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# ASSOCIATION OF INR QUALITY WITH COMPLICATIONS AMONG PATIENTS ON WARFARIN THERAPY IN HOSPITAL SULTAN ISMAIL PETRA, KELANTAN STATE

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## ABSTRACT

**Background:** Poor International Normalised Ratio (INR) quality of warfarin (time in therapeutic range (TTR) <70%) can lead to increased risk of complications (bleeding/thromboembolism). However, the association of INR quality (TTR) with warfarin complications in Hospital Sultan Ismail Petra (HSIP) is not well established. This study aimed to investigate the INR quality using TTR and its association with complications among patients on warfarin therapy in HSIP.

**Materials and Methods:** A total of 117 patients were recruited from INR Clinic and were retrospectively traced from the medical records office. TTR was computed using Rosendaal method and categorized into two groups (<70% or ≥ 70%). Clinical complications assessed were bleeding or thromboembolism (TE), defined based on hospitalization. Patients were followed from warfarin initiation to the first occurrence of complication. Chi-square test was used to evaluate the association of TTR with complications.

**Result:** Mean TTR was 55% with 57.3% of the total patients had TTR <70%. During observation, 12 complications (5 bleedings, 7 thromboembolisms) occurred in 10% of the patients, and those with TTR <70% were at higher risk. Patients with TTR <70% had a higher risk for any bleeding (RR: 2.99; 95% CI: 0.34 – 25.90) but a lower risk for any thromboembolism (RR: 0.56; 95% CI: 0.13 – 2.39). However, no statistically significant association was observed between TTR and overall complications (p = 0.94).

**Conclusion:** Bleeding and thromboembolism complications were associated with warfarin therapy, independently of INR control (TTR). Future study with a larger sample size is warranted to further validate this study's finding.

**Keywords:** warfarin, TTR, bleeding, thromboembolism, complications

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## 1.0 Introduction

Warfarin is a vitamin K antagonist, an oral anticoagulant with narrow therapeutic range and remains the mainstay for the prevention and treatment of thromboembolic disease (Ageno et al., 2012; Guyatt, Akl, Crowther, Gutterman, & Schuünemann, 2012). It produces an anticoagulant effect by interfering with cyclic interconversion of vitamin K and its 2, 3 epoxides (Friedman, Rosenberg, Hauschka, & Fitz-James, 1977). Inhibition of vitamin K in conversion cycle reduces anticoagulant activity by inhibiting the synthesis of clotting factors II (prothrombin), VII, IX, X, protein C and S. Warfarin is indicated for a wide range of clinical conditions such as prevention of cardio embolic ischemic stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or flutter, recent major surgery or immobility, heart valve replacement, ischemic stroke or other thrombotic events (Sacco et al., 2013).

International Normalized Ratios (INRs) for most indications of warfarin are between 2.0 to 3.0 for atrial fibrillation (Guyatt et al., 2012), and 2.5 to 3.5 for patients with mechanical heart valves (Rosendaal, Cannegieter, Van der Meer, & Briet, 1993). An INR target of 2.0 to 2.5 might be suitable for patients with mechanical prosthetic heart valves and persistent risk of bleeding (Friedman et al., 1977). Management and initiation of warfarin are often difficult and patients prescribed with warfarin will require continuous education and routine INR monitoring (Friedman et al., 1977). Time in therapeutic range (TTR) is calculated using a linear interpolation method developed by Rosendaal et al. (1993). TTR is often used to measure the quality of anticoagulation control and indicates the efficacy of patients' warfarin therapy (Connolly, Pogue, Eikelboom, & Investigators, 2008). According to Connolly et al. (2008), time in therapeutic range is defined as the duration of time (in days) the patient's INR within a therapeutic range.

