Managing oral anticoagulation therapy: improving clinical outcomes. A review

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SUMMARY
Many physicians are reluctant to prescribe oral anticoagulation therapy (OAT) because of the fear of haemorrhagic complications. Changes in patient health, lifestyle or diet and other drugs can alter the effectiveness of oral anticoagulants. These potential interferences, added to the fact that each individual has a different reaction to these drugs, requires that therapy is monitored regularly. This article aims to review those strategies which help to achieve optimal anticoagulation control and improve the outcomes of OAT. Relevant articles were identified through a search of MEDLINE and included publications reporting on intensity of anticoagulation, the initiation of therapy and the role of pharmacogenetics, the transition from primary to secondary care, management by specialized clinics using decision support software and home-testing. Implementation of these strategies would increase the use of oral anticoagulants by physicians and offers the potential to improve patient safety and reduce adverse events.

Keywords: oral anticoagulation therapy, practice improvement, warfarin

IDENTIFICATION OF OPTIMAL TARGET INTERNATIONAL NORMALIZED RATIO
The International Normalized Ratio (INR) is the recommended method for reporting results for the control of OAT (1). Defining an optimal INR target and range is an important step to improving the safety of OAT. This is the INR which aims to achieve a level of anticoagulation at which thromboembolic events are reduced without excessive bleeding. Anticoagulant-related bleeding complications are closely related to the intensity of anticoagulation (4). Standard warfarin therapy (with a target INR of 2–3) is associated with rates of major haemorrhage of up to 7–8% annually and a similar rate of recurrent or de novo thromboembolism with an overall serious adverse event rate of 15% annually (5). International guidelines of recommended target ranges depending on the indication for anticoagulation are widely available (1, 4). Recommendations may differ between guidelines, e.g. the American College of Chest Physicians recommend a target INR of 3–0 for mitral valve replacements (4), whereas
the British Committee for Standards in Haematology (BCSH) recommends a higher target INR of 3.5 (1). Bleeding risk is also influenced by patient characteristics such as age, history of bleeding and co-morbid conditions (4). The indications for OAT and target INR ranges as recommended by the recently updated BCSH guidelines are summarized in Table 1 (1).

The efficacy of OAT depends not only on defining the target INR but also maximizing the length of time the patient’s INR is maintained within the designated therapeutic range [time in therapeutic range (TTR)] as there is an increased risk of haemorrhage at INRs > 3.0 (6–9) and thromboembolic complications at INRs < 2.0 (4, 9). Recent data from the SPORTIF III and V studies demonstrates the poor outcomes associated with different levels of INR control. The incidence of death (4.2% vs. 1.69%), major bleeding (3.85% vs. 1.58%), myocardial infarction (1.38% vs. 0.62%) and stroke (2.1% vs. 1.07%) was more than doubled in the ‘poorly’ controlled patients (defined as being in range < 60% of the time) compared with patients who were in range more than 75% of the time ($P < 0.01$) (10). Van Walhaven and colleagues found that by maintaining the INR between two and three, one in every four haemorrhagic events and one in every 10 thrombotic events could be avoided (11). Even a 10% increase in time out of range has been associated with an increased risk of mortality (OR 1.29; $P < 0.001$), ischaemic stroke (OR 1.10; $P = 0.006$) and other thromboembolic events (OR 1.12; $P < 0.001$) (11). However, studies have found that anticoagulated patients have non-therapeutic INRs up to 80% of the time (12) (It is worth noting that when analysing the results of studies that report TTR as an outcome variable, a difference of 5–10% is considered significant) (13).

Table 1. Indications for oral anticoagulation and their target ranges (BCSH guidelines (1))

