**Time in range – Making a difference – Matthew Roberts, Julia Rollason, Sarah Warren.**

**Keywords –** Warfarin, Time in range, anticoagulation, anticoagulants **Key points**-

1. Patients taking warfarin will need regular INR blood tests to ensure that their levels remain within a set therapeutic range. If patients fall below this range they will be less protected from the chances of developing a VTE.
2. Warfarin’s narrow therapeutic index makes it difficult for some patients to remain within a set therapeutic range
3. Patients, taking warfarin, whose TIR was 60% or greater are shown to have a good prognosis with regards to thromboembolism and all cause death. This prognosis was worse for those patients who TIR was less than 40%
4. If suitable patients may benefit from switching from warfarin to a DOAC
5. Nursing interventions have shown to make a positive impact upon patients time in range. Increasing patient knowledge and suggesting positive changes in partnership with patients help improve patient outcomes and ensure the patient is involved in their care

**Abstract**

Warfarin is one of the most widely used anticoagulants in the United Kingdom. Patients taking warfarin need regular International Normalised Ratio (INR) blood tests to ensure that their levels remain within a set therapeutic range. Should patients fall below this range they will be at higher risk of developing a venous thromboembolism (VTE). If patients INR were to go above range they are at greater risk of bleeding. (Wan, Heneghan, Perera, Roberts, Hollowell, Glasziou, Bankhead & Yongyong, 2018) In order to achieve best patient safety it is vital that patients are kept within their set therapeutic range. The purpose of this service improvement was to address the issue of patients on Warfarin with a poor time in range (TIR) and to determine what could be done to improve these patients overall TIR.   
  
**Introduction**  
Warfarin is an anticoagulant that helps prevent blood clots, and are commonly prescribed to those at a highest risk of developing clots, to reduce their chances of Cardiovascular accident (CVA) or Myocardial Infarction (MI). Oral anticoagulants prevent clots from getting bigger and will prevent patients from developing further clots. Patients taking warfarin will need regular INR blood tests to ensure that their levels remain within a set therapeutic range. If patients fall below this range they will be less protected from the chances of developing a VTE. (Passman, 2016) Warfarin’s narrow therapeutic index makes it difficult for some patients to remain within a set therapeuric range. (Pirmohamed, 2006) A recent analysis of 6454 patients, taking warfarin for atrial fibrillation, found that patients INR was out of range for almost 50% of the time. (Boulanger, L., Kim, J., Friedman, M., Hauch, O., Foster, T., & Menzin, J., 2006). Individual responses to the medication are highly variable, and there are many other factors that should be considered when prescribing warfarin. These can range from patients diet, alcohol intake, body mass, drug interactions and patient compliance. (Hall & Wilkins, 2005) Ensuring patients remain within these limits will ensure greater safety and quality of life, this service is commonly monitored by Doctors surgery’s or anticoagulation nurse specialists who will educate patients and monitor their INR levels. (Connor, Wright, Fegan & May, 2002)  
  
**Background**Warfarin has proved to be a very efficient drug in the treatment and prevention of VTE. (Tideman, Tirimacco, St John & Roberts, 2015) Alnsasra, Haim, Senderey, et al (2019) noted that the benefit of anticoagulation in the elderly is positive, however the highest benefit in elderly patients treated with warfarin were those who achieved a TIR of 65% or higher. (NICE Guidelines, 2014) Jones, et al (2005) noted that even in patients who appear to have good control, instability of INR results has substantial implications for mortality and other clinical outcomes. An association was found between INR results outside the therapeutic range and an increased rate of hospitalisation, mortality and an increased likelihood of thromboembolic events. Wan, Et al, (2018) support this view however there are numerous challenges in ensuring that patients remain within their respective range (Kim, Park, Kang, Kim & Lee, 2019). There is a need for regular monitoring, which brings with it associated costs and burdens, and there are numerous other factors that can impact upon INR results. Molteni and Cimminiello (2014) discuss these issues and state the difficulties in keeping patients within 60% time in range, noting that anticoagulation nurse specialist services have proved very effective in this regard. This too is an important consideration as it has been noted that high warfarin dose fluctuation can lead to an increased risk of bleeding and thromboembolism. Conservative dosing was seen to be the less risky strategy when treating patients (Yu, Chen, Tsai & Hung, 2018)  
Patients, taking warfarin, whose TIR was 60% or greater are shown to have a good prognosis with regards to thromboembolism and all cause death. This prognosis was worse for those patients who TIR was less than 40% (Inoue, Kodani, Atarashi, Okumura, Yamashita, Okuyama, & Origasa,, 2018) It is important, therefore, to consider what impacts upon patients TIR and what can be done to act upon these factors where possible. In a well-managed warfarin therapy setting for patients with non-valvular AF, excessive alcohol use was found to be the greatest predictor of poor INR control (Bjork, Kadhim & Sjalander, 2018). Bjork, et al, suggested that patients other comorbidities such as hypertension, chronic obstructive disorder and renal failure, along with variables of frailty such as dementia, cancer and history of falls are also frequently associated with poor INR control and for patients such as these Direct Oral Anticoagulants (DOACs) may be an alternative treatment option. It is important, therefore, to understand why patients TIR may be poor and the choice of anticoagulant should be individualised for each patient. This should include considerations for the best estimate benefit versus the potential bleeding risk (Te, Chao, & Chen, 2019) A recent study by Tansey and Nugent (2018) showed that the majority of patients reviewed were only therapeutically anticoagulated for two thirds of the time, this was despite monitoring. For patients such as these DOACs could prove to be a more reliable form of anticoagulant, they also require less frequent monitoring which has significant advantages to both patients and healthcare resources (Kockaya, Carvus, Ozin, et al, 2018).  
The purpose of this service improvement was to determine how patients with a poor TIR could be best aided to ensure that their INR results remained within range for as long as possible, thus ensuring increased patient safety.