Based on 2016 European Society of Cardiology Guidelines for The Management of Atrial Fibrillation, the recommended TTR is ≥ 70%, as higher TTR corresponds with a good anticoagulation control (An et al., 2015; Kirchhof et al., 2016). Meanwhile, poor TTR is associated with an increased risk of complications such as bleeding or stroke/thromboembolism (Björck et al., 2016). TTR value is expected to be low in new patients, as the steady dose of warfarin was not yet established. Thus, at least 1 month is needed before the measurement of TTR (Razouki, Ozonoff, Zhao, Jasuja, & Rose, 2014). Bleeding is the most serious complication of warfarin in the prevention and treatment of thromboembolic events (Rosendaal et al., 1993). In contrast to warfarin's efficacy in reducing the risk of stroke by 64% and all-cause mortality by 26%, warfarin also confers an increased risk of hemorrhage, with intracranial bleeding as the most severe complication (Ogilvie, Welner, Cowell, & Lip, 2011). On the other hand, sub-optimal warfarin therapy is associated with an increased risk of recurrent thromboembolism by two-fold (Di Minno et al., 2017).

According to Björck et al. (2016) and Kirchhof et al. (2016), patients with TTR ≥70% is categorized as good anticoagulation control, with a lower risk of major bleeding and thromboembolism (Di Minno et al., 2017; Ogilvie et al., 2011). Meanwhile, several randomized controlled trials and observational studies had also concluded the relationship between poor TTR and a higher risk of stroke or bleeding in patients on warfarin therapy (Amin et al., 2014; Hirsh, 1991). A retrospective study carried out by Björck et al. (2016) found that patient with TTR ≥ 70% had a significantly lower prevalence of bleeding complications compared to other complications such as any other thromboembolism defined as arterial thromboembolism,

myocardial infarction and venous thromboembolism (Björck et al., 2016). In addition, a study conducted by An et al. (2015) identified the lowest major bleed rates were found in patients with TTR ≥ 55% and the events of major bleeding were highest in patients with TTR < 55%. This study also highlighted that the most common bleeding occurred was gastrointestinal bleeding with the percentage of 69.8% (An et al., 2015). A study by Liu et al. (2018) found that TTR ≤ 65% was associated with a 73% increased risk of death in comparison to TTR ≥ 65%.

From a study by Senoo and Lip (2016), it has been demonstrated TTR ≥ 65% was associated with 78% decreased risk for a combined endpoint of cardiovascular death/stroke and systemic embolism events. Meanwhile, from other retrospective longitudinal observational cohort study, the lowest stroke/thromboembolism risk was observed in patient with TTR ≥ 55% compared to patients with TTR ≤ 55% (An et al., 2015). From another observational study, the most common adverse event correlates with warfarin outcomes were ischemic stroke, ischemic heart disease and myocardial infarction (Wieloch et al., 2011). Razouki et al. (2014) found that patient with TTR <50% involved with higher number of stroke events, major bleeding and fatal cases with percentage of events per 100 person-years of 6.28%, 11.95% and 1.78% respectively compared to TTR ≥ 50%.

With that general concern in mind, this study was conducted to evaluate the TTR of patients on warfarin therapy; to investigate the prevalence of bleeding and thromboembolic complications of patients on warfarin therapy; and to determine the association of TTR with complications. The finding from this study is hopefully will serve as an overview of the overall quality of anticoagulation control among patients on warfarin therapy in Hospital Sultan Ismail Petra and might as well in Malaysian level.

## 2.0 Materials and Methods

This study employed a retrospective cross-sectional study design and was conducted in Hospital Sultan Ismail Petra (HSIP), Kuala Krai, Kelantan state of Malaysia from 1st January 2015 until 31st October 2018. Hospital Sultan Ismail Petra is one of the biggest and sophisticated hospitals in northeast region of Peninsular Malaysia and its pharmacy department has warfarin medication therapy adherence clinic (WMTAC) to provide comprehensive INR monitoring services for patients on warfarin therapy (Ab Aziz & Awang, 2019).

The study samples were all patients on warfarin enrolled in warfarin medication therapy adherence clinic, HSIP from 1st January 2015 until 31st October 2018 who fulfilled the study criteria. The study inclusion criteria were all patients aged 18 years old and above on warfarin enrolled in WMTAC, HSIP from 1st January 2015 until 31st October 2018. Patients who are on warfarin for less than one month were excluded from this study.