<table>
<thead>
<tr>
<th>Indication</th>
<th>Target range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous thromboembolism</td>
<td></td>
</tr>
<tr>
<td>Post-operative symptomatic calf vein thrombosis without any risk factors</td>
<td>2.0–3.0</td>
</tr>
<tr>
<td>Symptomatic calf vein thrombosis in non-surgical patients</td>
<td>2.0–3.0</td>
</tr>
<tr>
<td>Proximal DVT with transient risk factor</td>
<td>2.0–3.0</td>
</tr>
<tr>
<td>Pulmonary embolus and/or proximal vein thrombosis</td>
<td>2.0–3.0</td>
</tr>
<tr>
<td>Recurrent DVT and/or PE</td>
<td>2.0–3.0</td>
</tr>
<tr>
<td>Recurrent DVT and/or PE while on warfarin</td>
<td>2.5–3.5</td>
</tr>
<tr>
<td>Atrial fibrillation (AF)</td>
<td>2.0–3.0</td>
</tr>
<tr>
<td>AF or other high risk arrhythmias</td>
<td>2.0–3.0</td>
</tr>
<tr>
<td>Valve prostheses and other cardiac indications</td>
<td></td>
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<tr>
<td>Mechanical prosthesis valve</td>
<td></td>
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<tr>
<td>Aortic Valves</td>
<td></td>
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<tr>
<td>Bi-leaflet or tilting disk valve</td>
<td>2.5–3.5</td>
</tr>
<tr>
<td>Caged ball or disk valve</td>
<td>3.0–4.0</td>
</tr>
<tr>
<td>Mitral valves</td>
<td>3.0–4.0</td>
</tr>
<tr>
<td>Bioprosthetic heart valves (recommended for mitral valves, risk assessment for aortic)</td>
<td>2.0–3.0</td>
</tr>
<tr>
<td>Cardiomyopathy, mural thrombus or akinetic segment</td>
<td>2.0–3.0</td>
</tr>
<tr>
<td>Antiphospholipid antibody syndrome</td>
<td>2.0–3.0</td>
</tr>
<tr>
<td>TIA/Ischaemic stroke</td>
<td>2.5–3.5</td>
</tr>
<tr>
<td>Peripheral arterial thrombosis and grafts</td>
<td>2.0–3.0</td>
</tr>
<tr>
<td>Coronary artery thrombosis</td>
<td>2.0–3.0</td>
</tr>
<tr>
<td>Coronary artery graft thrombosis or stent thrombosis</td>
<td>2.5–3.5</td>
</tr>
</tbody>
</table>

INITIATION OF ANTICOAGULANT THERAPY

Achieving optimal anticoagulation is clearly important in protecting patients against haemorrhagic and thromboembolic events and this is especially important during the first few months of
anticoagulant therapy when the risk of haemorrhagic complications is greatest. One study reported 2,066 episodes of major bleeding per 100 patient-years during the initial 3 months of anticoagulation compared with 2.74 per 100 patient-years during the entire year after this period (14).

**Loading dose protocols**

Many dosing algorithms for the initiation of warfarin therapy have been developed. In the UK, the most widely published regimen was reported by Fennerty et al. in 1984 (15). Other studies suggest using less intense loading doses (16–18) (5 mg compared with 10 mg) to avoid dangerous over anticoagulation but even then this may be excessive in over 80% of elderly (>70 years) patients (19). Research in this area has focused on inpatient anticoagulation management with daily INR measurements to achieve rapid anticoagulation control.

Recommendations for the initiation of warfarin therapy differ depending on the indication for its use and the urgency in establishing therapeutic control, e.g. a patient with an acute pulmonary embolus would require more urgent and rapid anticoagulation than a geriatric outpatient diagnosed with AF. Less intense (<5 mg) initiation doses should be considered for the majority of patients being anticoagulated for AF in the outpatient setting without the inconvenience of daily INR monitoring (1, 20). The BCSH guidelines suggest 2 mg daily initially with further dose adjustments based on the INR which should be measured weekly (1).

**Knowledge of pharmacogenetics**

Regardless of the initial dose of warfarin prescribed, subsequent doses are adjusted according to trial and error based on the INR measurement until a stable maintenance dose is achieved. Knowledge of pharmacogenetics, along with other factors known to affect warfarin dose requirements, may help clinicians to more accurately predict the therapeutic dose of warfarin, and therefore reduce the time taken to reach therapeutic range, prolong the time in range and reduce the risk of bleeding and thrombotic complications (21–28).

Twenty per cent of Caucasians carry polymorphisms on the cytochrome P450 CYP2C9 gene (22). These patients metabolize warfarin more slowly, have significantly reduced warfarin dosage requirements, take longer to reach stable dosing and are two to three times more likely to have a haemorrhagic adverse event (22, 24). Polymorphisms on the vitamin K epoxide reductase complex subunit one (VKORC1) gene increases warfarin sensitivity (24, 29) and may also explain why some patients show warfarin ‘resistance’ and have much higher dosage requirements (30). The combination of these genetic variants together with clinical factors known to affect warfarin dosing, e.g. age, race, body surface area, concurrent medication and co-morbidity account for 56% of the variability in dose requirements (21).

