Introduction

Oral anticoagulation (OAC) therapy is the cornerstone in the prevention of morbidity and mortality due to venous thromboembolic events (thromboembolic stroke, pulmonary embolism, and recurrent thrombosis). Monitoring OAC therapy is imperative in maintaining the appropriate levels of anticoagulation, balancing the risk of thrombosis and bleeding. Monitoring long-term anticoagulation therapy is similar to monitoring blood glucose, HbA1c in diabetes, blood pressure in hypertension, and lipids in hypercholesterolaemia, and is required to adjust the duration and dosage of the OAC according to therapeutic response.

Monitoring Oral Anticoagulation with Vitamin K Antagonists

Vitamin K antagonists (VKAs) are the most widely used OACs. Despite certain limitations, VKAs have a vast clinical experience in addition to the published evidence, which has proven its efficacy, and thus, they remain the mainstay of OAC therapy.

Necessity of Monitoring Vitamin K Antagonist Therapy

Many factors interfere with VKA uptake and metabolism by the liver, including food, other medications, and comorbidities. A fixed low-dose regimen of VKAs is not very beneficial. Wide range of inter- and intra-patient variations in the dose requirement of VKAs that warrants the need of individualised dosage regimens to the desired international normalised ratio (INR) level. Thus, the primary objectives of monitoring VKA therapy are to help in deciding the initial VKA dose and the maintenance doses on the basis of level of anticoagulation.

Apart from the assistance in deciding the appropriate dosage regimen, monitoring helps in avoiding overcoagulation. With the help of routine monitoring, such dangerous situations can be detected well in time allowing dose adjustment, as well as actions taken to prevent recurrence of such situations.

How is Vitamin K Antagonist Therapy Monitored?

The prothrombin time (PT) test is the most common test used to monitor VKA therapy. It is expressed as INR. The PT signifies the reduction of three pro-coagulant clotting factors (i.e., II, VII, X) out of the four vitamin K-dependent clotting factors that are reduced by warfarin at a rate proportional to their respective half-lives. Thus, it would be safe to state that during the first few days of VKA therapy, the PT reflects mainly a reduction of factor VII during the half-life (approximately 6 hours). Consequently, the reduction of factors X and II contributes to prolongation of the PT. The time within the therapeutic range (TTR) is a good overall measure of the quality of antithrombotic treatment with VKAs. Wide variations in TTR have been observed. A country-wise analysis of randomised evaluation of long-term anticoagulation therapy (RE-LY) study data revealed that average TTR, excluding first week of treatment, varied from 44% in Taiwan to 77% in Sweden. Even a good level of TTR, such as nearly 75% in the Netherlands, suggests that INR values are either too low or too high in 25% of the time while anticoagulant therapy is continued. For achieving appropriate laboratory control, patients need to have their blood withdrawn about 20 times a year, which poses a significant burden. Thus, TTR provides a clearer picture of the quality of anticoagulation, guiding the clinicians to take appropriate steps to achieve better TTRs to balance the benefit-risk ratios.

Before initiating VKA therapy, the baseline INR should be determined and initial dose of VKAs should be administered. It is recommended that during the initiation phase, INR should be monitored every 2-4 days, until INR is in the target therapeutic range for two consecutive values. Once stabilised, INR should be monitored weekly. The interval
can be gradually increased up to every 4 weeks if the INR remains stable and within therapeutic range.\(^2\)

In the 9th edition of Evidence-based Management of Anticoagulant Therapy, American College of Chest Physicians (ACCP) recommends that rather than 4-week monitoring, the patients with consistently stable INRs can be monitored after every 12 weeks.\(^3\)

Whenever a new drug is being initiated, there is a risk of drug interaction. Thus, monitoring frequency should be increased with any substitution, deletion, or addition of any drug as a concomitant therapy during OAC.

**Self-management of Vitamin K Antagonist Therapy**

Self-management of VKA therapy is increasingly becoming popular, as it reduces patients’ inconvenience of visiting an outdoor anticoagulation clinic frequently for INR testing. It positively influences the quality of life, as well as the TTR, particularly in patients on long-term anticoagulant treatment.\(^1\) The Home INR Study (THINRS) reported that weekly home-based INR monitoring is as safe as clinical monitoring. Time in therapeutic INR range was significantly increased (7%) along with patient satisfaction with the anticoagulation therapy. Patients should be trained properly and competence in using home-based INR testing should be ensured.\(^4\)