The sample size was calculated for complications in warfarin-treated patients using power and sample size calculation software (Dupont & Plummer Jr, 1990) as well to compare two independent proportions. The largest estimated sample for each group was 56 using the proportion of insulin-accepting group by the factor of female (0.06) (Gallagher, Setakis, Plumb, Clemens, & van Staa, 2011), an estimated proportion of 0.25, 5% type 1 error and 80% power. Therefore, the total sample size required is 112 patients.

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Convenient sampling was the sampling method of choice. A total of 150 patients attending WMTAC follow-up at HSIP were traced through records of patients. After considering the inclusion and exclusion criteria, only 117 patients were eligible to participate in the study. Information collected from patients were socio-demographic characteristics (age, gender and ethnicity), clinical characteristics (indication of warfarin, complications and details of WTAC visit). These details were recorded in patient's proforma. Patients were followed-up from the first WMTAC clinic enrolment and TTR value were calculated after 1 month from first WMTAC clinic visit until the first outcome of interest, end of enrolment, death or whichever occurred first. This is because at least 1 month is needed before a steady dose of warfarin was established. Data collection process is summarized in Figure 1.

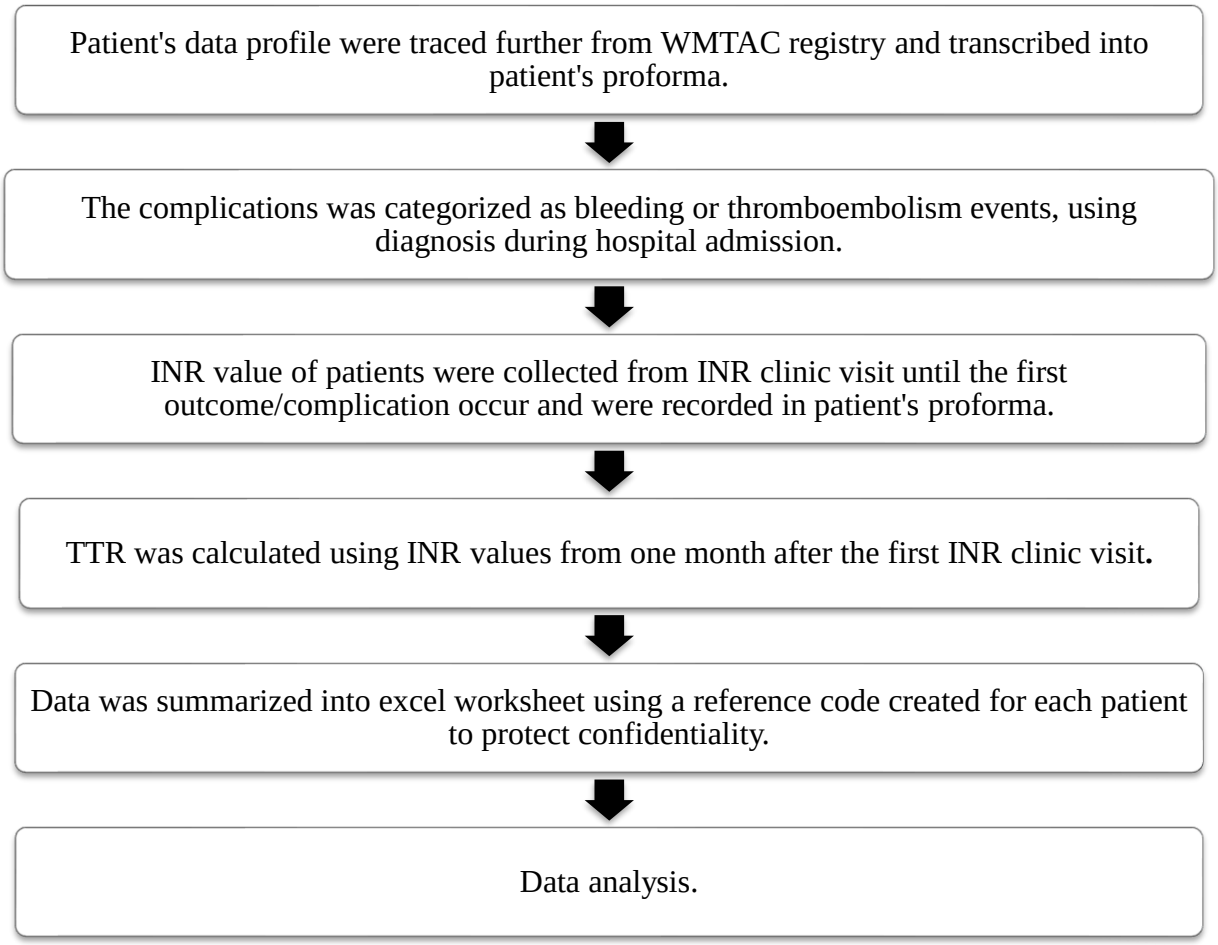


**Figure 1:** Summary of data collection process.

In this study, time in therapeutic range (TTR) is defined as percentage of time (in days) in which the patient's International Normalized Ratio (INR) values are within a desired range (Farsad,

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Abbasinazari, Dabagh, & Bakshandeh, 2016). Bleeding complications are defined as hospital admission which has bleeding diagnosis or as listed in ICD-10 (Liu et al., 2018). Thromboembolic complications are defined as hospital admission which has systemic embolism diagnosis or as listed in ICD-10 (Liu et al., 2018).

Data were analyzed by using SPSS software version 20. Time in therapeutic range (TTR) of patient were calculated using Rosendaal method (Rosendaal et al., 1993) and expressed by percentage of days. Mean, median and percentage of each group (TTR < 70%; TTR ≥ 70%) were calculated using SPSS. Descriptive analysis was used to present the prevalence of the bleeding and thromboembolism by the number