Warfarin is an oral anticoagulant that is commonly prescribed to people at high risk of developing blood clots, to reduce their chances of cardiovascular accident or myocardial infarction. Patients taking warfarin need regular international normalised ratio (INR) blood tests to ensure their blood levels remain within a set therapeutic range. If patients go above or below this range, the safety and efficacy of the drug is compromised. Warfarin’s narrow therapeutic index makes it difficult for some patients to remain in a set therapeutic range. This article describes an intervention whereby specialist anticoagulant nurses work with patients who have poor warfarin management to help them switch to new oral anticoagulants or increase their time in range to improve safety and quality of life.

Keywords Warfarin/Anticoagulants/ Patient safety/Medicines management

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In this article...
- Risks versus benefits of warfarin therapy
- Working with patients to improve safety and efficacy
- Increasing patients’ access to newer therapies

Safe anticoagulant management for patients taking warfarin

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Abstract Patients taking the anticoagulant warfarin to treat or prevent blood clots need regular international normalised ratio (INR) blood tests to ensure their blood levels remain within a set therapeutic range. Those who fall below this range are less protected from the risk of developing a venous thromboembolism, while patients who go above it are at greater risk of bleeding (Wan et al, 2018; Passman, 2016).

Ensuring patients on warfarin remain within the specified limits improves safety and quality of life, so they have their INR levels regularly monitored by GP surgeries or anticoagulation nurse specialists, who also educate them on warfarin and its use (Connor et al, 2002). Time in therapeutic range (TTR) is used to estimate the percentage of time a patient’s INR is within the desired treatment range or goal; it is widely used as an indicator of anticoagulation control and to assess the risks versus the benefits of warfarin therapy.

Warfarin’s narrow therapeutic index makes it difficult for some patients to remain within a set therapeutic range (Pirmohamed, 2006). An analysis of 6,454 patients taking warfarin for atrial fibrillation found their INR was out of range for almost half of the time (Boulanger et al, 2006). Individual responses to the medication are highly variable and, when prescribing warfarin, there are many other factors that need to be considered, which can influence warfarin response; these include a patient’s diet, alcohol intake, body mass, drug interactions and concordance (Hall and Wilkins, 2005).

Background Warfarin has proved to be an efficient drug in treating and preventing venous thromboembolism (Tideman et al, 2015). Alnassar et al (2019) noted a benefit for older people treated with anticoagulants, but found that those on warfarin benefited most if they achieved a TTR of ≥65% (National Institute for Health and Care Excellence, 2014). Jones et al (2005) noted...
that fluctuations in INR results had substantial implications for mortality and other clinical outcomes, even in patients who usually appeared to have good control; an association was noted between INR results outside the therapeutic range and increased rate of hospitalisation, mortality and likelihood of thromboembolic events. This view was also supported by Wan et al (2018).

“Fluctuations in international normalised ratio blood test results had substantial implications for mortality and other clinical outcomes”

There are many challenges in ensuring patients remain within their respective range (Kim et al, 2019). The need for regular monitoring brings associated costs and burdens, and there are other factors that can have an impact on INR results. Molteni and Cimminiello (2014) discussed these issues and the difficulties in keeping patients’ TTR within their target of 60%; they also noted that anticoagulation nurse specialist services have proved very effective in this.

Patients taking warfarin whose TTR was ≥65% were shown to have a much better prognosis relating to thromboembolism and all-cause death than those whose TTR was <40% (Inoue et al, 2018). It is therefore important to consider what factors have an effect on patients’ TTR and how to act on these when possible.

In a well-managed warfarin therapy setting for patients with non-valvular atrial fibrillation, excessive alcohol use was found to be the greatest predictor of poor INR control (Björck et al, 2019). The same study suggested other comorbidities (such as hypertension and renal failure) and variables of frailty (such as dementia, cancer and history of falls) were also frequently associated with poor INR control; in such cases direct oral anticoagulants (DOACs) may be an alternative treatment option.

