potentially at increased risk of haemorrhage or thrombosis, and should not be allowed to continue self-management.

Compliance in QC testing was variable, some patients performed too many tests, some patients performed too few and a minority of patients performed none at all. It was clear from the reasons given, that many patients did not fully understand the reasons or the importance of regular QC testing. The overall performance of internal and external quality QC was good, although poor performance in a minority of patients distorted the true figures. These discrepancies appeared to be largely because of the inappropriate handling of the QC preparations and difficulty in mixing the samples. It is clear that the role of QC testing must be fully explained during the patient education and training sessions prior to PST or PSM (Murray *et al*, 2003). Compliance in regular testing and performance of QC should be included in the contract between the anticoagulation clinic and the patient.

This study had several limitations. The variation between testing intervals during the study period and the previous

6 months, made direct comparisons of time in therapeutic range difficult, nevertheless, it was felt that it was important to explore this issue. The uptake for this trial was approximately 13%, suggesting that PSM and PST may be acceptable to only a minority of patients. However, it was felt that many patients found the clinical trial setting off-putting, and this may have contributed to the low uptake. This was an unblinded trial at a single centre. However, our intention was to compare self-testing with self-management within the context of a specialised anticoagulant clinic and, to our knowledge, this is the first published comparison of PST with PSM in warfarin patients.

It is clear that a high quality of OAT may be achieved through PSM. However, some patients demonstrating poor compliance are not suitable for self-management, and the importance of regular QC testing must be impressed on patients prior to PST or PSM. Excluding patients, who have previously demonstrated poor compliance, in terms of attendance at clinic or adherence to treatment from self-management or self-testing may lessen compliance problems. Accurate recording of INR results and warfarin dose should be kept by self-managing patients and it is essential that these should be regularly reviewed. We conclude that PSM is an effective mode of oral anticoagulant management for the majority of suitably trained patients.

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Authors contribution

CG and KW managed the study and are lead investigators. CG drafted the paper. HC is principal investigator and critically revised the paper. IJM and SJM participated in the study design and critically revised the paper. HC and SJM are the guarantors.

Conflict of interest

None.

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