of complications that occurred, recorded as percentage in total and it was divided for each group (TTR < 70%; TTR ≥ 70%). Chi-square test was used to find the association of TTR < 70% and TTR ≥ 70% with the prevalence of complications (bleeding or stroke/thromboembolism). A p-value of less than 0.05 was considered statistically significant. Overall relative risks of getting complication between TTR categories were calculated manually.

## 3.0 Result

### *3.1 Characteristics of patients*

A total of 117 patients with warfarin therapy were included in this study. The mean (±SD) age of patient was 57 (±15.58) with 88% of the patients aged less than 75 years old. Majority of the patients on warfarin therapy were male, Malay and had non-valvular atrial fibrillation. Details are shown in Table 1.

### *3.2 INR Quality (TTR)*

From 117 patients on warfarin therapy in HSIP, 57.3% of the patients had TTR < 70% and 42.7% of patients have TTR ≥ 70% with the mean TTR of 54.9%, which indicates majority of the patients on warfarin therapy at HSIP had poor INR quality. Details are shown in Table 2.

### *3.3 Complications and association with TTR*

During observation, there were 12 (10.2%) complications that had been reported with 5 (4.3%) were bleeding cases and 7 (6.0%) were thromboembolic cases. Those with TTR <70% were at higher risk of complications as 10.4% (n=7) of the complications occurred in patient with TTR<70% while 10% (n=5) in patients with TTR ≥70%. Patients with TTR <70% had a higher risk for any bleeding (RR: 2.94; 95% CI: 0.34 – 25.90) but a lower risk for any thromboembolism (RR: 0.56; 95% CI: 0.13 – 2.39). However, no statistical association was observed between TTR and overall complications (p = 0.94). Details are shown in Table 3.

**Table 1:** Characteristics of patients under Warfarin MTAC follow-up at Hospital Sultan Ismail Petra (n=117)

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| Characteristics | Frequency (%) |
|---|---|
| **Age*** | 57 (±15.58) |
| <75 years old | 103 (88.0%) |
| ≥75 years old | 14 (12.0%) |
| **Gender** | |
| Male | 70 (59.8%) |
| Female | 47 (40.2%) |
| **Ethnicity** | |
| Malay | 105 (89.7%) |
| Others | 12 (10.3%) |
| **Indication** | |
| Non valvular atrial fibrillation (NVAF) | 49 (41.9%) |
| Valvular atrial fibrillation | 13 (11.1%) |
| Deep vein thrombosis (DVT) | 17 (14.5%) |
| Pulmonary embolism (PE) | 4 (3.4%) |
| Post aortic valve repair | 4 (3.4%) |
| Post mitral valve repair | 5 (4.3%) |
| Others | 34 (21.4%) |