**Methods**NICE guidelines states that the gold standard for monitoring patients TIR is 65%, for this research patients 40% and below were chosen. This was due to time and staff restraints at the time of initiation. Within a large acute hospital trust the anticoagulation service had been addressing the issue of patients on Warfarin with a poor TIR for some time but the approach was being carried out in an ad-hoc manner, without a standardised procedure in place. It was hoped that by formalising this approach patients with a poor TIR could be identified and, through discussion with the patient, a clear method of improvement could be initiated. Patients would be contacted to determine possible reasons for the poor control and measures could be implemented that could potentially improve the TIR. This could involve patient education, changes to patient’s diet and lifestyle, change to methods taken for example, use of a dosette box, or exploring the possibility of switching the anticoagulant given, if appropriate, from Warfarin to a DOAC.  
A Senior Anticoagulation Nurse and the Clinical Nurse Specialist responsible for the development of the TIR project met to identify objectives regarding the implementation of work required to achieve the desired end result, which would be to improve a patient’s poor time in range or to implement the change of the anticoagulant from Warfarin to a DOAC. This was then presented to the Anticoagulation lead consultant and any suggested adjustments made to the process. The team involved requested that a report be written by DAWN Anticoagulation Clinical Software which would enable the identification of those patients with a poor time in range, using the NICE guidelines for Anticoagulation control as a framework. DAWN AC software also developed a new file in the patients’ anticoagulation records so that follow up and review dates could be entered.

A pathway was developed, which would be used, to identify and treat those patients with a poor TIR. A DOAC exclusion criteria was written, to be used in conjunction with this pathway, so ensuring those patients unsuitable for a DOAC would not be switched from Warfarin. A pro-forma for the switching of patients from Warfarin to a DOAC was created in order to document the findings from the investigations carried out when a patient was identified as having a poor TIR.  
Short codes were developed to standardise the information entered into a patient’s computerised record regarding the time in range investigations, reviews and outcomes. Standardised letters were written which would be used to send to the patient’s General Practioner (GP) informing them of the findings of any investigations into the poor time in range , and asking them to make a decision about the patient’s future anticoagulation drug. A spreadsheet was formulated to enter the findings from the first year of the TIR project so it could be used for audit purposes. Finally, a Standard Operating Procedure was developed for staff to follow, and to identify patients with a poor time in range, This document would help explain the process involved to either switch to a DOAC or to improve their TIR whilst remaining on Warfarin. Additional training was provided for staff to ensure they felt confident with the process. When these developments were in place staff were then able to contact patients and discuss their poor time and range in a clear and standardised manner. This would include increasing patient education, learning more about patients lifestyle choices and informing patients of suitability for DOACs.  
  
**Results**

Over the 12 month period 166 patients were identified who had an annual average time in range less than 40%. Where possible, each patient was contacted via telephone, or in person, to determine identifying causes of their poor time in range. In 82 (49%) of the 166 patients a reason for their poor TIR was not determined. (Figure 1) In the remaining 84 patients 8 main contributing factors were determined. Some of these were preventable, such as missed doses and increased alcohol intake. Whilst others were not thought to be preventable, for example hospital admissions and medical conditions. The biggest contributing factor was missed doses of warfarin, this was deemed, through patient feedback, due to memory problems or patients not taking doses as prescribed.

Figure 1

**Switching from warfarin to a DOAC**

Once patients had been reviewed, further information was collated to determine if they met the criteria to initiate a switch from warfarin to DOAC. This resulted in 59 out of the 166 patients being switched from warfarin to a DOAC. The DOAC drugs require significantly less blood test monitoring and hospital visits for the patients. There are also less interactions with other medications and alcohol. They are especially beneficial in patients who are difficult to bleed, require community phlebotomy or who require dosette boxes filled by pharmacy, or who find attending regular follow up difficult due to work commitments. Some patients were unsuitable, did not meet the criteria to be switched, or did not want to switch to a DOAC so remained on warfarin.  
  
