# Warfarin control in Hong Kong clinical practice

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# Abstract

Objectives: Time-in-therapeutic range (TTR) assesses safety and effectiveness of warfarin therapy using international normalized ratio (INR). This study aimed to investigate the status of TTR in Hong Kong and patients' economic and clinical outcomes. Predictors of poor warfarin control and patient's knowledge in warfarin therapy were assessed. Methods: A five-month observational study was conducted in Prince of Wales Hospital in Hong Kong. The TTRs calculated using Caucasian and Japanese therapeutic range were examined among patients on warfarin for at least one year. Patients' knowledge was assessed using the Oral Anticoagulation Knowledge (OAK) test. Results: A total of 259 patients were included in this study, with 174 of them completed the OAK test. Using Caucasian therapeutic range, calculated mean TTR was 40.2 ± 17.1%, compared that of 49.1 ± 16.1% with Japanese therapeutic range ($P<0.001$). Mean TTR in patients with atrial fibrillation was higher than those with prosthetic heart valve ($p<0.001$). Predictability of TTR on clinical outcomes and economic outcomes was comparable between Caucasian and Japanese therapeutic range. Patients with ideal TTR had fewer clinical complications and lower warfarin-related healthcare costs. Patients with younger age, concurrent use of aspirin, frusemide, famotidine, pantoprazole and simvastatin were associated with poorer TTR. Mean score of OAK test was 54.1%. Only 24 patients (13.8%) achieved the satisfactory overall score of ≥75% in the test. Conclusion: Warfarin use in Hong Kong patients was poorly controlled regardless of indication. Patients' knowledge towards warfarin use was suboptimal. More education to patients on warfarin use is warranted.


# Background

Warfarin, an oral vitamin K antagonist, has been widely used as anticoagulant therapy for treatment and prophylaxis of thromboembolic disease. It is commonly indicated in patients with atrial fibrillation (AF) or prosthetic heart valve (PHV) for thromboembolic prophylaxis. It is also indicated for treatment of deep vein thrombosis or pulmonary embolism. Patients with AF were at increased risk of mortality and morbidity, including increasing risk of stroke by 5-fold and risk of heart failure by 3-fold.[1,2] In patients with PHV, incidence of PHV thrombosis was 0.5 - 6% per patient-year, depending on the site of prostheses.[3] It was also reported that annual incidence of thrombotic emboli was 2.5 - 3.7% in patients with PHV.[4] Warfarin showed to reduce risk of stroke in patients with non-valvular AF significantly and reduce risk of embolism in patients with PHV.[5–7]

Warfarin has narrow therapeutic window. In order to ensure efficacy and safety of warfarin therapy, strict control of international normalized ratio (INR) is required. Evidence showed that risk of stroke increased dramatically with INR below 2, while risk of subdural haemorrhage increased drastically with INR above 4.[8,9] One measurement of INR at one time cannot reflect the appropriateness of long-term warfarin therapy. Instead, time-in-therapeutic range (TTR) is commonly used in clinical practice. As defined in European Society of Cardiology (ESC) guideline for the management of AF, ideal TTR is considered as 70%.[10] However, warfarin control in worldwide clinical practice is unsatisfactory. In Turkey, for patients using warfarin <15mg per week, their mean TTR was 53.76 ± 28.82%.[11] In the United States, the mean

TTR of AF patients using warfarin was 67.3 ± 14.4%.[12] Poor TTR is associated with increased risk of major haemorrhage, ischemic stroke and all-cause mortality.[13,14]

Hong Kong is currently following ESC Guidelines for the management of AF on warfarin control, which recommends INR control between 2.0 and 3.0 in patients with normal heart valve and between 2.5 and 3.5 in patients with PHV.[10] On the other hand, Japanese Guidelines for Pharmacotherapy of AF (JCS 2013) recommends INR control between 2.0 and 3.0 in patients <70 years old or with PHV and between 1.6 and 2.6 in those ≥70 years old.[15] The recommendation was based on a study showing that incidence rate of any events was lower at INR between 1.6 and 2.6.[16] It remains unknown if there would be additional benefit when Japanese guideline is used in our locality.

There are extensive drug-drug interactions, drug-herb interactions and drug-food interactions of warfarin, which potentially affect anticoagulation control.[17–20] To assure the anticoagulation effect of warfarin, patient education on warfarin is needed.[21] Improved patient's knowledge on warfarin therapy has shown to be associated with better anticoagulation control and fewer bleeding complications.[22,23] Yet, an epidemiological study revealed that only 1 in 6 AF patients had regular INR examination in China, while lacking in knowledge of the importance of regular INR checkups was common.[24]

The current project aimed to investigate the adequacy of warfarin control in clinical practice in Hong Kong using TTR and compared warfarin outcome prediction using Caucasian and Japanese INR therapeutic range respectively as primary endpoints. Predictors for poor warfarin control were determined as secondary endpoint in our study. Impact of TTR using Caucasian therapeutic range on both clinical and economic outcomes was investigated. Patient's knowledge in warfarin therapy and its predictors were also assessed.