*Mean (±SD)

**Table 2:** Distribution of patients by TTR categories at Hospital Sultan Ismail Petra (n=117)

| TTR* | Frequency (%) |
|---|---|
| <70 % | 67 (57.3%) |
| ≥70 % | 50 (42.7%) |

*TTR Mean (±SD) = 54.9 (±33.6)

**Table 3:** Prevalence of warfarin complications and its association with TTR among patients under Warfarin MTAC follow-up at Hospital Sultan Ismail Petra (n=117)

*CVA: cerebrovascular accident; DVT: deep vein thrombosis; UGIB: upper gastrointestinal bleeding.

| Complications | Number of complication events (%) (n=117) | | | RR | 95% CI | p-value |
|---|---|---|---|---|---|---|
| | TTR < 70% n = 67(57.3%) | TTR ≥ 70% n = 50 (42.7%) | Overall | | | |
| **Bleeding** | 4 (6.0%) | 1 (2.0%) | 5 (4.3%) | 2.94 | 0.34-25.00 | 0.39 |
| UGIB | 3 (4.5%) | 0 (0.0%) | 1 (0.9%) | | | |
| Haematuria | 1 (1.5%) | 1 (2.0%) | 2 (1.7%) | | | |
| **Thromboembolism** | 3 (4.5%) | 4 (8.0%) | 7 (6.0%) | 0.56 | 0.13-2.38 | 0.46 |
| CVA | 0 (0.0%) | 3 (6.0%) | 3 (2.6%) | | | |
| Recurrent DVT | 2 (3.0%) | 0 (0.0%) | 2 (2.3%) | | | |
| Left Occipital Infarct | 0 (0.0%) | 1 (2.0%) | 1 (1.7%) | | | |
| Myocardial Infarction | 1 (1.5%) | 0 (0.0%) | 1 (1.7%) | | | |
| **All complications** | 7 (10.4%) | 5 (10.0%) | 12 (10.2%) | 0.96 | 0.32-2.84 | 0.94 |

## 4.0 Discussion

In our study, the mean TTR of 55% indicates the poor control of INR among patients on warfarin therapy in Hospital Sultan Ismail Petra. A study by Gallagher et al. (2014) stated that average TTR >70% indicates a good efficacy and safety of the warfarin treatment. This is consistent with Björck et al. (2016) which reported that TTR ≥ 70% produces better treatment outcome and good control of INR. Meanwhile, TTR < 70% indicates a high INR variability and can lead to the development of complications.

In TTR < 70%, there was a higher prevalence of total complications. There were 7 complications occur in TTR < 70% (4 bleeding complications and 3 thromboembolic complications) compared to TTR ≥ 70% (1 bleeding complications and 4 thromboembolic complications) (Guyatt et al., 2012). Study by Björck et al. (2016) found that, prevalence of thromboembolism was higher in patients with TTR < 70% which contributed 6.8% of their patients and 5.4% of their patients had bleeding complications. Similar with current study, most of the patients on warfarin therapy in HSIP had thromboembolic complications (6.0%), meanwhile, 4.3% of the patients had bleeding complications.

Higher thromboembolic events occurred in TTR < 70% because lower TTR means high INR variability and poor INR control and it might cause complications to the patients because patient in this group received fewer benefits from the treatment. INR below the range may cause thromboembolism or stroke. Meanwhile, INR above the range may cause bleeding. From the

previous studies by Ogilvie et al. (2011) and Di Minno et al. (2017), despite warfarin's efficacy in reducing the risk of stroke and mortality, warfarin also confers an increased risk of haemorrhage. Besides, sub-optimal warfarin therapy was associated with an increased risk of recurrent thromboembolism.

An et al. (2015) observed the TTR <55% had almost twice the risk of major bleed (RR: 1.93; 95% CI: 1.74– 2.14) but lower risk for stroke (RR: 0.80; 95% CI: 0.67– 0.95). Meanwhile, Liu et al. (2018) showed patients with TTR <65% had a higher risk of both major bleeding (RR: 4.06; 95% CI: 3.71-4.43) and thromboembolism (RR: 2.18; 95% CI: 1.95-2.43). In other study by Kose et al. (2015) had reported that heart failure would increase the relative risk of embolism in patients with atrial fibrillation.

