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Should patients manage their own oral anticoagulation therapy?

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Editorial

Oral anticoagulant therapy has become more commonly prescribed for people of 65 years and over following the widening of its clinical indications to include thromboembolic prophylaxis in atrial fibrillation.[1] It is estimated that approximately 470 000 people in the UK, almost 1% of the population, are currently receiving oral anticoagulant therapy and this is growing. Due to its narrow therapeutic index and the intra-individual variation in dose requirement, there is a need to monitor the level of anticoagulation in each patient. In consequence, health systems have had to invest resources into monitoring services to cope with this development.

Degree of anticoagulation is measured using the International Normalised Ratio (INR) of the prothrombin time (PT). Patients have, until recently, been monitored and managed by their local general practitioner or at specialized hospital- based anticoagulation clinics. More recently, availability of small portable devices has enabled patient self-monitoring of anticoagulation and, following adequate education, self-adjustment of dose. This has enabled patients to have more control over frequency of monitoring and become more actively involved in managing their treatment. When portable monitors were first introduced, the initial research focused on their accuracy in comparison with routine laboratory measurements and whether patients found home monitors acceptable to use. These studies confirmed a high degree of similarity between home tests and clinic tests.[2,3,4] Studies to establish their clinical role were then undertaken.

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Patient self-management of oral anticoagulant therapy

Self-management would be a suitable model of oral anticoagulation therapy management if it could be shown to meet specific criteria. These are, firstly, improving therapeutic control, thereby decreasing complication risk, secondly, improving the patients' quality of life and thirdly, increasing cost-effectiveness, when compared with the current management strategies. The major criticisms of many of the studies so far reported are that self-managers and control patients have not been randomly selected and many data are not prospectively collected. Extrapolating results is also hampered by the diversity of management of the control groups, some managed by their family physicians, and some by specialist anticoagulation clinics, which results from different practices between countries.

Quality of therapeutic control

Ansell *et al.*[5] were early investigators of the therapeutic effectiveness of self-management of oral anticoagulation, comparing it with management by a specialist anticoagulation clinic at a tertiary medical institution. Their study demonstrate flaws in design about which it is important to be aware. It was a retrospective, and non-randomized, cohort study. Twenty patients, following education and training in PT monitoring and dosage adjustment, measured and managed their PT at home over an average of 7.5 years. Each measured PT every two weeks, unless a dosage adjustment was made, in which case a measurement was made the following week. The cohort were not representative of the anticoagulated population, their selection being based on a subjective assessment of their ability to perform measurements at home and the stability of their PT over the preceding months. The authors attempted to match control patients for age, gender, reason for anticoagula-

tion and duration of treatment, but could only match 75% (15/20) correctly, potentially affecting the outcome in what was a small study. As the criteria used to select the intervention group were not applied to the control group, it is likely to have included patients who would never have been considered for self-management, thus compounding the validity of the results. Quality of therapeutic control, measured as percentage of time in the therapeutic range, was a prime outcome measure. The self-management patients were within their therapeutic range 88.6% of the time, compared with 68.0% in the control group($p < 0.001$). There were also fewer dose changes in the study group compared with the controls (12 changes vs. 23 on average: $p < 0.001$). There were major complications in two of the self-managed patients (GI bleed and haematoma) and none in the control group. As the control patients were analysed retrospectively and so may have had complications that were not elicited, and because of the small sample size, the study however does not provide useful data on safety or complications.

Sawicki[6] performed a randomized, single-blind multicentre trial at five different centres in Germany, where the outcome measure was the deviation of INR values from the individual target range. The 83 control group patients were managed by a combination of family physicians and specialists. The 82 study patients were required to self-monitor at least one to two times per week, for six months. The intervention patients were retrained in their technique if they deviated >0.4 INR from the reference range. Fourteen patients dropped out, the reasons for which are unfortunately not given. Less than 29% of self-management patients were within the target range at baseline, rising to 57% at three months and 53% at six-month follow-up. Corresponding figures for the control group was 36%, 34% at three months and 43% at six months. The difference between the self-managed and control group was significant at three months (p =0.006) but was not significant at six months (p=0.22). The study time of six months was too short and the sample size too small to adequately examine the risk of complications or to conclude that self-management is safe.