# Methods

*Subject recruitment*

The single-center cohort study was conducted in Prince of Wales Hospital, Hong Kong. Prince of Wales Hospital is a regional acute hospital. It is a leading hospital in one of the seven clusters in Hong Kong under Hospital Authority, Hong Kong. Patients who received warfarin therapy in both Acute Coronary Syndrome (ACS) registry and warfarin clinic for at least one year and with their last visit from 1st January 2010 to 31st August 2015 were included. One year of warfarin therapy was assumed for patients to develop stable INR. Patients <41 years old and >90 years old were excluded, due to uncommon warfarin therapy in both age groups. Data for subject recruitment and subsequent subjects' profile review was retrieved through Clinical Management System, which is a regional computerized system for patient medical record.

*TTR summary*

Time-in-therapeutic range in our study was defined as the percentage derived by dividing the number of INR within the therapeutic range by total number of INR recorded.[12] The INR below therapeutic range was defined as sub-therapeutic, and that above therapeutic range was defined as supra-therapeutic. Ideal TTR was defined as 70%.[10]

Comparison of TTR was made between the two guidelines. The TTR of subgroups of individuals with different indications, using Caucasian therapeutic range, was also compared. Indication of warfarin for individual patient was categorized in four groups, respectively AF, PHV, both AF and PHV, and neither AF nor PHV (such as deep vein thrombosis and pulmonary embolism). Association of outcomes and adaption of either guidelines were subsequently determined.

*Predictors of suboptimal TTR*

Predictors of poor warfarin control, using Caucasian therapeutic range, were determined as secondary endpoint in our study. Patients were stratified into four quartiles according to TTR. Patients with TTR in Quartile 1 were considered to have poor warfarin control. Patients were compared across the four quartiles to identify predictors. Factors included were age, gender, co-morbidities, medication profile and patient's knowledge in warfarin therapy. For co-morbidities, hypertension, heart failure, thyroid disorder, liver dysfunction and diabetes mellitus were included. Ten commonly prescribed medications were chosen for medication profile comparison, based on a pilot study of 20 patients. The selected medications included aspirin, hydrochlorothiazide, metoprolol, diltiazem, diclofenac, famotidine, senna, simvastatin, lisinopril and pantoprazole. For other medications, if potential impact was suspected, further investigation was performed.

*Impact of TTR on clinical outcome*

Impact of TTR on clinical outcome was investigated, with TTR of patient stratified into four quartiles. Thrombotic events, bleeding complications and overall complication incidence were assessed. Stroke, pulmonary embolism, ACS and arterial embolism were included as thrombotic events in our study. Severity of bleeding complications was classified based on discussion at the Control of Anticoagulation Subcommittee of the International Society of Hemostasis and Thrombosis.[25] Major bleeding included: (1) fatal bleeding, and/or (2) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or (3) bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells. Otherwise, all non-major bleeds were considered as minor bleeds.

*Impact of TTR on economic outcome*

Impact of TTR, using Caucasian therapeutic range, on economic outcome was investigated. Costs were calculated per day of warfarin therapy so that the direct healthcare cost of patients could be calculated regardless of their length of warfarin therapy. Direct healthcare cost related to warfarin from the

healthcare provider perspectives was calculated using the Hong Kong government gazette.[25,26] Cost for INR checkups, procedures (including diagnostic tests except INR checkups, and surgery), hospitalization, medications, clinic visits and overall cost were compared respectively.

*Knowledge assessment*

Patient's knowledge in warfarin therapy was assessed using the Oral Anticoagulation Knowledge (OAK) test [see Additional file 1].[27] Question 14 of the original test was omitted in our study, as frequency of INR test and follow-up visit were determined by physicians in our locality. A "Don't know" option was included to minimize random guessing. Assessment was translated into Chinese [see Additional file 2] and done through phone interviews. Patient's knowledge was considered as satisfactory if score of 75% or above was achieved.[28] Results of individual questions in OAK test were analyzed to identify area of general knowledge deficiency. Predictors for OAK score performance were identified.

*Statistical analysis*

For descriptive statistics, frequency and percentages were used for categorical variables and mean ± SD was used for continuous variables. Wilcoxon signed rank test, Chi-square test, Fisher exact test and one-way ANOVA (Tukey method) were used for comparison of TTR using Caucasian and Japanese therapeutic ranges. Fisher's exact test and Mann-Whitney U test were used to determine impact of TTR on clinical and economic outcomes respectively. Ordinal regression model with stepwise selection was used to identify independent predictors for poor warfarin control. Multiple linear regression with stepwise selection for variables was used to determine predictors for OAK score. Two-sided P value was considered significant when <0.05. All statistical analysis was performed by IBM SPSS Statistic version 22.0 (IBM Corp. Armonk, NY: IBM Corp, 2013) and R version 3.5.3 (R Core Team, 2019).