**Nursing interventions undertaken to improve time in range**

In the process of talking to patients, via telephone conversations, and in person, the anticoagulation nurse specialists suggested various strategies to improve TIR for the patient, dependant on the findings of their conversations. These suggestions included advice to the patient to set phone reminders when warfarin was due, giving increased re-education and support, referring to a haematology consultant for complex cases, advising use of dossette boxes and switching to lower strength tablets. (Figure 2) Clear interventions were suggested to the patients. The majority of patients received verbal advice, with others receiving additional written information in addition to verbal advice. This included information on self-testing as well as further education on their medication.   
Of the 166 patients in the initial study, some patients had passed away, others had been swapped to a DOAC, and 55 patients remained on warfarin. These patients were contacted, their poor TIR was discussed in detail and their TIR 12 months prior to discussion was recorded. Their TIR was monitored over the course of 12 months and the percentage of TIR was again recorded 12 months post first discussion. Out of these 55 patients, 49 (89% of patients) saw an improvement in their range. The average increase for these patients was +22%. 6 patients (11% of patients) contacted did not improve their TIR, the average decline for these patients was -7%   
Figure 3

Figure 2  
  
Figure 3

**Discussion**Following the review of the results it can be noted that the interventions provided to patients have been successful. 89% of patients who received interventions improved their TIR within the following 12 months. The importance of this can be noted in a recent study by Wan, et al (2018) who noted that an improvement by as little 7% to patients TIR reduced major haemorrhage by 1 event per 100 patient years. Furthermore a reduction in thromboembolic event rate by 1 event per 100 patient years can be achieved by a 12% increase in TIR (Wan, Heneghan, & Perera et al, 2018). Those patients whose TIR did improve, did so on average of 22%, no doubt improving patient safety. Patients who are in range more frequently also require less nursing interventions and blood tests saving the trust large amounts of money each year. One likely cause of this improvement is due to increased patient education. Patients were contacted and their anticoagulation was discussed, this included lifestyle choices, compliance and understanding of their medication. Newell, Monagle and Johnston (2005) argued that there is a general acceptance that patients who have a better understanding of their warfarin therapy will experience fewer complications with their treatment. It was noted that an increase in warfarin based education resources could potentially help to improve patient knowledge and, therefore, therapeutic outcomes. (Nasser, Mullan, & Bajorek, 2012) Furthermore, such resources have been used to good effect in other clinical settings of chronic diseases and their drug therapy (Neafsey, Strickler, Shellman, & Chartier, 2002). A study by Bhatt, Russell, McCurdy and Liew (2018) argued that little evidence of additional benefit to patient knowledge was determined from further outpatient warfarin education. However, they did note that certain patients may benefit from additional education such as those with mild cognitive impairment or those from non-English-speaking backgrounds. It can be seen that further research into this area is needed in order to say with assurance that this was the cause of patients TIR improvement, but it is likely to have played a part for some.   
As well as education patients were given advice as to methods that may aid their warfarin therapy. Suggestions included advice to set reminders when warfarin was due and the use of dossette boxes. Patients were also referred to consultants for advice, while others were switched to lower dose strength tablets in the hope of gaining a tighter control over patients INRs. Telephone follow up services for recently discharged patients have shown to help achieve and maintain INR targets, (Sudas, Ayutthaya, Sakunrak & Dhippayom, 2018) and these conversations have arguably allowed patients the opportunity to make changes that are more suitable for them. During this study it was noted that a higher proportion of patients were identified as suitable for a DOAC than were actually switched. One area of further study would be to investigate further to determine the reasons for these patients not switching from warfarin to a DOAC.  
  
**Conclusion**  
In conclusion it can be seen that, as a result of the 12 month service improvement, 166 patients were identified as having poor TIR below 40% and two clear improvements were identified. Firstly, 35% of patients were switched to a DOAC. This will mean less hospital visits, monitoring will be required. DOACs also have fewer interactions with alcohol and other medications. The effectiveness of warfarin is dependent on the quality of control within the INRs therapeutic range. If this is not achieved patients may be better suited to switching therapy to a DOAC (Kim, et al, 2019) Secondly, 89% of the patients, who remained on warfarin and had a recording of TIR 12 months post intervention, showed an improvement in their TIR. Clear benefits were found from increasing nursing interventions in this patient group andfurther resources and time are needed to further develop this improvement. NICE guidelines (2014) state that anticoagulation should be reviewed for patients with 2 INR values higher than 5 or 1 INR value higher than 8 within the past 6 months and patients with 2 INR values less than 1.5 within the past 6 months. It would be beneficial to extend further study to include these patients to improve patient safety. Only patients with TIR of less than 40% were contacted in this study due to staffing limitations and resources. Nice Guidelines state that a TIR of 65% should be the gold standard so further support is needed in order to increase the scope of this service improvement to include all patients with a TIR of less than 65%. In doing so it can be seen that improvements can be made to patient experience and patient safety.

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