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A MULTICENTRE STUDY ON AVERAGE WARFARIN DOSE TO MAINTAIN THERAPEUTIC INTERNATIONAL NORMALISED RATIO WITH TIME IN THERAPEUTIC RANGE OF MORE THAN 75% IN ATRIAL FIBRILLATION PATIENTS

ANG KEE HOOI, **ISHMAH MUSFIRAH NAZARI, LOW SEOW HUEY, NG YINWEN, OON XIN YING AND VALLIYAMAI A/P SUPPIAH**
Pharmacy Department, Hospital Pulau Pinang, Georgetown, Pulau Pinang, Malaysia

ABSTRACT

Large interindividual variability and over-anticoagulation resulting bleeding complications due to narrow therapeutic index of warfarin has causes its pharmacodynamic activity to be highly variable. Studies shown that ethnicity, age and gender contribute to warfarin response variability. Good coagulation control of time in therapeutic range (TTR) > 75% was chosen to determine the average warfarin dose in atrial fibrillation (AF) among ethnicity, age and gender. Data from Warfarin Medication Therapy Adherence Clinic of selected Pulau Pinang hospitals were used for the analysis of average warfarin dose in AF among ethnicity, age and gender. Patients who fulfilled the inclusion criteria from 2015–2016 were followed up for a year. Five hundred and seventy-six patients were included. Two hundred and ten patients had good coagulation control of TTR > 75% with mean warfarin dose of 3.05 ± 1.25 mg. Only Chinese and Indian have significant difference in average warfarin dose with 2.86 ± 1.10 mg and 4.11 ± 1.40 mg, respectively (p = 0.008). Average warfarin dose was found not significantly different among gender and age. As for TTR achievement, 210 (36.4%) were able to achieve TTR > 75%, 134 patients achieved TTR 60%–75% and 232 patients has TTR < 60%. The median day to achieve three consecutive targeted international normalised ratio (INR) is 186.5 days for atrial fibrillation patient newly started on warfarin therapy in 2015 until 2016. Indian patients required a higher warfarin dose than Chinese patients. This study found that mean warfarin doses were not affected by age and sex.

*Corresponding author: kee_hooi_88@hotmail.com

INTRODUCTION

Warfarin is one of the most frequently prescribed oral anticoagulants to reduce thrombosis related risk, morbidity and mortality in patient with atrial fibrillation (AF), mechanical heart valves, deep vein thrombosis (DVT) and pulmonary embolism (PE) (Sonuga *et al.* 2016). Warfarin has been safe and effective treatment for stroke reduction in AF patients (Brass *et al.* 1997). However, warfarin initiation therapy has been impeded with two major issues which are large interindividual variability in maintenance dose and over-anticoagulation response, resulted bleeding complications (Ohara *et al.* 2014). Close monitoring of international normalised ratio (INR) and appropriate dosing are the utmost importance to ensure the warfarin therapeutic efficacy, as its narrow therapeutic index and large interindividual variability may cause its pharmacodynamic activity to be highly variable (Sonuga *et al.* 2016; Gan *et al.* 2011).

Malaysia is a multiracial country consisting of three major ethnic groups which are Malay, Chinese and Indian. Several studies have reported that racial differences do influence warfarin maintenance dose as the Asian population requires lower warfarin dose and the Indian patients requires higher warfarin dose to maintain therapeutic INR compared to other races (Gan *et al.* 2011; Lal *et al.* 2008*;* Dang, Hambleton and Kayser 2005). Studies also shown that age and gender have significant contribution in warfarin response variability (Khoury and Sheikh-Taha 2014).

