ANTICOAGULATION IN PATIENTS WITH THROMBOEMBOLIC DISEASE

R C Tait

Background: Vitamin K antagonist treatment is effective for prevention and treatment of thromboembolic events but frequent laboratory control and dose adjustment are essential. Small portable devices have enabled patient self-monitoring of anticoagulation and self-adjustment of the dose. We compared this self-management of oral anticoagulant therapy with conventional management by a specialist anticoagulation clinic in a randomised cross-over study. Methods: 50 patients on long-term oral anticoagulant treatment were included in a randomised controlled crossover study. Patients were self-managed or were managed by the anticoagulation clinic for a period of 3 months. After this period the alternative strategy was followed for each patient. Prothrombin time (expressed as international normalised ratio [INR]) were measured at intervals of 1–2 weeks in both periods without knowledge of type of management. The primary endpoint was the number of measurements within the therapeutic range (therapeutic target value ±0.5 INR units). Findings: There was no significant difference in the overall quality of control of anticoagulation between the two study periods. Patients were for 55% and for 49% of the treatment period within a range of ±0.5 from the therapeutic target INR during self-management and anticoagulation clinic management, respectively (p=0.06). The proportion of patients who spent most time in the therapeutic target range was larger during self-management than during anticoagulation clinic-guided management. The odds ratio for a better control of anticoagulation (defined as the period of time in the therapeutic target range) during self-management compared with anticoagulation clinic-guided management was 4.6 (95% CI 2.1–10.2). A patient satisfaction assessment showed superiority of self-management over conventional care. Interpretation: Self-management of INR in the population in this study is feasible and appears to result in control of anticoagulation that is at least equivalent to management by a specialist anticoagulation clinic. It is also better appreciated by patients. Larger studies are required to assess the effect of this novel management strategy on the incidence of thromboembolic or bleeding complications. (Lancet 2000;356:97–102)
subsequent incidence of recurrent DVT and PE. Such prolonged oral anticoagulant treatment—in many cases 6 months and in some cases 1 year—has to be acceptable to the patient, both in terms of benefit:risk ratio and convenience of anticoagulant control. The haemorrhagic complications of oral anticoagulant therapy may be reduced by high quality anticoagulant control, maintaining the international normalised ratio (INR) within the desired therapeutic range. Traditionally, this has been achieved by frequent attendance at specialised hospital based anticoagulant clinics. Fortunately, the recent availability of portable near patient INR testing equipment and computerised warfarin dosing algorithms have allowed small and convenient community based anticoagulant clinics to be established. Of course, the same technologies can facilitate patient self-testing and self-dosing which, when combined, will allow patient self-management of oral anticoagulant therapy. Resourcing issues as well as anxieties over devolving total anticoagulant care to the patient have delayed assessment of patient self-management in the UK. However, several randomised controlled trials have been undertaken in Germany and the Netherlands including that by Cromheecke et al which provides the introductory article for this review. These recent studies have demonstrated adequate efficacy and safety of self-management programmes and it simply remains for logistical, patient selection, and resourcing issues to be resolved before oral anticoagulant self-management, analogous to diabetic self-management of insulin therapy, may become the norm.

This review summarises the evidence base that supports our current anticoagulant management strategies and discusses the emerging technology and treatments that are likely to shape self-management strategies for venous thromboembolic disease in the future.