A recent pilot study on the impact of a novel patient self-management programme on management of VKA therapy was conducted for 3 months. The study enrolled 44 patients with atrial fibrillation (AF), who were on long-term anticoagulation therapy. The patients acted as their own controls; after 3 months of initial monitoring anticoagulation at outdoor clinics, self-testing programme was introduced for the next 3 months. The outcomes measured included TTR, number of INR tests performed, and episodes of major bleeding or thrombosis. No differences in the TTR were observed. The number of INR tests increased from 2.97, before the implementation of self-management programme to 4.38, during the self-management. The study concluded that self-management of VKA therapy was as effective as the outdoor INR testing, thus reducing the patient inconvenience to a significant extent.\(^5\)

American College of Chest Physicians recommends the practice of self-management of patients over outdoor INR monitoring, in patients who are motivated, and can demonstrate competency in self-management strategies.\(^6\)

**Managing Under- or Overcoagulation with Vitamin K Antagonists**

Several measures can be taken to improve TTR in patients on VKA therapy. These include:\(^1\)

- Reminding the clinician to check if patient has problems that may hamper adequate medication intake (poor network, treatment of co-morbid conditions, etc.).
- Supervision of medication intake, involving nurse, family or neighbours. Such a scenario is often encountered in anticoagulation clinics, as in about 40% of the cases, elderly population, due to co-morbidities, need blood samples taken at home.

**Management of Bleeding with Vitamin K Antagonists**

The prominent feature of anticoagulant overdose is bleeding, which may be manifested as nasal bleeds, haematemesis, haemoptysis, gastrointestinal bleeding, vaginal bleeding, haematuria, cutaneous haemorrhages, gingival bleeding, haematoma, and bleeding into joints or menorrhagia. In case of bleeding with VKAs, following precautions should be taken:\(^6\):

1. Reduce INR to a safe level (< 5) if excessive increase in PT and/or INR occur without bleeding or prospective surgery.
2. In case of serious bleeding, reduce INR to 1 as soon as possible.
3. In case of elective or urgent surgery, reduce INR to 1-1.5 at the time of surgery.

Temporary reduction in INR can be done by withdrawing anticoagulant therapy, and oral or parenteral vitamin K administration.

In case of moderate bleeding, vitamin K1 2-5 mg should be given orally.

In case of severe bleeding, vitamin K1 5-10 mg should be injected intravenously very slowly (at a rate < 1 mg/minute). Additional doses (up to a maximum of 40 mg daily) should be given at 4-hour intervals.

In case of serious overdose or life-threatening bleeding, immediate restoration of clotting factors can be achieved by transfusion of fresh frozen plasma or whole blood or prothrombin (factor IX) complex concentrate, along with vitamin K.

**Initiating Anticoagulant Therapy after Intracranial Haemorrhage**

Intracranial haemorrhage (ICH) is the most feared and fatal complications of OAC. Once occurred, it is not certain how long after symptom onset the risk of ongoing bleeding continues. Clearly, the risk is high on the first day, but small after the first few days. The European Stroke Initiative recommends that patients with a strong indication for anticoagulation, such as a history of embolic stroke with AF, should be restarted on VKAs after 10-14 days, depending on the risk of thromboembolism and ICH recurrence. The American Heart Association suggests that, in patients with a very high risk of thromboembolism for whom restarting
VKA is considered, it may be restarted 7-10 days after ICH onset.7

**No Need of Monitoring Newer Oral Anticoagulant Therapy**

The newer oral anticoagulants (NOACs) are being promoted as there is no need of monitoring, illustrated by paper headlines ‘Funeral of anticoagulation clinics.’ The assumption is that in contrast to VKAs, NOACs neither require monitoring with laboratory tests, nor frequent dose adjustment. This is attributed to reduced food and drug interactions, contributing to increased pharmacokinetic stability.1

**Why Risky?**

Newer oral anticoagulants have been developed to abolish the need of monitoring and dosage adjustments. As a result, all patients have a prescription and a single advice, but no formal support or laboratory control. Such a development is potentially harmful to the patient, and needs critical consideration of causes and consequences.1

It should be understood that though routine monitoring causes inconvenience to patients, such practice is actually very beneficial. The occurrence of potentially harmful situations, such as overcoagulation, can be detected well in time, and appropriate dosage adjustments can be done to prevent worsening of the situation. Such incidents also alert the clinicians and the recurrence of overcoagulation can be prevented in future.8