A priori knowledge of a patient’s genotype may improve warfarin therapy as demonstrated by Caraco et al. (25). Patients were randomly assigned to receive warfarin by a standard algorithm or a pharmacokinetic-based one. The first therapeutic INR and stable anticoagulation were reached 2.73 and 18.1 days earlier using the pharmacokinetic-based model (P < 0.001). Study patients experienced less minor bleeding complications (3.2% vs. 12.5%; P < 0.02 respectively) and spent more time in therapeutic range (80.4% vs. 63.4%; P < 0.001 respectively). Several other dosing algorithms have been reported in the literature which take into account genetic factors in an attempt to minimize the risk of bleeding (23, 26–28).

The US Food and Drug Administration has recently updated the product label for warfarin to include information on the potential benefits of genetic testing to guide warfarin treatment. However, before genetic-based warfarin dosing models are routinely applied, pharmacogenetic tests are required to provide quick results to clinicians for dose optimization prior to and during initiation. The Verigene System® (Nanosphere Inc., Northbrook, IL, USA) and the DoseAdvise® genetic test (Kimball Genetics Inc., Denver, CO, USA) have a 1-day turnaround time. The Verigene® system costs 38 000 Euros and each test costs 55 Euros. Genetic testing for the three SNPs using the DoseAdvise® system costs 337 Euros. One study estimated that the use of CYP2C9 genotyping could potentially avoid 85 000 serious bleeding events and 17 000 strokes annually in the US and reduce healthcare spending by $1.1 billion (31). Further study is needed to determine more precisely the effect of
pharmacogenetics on clinical outcomes and the cost-effectiveness of such an intervention.

Transfer of care from secondary to primary care

The transfer of warfarin management from secondary to primary care is associated with increased adverse effects (32) and loss of anticoagulation control (33) with poor communication and unsafe arrangements between healthcare teams being identified as an area of risk by the National Patients Safety Agency (NPSA), UK (32, 34). Specific information concerning the clinical indication, target INR, intended duration of therapy, current prescription and recent laboratory test results must be provided to the new healthcare provider to ensure a smooth transition and optimal patient care during this time (34).

Patient education

Lack of compliance is another important factor that contributes to poor outcomes (35). Patients who have a poor understanding of the indications and potential adverse effects of warfarin are more likely to be non-compliant than those who receive education (36). Counselling patients with respect to their anticoagulant treatment is fundamental and significantly improves patient’s knowledge and quality of anticoagulation (12, 37–40).

In a large study of over 15,000 elderly patients (>80 years), perceived lack of education was associated with poor outcomes (12). In this study, only 21% of patients believed their education to be satisfactory and this corresponded to an average TTR of 45–1%. Seventeen per cent declared their education to be insufficient and the 61% of patients who declared they received no education at all spent only 20% of time in therapeutic range ($P < 0.001$).

Verbal and written information should be provided at the start of therapy, at hospital discharge and on the first anticoagulant clinic appointment (34). Booklets aimed at patient education are available and are a useful supplement to the healthcare provider’s advice. Patient education should highlight the side-effects of warfarin, the potential for drug–drug and drug–food interactions, advice on birth control, the importance of compliance and the need for regular monitoring (41).

IMPROVING THE DELIVERY OF ORAL ANTICOAGULATION CARE

Different models of managing OAT have evolved and use of specialized clinics and computerized dosing are two strategies that have been proposed to improve the success of warfarin management. Increased frequency of testing facilitated through patient self-monitoring programmes may also have a positive impact on anticoagulation control.

Coordinated anticoagulation care by a specialized anticoagulant management service

One strategy proposed for improving warfarin management is the establishment of a specialized anticoagulant management service (AMS) involving healthcare professionals with knowledge and skill in the coordination and management of OAT (42, 43). This enables an organized system of follow-up, reliable INR monitoring and good patient communication and education.

Studies have shown that when compared with OAT management by a primary care physician, management by a specialized AMS achieves better anticoagulant control in terms of TTR and reduces complication rates by up to 50–90% (42). A review by Ansell et al. (44) indicated a combined rate of major haemorrhage and of recurrent or de novo thromboembolism of 15% per patient per year of therapy for those having their OAT managed by their primary care physician. This risk was reduced by more than 40% when patients were managed by an AMS. A study comparing both management approaches [specialized service vs. usual care (UC)] in the same patients found that, although bleeding and thrombotic outcomes were similar in the AMS and the UC group, the patients spent significantly more time in range during the AMS treatment period compared with during the UC period (68% and 58%; $P < 0.001$) (43).