**Initial anticoagulation following acute venous thrombosis**

In the 1940s and 1950s anticoagulant strategies for treatment of venous thrombosis were simply based on uncontrolled observations. The first randomised study to demonstrate the efficacy of heparin and oral anticoagulation (albeit for only 14 days) was reported in 1960. However, it has taken a further 40 years to determine the optimal intensity and duration of anticoagulant treatment. The importance of achieving early therapeutic heparinisation was demonstrated by Basu et al. In a cohort of 162 patients with acute venous thrombosis, all five patients suffering early recurrence (within days of the initial event) had subtherapeutic heparin levels. Similarly, Hull et al observed a 15-fold higher recurrence rate over 3 months in patients with proximal DVT whose heparin treatment was subtherapeutic at 24 hours. A subsequent study showed that the duration of heparin therapy (traditionally 10 days) could safely be reduced to 5 days assuming oral anticoagulants were started on day 1. This led some researchers to question the requirement for the initial course of heparin. However, its importance was confirmed by Brandjes et al in a randomised controlled study in which 120 patients with proximal DVT received treatment with oral anticoagulants for 3 months commencing on day 1. Only half the cohort received initial intravenous unfractionated heparin. During the first 6 months following the initial DVT symptomatic extension or recurrent thrombosis was documented in 20% of cases who did not receive heparin compared with 6.7% of those who did. Furthermore, asymptomatic extension of DVT at 1 week was significantly less common in the group receiving heparin (8.2% vs 39.6%; p<0.001). Interestingly, the reduction in symptomatic recurrences in the heparin treated group extended well beyond the initial phase of anticoagulation.

**Low molecular weight heparins in the treatment of acute venous thrombosis**

Low molecular weight heparins (LMWHs) are prepared from unfractionated heparin by controlled depolymerisation yielding polysaccharides with a mean molecular weight of 4000–6000 compared with 12 000–14 000 in unfractionated heparin. These smaller polysaccharides have a relatively higher anti-Xa than anti-IIa activity and, following subcutaneous administration, are readily absorbed resulting in a bioavailability approaching 100%. They are less prone to endothelial sequestration and consequently have a longer half life. These properties mean that LMWH gives a highly predictable dose response compared with unfractionated heparin.

Early studies comparing LMWH with unfractionated heparin in the treatment of DVT indicated superior improvement in venogram appearances with LMWH. Subsequent studies with harder clinical end points (recurrent venous thrombosis, mortality, and major haemorrhage) established that LMWH was at least as safe and effective as unfractionated heparin in the treatment of DVT and PE. These findings paved the way for successful trials of LMWH in outpatient treatment of venous thrombosis. Subsequently, a series of meta-analyses has confirmed their superiority over unfractionated heparin with significantly better clot reduction and lower rates of mortality, recurrent thrombosis, and major haemorrhage. These findings, together with other advantages of LMWH (box), now make it the heparin of choice in the treatment of acute DVT and PE.

<table>
<thead>
<tr>
<th>Advantages of low molecular weight heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior pharmacokinetic profile allowing predictable dose response</td>
</tr>
<tr>
<td>No need to monitor blood levels (except in significant renal impairment or patients at extremes of normal weight range)</td>
</tr>
<tr>
<td>Logistic advantages of once daily subcutaneous dosing</td>
</tr>
<tr>
<td>Facilitates outpatient management of venous thrombosis</td>
</tr>
<tr>
<td>Superior efficacy in treatment of DVT</td>
</tr>
<tr>
<td>Improved clot reduction</td>
</tr>
<tr>
<td>Lower overall mortality</td>
</tr>
<tr>
<td>Fewer recurrent thromboses</td>
</tr>
<tr>
<td>Superior side effect profile</td>
</tr>
<tr>
<td>Less haemorrhage</td>
</tr>
<tr>
<td>Lower risk of heparin induced thrombocytopenia</td>
</tr>
<tr>
<td>Lower risk of osteoporosis</td>
</tr>
<tr>
<td>At least equivalent efficacy in treatment of PE</td>
</tr>
<tr>
<td>Superior cost effectiveness in treatment of DVT</td>
</tr>
</tbody>
</table>