Many previous studies had showed significant association of TTR with complications (An et al., 2015; Liu et al., 2018; Ogilvie et al., 2011). In all these studies, lower TTR values were associated with the higher prevalence of complications. However, studies from Razouki et al. (2014) found that complications related to warfarin therapy were independent of TTR, which was similar with current study.

There are many factors that can lead to INR variability of the patients. Okumura et al. (2011) highlighted that, dose of warfarin may affect TTR value. When patients needed higher dose of warfarin, there will be high INR variability of the patients and might increase the risk of hemorrhage. High INR variability indicated unstable anticoagulation meanwhile low INR variability signified stable anticoagulation (Björck et al., 2016). Doses of warfarin was also different in patients that aged >75 years old in comparison with patient <75 years old. Thus, optimization of dose adjustment must be done in obtaining higher TTR value in each patient. Besides, Singer et al. (2013) also studied the factor of geographical region would affect the TTR of the patient. The ability of the patient to access hospital also may affect the TTR of the patient. Patients who stayed in rural area and difficult to meet physicians have tendency to had variation in INR readings as they did not obtain proper scheduled monitoring from physicians. A study by Wieloch et al. (2011) and Kose et al. (2015) stated that age, sex, smoking status, comorbidities, alcohol abuse, and polypharmacy were correlated with the TTR value of patients. In another study conducted by Phillips and Ansell (2008), there was a relationship between patient's knowledge and adherence with the quality of INR. Based on the above findings, it can be concluded that the risk factor for INR quality is multifactorial.

The most widely used method to measure INR control is by calculating the TTR value using Rosendaal method (Rosendaal et al., 1993). However, there were other measures available to find the INR control such as INR variability as calculated by Fihn's method (Razouki et al., 2014) and SAMe TT2R2 score (Apostolakis, Sullivan, Olshansky, & Lip, 2013). Both measures had been shown to predict warfarin-related adverse events more precisely (Apostolakis et al., 2013; Razouki et al., 2014). The INR variability by Fihn's method was calculated as a time-weighted variance of the INR around the target INR and reflects the degree to which a patient-achieved INR deviates from his or her target INR or previous INR measurement. Meanwhile, the SAMe TT2R2 score was proposed and validated by Apostolakis et al. (2013) in order to predict patients who are likely to do well on warfarin therapy with good average TTR.

Among the limitations of this study was small sample size which could lead to higher variability and bias to the outcomes. Moreover, it was a single-centred study that was only conducted in

HSIP. Thus, it may not represent general population in Malaysia. Studies with larger sample size involving other different settings should be carried out to better represent Malaysian population. Moreover, further studies should include co-morbidities, concurrent medications, smoking status and socio-demographic factors to investigate their influence towards the complications.

## 5.0 Conclusion and recommendation

In conclusion, patients on warfarin therapy at HSIP had poor INR quality, which most of the patient have TTR value < 70%. Only small percentage of patients achieving TTR ≥ 70%. Furthermore, the outcomes of bleeding and thromboembolic are came from patients with TTR < 70% which are 7 out of 12 total events in this study.

However, there was no statistically significant association of INR quality with warfarin complications. The occurrence of complications that associated with warfarin therapy were independently of INR control (TTR). Hence, it is necessary for patient to be well educated and understand importance of compliance to warfarin therapy to reduce risk of bleeding or thromboembolism in the future.

A better measurement tool would be needed in predicting warfarin control so clinicians can decide whether to switch suitable patients to direct oral anticoagulants (DOACs). Besides, current protocol for INR clinic should be revised periodically such as monitoring intervals and frequency of clinic days. Efforts should be made to maintain good INR control such as to educate patients on knowledge of complications and emphasize on compliance through counselling and to do home medication review for patient with poor INR control.

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## Declaration

The authors declare that this manuscript has never been published in any other journal

## Authors contribution:

Author 1,2,3,4,5: information gathering, data entry, data analysis and manuscript drafting.

Author 6: data analysis, manuscript editing and review.

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