The Managing Anticoagulation Services Trial is the largest randomized controlled trial of AMS vs. care by a primary care physician to date. However, it failed to show a significant difference in the quality of anticoagulant control between AMS and UC (intervention effect: 5%, 95% CI: −5% to 14%; $P = 0.32$) but concluded that an AMS is an especially reasonable consideration in a practice setting in which TTR is < 50% (45).
Use of computerized decision support systems

Computer programs that predict dosage adjustments of oral anticoagulants and the time interval to the next test have been shown to improve the quality and efficiency of OAT and are being increasingly used in practice (46–49).

A review of the effects of computerized decision support systems (CDSS) on the quality of OAT identified nine trials including 1336 patients and concluded that the use of a computer for anticoagulation optimization increased by 29% the proportion of visits where patients were ‘appropriately treated’ (OR 1.29; 95% CI 1.12–1.49) (47). In terms of clinical outcomes there was a trend towards a reduced incidence of major haemorrhage in the CDSS groups vs. the control groups (2.0% vs. 3.9%) (47). More recently the results of the APROAT study showed that patients in the CDSS group achieved a stable anticoagulation significantly faster (39% vs. 27%; P < 0.01) in the first month of the stabilization phase and TTR was increased from 68.7% to 71.2% (P < 0.001) during the maintenance phase compared with UC (48).

As well as the improved quality of therapeutic control compared with manual dosing, these expert support systems can reduce the reliance on physician delivery of OAT. Because dosing recommendations are consistent and reliable, other healthcare professionals, e.g. pharmacist and nurses are better equipped to become directly involved in the management of patients on warfarin (50).

Frequency of testing

Studies suggest that adverse events can be reduced and TTR maximized by more frequent testing of the INR (7, 51–53). When monitored monthly, around half of patient’s INRs remain within target range, compared with 90% when monitored every second day (52). However, this relationship between test frequency and TTR is not definitive as studies compare UC with patient self-testing (PST) or patient self-management (PSM), the advantages of which (patient empowerment, education etc.) may contribute to the improvements achieved (13).

Point of care INR monitoring

Patient self-testing involves the patients measuring their INR themselves, with dose adjustment by the healthcare professional. PSM, whereby the patient measures their INR and adjusts their own dose requires intensive patient training/education and is not yet commonly used, but has also been shown to a safe and effective approach that may be suitable for some patients (38–40, 53–65). The testing frequency for both models is usually weekly (5).

A systematic review and meta-analysis of the literature showed that PST/PSM reduced thromboembolic events by 55% (OR 0.45; 95% CI 0.30–0.68), reduced major haemorrhage by one-third (OR 0.65; 95% CI 0.42–0.99) and was associated with a significant reduction in death from all causes (OR 0.61; 95% CI 0.38–0.98). All studies reported improvements in TTR, six out of the 14 of which were statistically significant (59).

The quality of therapeutic control achieved by PSM has been reported as being comparable with that of PST (TTR 69.9% vs. 71.8%; P = 0.46) (54). Both groups combined showed a significant improvement over the previous 6 months in AMS (71% vs. 62.5%; P = 0.04).

Study setting has the greatest effect on anticoagulation control (66) and ‘high quality anticoagulation management’ should be the standard against which the relative effectiveness of PST/PSM is measured (13, 66). Studies comparing clinical outcomes have shown superiority of PST/PSM over primary care physicians (53, 60) but the improvements are much less when compared with a specialized AMS (61, 62).

A novel concept involves the use of an expert system which enables the caregiver to supervise PST patients remotely (CoagCare®, ZyCare Inc., Chapel Hill, NC, USA). Instead of the patient contacting the caregiver by phone, fax or e-mail which is the usual scenario, using this system, patients enter their INR onto a web-based internet system which provides dose and testing instructions. The use of this system in Ireland is currently being investigated in a randomized controlled trial but a preliminary trial has shown an improvement in TTR using this system compared with UC in an AMS (73.5% vs. 63.5%; P = 0.008) (67).