According to Ansell *et al.* (2004), there is strong relationship between time in therapeutic range (TTR) and events of bleeding or thromboembolism for INR above or below targeted range. Therefore, TTR is often used to represent the coagulation control for warfarin. In ACTIVE W study, association of centre TTR and outcomes were evaluated. The median centre TTR of ACTIVE W study was 65% and warfarin requires median centre TTR > 65% to reduce vascular events as compared to combination of clopidogrel and aspirin (Pokorney *et al.* 2015). The study reported that TTR < 58% do not generate any clinical benefits (Pokorney *et al.* 2015). Good INR control was defined by Rosendaal *et al.* (1993) as TTR ≥ 75% during study period using the Rosendaal *et al.*'s method. In White *et al.* (2007) study, good control group (TTR > 75%) has lower rates of annual mortality and major bleeding (1.69% and 1.58%, respectively) as compared to moderate control group (TTR 65%–75%) 1.84% and 1.96%, respectively and poor control group (TTR < 60%) 4.20% and 3.85%, respectively. Furthermore, poor control group reported to have higher rates of myocardial infarction (1.38% versus 0.62%) and stroke or systemic embolic event (2.10% versus 1.07%) compared to good control group (White *et al.* 2007).

The objectives of the study were to determine the average warfarin dose in AF patients for TTR more than 75% among different ethnicity, age group and gender, to determine the TTR of warfarin in Pulau Pinang population, and to determine the median day to achieve a stable therapeutic INR. TTR of more than 75% is used, to determine the average warfarin dose in AF patients of different ethnicity, age and gender.

METHODS

Study Design and Study Population

This is a retrospective study conducted in four hospitals in Pulau Pinang which was approved by the National Medical Research Register (NMRR) and the Medical Research and Ethics Committee (MREC). All AF patients who are currently under follow up in Warfarin Medication Therapy Adherence Clinic (WMTAC) of Hospital Pulau Pinang, Hospital Seberang Jaya, Hospital Bukit Mertajam and Hospital Kepala Batas during January 2015 until December 2016 were included. This study was conducted over a period of 4 months inclusive of study protocol preparation, study approval application, data collection approval from hospital directors of respective hospitals, data collection, data analysis and dissertation preparation.

All adult patients who are on warfarin for at least a year, with a desired INR range of 2.0–3.0 and have stable INR from 2015–2016 were included. We excluded patients younger than 18 years old, with tuberculosis, pregnant women, patients who defaulted follow up at WMTAC, discontinued warfarin therapy at any point of the study, has interruption in the warfarin therapy for > 7 days, has a change in INR target within the study period and patients on warfarin for other indications other than AF.

Data Collection

Case notes of patients were reviewed and data such as age, gender, race, date of clinic appointment, present recommended dose of warfarin and present INR were collected. The patient ethnicity was defined according to national identification documents. During data collection period, we were notified that WMTAC patient under Hospital Seberang Jaya has different blood taking method which uses the conventional laboratory method to test for coagulation profile of INR. As compared to other hospitals, coagulometer were used in INR monitoring. Thus, patients' data from Hospital Seberang Jaya were excluded to prevent systematic error. The coagulometer used by Hospital Pulau Pinang is CoaguChek Pro II, Hospital Kepala Batas is CoaguChek XS and Hospital Bukit Mertajam is CoaguChek.

STATISTICAL ANALYSIS

A total of 576 records met the inclusion criteria and were analysed using descriptive statistic to ensure the data (average warfarin dose) collected is normally distributed. To analyse the average warfarin dose between gender the independent sample-t test was used. Factor of race was analysed using analysis of variance (ANOVA), followed by post-hoc test. For correlation of age factor and average warfarin dose, Pearson correlation test was used. All data were expressed as means and standard deviation. If the value of $p < 0.05$ then was considered statistically significant.
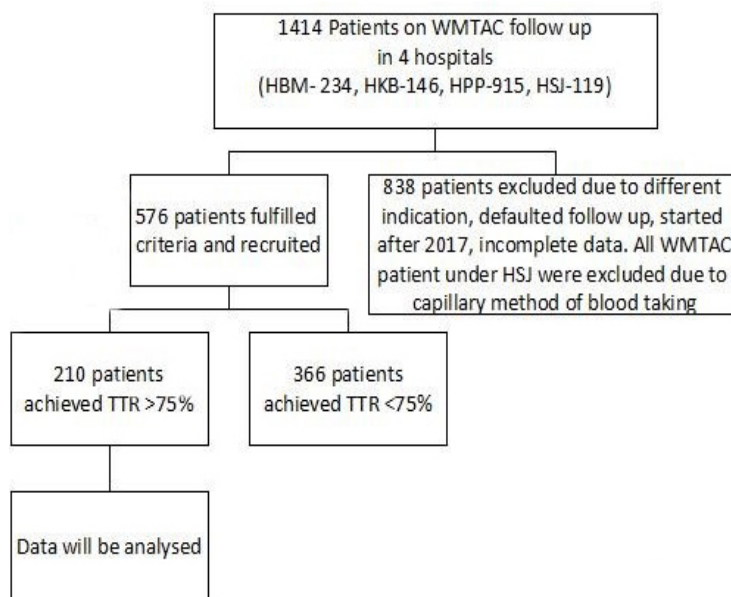
Key Definitions

