Original Article

Comparison of Medication Adherence and Treatment Persistence between New Oral Anticoagulant and Warfarin among Patients

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Abstract

Introduction: This study aimed to compare medication adherence and treatment persistence of patients on warfarin versus rivaroxaban in Singapore. A secondary objective was to identify significant covariates influencing adherence. Materials and Methods: A retrospective cohort study was conducted where data from September 2009 to October 2014 was retrieved from the hospital electronic databases. Prescription records of rivaroxaban patients with 3 months or more of continuous prescription were extracted and compared against those of patients on warfarin. Primary outcome of adherence was determined based on the medication possession ratio (MPR), while treatment persistence was determined by outpatient clinic appointment gaps. Results: A total of 94 rivaroxaban and 137 warfarin users were analysed by complete case analysis. The MPR of warfarin patients was lower than rivaroxaban patients by 10% (95% CI, 6.4% to 13.6%; *P* <0.0001). Also, there were more warfarin patients who had gaps in treatment persistence compared to those prescribed rivaroxaban (8.0% vs 1.1%; *P* = 0.03). Significant factors affecting medication adherence were age and duration of anticoagulant use. For every 10-year increase in age, MPR increased by 1.7% (95% CI, 0.7% to 2.8%). Similarly, for every year increase in duration of use, MPR increased by 1.8% (95% CI, 0.6% to 3.0%). Race, gender, concomitant medication and type of residence were not found to be significant covariates in the multivariable analysis. Conclusion: Patients on rivaroxaban are likely to be more adherent to their prescribed oral anticoagulant with increasing age and duration of treatment influencing adherence.

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Key words: Compliance, Medication possession ratio, Oral anticoagulation, Rivaroxaban

Introduction

Rivaroxaban is a non-vitamin K oral anticoagulant (NOAC) approved for use in Singapore since 2008 for the prevention of venous thromboembolism in patients undergoing total hip and knee replacement surgery. In March 2012, the registered indication was expanded to include prevention of stroke and systemic embolism in subjects with non-valvular atrial fibrillation, treatment of deep vein thrombosis (DVT), and the prevention of recurrent DVT and pulmonary embolism (PE).[1]

Clinical trials and meta-analysis have demonstrated rivaroxaban's equivalent efficacy and similar major bleeding rates as compared to warfarin.[2-4] Additionally, rivaroxaban has fewer drug interactions and do not require dose titration in routine use. In practice, patients are recommended for annual re-evaluation of renal function to ensure continued safe use of the drug.[5] This is in contrast to warfarin which requires frequent monitoring and dose titration.

The advantage of less frequent visits to healthcare centres in routine care has ironically been reported to translate to poorer medication adherence.[6-8] Unlike patients taking warfarin whose compliance can be gauged from measured international normalised ratios (INRs), patients taking NOACs will typically have no objective measures of their state of compliance.

A number of studies on this matter have shown conflicting

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medication adherence results.[9-11] Warfarin is currently classified as a "standard drug" in Singapore, costing around S$0.10 per dose, whereas rivaroxaban, a "non-standard drug", costs about S$5 per dose. In an in-house survey conducted in 2010 among 93 anticoagulation clinic patients in Singapore General Hospital (SGH), 81.7% of the patients were not willing to switch from warfarin to NOACs if given a choice, and the top reason for this was higher drug costs of proprietary NOACs compared to generic warfarin (92.1%).[12] Culturally, with Asians' limited risk-taking and thrift mentality, the 50-fold difference in drug price was hypothesised to discourage patients from taking rivaroxaban regularly. Coupled with the lack of regular monitoring and reminders during clinic or pharmacy visits, these factors may translate into poorer medication adherence.

The sum effect of these factors on NOACs adherence and persistence among our patients treated for acute venous thrombosis is currently not known. We therefore studied a group of patients who had been anticoagulated for venous thrombosis to determine if there were important differences in medication adherence and treatment persistence between patients taking NOACs and warfarin. This paper reports our findings.

Materials and Methods

Study Design

This retrospective, single centre, cohort study was conducted in SGH, a Joint Commission International (JCI) accredited 1700-bed acute care academic medical centre in Singapore. Prescription and dispensing records from October 2009 to October 2014 were retrieved electronically from patients who were prescribed the 2 commonly used oral anticoagulants—warfarin and rivaroxaban. The index anticoagulant of each patient was determined based on the first prescription of either warfarin or rivaroxaban. Patients satisfying the following criteria were included in the analysis: 1) anticoagulated for treatment of DVT or PE; 2) at least 3 months of continuous anticoagulation on either warfarin or rivaroxaban; 3) anticoagulant therapy managed in SGH. Exclusion criteria included: 1) patients with incomplete demographic data in electronic record; 2) patients whose anticoagulation therapy was stopped for medical reasons; 3) lost to follow-up.