Home-testing of the INR facilitates increased frequency of testing, but this may not be the sole reason for improvements in anticoagulation control. Most PST/PSM programmes include detailed patient education sessions (53, 55). Knowledge
about warfarin therapy has been positively correlated with improved outcomes (12, 38, 39) and this may improve the quality of anticoagulation management above and beyond the direct effects of increased INR testing (13). This was demonstrated by Piso et al. (40) who analysed the quality of anticoagulation before, during and after a period of PSM. Improvements were seen during PSM which persisted even after PSM had ceased, suggesting that the increased patient knowledge as a result of the training and education received had a positive impact on the quality of anticoagulation even without self-management. This, together with the suggestion that patients enrolled on these studies are a highly motivated, competent and perhaps more compliant cohort may have contributed to the improvements in TTR seen (56).

PST/PSM has the potential to improve quality of life though only a few studies have considered this outcome measure (38, 53, 55, 57, 58). These programmes relieve the burden of frequent, time consuming visits to clinics and allows greater independence and freedom when travelling (53). Patients may feel more empowered and reassured and worry less about bleeding complications although ‘increased anxiety and obsession with health’ have also been reported (55).

Near patient testing programmes should be reviewed and audited at regular intervals to ensure the point-of-care (POC) meters continue to give precise and accurate results (34, 68). The UK National External Quality Assessment Scheme (NEQAS) provides a comprehensive external quality assurance service for POC monitors through one of two options. The first is to compare the POC device with a clinic-based POC machine which is itself registered with NEQAS. Second, the POC meter may be compared with a venous blood sample sent to a laboratory which participates in NEQAS (in both instances INR results should be within 0 to 5 INR units of each other) (68).

Based on the SMART study in 2005 the cost of PSM was reported to be three times more expensive than standard care (£417stg vs. £122stg per patient/year) (63). This may have been a result of the increased frequency of testing in the PSM group as dictated by the study protocol (every 12/4 days vs. every 37/9 days in the control group). McCallon et al. (64) assessed the cost effectiveness of PSM outside trial conditions and concluded that PSM was not cost effective compared with standard care but that ‘the extra cost must be weighed against the increased autonomy and control PSM offers patients and the reduction in workload it offers busy oral anticoagulation clinics’.

On the other hand, PSM was found to be a cost-effective strategy in the Canadian healthcare system when the incremental cost and health benefits of PSM were compared with that of physician management over a 5-year period (65). The costs of PST have not yet been evaluated but may be higher again due to increased contact time with health professionals for INR interpretation and dose adjustment.

### REGULAR AUDIT OF THE ANTICOAGULANT SERVICE

Regular audit should be an integral part of every AMS (1, 34). Laboratory measurements, dosing, level of therapeutic INR control, clinical outcomes, patient satisfaction and clinic administration (e.g. follow-up on patients failing to attend clinic) should be systematically reviewed (34). Standards for audit have been outlined by the BCSH and are listed in Table 2 (1). The NPSA has highlighted inadequate audit of anticoagulant services and/or failure to act on audit results as a major factor that increases the risk of patient harm associated with OAT (34). In this report the NPSA recommends the use of CDSS for decision support and audit. In addition to dosing guidelines, these packages can generate the reports and necessary statistics, such as TTR which can be used to identify areas for improvement.

### Table 2. Standards for audit

1. Provision of adequate data for safe transfer of anticoagulant follow-up
2. Provision of patient held information (yellow books) for patients on hospital discharge
3. Patient information: awareness of need for anticoagulation and possible side-effects
4. Hospital notes contain information that the patient is currently on warfarin
5. The use of heparin/warfarin dosage schedules according to BCSH standards
6. Follow-up arrangements for patients failing to attend appointments
7. Achievement of target INR: 60% of INRs within 0.5 INR units and 80% within 0.75 INR units of target

improvement and continuously monitor the quality of the AMS.

**CONCLUSION**

Currently, approximately 1.5% of the Irish population requires warfarin therapy and this figure is expected to rise by at least 10% per year. The adverse event rates associated with OAT are dependent on the model of care used to manage warfarin therapy with better outcomes associated with the use of specialized AMS and CDSS, increased test frequency and home monitoring. Dosing algorithms that incorporate both clinical and genetic factors will undoubtedly increase the capacity to improve dosing of warfarin. Implementation of these strategies has the potential to improve clinical outcomes. This would ultimately reduce the morbidity and mortality associated with the numerous conditions for which OAT is indicated, while making OAT more convenient for both patients and physicians.

**REFERENCES**