INR stabilisation is the achievement of stable therapeutic INR defined as the first three consecutive INR values in range of 2.0–3.0 after the initiation of warfarin therapy (Nelson *et al.* 2014).

INR stabilisation time was defined as the time between the first visit and the third of the three consecutive in-range INR values. INR patterns were expressed using percentage of TTR (Nelson *et al.* 2014).

TTR was calculated based on Rosendaal *et al.*'s (1993) method, which uses linear interpolation to assign an INR value to each day between successive observed INR values (Nelson *et al.* 2014). This approach assumes that INR is linearly increasing or decreasing between measurements and produces a percentage of days when the INR measurements are within a pre-specified range (Nelson *et al.* 2014).

RESULTS

A total number of 1,414 patient were followed up under WMTAC warfarin clinic of the four selected hospitals. The number of patient under WMTAC follow up in Hospital Bukit Mertajam, Hospital Kepala Batas, Hospital Pulau Pinang and Hospital Seberang Jaya is 234, 146, 915 and 119, respectively. Eight hundred and thirty-eight patients were excluded from the study and the remaining 576 patients who fulfilled the criteria were selected for this study as shown in Figure 1.

Figure 1: Flowchart of study sample selection of AF patients with TTR > 75%.

Microsoft Excel were formulated according to Rosendaal *et al.*'s (1993) method shows that only 210 patient has TTR more than 75%. The data is normally distributed and positively skewed. The mean and median of the mean warfarin dose is 3 mg for the whole of study population. Table 1 summarises the patients' characteristics. The mean dose of warfarin for TTR more than 75% is 3.05 mg ± 1.25 mg. The average warfarin dose was not significantly different among the gender male and female (*p* = 0.11) according to independent-sample
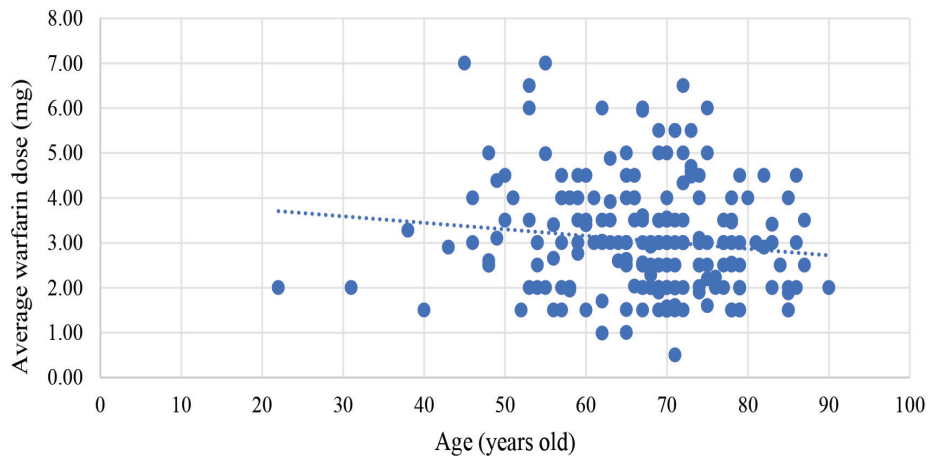
t-test. The influence of race on the mean warfarin dose appear to be present in between Chinese and Indian races only based on the result of ANOVA test followed by post-hoc test ($p = 0.008$).