*Ethics approval*

The study was approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (reference number: CRE 2013.667). Informed verbal consent was obtained from subjects who participated in the knowledge assessment. Verbal consent was obtained because the knowledge assessment was done by telephone interview.

# Results

*Baseline characteristics*

A total of 259 patients met the inclusion criteria and was included in the study. Among these 48.6% (n=126) were male. Mean age of all subjects was 67.9 ± 10.4 years. The demographic characteristics of study patients were shown in table 1.

*TTR summary*

The overall mean INR value was 2.3 ± 0.3. Using Caucasian therapeutic range, 34.5% of all measured INR values were in the therapeutic range, whereas 53.8% were sub-therapeutic, and 11.8% were supra-therapeutic. Overall TTR was 40.2 ± 17.1%. The mean proportion of duration individual's INR being sub-therapeutic and supra-therapeutic were 47.8 ± 19.0% and 12.3 ± 9.3%, respectively. Among all, 7.7% of subjects were with ideal TTR during the inclusion period.

For Japanese therapeutic range, 44.1% of all measured INR values were in the therapeutic range, whereas 36.2% were sub-therapeutic, and 19.6% were supra-therapeutic. Overall TTR was 49.1 ± 16.1%. The TTR was significantly higher than that of using Caucasian therapeutic range (P<0.001). The mean proportion of duration individual's INR being sub-therapeutic and supra-therapeutic were 30.6 ± 18.2% and 20.3 ± 11.4%, respectively. There were 12.4% of all subjects with ideal TTR.

Proportion of patients with ideal TTR were found to be statistically different among different subgroups of indications using Caucasian therapeutic range, as shown in table 1. Mean TTR of each indication of warfarin was calculated and compared within each therapeutic range group and among two therapeutic range groups (table 2). Within Caucasian therapeutic range, mean TTR with indication for AF was significantly higher than that of PHV (p<0.001), and that of both AF and PHV (p<0.001). Mean TTR with indication for neither AF nor PHV was also significantly higher than that of PHV (p=0.038). As with Japanese therapeutic range, mean TTR with indication for AF was significantly higher than that of both AF and PHV (p<0.001). Mean TTR using Japanese therapeutic range was significantly higher than that using Caucasian therapeutic range within each indication category.

*Predictors of suboptimal TTR*

Subjects were divided into four quartiles upon their TTR according to Caucasian therapeutic range (table 3). Predictors were determined upon regression across the four quartiles. Adjusted OR (aOR) for poor TTR was calculated. Results showed that younger age, concurrent use of aspirin, frusemide, famotidine, pantoprazole or simvastatin were associated with poorer TTR.

*Impact of TTR on clinical outcome*

Clinical outcomes were compared between two therapeutic ranges (table 4). Out of 259 patients, 35.9% of subjects experienced complications including thrombotic events and bleeding complications. Out of the 39 patients with thrombotic events, 41.0% of them had recurrent non-ST elevation myocardial infarction and 33.3% had stroke. For bleeding complications, 68.8% had minor bleeding while 31.3% of them experienced major bleeding episodes. People with ideal TTR had significantly fewer overall complications and bleeding complications, compared to those with non-ideal TTR, in both Caucasian and Japanese therapeutic range. Additionally, there were fewer thrombotic events in patients with ideal TTR using Japanese therapeutic range. All patients who had complications were those with non-ideal TTR, using Caucasian therapeutic range.

Patients were further stratified into quartiles based on TTR using Caucasian therapeutic range (table 5). Percentage of patients having overall complications and bleeding complications decreased from Quartile 1 to Quartile 4. Statistical test showed that there is a trend between each tested clinical outcome and TTR.

*Impact of TTR on economic outcome*

Healthcare costs were all expressed in terms of United States dollar (USD) per year (USD $1 = Hong Kong Dollar $7.8), as shown in table 4. Including all services related to warfarin, patients on average needed to spend USD $809.9/year. For economic outcomes, cost of INR checkups, cost of clinical visits and total healthcare cost were significantly lower in patients with ideal TTR in both Caucasian and Japanese therapeutic range. Patients with ideal Japanese TTR also had lower cost of hospitalization.