**Duration of oral anticoagulant therapy**

The need for oral anticoagulant therapy after initial heparin treatment was established in two separate studies. In 1979 Hull et al randomised patients with DVT to receive either oral anticoagulant or low dose subcutaneous heparin (5000 units twice daily unfractionated heparin) for 3 months following 14 days of intravenous heparin. During the 12 week follow up period none of the patients receiving warfarin suffered recurrent venous thromboembolism compared with 26% in the low dose heparin group. Major haemorrhage was
significantly more common in the warfarin treated group (12% vs 0%). In 1985 Lagerstedt et al.\(^1\) reported on a study of patients with isolated calf vein DVT who, after 5–7 days of treatment with intravenous heparin, were randomised to receive oral anticoagulant therapy for 3 months or no further treatment. The rate of recurrent thrombosis was significantly less in the warfarin treated group both at 3 months (0% vs 29%) and at 1 year (4.3% vs 67.8%). This suggested that oral anticoagulant therapy for 3 months was sufficient to prevent recurrent thrombotic events following isolated distal DVT. However, the optimal duration of anticoagulant therapy for proximal DVT and PE remains to be established. Between 1970 and 1990 there was a trend toward shorter periods of oral anticoagulant therapy. This was apparently supported by several small, poorly powered studies that failed to demonstrate any difference in recurrent thrombosis rates following treatment for 4 or 6 weeks compared with 6 months.\(^{20,21}\) However, the first large study to address this issue,\(^22\) conducted by the British Thoracic Society, demonstrated a significantly lower recurrence rate with 3 months of treatment compared with 4 weeks (4% vs 7.8% during a 12 month follow up period; \(p=0.04\)). An unfortunate weakness of this study was that objective diagnosis was obtained for only 71% of the initial thrombotic events and 42% of the recurrences. However, the study did show that patients with DVT following temporary risk factors such as surgery had a low risk of recurrent thrombosis, even after just 4 weeks of oral anticoagulant therapy. This finding was confirmed in a subsequent study by Levine et al.\(^23\)

Schulman et al.\(^24\) compared oral anticoagulant therapy for 6 weeks and 6 months (target INR 2.0–2.85) for treatment of a first episode of DVT or PE. At 2 years the odds ratio for recurrence in the 6 week group was 2.1 (CI 1.4 to 3.1; 18.1% recurrences vs 9.5%). Subgroup analysis revealed lower recurrence rates in patients with transient risk factors and higher than average recurrence rates in patients with persisting risk factors or idiopathic DVT or PE. Furthermore, recurrence rates were higher following PE than after proximal DVT (table 1). The differences were seen irrespective of the duration of anticoagulant therapy. The same authors\(^25\) also showed that, following a second episode of DVT or PE, indefinite oral anticoagulant therapy (compared with treatment for 6 months) greatly reduced the risk of further recurrences (table 1). However, this reduction was achieved at a cost of increased episodes of major bleeding (8.6% vs 2.7% during 4 years of follow up, \(p=0.084\)).

The main difference in recurrence rates between patients treated for 6 weeks and those treated for 6 months resulted from an early accumulation of recurrent events following cessation of oral anticoagulants at 6 weeks. The same phenomenon of early recurrent events was noted in a study of patients with a first episode of idiopathic DVT or PE who were randomised in a double blind study to receive oral anticoagulant treatment for 3 or 24 months.\(^26\) The study was terminated prematurely because follow up at 12 months revealed astonishingly higher recurrence rates in the group treated for 3 months (27.4% vs 1.3%, \(p=0.001\)). From this study it would appear that the high recurrence rates following idiopathic thrombosis cannot be overcome by longer term, but not indefinite, anticoagulant therapy. In the WODIT study\(^27\) treatment of the first episode of idiopathic DVT with oral anticoagulant therapy for 3 and 12 months was compared. Not surprisingly, recurrence rates at 12 months were significantly higher in the short term treatment group (7.5% vs 1.5%). However, at 2 years the recurrence rates were not significantly different (14.4% vs 11.8%). Furthermore, major bleeding was four times more common in the longer treatment group (absolute risk 3%/year on treatment).

### Maximising the benefit:risk ratio of longer term oral anticoagulant therapy

Clearly, there are categories of patients with DVT and PE who merit receiving treatment with oral anticoagulants for at least 6 months. This is particularly true for patients with persisting risk factors (particularly cancer) or primary idiopathic thrombosis. Careful patient selection of those individuals at highest risk of recurrent thrombosis will therefore help to maximise the benefits of longer term anticoagulation. The main health cost of such treatment is increased episodes of major haemorrhage which, with standard anticoagulant therapy, occur at an absolute rate of around 3%/year with one in four events being fatal.\(^{36,37}\) Risk factors for major haemorrhage include older age, polypharmacy, comorbid disease, and higher achieved INR.\(^{36,37}\) Here again, patient selection is critical, as is anticoagulant control which should aim to achieve the lowest possible INR below which the optimal antithrombotic effect is lost.