It is important to understand why patients’ TTR may be poor and to individualise the choice of anticoagulant for each patient. For example, the DOAC rivaroxaban needs to be taken with food but apixaban (another DOAC) does not, and so may be more appropriate for patients who do not eat regularly or those who have a poor appetite.

DOACs have the advantage of having a wider therapeutic window than warfarin and require less-frequent monitoring and hospital visits; this results in significant advantages for patients and healthcare resources (Kockaya et al, 2018). DOACs also have fewer interactions with alcohol and other medications, and are especially beneficial for patients:

- From whom it is difficult to obtain a blood sample;
- Who require community phlebotomy or dosette boxes filled by a pharmacy;
- Who find it difficult to attend regular follow-up appointments due to work commitments.

One concern with DOACs is medication adherence; warfarin’s long half-life of approximately 40 hours is an advantage for patients who may occasionally miss doses. The twice-daily dosing regimen of some DOACs may be more difficult for some patients to adhere to than a daily schedule; conversely, the impact of a missed dose may be greater with DOACs that are taken daily. Ongoing adherence is extremely important to attain good clinical outcomes (Bauer, 2013).

**Service improvement programme**

In 2017, Nottingham University Hospitals NHS Trust embarked on a service improvement programme to help patients on warfarin with a poor TTR maximise their time in the therapeutic range to improve safety and quality of life. The study began on June 2017 and ended in May 2018.

**Aims**

The trust’s anticoagulation service had already been working in an ad-hoc way to address the issue of patients who were prescribed warfarin but had a poor TTR. The aim was to provide a more standardised approach by systematically identifying and contacting patients with a poor TTR, and initiating improvement through discussion with the patient.

A TTR of 65% is the gold standard set by the National Institute for Health and Care Excellence in 2014; time and staff constraints when this project was initiated meant patients were selected with a TTR of <40%. It was proposed that anticoagulation nurse specialists would contact these patients to:

- Determine possible reasons for poor control;
- Help them implement measures that could improve their TTR, including further education, changes to diet and lifestyle, help with managing their medication (for example, using a dosette box) or, where appropriate, exploring the possibility of switching from warfarin to a DOAC.

**Method**

The clinical nurse specialist leading the project met with a senior anticoagulation nurse to agree objectives for implementing the work to achieve one of two desired outcomes: switching the anticoagulant from warfarin to a DOAC; or, for patients who needed to stay on warfarin, improving their TTR.

The proposal was presented to the anticoagulation lead consultant and suggested adjustments were made. DAWN anticoagulation clinical management software was used to:

- Write a report to identify those patients...
Results
The team identified 166 patients prescribed warfarin who had an average TTR of $<40\%$ over the previous 12 months. In nearly half of cases ($n=82, 49\%$), the reason for patients’ poor TTR was not clear; for the remaining 84 patients, eight main contributing factors were identified (Fig 1). Some of these were preventable, such as missed doses and increased alcohol intake; others were considered non-preventable – for example, hospital admissions and medical conditions.

The biggest contributing factor was missed doses of warfarin, which patient feedback indicated was due to memory problems or patients not taking doses as prescribed.

Switching to a DOAC
Once patients had been reviewed, staff collated information to determine whether they met the criteria to initiate a switch from warfarin to a DOAC. This led to 59 (36\%) of the 166 patients being switched from warfarin to a DOAC. Those patients who were unsuitable for DOACs ($n=107, 64\%$), did not meet the criteria to be switched, or did not want to switch to a DOAC remained on warfarin.