Cromheecke *et al.*[7] performed a randomized crossover comparison of self-management and anticoagulation clinic management in 50 patients on long-term therapy for six months. The study eliminated the problem of incorrectly matched controls with its crossover design. Patients were educated and trained in self-management before randomization. INR was measured at intervals of one to two weeks in both periods. In the self-managed group, 55% of INRs were <0.5 from the target INR, compared to 49% in the control group (p = 0.006). The odds ratio for better control, defined as the period of time in the therapeutic range during self-management, was 4.6 (95% CI 2.1–10.2). A patient satisfaction assessment showed superiority for self-management of anticoagulation. Three minor bleeding episodes were recorded by the 50 patients of the clinic-managed group (all of whom were out of their target range at the time of event) and one minor bleeding episode in the self-management group. There were no episodes of major bleeding. The study was too small and too short to provide data valid for assessment of risk.

Hasenkam *et al.*[8] also observed patients who received oral anticoagulant therapy following heart valve replacements, for at least a nine-month period. However, the sample size was only 21 patients and their selection was not random but was due to their 'anticipated high level of compliance judged at interview'. The study group was compared with 20 patients whose medical files were retrospectively collected and matched with the study patients, giving the possibility of selection bias. The reliability of medical records to contain accurate and necessary information is questionable. The study patients were within their therapeutic range 77% of the time, compared with 53% for the control patients. In the training period, parallel laboratory INR measurements were made at three to four-week intervals. These showed the mean deviation of laboratory and Coaguchek INR was 7.8%, but each patient had a constant characteristic deviation from –11 to +21%. Following the study of nine months, 19 of the study patients wanted to continue with self-management. The small sample size, the non-randomized design and the partly retrospectively collected data limit the usefulness of the results and do not allow comment on the relative safety of self-management.

Effect on outcomes of thromboembolism or bleeding

The randomized prospective study of Kortke *et al.*[9] of self-management following heart-valve

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replacement in 600 patients, ensured no variation in the indication for therapy. The majority (74.5%) had received aortic value replacements. Subjects were randomized into the control group (295 patients), who were managed by family practitioners, or the intervention group (305 patients), who monitored their INR values at home. The randomization eliminates selection bias and the study also has the advantage of a larger sample size, a prospective design and a longer study period of 25–51 months. In the control group, 62% of recorded values were in the target therapeutic range over the entire study period, compared to 79% in the self-managed group ($p \leq 0.001$).

Patients recorded complications themselves, which were checked by the investigators. This was a potentially flawed reporting system, as some patients may have been more motivated to report complications than others. The researchers had specific definitions and grades for both thromboembolic and haemorrhagic complications. There were 74 recorded Grade III (most severe) thrombotic and haemorrhagic complications, 42 in the self-management group, 29 in the control group, $p < 0.05$. Most were haemorrhagic. More than 98% of the self-managed group were free of Grade III complications after two years. Complications were at their highest in the first 11 months postoperatively. Twenty-five patients (8.3%) gave back their PT monitors and were excluded from the study, but reasons for discontinuing therapy are not given. The authors supported beginning self-management immediately after heart valve replacement as, over a two-year period, nearly 80% of self-recorded INR were in the therapeutic range in patients managing their own anticoagulation, as opposed to 64.9% monitored by family practitioners ($p<0.001$).