Studies comparing different ranges of INR suggest that a target range of 2.0–3.0 is optimal.\(^36\) This is further supported by evidence that INRs below 1.9 are associated with a higher rate of recurrent thrombosis,\(^38\) while INRs of 2.0–3.0 are associated with a low risk of bleeding.\(^39\) The risk of bleeding should also be reduced if the INR can be maintained within this optimal therapeutic window. This is particularly pertinent during the initial phases of oral anticoagulant therapy when the risks of over-anticoagulation and bleeding are significantly higher.\(^20,21\) The use of an established induction algorithm is critical. Typically, a 10 mg warfarin induction regime can be used.\(^40\) However, in older patients there may be merit in using a lower dose regime that may take longer to achieve a therapeutic INR but have less likelihood of achieving dangerously supratherapeutic INR levels.\(^41\) Balancing the risk of recurrent thrombosis (case fatality rate 4%),\(^42\) although perhaps higher if the initial thrombosis is a PE\(^43\) against the risk of major haemorrhage (case fatality rate 25%) is important when determining the optimal duration and intensity of warfarin therapy for an individual patient. The patient’s age, risk factors for bleeding, and details of the initial DVT or PE should be taken into consideration.\(^41,44\) These concepts and the existing evidence base form the basis of national guidelines, both in the UK\(^44\) and the USA.\(^45\)
Monitoring oral anticoagulant therapy

It is assumed that tight control of anticoagulant therapy during the maintenance phase, which may last from 3 months to many years, will maximise the antithrombotic efficacy and reduce the risk of haemorrhagic complications. However, the model of care used to provide the service can radically affect the quality of anticoagulant control. Traditionally, in the UK, patients will attend a hospital based specialised anticoagulant clinic to have their INR tested from either a capillary or venous blood sample with dose adjustment advice being given by an experienced physician. Such systems provide rather modest INR control with only 50–60% of INR results, or a similar proportion of time, being in the specified target range.56–58 These models do, however, appear to be superior to systems in the USA46 and Germany59 where, historically, anticoagulant control has been left to family practitioners when percentage results in target range is nearer 40%. This performance can be improved by introduction of specialised anticoagulant services.51

Computerised decision support software for anticoagulant dosing

In an attempt to further improve the quality of anticoagulant control and to devolve some of the ever expanding service to less experienced medical and paramedical staff, computer programmes were designed to assist in oral anticoagulant dosing. Early studies with three different programmes showed that they were as effective as experienced medical staff in reaching target INRs.60 One of the programmes (Anticoagulation Management Support System, Soft-top Information Systems, Warwick, UK) has proved successful in the primary care setting and another system (DAWN, 4S Information Systems, Cumbria, UK) is already in widespread use in the secondary care sector throughout the UK. It is estimated that around 150 hospitals use this system to monitor approximately 300 000 patients. This system was tested in both primary and secondary care settings.51–55

Currently available equipment includes ProTime (ITC Technidyne), TAS (Diagnostic Testing), and CoaguChek (Roche Diagnostics). The CoaguChek system is the most widely tested and utilised in Europe. However, all three systems have been shown to be robust and reliable with acceptable accuracy and reproducibility of INR results compared with standard laboratory techniques.51 56–58

Importantly, these devices can be subject to internal quality control and, in most cases, additional external quality assessment. Their development has now paved the way for decentralisation of INR testing.