When focusing on Caucasian therapeutic range, healthcare provider needed to pay an addition of USD $530.1/year considering direct healthcare cost related to warfarin for each patient with non-ideal TTR, compared with a patient with ideal TTR. The average additional cost composed of USD $374.3/year for INR checkups and USD $9.0/year for clinic visits. Cost for hospitalization was USD $25.1/year for a patient with non-ideal TTR, compared to USD $0.3/year for a patient with ideal TTR. In conversion, patients with non-ideal TTR were hospitalized for approximately 2 days per year while those with ideal TTR were unlikely to be hospitalized.

*Knowledge assessment*

A total of 174 completed OAK test, with mean score of 54.1% based on percentage correct out of 19 questions. The mean duration of warfarin therapy of this subgroup of patients within the study period was 4.8 ± 1.4 year. Only 24 patients (13.8%) achieved the satisfactory overall score of ≥75% in the test. Out of 19 questions, only four questions were answered correctly by ≥70% of respondents (table 6). Patients generally knew how to differentiate different strengths of warfarin (question 2, 81.6%), the reason for taking warfarin (question 8, 82.8%), what INR is (question 7, 83.3%) and when they should monitor sign of bleeding (question 15, 70.7%).

However, only half of the respondents knew the importance of dietary modifications (question 4, 50.6%), which vitamin warfarin interacts with (question 5, 44.8%), interpretation of INR test results (questions 9, 52.3%; question 20, 47.1%), when they should seek an immediate medical attention (question 11; 50.6%) and management for missing a dose (question 16, 48.9%). Approximately one-fourth of respondents gave the exactly opposite answer regarding interpretation of INR. Respondents perceived that there would be increased bleeding risk for INR below therapeutic range and increased thrombotic risk for INR above therapeutic range.

Patient knowledge regarding medication interactions with warfarin (questions 6, 35.6%, question 10, 21.8%) and the consequence of missing or skipping a dose (question 1, 28.2%; question 12, 25.3%) was insufficient. Nearly half of respondents believed no effect on missing one dose of warfarin.

Results from multiple linear regression showed that respondents with increasing age (adjusted β = -0.17, 95% CI (-0.23, -0.11), p = 0.001) or comorbid with diabetes (adjusted β = -1.21, 95% CI (-2.29, -0.12), p = 0.03) were more likely to score low in OAK test. On the contrary, respondents with concurrent hypertension (adjusted β = 1.68, 95% CI (0.56, 2.80), p = 0.004) or thyroid dysfunction (adjusted β = 2.38, 95% CI (0.80, 3.97), p = 0.003) were more likely to score high in OAK test. Respondents with better TTR were more likely to score high in OAK, yet marginally insignificant (adjusted β = 2.73, 95% CI (-0.21, 5.68), p = 0.069).

# Discussion

*Major findings*

Overall, we found that only 34.5% of all INR values drawn on patients on warfarin were in therapeutic range, resulting in a mean patient-level TTR of 40.2%. Ideal TTR was achieved by only 7.7% of subjects. Mean TTR calculated form Japanese therapeutic range is higher (49.1%), with similar ability in predicting outcomes as Caucasian therapeutic range. Patients with non-ideal TTR had worse economic and clinical outcomes than those with ideal TTR. We also found that younger age, concurrent use of aspirin, frusemide, famotidine, pantoprazole and simvastatin were associated with poorer TTR in patients with warfarin use. Patients' knowledge in warfarin therapy was unsatisfactory with a mean score of 54.1%, while patients with increasing age or comorbid with diabetes were associated with poorer performance in OAK test.

*Status of warfarin control in Hong Kong*

Mean TTR observed in our study was lower than that of western results. A meta-analysis of 40 Caucasian studies identified a mean TTR of 75.2% in months 4 to 12 or longer of warfarin management.[29] The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) identified a mean TTR of 50.4% in East Asia region.[30] A study focusing on warfarin use in Japanese population using Japanese guideline recommended therapeutic range showed an overall TTR of 69.7% in non-valvular AF patients.[31] Studies in Hong Kong reported that the mean TTR for a target INR of 2.0 to 3.0 in Chinese patients with AF improved from 24.2% to 39.7% in the past decade.[32,33] Results from our study showed a better warfarin control in AF population (mean TTR 48.0%) compared to past local data, yet remained unsatisfactory. A 5-year retrospective cohort study from Swedish registries reported a mean TTR of 72.5% in patients with mechanical heart valve prosthesis, while another study in Malaysia showed that mean TTR in patients with mechanical heart valve(s) replacement was 47.48%.[34,35] Mean TTR in patients with PHV in this study was 30.5%, lower than the previously reported findings. Our study also demonstrated that warfarin control in patients with PHV was worse that patients with AF.