Table 1: Average warfarin dose among patients based on gender and race.

Characteristics	Patients	Average dose (mg)	*p*-value
All	$N = 210$	3.05 ± 1.25 (0.5–7.0)	
Sex (*n*, %)			
Male	120 (57.1%)	3.16 ± 1.35	0.11 i
Female	90 (42.9%)	2.90 ± 1.09	
Ethnic group (*n*, %)			
Malay	62 (29.5%)	3.36 ± 1.55	
Chinese	161 (76.7%)	*2.86 ± 1.10	0.0008 p
Indian	12 (5.7%)	*4.11 ± 1.40	
Others	1 (0.5%)	5.00	

Notes: i = Independent sample *t*-test, *p* = post-hoc test; *the result showed statistically significant different of mean warfarin dose among Chinese and Indian population.

Based on Figure 2, there was a pronounced decrease of mean warfarin dose with increasing age of patient. The mean warfarin dose among the age of patient were analysed using Pearson correlation showed weak negative correlation (Pearson value = −0.125). From Table 2, the frequency of patient achieve TTR more than 75% was 210 represented only 36.4%, 232 of the patient has less than 60% of TTR and 134 of them achieved TTR 60%–75% range. The median day to achieve three consecutive targeted INR is 186.5 days for atrial fibrillation patient newly started on warfarin therapy in 2015 until 2016.

Figure 2: Correlation between age of patient (years old) and average warfarin dose (mg).

Table 2: Time in therapeutic range of atrial fibrillation patient.

TTR	Patients (*n*, %)
All (mean = 65.9% ± 22.1%)	576
< 60%	232 (40.3%)
60%–75%	134 (23.3%)
> 75%	210 (36.4%)

DISCUSSION

Ethnicity

Reports suggested that racial background may influence warfarin dose requirements. According to our findings, Indian patients require the highest dose of warfarin, which was 4.11 ± 1.40 mg. On the other hand, Chinese patients and Malay patients require a much lower average maintenance dose of warfarin compared to the Indian patients, which were 2.86 ± 1.10 mg and 3.356 ± 1.55 mg, respectively. However, the difference was only significant between the Indians and the Chinese (*p* = 0.0008).

This finding is similar compared with previous study by Gan *et al.* (2011) who found that Indian patients require a significantly higher average warfarin dose compared to Malay and Chinese patients (4.9 ± 1.8 mg, 3.5 ± 1.3 mg and 3.3 ± 1.1 mg, respectively). Lal *et al.* (2008) also reported that the daily warfarin doses were significantly higher in Indians compared to Malays and Chinese (6.21 ± 2.94 mg, 3.28 ± 1.39 mg and 3.68 ± 1.68 mg) (*p* < 0.001 in each case). The difference between our findings and the findings of the previous studies could be due to difference in the target INR and indication of warfarin. Gan *et al.* (2011) included patients with target therapeutic INR of 2.0–3.5, whereas our study included patients with target INR of 2.0–3.0. Lal *et al.* (2008) on the other hand had a wider exclusion criterion compared to our study, as they excluded patients with congestive heart failure (New York Heart Association [NYHA] class 3 or greater), liver cirrhosis or thyroid disease and patients on medications known to interact with warfarin. Besides, both studies included patients of all indications of warfarin, whereas our study included only patients with atrial fibrillation (Gan *et al.* 2011; Lal *et al.* 2008). Difference in average warfarin requirement among various ethnicity can be explained by the genetic variants of vitamin K epoxide oxidase reductase complex subunit 1 (VKORC1). VKORC1 GG genotype was more commonly seen in Indian patients, whereas AA genotype is more frequent in Malay and Chinese. It was shown that the non-A/non-A genotype require a higher mean daily dose. Polymorphism of the CYP2C9*2 alleles and CYP2C9*3 alleles will also reduce the warfarin enzymatic activity which lead to reduced clearance of warfarin and result in a lower warfarin dose requirement (Gan *et al.* 2011; Absher, Moore and Parker 2002*).* Furthermore, genetic mutation in the factor IX propeptide will also cause selective reduction in factor IX during treatment with coumarin drugs and cause the levels of other vitamin K-dependent coagulation factors to decrease to 30% to 40% of normal values. These findings are significant in presenting the need to include such requirement in warfarin dose initiation and maintenance, as certain genotypes can be associated with higher risk of adverse events (Ansell *et al.* 2008).