Statistical Analysis and Sample Size Calculation

Using Lehr's approximation and Cohen's standardised effect size of 0.5, with α at 0.05 and β at 0.10, a minimum of 84 patients in each group were required to detect the anticipated difference, assuming 1:1 allocation ratio. Patient demographics, type of anticoagulant prescribed and adherence were summarised using frequency and percentages for categorical variables, and means and standard deviation for continuous variables which were normally distributed. Where the data were skewed, median and range were presented. Independent sample t-test was used for comparing mean differences of continuous data if they were approximately normal; otherwise, the Mann-Whitney U test was applied. Fisher's exact test was used for comparing differences in proportions between the 2 treatment arms with respect to baseline demographics. To identify factors affecting adherence, multivariable linear regression was performed, and the following patient demographics—age, gender, ethnicity, duration of anticoagulant used, housing type and number of concomitant medicines—were considered for inclusion in the model. These factors were chosen as they are known surrogates affecting general medication adherence.[13-15] All the analyses were performed using STATA Version 13.1 (College Station, TX: StataCorp LP) assuming a 2-sided test at the conventional 5% level of significance.

Data Collection

Prescription records of rivaroxaban and warfarin were obtained from the institution's computerised physician order entry system (CPOE) (Sunrise Clinical Manager; Eclipsys, Atlanta, Georgia). Pharmacy refill records of patients were extracted from the electronic dispensing system (MaxCare; iSoft, Adelaide, South Australia). The records of patients taking rivaroxaban were then compared with patients taking warfarin to estimate differences in adherence.

The Singhealth Centralized Institution Review Board (CIRB) approved this study protocol. The study also conforms to the provisions of the Declaration of Helsinki and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Outcome Measures

The primary outcome measure of this study is medication adherence and treatment persistence. Medication adherence is generally defined as the extent to which patients take the medications as prescribed. In this study, it was calculated using the medication possession ratio (MPR) as follows:

$$MPR = \frac{\textbf{Duration of refills collected from pharmacy}}{\textbf{Duration of intended treatment or follow-up}}$$

As for treatment persistence, it is defined as the absence of gap in follow-up medical appointments. Presence of appointment gap, regardless of the duration or reason, is considered as treatment non-persistence. Secondary objective is to determine if there are any other variables that may have contributed to the difference in the adherence between the 2 regimes apart from anticoagulant choice.

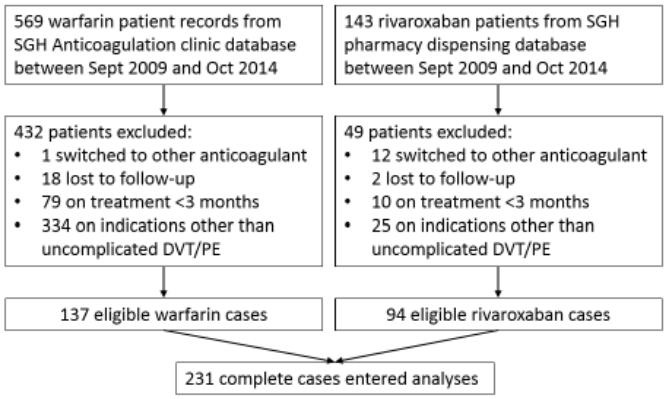

Fig. 1. Screening and enrolment flowchart.

Results

Of the 896 patients screened between September 2009 and October 2014, 231 met the inclusion criteria and were included in the data analysis (Fig. 1). Of these, 94 were on rivaroxaban and 137 were taking warfarin for treatment of DVT and/or PE for at least 3 months. Their characteristics are presented in Table 1.

The median time in therapeutic range (TTR) of the warfarin patients included in the study was 60%, with a median duration of use of 6.5 months and 6 clinic visits. The mean age and gender distributions of warfarin users did not differ significantly from those in the rivaroxaban arm. Rivaroxaban patients had a significantly higher median number of concurrent regular medications compared to those on warfarin (7.5 vs 6.5; $P = 0.0001$). More rivaroxaban users resided in 5-room flats, executive units, condominiums and landed properties (23.4% vs 12.4%) while most warfarin users resided in 1-room to 4-room flats (87.6% vs 76.6%). However between both groups, the distribution of patients across the housing types was not significantly different ($P = 0.149$).