The lower TTR in Hong Kong compared with western countries could attribute to ethnicity. Geographical profile difference in genetic polymorphisms between Hong Kong and Western countries could lead to differences in warfarin metabolism and thus dosing warfarin.[36] Moreover, it was suggested by previous

evidence that East Asian was more likely to experience intracranial haemorrhage compared to Caucasian with comparable level of warfarin control.[37] INR target for patients was not known in our study, therefore possibility of physician targeting at lower INR range could not be ruled out. When therapeutic range suggested by Japanese guideline was employed (INR 2.0-3.0 for patients with AF aged <70 years old, INR 1.6-2.6 for patients with AF aged ≥70 years old, INR 2.0-3.0 for patients with PHV), TTR was improved to 53.4% for AF patients and 48.0% for PHV patients. Warfarin control remained unsatisfactory in Hong Kong population despite using a lower range of recommended standard for Asian population.

*Caucasian vs Japanese therapeutic range*

The overall predicting ability of both Caucasian and Japanese therapeutic range were similar. The calculated ORs for each economic outcome across Caucasian and Japanese therapeutic range were similar, except for cost of hospitalization. For clinical outcomes, it is not possible to calculated ORs for each item comparing ideal TTR to non-ideal TTR, given that there was no complication event for ideal TTR group. On the contrary, there were complications in the ideal TTR group under calculation with Japanese therapeutic range. The ORs calculated showed that there was predictability of Japanese therapeutic range on clinical outcomes. It is possible for patients in Hong Kong to set a lower INR target, such as Japanese therapeutic range. However, a larger, well-designed randomized controlled trial would be needed to establish non-inferiority in clinical outcomes and superiority in economic outcomes of using Japanese therapeutic range compared to current practice.

*Impact of TTR on outcomes*

Level of warfarin control was shown to be associated with clinical outcomes. Study in patients with non-valvular AF revealed that for every 10% increase in TTR, thrombotic event rates among patients treated with warfarin decreased by 0.32%/patient year.[38] A systematic review of 47 studies with TTR ranging from 29% to 75% also found that TTR was negatively correlated with major bleeding and thromboembolic events.[39] Results from our study agreed with the association of TTR with clinical outcome, showing that patients with poorer TTR were more likely to experience overall complications, thrombotic events and bleeding complications.

It was also shown that TTR was associated with economic outcomes. Previous study showed that AF patients in the US with TTR<60% had higher total healthcare and stroke-related costs.[40] Our study demonstrated similar result with TTR cut-off at 70%. With better warfarin control, corresponding healthcare expenses can be reduced accordingly, of which the government is responsible for most expenses currently.

*Predictors for suboptimal TTR*

Predictors for suboptimal TTR were investigated in the study. Multiple studies mentioned heart failure as highly associated with poor warfarin control, yet it was not demonstrated in this study. [12,31] Instead this study showed that younger patients were more likely to have poor TTR. This finding was also supported

by previous studies worldwide.[30,41,42] It could be possible correlated with higher medication adherence in the elderly population. Previous studies in Hong Kong hypertensive patients showed that patients with advanced age were associated with good medication adherence, possible due to better health consciousness in elderly population.[43,44] Contradictorily, our study showed that patients with advance age were more likely to achieve low score in OAK test, while higher score in OAK test had marginally better TTR. One of the limitations was that OAK test was not performed in all recruited subjects in this study. Moreover, concurrent use of aspirin, frusemide, famotidine, pantoprazole or simvastatin was more likely to have poor TTR. Despite common concurrent use of simvastatin and warfarin, study by Andersson et al. showed that the anticoagulant effect of warfarin, as measured by INR, was 8–27% higher in simvastatin-treated patients, due to CYP 2C9*3 polymorphism.[45,46] Regarding concurrent use of warfarin and pantoprazole, there had been reported alteration on warfarin absorption and metabolism under influence of proton pump inhibitors, which could be possible explanation to the findings from our study.[47–49] Yet, despite the theoretical interaction, there was lacking clinical evidence between warfarin and pantoprazole.[50,51] Patients with aspirin were more likely to have poor TTR. Concurrent use of aspirin and warfarin increases risk of major bleeding, which could possibly lead to physician more conservative regarding level of anticoagulation control.[52] Evidence showed that use of aspirin and poor TTR were independently associated with higher bleeding risk, while poor TTR was independently contributing to all-cause mortality.[53] Therefore, despite the concurrent use of aspirin, optimal TTR should be achieved with regards to appropriate INR therapeutic range in order to reduce complication.

*Patients' knowledge in warfarin therapy*

According to validation studies performed by Zeolla et al., an achievable benchmark mean OAK score in long term warfarin users (mean duration of warfarin use is 5.5 years) was 72%.[27] A study done in Malaysia found that only 11.2% of patients achieved the satisfactory score, with a mean OAK score of 48% for the whole sample.[54] Similar results were obtained from our study, with a mean score of 54.1% and 13.8% of patients achieving 75% or above. This could attribute to tight medical consultation time, leading to lack of education on respective disease and medication.[55] Medical jargons in OAK test may not be easily understood by subjects. For example, physicians generally use "thickness of blood" for simplified description of coagulability. For such, patients may not be able to correlate wordings with INR values. Patients with advanced age were more likely to score low in OAK test, which was supported by previous study reporting on negative correlation between age and warfarin knowledge.[56] Yet, observed relationship between comorbidities and warfarin knowledge requires further study to establish underlying explanation.