Age

Our present study found that the average warfarin dose requirement decreases with age, with the mean warfarin dose ranging from 2.67 ± 0.93 mg for age group > 75 years old–3.38 ± 1.40 mg for age group ≤ 45 years old. However, the association between age and mean warfarin dose was not significant ($p = 0.11$). On the contrary, previous study done by Khoury and Sheikh-Taha (2014) found a significant association between increasing age and the average maintenance dose of warfarin. Khoury and Sheikh-Taha (2014) reported that the mean total weekly dose (TWD) of patients in group 20–29 years old, 30–39 years old and 40–49 years old was two times higher compared to group 80–89 years old (~51 mg versus 24.82 mg; $p < 0.05$). The difference between our findings and the findings by Khoury and Sheikh-Taha (2014) could be due to the presence of confounding variables in our present study, such as concomitant drugs with major interactions with warfarin, smoking and alcohol consumptions as Khoury and Sheikh-Taha (2014) excluded all such patients. Besides, the indication for warfarin included by Khoury and Sheikh-Taha (2014) was either AF or venous thromboembolism, whereas our study included only AF patients. Liew *et al.* (2013) on the other hand reported that warfarin dosage requirement correlated negatively with age, decreasing by 1.1 mg per decade within the age range of 45–85 years old, irrespective of body weight, ethnicity, or sex differences ($p < 0.001$). Garcia *et al.* (2005) also reported that the TWD declines by 0.4 mg per year of life.

It was suggested that the decreased serum proteins, metabolic activities and excretion through the kidneys of elderly patients contributed to the increased sensitivity to warfarin (Shepherd *et al.* 1977).

However, Shepherd *et al*. (1977) revealed that there was no appreciable difference in the pharmacokinetics of warfarin, i.e. the plasma half-life, apparent volume of distribution, plasma clearance and plasma warfarin metabolite levels, between younger and older patients. This suggests that increase in age-dependent warfarin sensitivity did not influenced by pharmacokinetic factors. Elderly patients are more likely to take multiple medications which may increase the risk of drug-drug interactions that possibly potentiate warfarin effects (Garcia *et al.* 2005). Inhibition of synthesis of vitamin K dependent clotting factors are much greater in elderly compared to young patients at similar warfarin plasma concentrations (Mangoni and Jackson 2004). Furthermore, the differences in intake of vitamin K containing food will also affect the average dose of warfarin in patients.

Gender

According to our findings, male patients require an approximately 0.26 mg higher mean daily warfarin dose than women but was not statistically significant ($p = 0.06$). This finding is similar compared with previous studies by Whitley *et al*. (2007) who reported that female patients require 0.36 mg lower total daily warfarin dose than males. Khoury and Sheikh-Taha (2014) reported that women required a 0.46 mg lower total daily dose of warfarin than men. Both studies showed that the differences were insignificant.

Conversely, several published articles cite gender to be an important factor in predicting warfarin dose (Garcia *et al.* 2005; Liew *et al.* 2013; Ansell *et al.* 2004; Absher, Moore and Parker 2002; Oates *et al.* 1998). Ansell *et al.* (2004) showed that women require an average of 0.64 mg lower of warfarin dose per day. Regardless of the effect gender plays in warfarin dosing, studies are consistent in reporting lower doses required for women compared with men.

The sensitivity difference in each gender could be contributed by the biological difference between men and women. Generally, men are bigger in size than women, which leads to a larger distribution volumes and faster warfarin clearance. In addition, glomerular filtration, renal tubular secretion and reabsorption are faster in men. This may result in faster clearance of warfarin in men compared to women as warfarin is mainly eliminated renally (~92%) (Schwartz 2003).