Patient self-management of anticoagulant therapy

There are two separate components to patient self-management of anticoagulant therapy. Firstly, there is a self-testing component where suitable trained patients with moderate dexterity will obtain their own capillary blood sample and measure the INR using one of the above near patient testing devices. The second component is the interpretation of the INR result and subsequent alteration in anticoagulant dose if appropriate. This requires the patient to have considerable understanding of anticoagulant control since poor or erroneous adjustment is likely to lead to poor quality control and therefore higher risks of haemorrhage or thromboembolism. These risks are considerable but, perhaps, little different from the risks associated with self-adjustment of insulin dose in diabetic patients. As well as education, patients may be given written dose adjustment algorithms or even computerised decision support software (either on their home computer or small palm top device) to guide their decisions on dose adjustment.

Patient self-testing

Several studies using patient self-testing devices appear to show a high level of satisfaction and, in some cases, improved anticoagulant control. In a feasibility study a group of 40 patients monitored their own treatment over a period of 6–12 months at home.60 There was good agreement between patient self-test results and laboratory results and 97% of patients preferred the home testing system to standard management. A randomised controlled trial of 325 elderly patients with a variety of indications for anticoagulation showed that self-testing at home (followed by dosing advice from the investigator) compared with anticoagulant management by patients’ private physicians resulted in significantly fewer haemorrhagic events over a 6 month period (5.7% v 12%).61 This difference in outcome events may, however, reflect a superior quality of dosing advice in the self-testing group rather than any difference in the model of INR determination. In a small randomised controlled trial White et al62 showed that patient self-testing (followed by dosing advice from the patient’s health care provider) yielded better therapeutic anticoagulant control than attendance at an anticoagulant clinic (median time in target range 93% v 75%; p=0.003).

Patient self-management

Early observational studies of patient self-management (self-testing followed by self-dosing) appeared to show improved therapeutic control, patient satisfaction, and perhaps lower complication rates.63–65 In a large survey undertaken by Heidinger et al66 INR and clinical data were collated from 1375 patients (out of a possible 3000 already undertaking anticoagulant self-management for more than 3 months). The indications for anticoagulation in the group consisted mainly of atrial fibrillation or venous thrombosis. Review of 1428 patient years of data indicated that 69% of results lay within the INR target range of 2.0–3.0 and that the incidence of major haemorrhage and thromboembolism was relatively low (1.61%/year and 1.12%/year, respectively).

It is quite possible that many of these observational studies were subject to a high degree of patient selection and therefore more valuable data on the merits of patient self-management would come from prospective randomised
controlled trials. Four such studies, including the introductory article by Cromheecke et al, have now been published and the details and results are summarised in Table 2. A fifth randomised study has also appeared in abstract form where patient self-management was compared with family practitioner management. There were no differences in clinical events although the study was not powered for this purpose.

The collective evidence from these studies clearly indicates that patients can safely self-manage their own oral anticoagulation. However, exactly why some studies show superior anticoagulant control during self-management requires closer scrutiny. Comparison between studies is difficult because the width of target range varies from study to study. Also, in several studies the comparator group consists of general practitioner management which is historically poorer than current UK practice. In the studies where the comparator group was managed in an anticoagulant clinic, the differences were more marked which suggests that more frequent INR testing may lead to improved control. Of course, the education and training received by self-managed patients may also play a part. It is quite possible that the greater responsibility and autonomy afforded to self-managed patients could have a subtle positive impact on patient compliance.