*Limitations of study*

This study has several important limitations. This was a single centre study with limited sample size and skewed distribution on warfarin indication. The target INR range for patients was unknown. For example, although the standard goal is 2.0-3.0 for normal valve, 2.5-3.5 for mechanical valve for Caucasian

therapeutic range, it is possible that some physicians may have set a lower goal of 1.5-2.5 in patients with higher risk of bleeding. The TTR of patient could be affected by withholding the medication due to procedures, such as dental procedures. Moreover, the impact of TTR on cost of medications was not investigated. Since the Hong Kong government gazette only provided costs for 1mg, 3mg and 5mg warfarin and most patients were taking various warfarin doses corrected to 0.5mg, the exact medication costs could not be calculated. For other related medications, including vitamin K1, duration of use might not be specified such that exact amount of use could not be determined. Also, we were unable to account for diet, traditional Chinese medicine or complementary alternative medications and medication non-compliance as predictors for warfarin control. As a result, our model may not be able to most appropriately predict factors for poor warfarin control. The OAK test had been amended to fit our locality situation. A further validation test is required for the amended tool in Chinese version.

# Conclusions

Warfarin use in Hong Kong patients was poorly controlled regardless of indication. Patients indicated for stroke prevention with AF had better warfarin control, compared to those indicated for PHV. With Japanese therapeutic range, level of warfarin control remained unsatisfactory. Our study showed that TTR could be a predictor for both economic and clinical outcomes. Several influential factors on TTR in Hong Kong patients undergoing long-term warfarin therapy had been identified. To highlight, younger age, concurrent aspirin or simvastatin were found to be independent predictors of poor warfarin control. Patients had poor knowledge on INR value and interpretation. More education should also be done on drug-drug interactions of warfarin and consequences of missed dose.

# Abbreviations

ACS: Acute Coronary Syndrome

AF: Atrial Fibrillation

aOR: Adjusted Odds Ratio

ESC: European Society of Cardiology

INR: International Normalized Ratio

JCS 2013: Japanese Guideline for Pharmacotherapy of Atrial Fibrillation

OAK: Oral Anticoagulation Knowledge

PHV: Prosthetic Heart Valve

ROCKET AF: The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation

TTR: Time-in-therapeutic range

USD: United States dollars

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# Tables

| | Overall | Caucasian therapeutic range | | | Japanese therapeutic range | | |
|---|---|---|---|---|---|---|---|
| | | Ideal TTR | Non-Ideal TTR | P | Ideal TTR | Non-Ideal TTR | P |
| | N=259 | N=20 | N=239 | | N=32 | N=227 | |
| Demographics | | | | | | | |
| Age, mean (SD) | 67.9 (10.4) | 67.8 (9.9) | 67.9 (10.4) | 0.973 | 68.8 (11.3) | 67.8 (10.2) | 0.612 |
| Male sex | 126 (48.6%) | 11 (55.0%) | 115 (48.1%) | 0.554 | 19 (59.4%) | 107 (47.1%) | 0.195 |
| Indication of warfarin | | | | **0.009** | | | 0.184 |
| AF | 127 (49.0%) | 17 (85.0%) | 110 (46.0%) | | 21 (65.6%) | 106 (46.7%) | |
| PHV | 52 (20.1%) | 1 (5.0%) | 51 (21.3%) | | 6 (18.8%) | 46 (20.3%) | |
| Both AF and PHV | 63 (24.3%) | 1 (5.0%) | 62 (25.9%) | | 4 (12.5%) | 59 (26.0%) | |
| Neither AF nor PHV | 17 (6.6%) | 1 (5.0%) | 16 (6.7%) | | 1 (3.1%) | 16 (7.0%) | |

Table 1. Demographics and indication of warfarin using Caucasian and Japanese therapeutic range
Unless specified, counts of subjects were shown, with brackets showing percentage of subjects within the TTR category using specific therapeutic range.

| | Caucasian therapeutic range | | | Japanese therapeutic range | | | |
|---|---|---|---|---|---|---|---|
| | Mean TTR | SD | P * | Mean TTR | SD | P* | P** |
| Indication of warfarin | | | **<0.001** | | | **<0.001** | |
| AF | 48.0% | 16.3% | | 53.4% | 16.3% | | **<0.001** |
| PHV | 30.5% | 13.9% | | 48.0% | 14.5% | | **<0.001** |
| Both AF and PHV | 32.0% | 13.6% | | 42.9% | 15.2% | | **<0.001** |
| Neither AF nor PHV | 41.9% | 14.7% | | 43.0% | 14.3% | | **<0.001** |