Average TTR of Penang Population

TTR is the optimal measure of INR control and has a significant relationship with adverse outcomes in all studies. This is shown by Jones *et al.* (2005) who reported that a 10% increase in time out of therapeutic range in AF patient was associated with an increased risk of ischemic stroke (odds ratio = 1.10; *p* = 0.006). Wan *et al.* (2008) also reported that a 6.9% increase in TTR significantly reduced major haemorrhage by 1 event per 100 patient-years (95% CI: 0.29 to 1.71 events) and an 11.9% increase in TTR reduced thromboembolic events by 1 event per 100 patient-years (95% CI: 0.01 to 2.02 events). A similar study by Connolly *et al.* (2008) also showed a 5% improvement in TTR across UK anticoagulation clinics would prevent 400–500 strokes per year. These studies signify the importance of a high TTR value as it represents the quality of anticoagulation treatment.

In the present study, we found that the average TTR of the Pulau Pinang population was 65.9% ± 22.1% which is comparable with previously reported studies. Edwards *et al.* (2014) and Thanimalai *et al.* (2013) reported the average TTR of 66% and 65.1% in patients in Sarawak, Malaysia and Hospital Kuala Lumpur, respectively. Whereas Yap *et al.* (2017) and Ainina, Farhana and Nur'ain (2015) reported a slightly lower average TTR of 52% ± 18.7% in National Heart Institute, Kuala Lumpur and 60.6% ± 19.1% in in Hospital Kemaman, Terengganu, respectively.

A marked benefit was found against stroke and total vascular events for patients on oral anticoagulant treated at centres that had mean TTRs above the study median of 65%; no apparent benefit was found for the other half of patients with mean TTRs below 65% (Connolly *et al.* 2008). It was shown that average TTR > 65% reduced vascular events by > 2-fold (relative risk, 2.14; 95% CI: 1.61 to 2.85; *p* < 0.0001) compared to TTR < 65% whereas TTR < 58% would not generate a net clinical benefit (Connolly *et al.* 2008). Veeger *et al.* (2005) reported increased rates of recurrent venous thromboembolism and major bleeding when patients with TTR < 45% were compared with those having TTR > 65%.

White *et al.* (2007) categorised patients into poor control group, (< 60%) moderate control group (TTR 60%–75%) and good control group (TTR > 75%) and demonstrated that poor control group have a higher risk of myocardial infarction, stroke and systemic embolism event. Our results showed that 232 out of 576 patients (40.3%) have poor INR control (TTR < 60%), 134 out of 576 patients (23.3%) have moderate INR control (TTR 60%–75%) and 210 out of 576 patients (36.4%) have good INR control (TTR > 75%) (White *et al.* 2007). The study by White *et al.* (2007) showed that the annual mortality (4.20%) and major bleeding (3.85%) of the poor control group is higher compared with the moderate control group (TTR 60%–75%) (1.84% and 1.96%).

There are several factors associated with poor anticoagulation control which lead to a low TTR value. Several studies reported patients who are females, advanced age (> 75 years old) and heart failure are associated with poor INR control (Melamed *et al.* 2011; Costa *et al.* 2012; Zubaid *et al.* 2013). This may be associated with the significantly higher thrombin levels in females compared to males as reported by Lim *et al.* (2014). Lim *et al.* (2014) reported that plasma thrombin levels correlated well with TTR status, with higher levels found in patients with suboptimal INR control. Thrombin levels may be a

useful marker in reflecting the quality of anticoagulation and in identifying poorly controlled warfarin patients. Adherence to medication is one of the factors of a significant decrease in good control rates observed by *Farsad et al.* (2016) when the patients were prescribed more than four medications. It suggested that the number of prescribed medications may be an important factor in influencing patient adherence to warfarin therapy that can affect TTR indirectly. This is supported by Zullig *et al.* (2015), who reported that having too many medications to take is a barrier to medication adherence.