Frequency of testing

The reasons why self-managed patients appear to have better control has been debated. Authors have suggested that the increased frequency of testing, which can be provided by home PT testing, has a positive effect on the percentage of time in the therapeutic range. The results of Ansell *et al.*[5] demonstrated this relationship, with the study group monitoring their PT values 2153 times in comparison with 1608 times in the control group over 44.7 months vs. 42.5 months respectively. A more striking difference in testing frequency is seen in the study of Kortke *et al.*[9] The control group submitted 4599 INR values compared with 23 693 values by the self-managed group, over a similar number of patient-years (943 vs 973). Hasenkam *et al.*[8] ensured that the study patients measured their INRs at least weekly, whereas the control patients measured at least every eight weeks, although this varied from patient to patient. Cromheecke *et al.*[7] also reported that frequency of INR testing was increased in the self-managed group when compared with the clinic managed groups (every 8.6 days vs. 9.0 days). However, there was only a slight difference in the frequency of monitoring in this study when compared to the others, and yet the author still detected a difference between the level of control. In a study designed to test the hypothesis that increased frequency of testing would lead to better control of anticoagulation, 2733 weekly INR measures were carried out by 49 patients, using self-management and 539 tests in 53 patients having standard management, over the same period.[10] The deviation from target INR was smaller in the self-management group ($p < 0.0001$), with more values being in the target range (86.2% vs 80.1% at INR range 2.5–4.5; 82.2 vs 68.9 at INR range 2–3). Achieved INR was almost identical to target INR in patients using self-management but significantly below ($p < 0.005$) the target INR in patients on high intensity anticoagulation having standard management (target INR 3.5, achieved INR 3.19 (3.05–3.34)). This may reflect a nervousness on the part of clinic staff associated with what they would consider higher INR targets than those with which they are most familiar.

It has been suggested that, if monitoring occurs monthly, only 50–60% of patients remain in their target range. This increases to 77–85% of patients if weekly monitoring occurs and up to 92% of patients if monitoring is every three days.[2] It would be unrealistic to expect an anticoagulation clinic to be able to monitor patients every three days, but home monitoring does allow for this possibility. It has been postulated that a threshold may exist beyond which there is no further beneficial effect of increased testing and this has been suggested as between two and four days.[11] This is understandable, given the delay between warfarin ingestion and its effect upon clotting factor synthesis.

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Self-management by older people

In a study of 325 patients of 65 years or over, designed to assess the effect of a programme to educate patients about warfarin, train them to increase their participation, self-monitor prothrombin time and alter their warfarin dose according to guidelines, the proportion of time during which the INR was in the therapeutic range was higher in the intervention group than in the usual-care group (56% vs 32%; $p < 0.001$).[12] Major bleeding was more common at six months in the group who received 'usual care' from their primary physician than in the intervention group (cumulative incidence, 12% vs. 5.6%; p, 0.05). After six months, major bleeding occurred with similar frequencies in the intervention and usual-care groups. These findings suggest that education and self-management reduce the likelihood of major bleeding and would lead to safer and more effective use of warfarin therapy in older patients.

Heidinger *et al.*[13] studied patients receiving the therapy for the treatment of atrial fibrillation or deep vein thrombosis. As thromboembolic prophylaxis for patients in atrial fibrillation in those of 65 years and older accounts for the increase in use of warfarin over the last decade to just under 1% of the UK population and rising, research in this group is particularly important. They examined 1375 patients in Germany who had been anticoagulated for at least three months, 1428 patient years of observation in total. Sixty-nine per cent of INR values in patients with atrial fibrillation and similarly in patients with deep vein thrombosis were within the therapeutic target range. This is rather low in comparison with other study groups, but the study does not detail how often patients were measuring their INR. There was an incidence of bleeding of 1.69% per patient year in those with atrial fibrillation (AF) and 1.52% in those receiving therapy for deep vein thrombosis (DVT). The incidence for thromboembolic complications was 1.04% per patient year in those with AF and 1.21% in those with DVT.

Further information about the elderly in atrial fibrillation would be particularly important, as a decision that the likely benefits will outweigh risks is required in each individual before embarking upon anticoagulation. An open, randomized study is under way in Germany,[14] aiming to investigate the benefits and costs of self-management of oral anticoagulation in patients with atrial fibrillation. Results of the two-year study, which aims to randomize 2000 patients to self-management or usual care, and report on thromboembolic and haemorrhagic complications, INR values and cost efficiency, should provide useful information.