Table 2. TTR with different indications of warfarin using Caucasian therapeutic range.
* P value was calculated using one-way ANOVA test, comparing mean TTR within each therapeutic range respectively.
** P value was calculated using paired t-test, comparing mean TTR using Caucasian and Japanese therapeutic range.

| | Quartile 1 N=65 | Quartile 2 N=65 | Quartile 3 N=65 | Quartile 4 N=64 | aOR for poor TTR (95% CI) | P |
|---|---|---|---|---|---|---|
| TTR, range | 0 – 27.8% | 27.9 – 38.5% | 38.5 – 50% | 50.0 – 93.3% | | |
| Demographics | | | | | | |
| Age, mean (SD) | 64.9 (10.0) | 67.2 (10.8) | 70.4 (10.3) | 69.0 (9.7) | **0.94 (0.92, 0.97)** | **<0.001** |
| Male sex | 35 (53.8%) | 26 (40.0%) | 28 (43.1%) | 37 (57.8%) | -- | |
| Past medical history | | | | | | |
| Hypertension | 23 (35.4%) | 28 (43.1%) | 29 (44.6%) | 27 (42.2%) | -- | |
| Heart failure | 28 (43.1%) | 31 (47.7%) | 24 (36.9%) | 23 (35.9%) | -- | |
| Thyroid disorder | 8 (12.3%) | 7 (10.8%) | 4 (6.2%) | 8 (12.5%) | -- | |
| Liver dysfunction | 11 (16.9%) | 11 (16.9%) | 3 (4.6%) | 9 (14.1%) | -- | |
| Diabetes mellitus | 17 (26.2%) | 22 (33.8%) | 24 (36.9%) | 15 (23.4%) | -- | |
| Medication | | | | | | |
| Aspirin | 22 (33.8%) | 26 (40.0%) | 32 (49.2%) | 9 (14.1%) | **1.70 (0.97, 3.00)** | **0.033** |
| Frusemide | 47 (72.3%) | 41 (63.1%) | 32 (49.2%) | 26 (40.6%) | **2.59 (1.62, 4.18)** | **<0.001** |
| Carvedilol | 9 (13.8%) | 12 (18.5%) | 15 (23.1%) | 4 (6.3%) | -- | |
| Diltiazem | 8 (12.3%) | 8 (12.3%) | 6 (9.2%) | 12 (18.8%) | -- | |
| Diclofenac | 4 (6.2%) | 6 (9.2%) | 6 (9.2%) | 6 (9.4%) | 0.55 (0.24, 1.23) | 0.073 |
| Famotidine | 39 (60.0%) | 43 (66.2%) | 39 (60.0%) | 27 (42.2%) | **1.67 (1.03, 2.71)** | **0.020** |
| Senna | 29 (44.6%) | 25 (38.5%) | 24 (36.9%) | 17 (26.6%) | **--** | |
| Pantoprazole | 25 (38.5%) | 22 (33.8%) | 20 (30.8%) | 11 (17.2%) | **1.61 (0.97, 2.68)** | **0.033** |
| Lisinopril | 28 (43.1%) | 27 (41.5%) | 27 (41.5%) | 19 (29.7%) | -- | |
| Simvastatin | 34 (52.3%) | 29 (44.6%) | 32 (49.2%) | 19 (29.7%) | **1.66 (1.00, 2.76)** | **0.026** |

Table 3. Predictors of poor TTR using Caucasian therapeutic range.
Unless specified, counts of subjects were shown, with brackets showing percentage of subjects within the quartile. Patients with TTR in Quartile 1 were considered to have poor warfarin control. Ordinal regression, with stepwise selection, was adopted to identify predictors across four quartiles.