INR STABILISATION TIME

Difficulties in achieving therapeutic INR for newly initiated warfarin patients are commonly focused by most of the studies, only fewer studies focus on achievement of INR stabilisation time (Nelson *et al.* 2014). In this study, we aimed to find the INR stabilisation time and found that the median day to achieve three consecutive targeted INR is 186.5 days for 111 AF patients (97.4%) who are newly started on warfarin therapy in 2015 until 2016.

In the study conducted by Nelson *et al.* (2014), data of 15,276 non-valvular atrial fibrillation (NVAF) patients with ≥ 3 INR values were analysed from a large United States electronic database collected from 2006 to 2010 and were followed from warfarin initiation to the first ≥ 90-day gap or end of the data time frame. Nelson *et al.* (2014) found that the mean days to INR stabilisation for INR stabilisation achievers (75.1%) was 129.1 ± 2.4 days. As for Rombouts, Rosendaal and van der Meer (2009), (N = 13,443) which studies on the risk factors of subtherapeutic INR patients, the INR stability was defined as four consecutive in range INR measurements and further defined as 2.0–3.5 for low-intensity treatment and 2.5–4.0 for high-intensity treatment. Rombouts, Rosendaal and van der Meer (2009) found that 55% patients achieved INR stabilisation with the average time to stabilisation of 12 weeks. Witt *et al.* (2009) analysed data of 6,073 patients receiving warfarin retrospectively to identify the determinants of stable INR and has defined INR stabilisation as having all INR within the therapeutic range for any continuous 6-month period and found that 41% of their patients achieved INR stabilisation. The difference probably is due to the fact that the definition of time to INR stabilisation, number of consecutive in range INR measurements, duration of patient monitoring and inclusion of various warfarin indications were differed in each study as there are no standard to determine the appropriate criteria of INR stabilisation. Besides, the number of INR measurements or follow ups and the large sample size difference could be the factors of the difference of the INR stabilisation time.

CONCLUSION

In conclusion, this study found that the average warfarin dose in AF patient to achieve therapeutic INR range of 2–3 with TTR > 75% is 3.05 ± 1.25 mg. Indian patients required a statistically significantly higher warfarin dose than Chinese patients. Mean warfarin doses were not affected by age and sex. The average TTR among 576 patients in our study is 65.9% ± 22.1%. The median day to achieve three consecutive targeted INR is 186.5 days for 111 AF patients (97.4%) who were newly started on warfarin therapy in 2015 until 2016.

LIMITATIONS

There are few limitations of this study. This study is a retrospective and relies upon extraction of data from administrative databases and medical records. Factors such as Vitamin K intake, comorbidities and concomitant drugs used could be affecting warfarin dose in clinical decision were not collected in view that the data may not be updated. Our study has a relatively small sample size and may not be adequately powered to detect a statistically significant difference. This is because the small sample size under-represents various ethnic groups, as well as age group, thus possibly prevents us from drawing conclusions regarding warfarin requirements in these individuals. Rosendaal *et al.*'s (1993) method may also be biased by individual INR values that are far outside of TTR as Rosendaal *et al.*'s (1993) method assumes that the change in INR over time is linear between each timepoint, which may not be true. This may lead to an over-estimation or an under-estimation of TTR value for patients. This research is a multicentre study and involves three different hospitals. The different types of coagulometer used by the hospitals may lead to variability in the INR reading due to the respective standard errors.

RECOMMENDATIONS

These observations suggest that the current initiation and maintenance doses of warfarin may be reviewed and tailored to patients to reduce the risk of inadequate therapy in Indian patients and excessive anticoagulation in the Chinese patients. Further studies with a greater samples size in this area may more precisely predict the average warfarin dose among these different patient-specific factors. More effort should also be taken to improve the TTR of patients in the poor and moderate control group. The recent American College of Chest Physician guidelines have suggested the practice of three techniques to improve TTR namely establishing anticoagulation clinics, application of computerised dose adjustment systems and patient self-monitoring. However, the use of computerised dose adjustment systems and patient self-monitoring warrant further evaluation before its implementation in a primary care setting.

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