Patient satisfaction and quality of life

It has been postulated that patients, through self-management of their oral anticoagulation therapy, would increase their compliance and satisfaction with treatment. Many of the studies cited assessed patient satisfaction. Sawicki *et al.*[6] measured treatment-related quality of life by a 40-item questionnaire, administered at baseline and at six-month follow-up. General treatment satisfaction and daily hassles scores improved in the self-management group ($p < 0.001$ and $p = 0.01$), whereas self-efficacy and distress improved in both groups but significantly more so in the self-managed group ($p = 0.003$ and $p = 0.006$). No significant effect on strained social networks was identified.

Ansell *et al.*[5] used a satisfaction survey to assess the 'comfort level' of patients with self-management, their training and ability to perform PT measurement. The topics included adequacy of training, initial confidence with testing and confidence after three months, and practical aspects of machine operation. Of the 17/20 patients in the self-management group who completed it, 11 stated that routine management caused more anxiety and that they preferred self-management. The reasons why either method may cause greater anxiety were not explored in depth. However, the results appeared to support the notion that self-management is preferred by many patients.

Kulinna *et al.*[15] performed a prospective cohort study of INR self-monitoring on 100 patients and measured quality-of-life changes. They found that the highest improvement in score following self-monitoring was in independence and organization of vacation/spare time, thus empowering patients to organize their time more efficiently when not depending on a clinic-based service. Similar results were noted by Anderson and Hirsch,[16] who evaluated the feasibility and accuracy of home use of the portable PT monitor in a prospective cohort study of 40 patients. Thirty-four patients preferred using the portable home monitor and 97% suggested that they had a 'greater sense of control and

involvement in therapy management' (P<0.001). When asked about the method that caused more anxiety, no significant difference was found between the two methods.

Cromheecke *et al.*[7] gave 50 self-managed and 44 clinic-managed patients a structured, validated 32-item questionnaire to subjectively measure their quality of care and satisfaction with treatment, worries and social issues. Significant differences in favour of the self-management group were achieved for general treatment satisfaction ($p = 0.015$), self-efficacy ($p < 0.001$), daily anxieties ($p < 0.001$), distress ($p = 0.022$) and strain (social issues) ($p < 0.001$).

Training

Training requirements in self-management must differ between patients, but this has been little studied. In their training centre, Morsdorf *et al.*,[17] recruited 50 patients who took part in a standardized training course for self-management. Patients (36 men, 14 women) were preselected according to the guidelines of the German Association for Self-management of Oral Anticoagulation and were all trained by the same physician. The complete course took an average of eight sessions. Patients older than 59 years needed significantly more training time in theory than younger patients; they did not need more training time in practical matters. During the study period, the values of International Normalised Ratio (INR), measured in venous blood samples and by self-assessment, were comparable for both groups. There was a good overall correlation between self-controlled INRs and laboratory assays, but the self-assayed INRs were significantly lower than those from the venous blood samples. There was no difference in the success of self-management between those initiating self-management of oral anticoagulation from the time of commencement and those who had been initially managed in a clinic for more than six months.

Anderson and Hirsch[16] reported that 40% of patients experienced an initial difficulty with operating the monitor, particularly with application of blood on to the cartridge. These difficulties were overcome with further training, but raise the possibility of problems for those with disorders which may limit their manual dexterity, for example rheumatoid arthritis. Furthermore, Cromheecke *et al.*[7] commented that a potential limitation of self-management was discovered in one patient who could not self-manage due to progressive visual impairment. Patient factors that may prevent self-management have been inadequately investigated in the studies, with little detail being given as to the factors which make patients decide to stop using the portable home monitor. Studies in older people, who may have co-morbid conditions that could hinder their use of home monitors, would be particularly valuable.