| | Overall | Caucasian therapeutic range | | | | Japanese therapeutic range | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Ideal TTR | Non-ideal TTR | OR (95%CI) | P | Ideal TTR | Non-Ideal TTR | OR (95%CI) | P |
| | N=259 | N=20 | N=239 | | | N=32 | N=227 | | |
| Clinical outcomes | | | | | | | | | |
| Complications | 93 (35.9%) | 0 | 93 (38.9%) | -- | **0.001*** | 4 (12.5%) | 89 (39.2%) | **0.23 (0.06, 0.61)** | **0.002**** |
| Thrombotic events | 39 (15.1%) | 0 | 39 (16.3%) | -- | 0.051* | 1 (3.1%) | 38 (16.7%) | **0.18 (0.01, 0.89)** | **0.032**** |
| Bleeding complications | 64 (24.7%) | 0 | 64 (26.8%) | -- | **0.005*** | 3 (9.4%) | 61 (26.9%) | **0.30 (0.07, 0.88)** | **0.026**** |
| Economic outcomes | | | | | | | | | |
| Cost of INR checkups | 605.8 (450.8) | 260.5 (87.4) | 634.8 (458.0) | **0.99 (0.98, 0.99)** | **<0.001**** | 303.7 (100.4) | 648.5 (465.7) | **0.99 (0.99, 1.00)** | **<0.001**** |
| Cost of procedures | 105.8 (332.3) | 2.7 (12.1) | 114.4 (344.6) | 0.98 (0.95, 1.02) | 0.296** | 7.7 (23.0) | 119.7 (352.9) | 0.99 (0.98, 1.00) | 0.148** |
| Cost of hospitalization | 23.1 (52.0) | 0.3 (1.2) | 25.1 (53.7) | 0.71 (0.49, 1.02) | 0.061** | 3.0 (7.6) | 26.0 (54.9) | **0.94 (0.89, 0.99)** | **0.015**** |
| Cost of clinical visits | 38.7 (22.5) | 30.4 (12.3) | 39.4 (23.0) | **0.93 (0.87, 0.98)** | **0.007**** | 30.6 (11.1) | 39.9 (23.4) | **0.92 (0.88, 0.97)** | **0.002**** |
| Total healthcare cost | 809.9 (630.5) | 320.9 (101.6) | 851.0 (639.1) | **0.99 (0.98, 0.99)** | **<0.001**** | 373.8 (122.2) | 871.7 (649.0) | **0.99 (0.99, 1.00)** | **<0.001**** |

Table 4. Clinical and economic outcomes using Caucasian and Japanese therapeutic range
For clinical outcomes, counts of subjects were shown, with brackets showing percentage of subjects within the TTR category using specific therapeutic range. For economic outcomes, cost is expressed as mean (SD), in terms of United States dollars (USD) per year.
* P value was calculated using Fisher's exact test, comparing counts across ideal TTR and non-ideal TTR groups.
** P value was calculated for OR.

| | Quartile 1 N=65 | Quartile 2 N=65 | Quartile 3 N=65 | Quartile 4 N=64 | P |
|---|---|---|---|---|---|
| Clinical outcomes | | | | | |
| Complications | 32 (49.2%) | 30 (46.2%) | 21 (32.3%) | 10 (15.6%) | **<0.001** |
| Thrombotic events | 11 (16.9%) | 14 (21.5%) | 12 (18.5%) | 2 (3.1%) | **0.027** |
| Bleeding complications | 25 (38.5%) | 20 (30.8%) | 11 (16.9%) | 8 (12.5%) | **<0.001** |

Table 5. Clinical outcomes of four quartiles using Caucasian therapeutic range.
Counts of subjects were shown, with brackets showing percentage of subjects within the quartile. Patients with TTR in Quartile 1 were considered to have poor warfarin control. Mantel-Haenszel Chi-squared test for trends was adopted to test for significance the outcome effect across four quartiles.

| | Answered correctly | Do not know |
|---|---|---|
| Q1: Consequence of missing one dose | 28.2% | 16.7% |
| Q2: Knowledge on distinguishing between different strength of warfarin | 81.6% | 17.2% |
| Q3: Condition to seek medical attention | 69.0% | 28.7% |
| Q4: Eating a large amount of leafy green vegetables while taking warfarin | 50.6% | 30.0% |
| Q5: Type of vitamin which interacts with warfarin | 44.8% | 51.7% |
| Q6: Significance of drug-drug interaction with warfarin | 35.6% | 21.3% |
| Q7: Knowledge on PT/INR test | 83.3% | 8.6% |
| Q8: Indication of warfarin | 82.8% | 10.9% |
| Q9: Consequences of a PT/INR value below therapeutic range | 52.3% | 23.6% |
| Q10: Knowledge on drug-drug interaction of warfarin with aspirin or NSAID | 21.8% | 54.6% |
| Q11: Condition to seek medical attention | 50.6% | 17.8% |
| Q12: Consequence of skipping dose | 25.3% | 44.8% |
| Q13: Effect of alcohol during taking warfarin | 55.8% | 36.2% |
| Q15: Knowledge on monitoring bleeding signs | 70.7% | 13.8% |
| Q16: Management for missing dose | 48.9% | 28.2% |
| Q17: Knowledge on food-drug interaction | 68.4% | 4.6% |
| Q18: Precautions before PT/INR check | 55.8% | 35.6% |
| Q19: Knowledge on over-the-counter products interacting with warfarin | 55.2% | 28.2% |
| Q20: Consequence of a PT/INR value above target range | 47.1% | 24.1% |

Table 6. Results of OAK test.

# Supplementary Files

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