Table 2 details the MPR of the warfarin and rivaroxaban users, along with the non-persistence of therapy. The MPR in the rivaroxaban arm was significantly better than that of the warfarin user arm (0.904 ± 0.094 vs 0.804 ± 0.159). On average, rivaroxaban users have 0.100 (95% CI, 0.064 to 0.136; $P < 0.0001$) higher MPR than warfarin users.

There were also significantly more people failing to adhere to outpatient appointments in the warfarin group compared to the rivaroxaban group (8.03% vs 1.06%; $P = 0.030$).

In the linear regression analysis performed to predict factors affecting MPR, effect of drug choice (warfarin vs rivaroxaban) on MPR was assessed in the presence of other significant covariates. We observed that using rivaroxaban

Table 1. Baseline Characteristics of Study Subjects

Characteristics	Warfarin (n = 137)	Rivaroxaban (n = 94)	*P* Value
Mean age in years (SD)	62.33 (1.44)	63.32 (1.60)	0.654
Gender, n (%)			
Male	59 (43.1)	49 (52.1)	0.183
Female	78 (56.9)	45 (47.9)	
Ethnicity, n (%)			
Chinese	90 (65.7)	69 (73.4)	0.231
Indian	22 (16.1)	7 (7.5)	
Malay	15 (11.0)	12 (12.8)	
Eurasian	8 (5.8)	3 (3.2)	
Others	2 (1.5)	3 (3.2)	
Mean duration of anticoagulant used, months (SD)	11.10 (1.85)	10.47 (0.79)	0.788
Median number of concomitant medicines (range)	6.5 (2 – 10)	7.5 (0 – 18)	0.0001
Housing type, n (%)			
1- or 2-room flat	16 (11.7)	7 (7.5)	0.149
3-room flat	36 (26.3)	21 (22.3)	
4-room flat	68 (49.6)	44 (46.8)	
5-room flat/executive/condominium/ landed	17 (12.4)	22 (23.4)	

SD: Standard deviation

Table 2. Univariate Analysis of the Association of MPR and Persistence with Warfarin or Rivaroxaban

	Warfarin	Rivaroxaban	Effect Estimate (95% CI)	*P* Value
Mean MPR (SD)	0.804 (0.159)	0.904 (0.094)	0.100 (0.064 – 0.136)	<0.0001
Non-persistence	11 (8.03%)	1 (1.06%)	0.123 (0.003 – 0.880)	0.030

MPR: Medication possession ratio; SD: Standard deviation

as the choice of anticoagulant resulted in 10% increase in medication adherence (95% CI, 6.4% to 13.6%; P <0.001), while every 10-year increase in age and every year increase in duration of use improved adherence by 1.7% (95% CI, 0.7% to 2.8%, P = 0.001) and 1.8% (95% CI, 0.6% to 3.0%, P = 0.003) respectively (Table 3).

Discussion

Poor medication adherence is common in clinical settings and may not be evident in the absence of objective laboratory monitoring. Contrary to our initial hypothesis, it was found that adherence as measured by MPR was better among rivaroxaban patients despite the higher treatment costs and lower monitoring intensity. The result is in line with some existing studies that reported better adherence in NOAC including rivaroxaban.[16-18] Also, rivaroxaban patients in this study were more persistent with their therapy compared with those using warfarin. Several reasons could potentially explain these observations.

Firstly, patients prescribed with rivaroxaban were a select group of patients. Rivaroxaban is currently listed as a non-standard medication in our institution and is not entitled to subsidy. As such, it tended to be prescribed to those of higher economic status who were willing to pay the price premium. Prior to prescription, the physicians would normally discuss cost of treatment with their patients and respect their choices. Importance of medication adherence was also constantly reinforced by physicians and pharmacists at the point of prescribing and dispensing rivaroxaban. This combination of factors may have limited the impact of cost on adherence among rivaroxaban patients.

Secondly, rivaroxaban is taken once a day like warfarin and offers additional advantages like not requiring routine blood tests, along with fewer interactions. These conveniences could have paradoxically led to better adherence as patients are more assured of its efficacy and less concerned with side effects. In a survey on the use of warfarin and dabigatran in patients with atrial fibrillation, patients reported higher satisfaction (e.g. no need for dietary restrictions, ease of handling missed doses, less checkups, less concerns with possible interactions with other concurrent medications or supplements) with the use of dabigatran than warfarin therapy.[19] This is despite the greater incidences of adverse effects as they believed that the convenience and benefits of NOAC outweighed the marginal increase in risks and thus were more willing to take their medications consistently. This may similarly be expected in our patients on rivaroxaban.