The fixed-dose regimen of NOACs is an issue of debate. The concept of fixed dose does not apply well in clinical situations. The pharmacokinetic studies have reported considerable variation in plasma levels of dabigatran. While many patients may achieve the desired range of plasma concentration, several of the patients may be under- or overexposed, and thus a variability in the therapeutic response. Some may argue that the overall performance of NOACs was non-inferior or better than INR-adjusted dose of warfarin. But it should be reminded that these results were obtained in very carefully selected patients (excluding those with assumed poor compliance, renal insufficiency, and bleeding risks). Even in such a selected patient population, the incidence of bleeding and other side effects was significant. In order to achieve better efficacy and safety with NOACs, an optimal dose for individual patients need to be identified, where laboratory-based dose adjustment will have an important role.1

Another issue associated with not monitoring NOACs is that there is a risk of losing track of the patient during long-term treatment. As majority of AF patients do not require long-term follow-up with cardiologist, general practitioners maintain the continuation of medication by prescription. If the therapy is not monitored routinely, there will be no routine check on side effects, tolerance, and adherence. In unmonitored conditions, medication adherence levels are not better than 50%.1

The third issue with NOACs is that measurement of anticoagulant effect is required in certain acute conditions, such as suspected under- or overdosing, co-morbidity, potential interactions, surgical interventions, and cardioversion, acute renal impairment (with dehydration or use of antibiotics). In addition, measurement of anticoagulant effects may also be required while taking decision on dual or triple antithrombotic therapy.1

Also, in case of emergency situations such as major bleeding, laboratory tests can provide information on the amount of anticoagulant still present and to decide the dose of antidotes accordingly.1

Further, with the reduced frequency of clinic visits, the opportunity for clinicians to educate the patients is also reduced. Another disadvantage is to confirm the incidence of therapy failure. With VKAs, monitoring INR can determine whether or not treatment failure is a result of warfarin resistance. However, with no monitoring, determining resistance or therapy failure of newer anticoagulants is not possible.9

**Assay Methods**

Although reliable assays for the estimation of anticoagulation with NOACs are not widely available, the results of a panel of common commercial assays for monitoring the effects of dabigatran in plasma have been published. This comparative study reveals that an assay based on assessing the direct antithrombin effect is optimal for recording the anticoagulant effects over a wide range of dabigatran concentrations. Such assays will assist in improving the quality of NOAC therapy and reducing the risk of unwanted bleeding complications.1

**Managing Overdose/Overcoagulation**

The rise in gastrointestinal bleeding with novel agents is a cause of concern, particularly in elderly population. In the absence of a specific antidote to reverse their effect, management of life-threatening bleeding episodes is difficult.8 The only reversal option for direct thrombin inhibitors is fresh frozen plasma, or factor Xa concentrate, but it requires hospitalisation and increases the cost.8 Also, the perioperative reversal and bridging of anticoagulation with the novel agents are not yet determined. Some may argue that shorter half-lives of the novel anticoagulants are helpful, but even that is applicable only in non-urgent situations. In case of emergencies, there is no established therapeutic procedure.8

It has been now well recognised that the absence of proper laboratory tests as well as the lack of antidotes is a major limitation in the safe introduction of NOACs. The best laboratory assays on a 24-hour basis should be
made available to facilitate optimal drug management in emergency conditions such as an urgent surgery.¹

A suitable point-of-care test is available in a few countries, but rest of the world is still not ready. Several steps can be taken toward a better management of anticoagulant therapy, of which a few are as follows¹:

1. A general shift toward thrombosis care, aiming to provide good quality management of patients with thrombosis, should be initiated. Such a strategy will encompass describing and organising the entire chain of care. Optimal communications such as protocols, based on guidelines, are crucial in situations such as perioperative management of anticoagulation.

2. Pharmaceutical companies should provide all the relevant data on drug levels and coagulation test responses, which may help in when to expect over- and undercoagulation based on the drug levels, in situations where such tests are unavailable.

3. It should be realised that the already existing complex issue of thrombosis management is increasingly becoming more complex with the introduction of newer agents.¹ All efforts should be made to maximise the benefits and reduce the risk to the patients.

**Summary**

Although VKAs are often criticised for the need of frequent monitoring, such a practice is very beneficial. Recommended 12-weekly monitoring, rather than 4-weekly, in patients with consistently stable INRs may help reduce patient inconvenience. The recommended use of patient self-management of anticoagulation in motivated and competent patients is further very helpful. In the absence of laboratory tests and antidotes to reverse their effects, the use of NOACs is quite challenging.

**References**