The ability of patients on chronic oral anticoagulation therapy (OAT) to self-adjust their dose without specific training and the integration of a portable PT monitor (Coaguchek) for home use into routine patient care in anticoagulation clinics, has been evaluated in a nested case-control study, conducted in four centres of the Italian Federation of Anticoagulation Clinics (FCSA).[18] Patients ($n = 78$) on stable OAT for at least six months (47 men, 31 women, aged 18–75 years) were enrolled on a volunteer basis after passing an abbreviated mental test. After three instruction sessions on the use of the monitoring equipment, subjects performed the PT test at home, communicated the INR results to the Centre and suggested the dose adjustment and date for next control as they thought appropriate. However, they were requested to follow the prescription made by the Centre. Controls (78 subjects) matched by age (± 5 years), sex and therapeutic range were selected from among those who attended the anticoagulation clinics and managed by usual care. Time spent in the therapeutic range during the study was the same (80%) for cases and controls. It seems therefore, that some patients can acquire satisfactory ability for self-adjustment of dose without specific training.

Cost-effectiveness

The cost-effectiveness of self-management has been inadequately investigated, especially in relation to the UK. Estimates have assumed that self-management results in increased time in the therapeutic range, reduces complication rates and results in less time in hospital. Self-management may reduce the need for specialist anticoagulant clinics, travel and associated costs. Samsa[11] estimates that the cost of an 'adverse event' is approximately $50 000. This is vastly more than Eckman and Pauker's[19] estimation, which is between $3 000 and $12 000 for haemorrhagic complica-

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tions and between $5 000 and $18 000 for thromboembolic complications, depending on outcome. However, Ansell[20] estimated that the combined savings by lowering the incidence of complications was approximately $835 per patient year. Thus estimations of cost-effectiveness are widely incongruent. It is possible that it could cost more than standard management.

Self-management itself has expenses such as the cost of the machine, currently £399 + VAT. For each test, the patient needs to use a new cartridge that costs £2.50 each. Furthermore, the cost of training programmes and the employment of training personnel have to be included. As a result, cost-effectiveness may be best for those patients who are on long-term therapy.

Conclusion

All of the studies examining quality of control conclude that self-management patients spend a significantly increased percentage of time within their therapeutic range, compared with control groups. Furthermore, this trend appears to remain, regardless of clinical indication for anticoagulant therapy. They don't provide information about outliers who are most at risk of complications. There are important limitations in some of the study designs, principally in the adequate selection of control groups and the analysis of retrospective data. However, aside from these limitations, the randomized-controlled trials which have been performed indicate that self-management leads to better control of INR, probably as a result of increased frequency of testing.

A major problem with the studies is that the sample sizes are too small to ensure that adequate assessment of complication risk could be ascertained, particularly in the time-limited periods of observation. Results obtained from non-randomized studies which show good control in the self-management group, and suggest a low risk of complications[21] are interesting. There remains a need for larger, randomized long-term studies to investigate the risk of complications. The evidence is as yet inconclusive as to whether there is a difference in complication risk between clinic-managed and self-managed patients. The outcome measure of time in the therapeutic range, which is associated with the risk of complications, must at present act as a surrogate but unsatisfactory marker of reduced risk.

Although studies indicate an improvement in quality-of-life measures, patient satisfaction and preference for self-management, there are flaws in study design here too. For example, in the studies of Ansell *et al.*[5] and Hasenkam *et al.*,[8] patients were selected subjectively by the investigators and so were likely to be highly motivated individuals. It is clear that not all patients would be able to undertake self-management, due, for example, to visual impairment or problems with operating the home monitor. Reasons for dropping out from self-management is not discussed in the studies, but are important. It would be relevant to know whether conditions such as arthritis of the hands, poor eyesight, or poor comprehension, all more common in old age, were responsible. Further randomized investigations to determine for which patients self-management is appropriate are required. The potential cost-effectiveness of the scheme requires careful assessment, particularly in the context of the UK's health service, as the majority of research thus far has been based in other countries.

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