Patients remaining on warfarin
Of the 166 patients originally contacted, nine (5\%) died, 59 had their medication switched to DOACs (36\%) and 55 (33\%)

“Patients outside the therapeutic range had increased rate of hospitalisation, mortality and likelihood of thromboembolic events”

Training was provided to ensure staff were confident with the process. These measures allowed staff to:

- Identify patients on warfarin with poor TTR ($<40\%$) over the previous 12 months;
- Contact these patients by telephone or in person to try and establish the reasons for their poor TTR;
- Establish which patients were suitable to be switched from warfarin to a DOAC, and contact them to inform them of their suitability for a DOAC;
- Contact patients who needed to remain on warfarin to discuss in a clear and structured way how they might improve their TTR, including:
  - Educating them further on the use of warfarin
  - Learning more about their lifestyle choices
  - Helping them to better manage their medication;
- Measure the effect of these interventions on patients’ TTRs over a 12-month period.

DOAC = direct oral anticoagulant; DNA = did not attend
remained on warfarin after 12 months (Fig 2). Of the remainder (n=43, 26%), some stopped warfarin, others moved out of the area, were seen by another service or did not attend clinic (Fig 2).

The anticoagulation nurse specialists contacted the 55 patients who remained on warfarin and discussed in detail their poor TTR with them. In the course of talking with patients, the nurses suggested various strategies for them to improve their TTRs. These included:
- Advising the patient to set telephone reminders for when they were due to take their warfarin;
- Providing re-education and support;
- Referring complex cases to a haematology consultant;
- Advising on the use of dossette boxes;
- Switching to lower-strength tablets.

The majority of patients received verbal advice only. The treatment was usually discussed with them and they were asked if they wanted any written information; some said yes, others did not feel it was necessary. This included information on self-testing with home-testing kits, as well as further education on their medication.

Patients’ TTR was then monitored over a 12-month period to see whether there was any improvement compared with their TTR in the 12 months before the intervention. Of the 55 patients contacted, 49 (89%) saw an improvement in TTR after discussion with the nurse. The average increase in TTR for these patients was 22% over a 12-month period. Six patients (11%) saw no improvement, with TTR in these patients declining by an average of 7%.

**Discussion**

Wan et al (2018) showed that a 7% improvement in TTR reduces major haemorrhage by one event for every 100 patient years; and a 12% improvement reduces thromboembolic events by the same amount. The nurse interventions in this project achieved an average 22% improvement in TTR for the majority of patients remaining on warfarin, thereby increasing patient safety.

One likely cause of the improvement for our patients was increased patient education. Patients chosen to receive the intervention were contacted and their anti-coagulation discussed with them, including lifestyle choices, concordance and understanding of their medication. Newell et al (2005) argued that it is generally accepted that patients who have a better understanding of their warfarin therapy will experience fewer complications with their treatment. Nasser et al (2012) also proposed that an increase in warfarin-based education resources could perhaps help improve patient knowledge and, as such, therapeutic outcomes. Such resources have been used to good effect in other clinical settings for chronic diseases and their drug therapy (Neafsey et al, 2002).

Bhatt et al’s (2018) study, however, found little evidence that more warfarin education produced extra benefit in terms of increasing patient knowledge; the researchers highlighted potential issues to be aware of when counselling patients, such as poor understanding among those whose first language is not English. More research is needed but it is likely that this project’s increased patient education did help some patients to improve their TTRs.

As well as education, patients were also given practical advice on how to improve their warfarin therapy, such as setting reminders when warfarin was due and using dossette boxes. Some were also referred to consultants for advice and others were switched to lower-dose tablets in the hope of gaining tighter control over INRs. Sudas Na Ayutthaya et al (2018) found telephone follow-up services helped achieve and maintain INR targets in recently discharged patients; such conversations may give patients the opportunity to make changes that are more suitable for them.

**Conclusion**

The effectiveness of warfarin depends on patients’ success in keeping their blood levels within a narrow therapeutic range. If this is not achieved, some patients may be better switching to a DOAC, which requires fewer hospital visits and less monitoring. Patients who remain on warfarin can benefit from increased nursing interventions. Resource and staffing constraints meant this intervention was only given to patients with a TTR of <40%; as 65% is the gold standard recommended by NICE (2014), extending it to all patients with a TTR <65% could further improve patient safety and quality of life. NT

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**References**