Thirdly, socioeconomic status and a medical co-payment system have been reported to affect medication adherence.[20] In our study, we used housing type as a surrogate marker for the socioeconomic status of patients, as in other studies on chronic conditions.[21-23] These studies have found an association between community dwelling type and medication adherence in patients; it was reported that patients at the lower end of the social economic ladder, based on the type of residence, were more likely to have poorer medication adherence as this group of patients had limited access to healthcare monitoring and treatment, or fail to adhere to their medication regimens as a result of their inability to acquire adequate supply of medications. While many aspects of such studies are not applicable in Singapore, our co-payment system of healthcare did influence the selection of patients who chose to use rivaroxaban. In our sampling distributions, we noted that patients on rivaroxaban were economically better-off than patients on warfarin. Aspects of socioeconomic status which

Table 3. Factors Affecting MPR

Factors	Coefficient	95% CI	*P* Value	R^2
Rivaroxaban vs warfarin	0.099	0.064 – 0.133	<0.001	0.180
Age	0.00174*	$6.99x10^{-4}$ – $2.80x10^{-3}$	0.001	
Duration of use	0.00149†	$5.01x10^{-4}$ – $2.48x10^{-3}$	0.003	

*Coefficient is presented in terms of per year increase for age.

†Coefficient is presented in terms of per month increase for duration of use.

MPR: Medication possession ratio

are known to influence adherence invariably contributed to adherence difference.

Treatment persistence was notably higher in rivaroxaban group in our study, which is consistent with studies performed overseas with other NOACs.[24,25] As warfarin patients have more clinic visits, the likelihood of missing some of their appointments intentionally or otherwise was likely to be higher.

In this study, it was found that the choice of drug (warfarin vs rivaroxaban) alone explained about 11.5% of the variation in MPR. When age and duration of use were added into the regression model, they explained 18% collectively. It echoes the findings of many previous studies that medication adherence is a multifaceted problem involving the interplay of many varying factors. Screening by doctors and pharmacists during prescribing and dispensing counselling together with other usual safeguards, may potentially help to further reduce the risk of medication non-adherence among this group of patients in our care setting.

There are several strengths in this study. Firstly, this is a focused local study to evaluate adherence to rivaroxaban as compared to warfarin, and the results of this study can provide insights into differences in adherence between NOACs and warfarin among our patients in Singapore. This can potentially be applied to other conditions requiring anticoagulation like atrial fibrillation. Secondly, results from the secondary analysis may help physicians assess and select the most appropriate patients who are likely to be older and been taking anticoagulants for longer periods.

There are a number of limitations in this study. Firstly, given the retrospective nature of the study, the allocation of patients into either warfarin or rivaroxaban arm was not at random but based on physicians' subjective assessment of patients' ability to afford the medications and perceived adherence at the point of treatment prescription. This clearly represented a selection bias which could influence the study findings. However, this selection bias also best reflect real world practice in our care setting and yielded findings that are devoid of the controlled environment of a randomised study. The results may, in turn, have higher relevance and applicability. Secondly, the presence of refills in the electronic database does not necessarily mean that the patient actually consumed the medications. Therein lies the assumption that patients are adherent to their medications as long as they return for a refill, which may thus lead to an overestimation of adherence. Thirdly, we did not have, for instance, sufficient data on possible confounders such as education status, personal income data, occupation, mobility and caregiver availability. As a result, we cannot rule out the possibility of residual confounding from unmeasured causal factors that were unevenly distributed between treatment groups and this could have influenced our results. Besides, sample size of the study was calculated to detect differences in MPR between the warfarin and rivaroxaban arm. Failure to detect significant differences among some suspected factors could potentially be due to insufficient power to detect them. Though inconclusive, the exploratory findings do provide important insights into other possible influencing factors that may warrant investigating in future studies.

Conclusion

The results of this study suggest that adherence with rivaroxaban may be superior to warfarin for the treatment of DVT/PE in Singapore despite it being more costly. Indicators of medication non-adherence need to be evaluated apart from other clinically relevant parameters like renal function and full blood count when deciding on the choice of anticoagulant to be administered to patients to optimise treatment outcome.

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