### Table 2 Randomised controlled trials of anticoagulant self-management

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Comparator group</th>
<th>Training</th>
<th>INR frequency</th>
<th>Anticoagulant control (% INR in target)</th>
<th>Clinical events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cromheecke et al (2000)</td>
<td>Randomised crossover; 50 patients; mixed indications; stable anticoagulation (3 months); 3 months duration each arm</td>
<td>Anticoagulant clinic ≤ computer dosing</td>
<td>4 hours</td>
<td>8.6 days v 9 days</td>
<td>55% v 49% (p=0.06)</td>
<td>No difference</td>
</tr>
<tr>
<td>Watzke et al (2000)</td>
<td>Randomised; 102 patients; mixed indications; stable anticoagulation (&gt;6 months); 12 months follow up</td>
<td>Anticoagulant clinic</td>
<td>3 hours</td>
<td>6.6 days v 36 days</td>
<td>86.2% v 80.1% (target 2.5–4.5) 82.2% v 68.9% (target 2.0–3.0)</td>
<td>No difference</td>
</tr>
<tr>
<td>Koercke et al (2000)</td>
<td>Randomised; 600 prosthetic valve patients; from early after surgery; 24 months follow up</td>
<td>Family practitioner management</td>
<td>During days 6–11 postoperative</td>
<td>9.4 days v 45 days</td>
<td>78.3% v 60.5% (p&lt;0.001)</td>
<td>9.5% v 15.3% admissions</td>
</tr>
<tr>
<td>Sawicki (1999)</td>
<td>Randomised; 179 patients; mixed indications; stable anticoagulation (approx 2 years); 6 months follow up</td>
<td>Family practitioner management</td>
<td>3–5 hours</td>
<td>&lt;7 days v 14 days</td>
<td>53% v 43% at 6 months, mean deviation from target 0.65 v 0.83 (p=0.03)</td>
<td>No difference</td>
</tr>
</tbody>
</table>

**What are the patient training requirements?**

The content and duration of training required is becoming clearer. Some studies used a 6 week programme, claiming that all patients could safely self-manage by 30 weeks. However, most of the recent studies successfully employed a shorter programme of 3–10 hours in small group sessions spread over several weeks. In Germany the training of both trainers and patients appears to be well standardised.

Programmes typically include theoretical aspects of anticoagulation, practical sessions on near patient testing and dose adjustment scenarios, with patients being required to pass a test before commencing self-management. The dropout rates appear to be relatively low (less than 10%) and are most often due to difficulty in self-testing (either poor blood sampling technique or difficulty in handling the near patient testing device).

It is likely that this figure would be higher if an element of preselection had been avoided. Noticeably, the mean age of patients in the study by Cromheecke et al was only 42 years. Although the authors found no adverse effect of age or inferior educational background, other studies have commented on poorer control and longer waiting times in such patients. In some studies, training for self-dosing included written dose adjustment algorithms but none have yet used computer decision support software which could easily be deployed on a home computer. This could lead to further improvement in control and give the patient added reassurance.

Patient selection for self-management protocols is important. Clearly, candidates will require modest visual insights into the patient's condition and ability to manage their oral anticoagulation.
Learning points

- Heparin should be commenced as soon as DVT/PE are considered likely, because achieving early therapeutic anticoagulation can reduce the risk of thrombus extension and recurrence.
- Low molecular weight heparins appear to be superior to unfractionated heparin.
- The duration of oral anticoagulant therapy requires a balancing of benefits against risks for each individual patient.
- Higher quality anticoagulant control can be achieved by trained staff assisted by computer decision support software.
- Patient self-management appears to provide at least equivalent quality anticoagulant control with superior patient satisfaction compared with standard management.
- In the UK it remains to be determined how self-management will compare, in terms of clinical and cost effectiveness, with the specialised computer assisted services currently available.

Conclusion

The availability of LMWH has greatly improved our initial management of venous thrombosis. Optimal intensities for oral anticoagulation have been established and we are now able to select those patients who merit longer term treatment. However, the need for regular INR monitoring continues to place a financial, physical, and mental burden on the NHS and its staff. The advent of anticoagulant self-management may well release some of this burden in the future, but still requires formal assessment against current gold standard anticoagulant services in the UK. Even if it proves only equivalent to these services, its selective implementation—given the appropriate resourcing and training infrastructure—may lead to improved patient satisfaction. Anticoagulant clinics will still be required, although their role may move more towards continuing education for the patients and quality control of their INR testing devices. The days of empty anticoagulant clinics must await the availability of novel oral anticoagulants that require no monitoring.13

References


Anticoagulation in patients with thromboembolic disease

R C Tait

Thorax 2001 56: ii30-ii37

Updated information and services can be found at:
http://thorax.bmj.com/content/56/suppl_2/ii30

These include:

References
This article cites 65 articles, 7 of which you can access for free at:
http://thorax.bmj.com/content/56/suppl_2/ii30#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Venous thromboembolism (157)
Patients (155)
Pulmonary embolism (140)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/