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Comparison of three medication adherence measures in patients taking warfarin

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Abstract In order to improve warfarin adherence, we must first know the rate of non-adherence and the reasons for it. Assessment of warfarin adherence is important in improving patients' warfarin-taking behavior and International Normalized Ratio (INR) control. This study aimed to compare three medication adherence measures in patients taking warfarin: the 8-item Morisky Medication Adherence Scale (MMAS), the 100-point Visual Analogue Scale (VAS) and medication refill adherence (MRA). A cross-sectional observational study was conducted in a convenience sample of 174 patients taking warfarin at an anticoagulation clinic. A survey questionnaire that included the MMAS, VAS, and demographic and warfarin-related clinical questions was administered to patients in English or Chinese depending on their preferences. The MRA and INR values were retrieved from hospital electronic databases. Most participants were adherent to warfarin as indicated by the three measures. A weak association was found between the MMAS and the other two adherence measures. The MMAS and MRA were associated with the percentage of INRs within range in the past 2 weeks. Moreover, the MRA was weakly associated with time within the therapeutic INR range in the past 3 months and 2 weeks. The findings provide insights into the differences among three medication adherence measures and may assist healthcare providers to select the most suitable measure for the assessment of warfarin adherence.

Keywords Adherence · Warfarin · Anticoagulation · Morisky medication adherence scale · Visual analogue scale · Medication refill adherence

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Introduction

Warfarin has been the most commonly used vitamin K antagonist to prevent thromboembolism in the past few decades [1]. A major concern of warfarin lies in its narrow therapeutic range and considerable variability in inter-individual responses, which may lead to the occurrences of out-of-range International Normalized Ratio (INR) values in clinical practice [1]. Subtherapeutic INRs are associated with a higher risk of thromboembolism, which can lead to ischemic stroke and even death; supratherapeutic INRs can lead to warfarin-induced hemorrhage, which is the most common adverse effect of warfarin and can result in different levels of long-term disabilities and even death [2–4]. Studies have shown that almost one-third of INRs in patients treated with warfarin are either below or above the therapeutic range [5, 6], subjecting patients to the dangers of thromboembolism and hemorrhage, respectively [2–4].

Non-adherence to warfarin is one of the major contributors to out-of-range INRs and subsequent complications [6, 7]. Assessment of patient adherence to warfarin is essential, as it enables the identification of non-adherent patients and elicits a better understanding of those patients' barriers to adherence. This information can assist in improving adherence to warfarin regimens, thus enhancing anticoagulation control. In addition, assessment of adherence to warfarin therapy can help healthcare providers

judge if the occurrence of out-of-range INRs is caused by poor warfarin adherence or variability in individual responses to warfarin doses, and then effective interventions can be implemented to achieve good INR control.

There is no best method to evaluate adherence to medication regimens. Each method has its own advantages and disadvantages [8, 9]. The selection of medication adherence measures is important, and they need to be specifically chosen for the population and medication in question; a measure suitable for one clinical setting may not be applicable to another. Therefore, evaluation and comparison of medication adherence measures are needed prior to their application in order to determine the most suitable measure for the medications and populations under investigation. The aim of this study was to examine the associations among three commonly used measures of medication adherence: the 8-item Morisky Medication Adherence Scale (MMAS), the Visual Analogue Scale (VAS) and medication refill adherence (MRA) in patients taking warfarin. In addition, the three measures' associations with patients' INR control were also evaluated.

Methods

Data collection

A cross-sectional survey was conducted from September to December, 2011, in a convenience sample (i.e. using the most readily available patients) of patients taking warfarin in an outpatient anticoagulation clinic (ACC) of the Singapore General Hospital (SGH). The target sample size was 155 in order to have a power of 0.8 to detect a small correlation ($r = 0.25$) between warfarin adherence and the percentage of INRs within the therapeutic range at the 5 % significance level, assuming 20 % incomplete responses.

The survey questionnaire included the 8-item MMAS, the VAS, socio-demographics and warfarin-related clinical questions (e.g. indications for warfarin). Two interviewers received training on the standardized administration process and data-coding procedure. Potentially eligible patients were approached by referral from the ACC pharmacists. Patients were eligible if they were age 21 or older, on warfarin therapy for at least 3 months and able to comprehend English or Chinese. Proxies (i.e. next of kin) were approached if they looked after the patient for his or her warfarin treatment. Respondents who consented to participate were interviewed face-to-face and were asked to complete either an English or Chinese version of the questionnaire, depending on their language preferences. The Chinese version of the 8-item MMAS was developed and evaluated by a panel of multi-disciplinary and bilingual clinical experts based on their clinical expertise and/or experience in validation and translation of patient-reported measures. The expert panel included one clinical pharmacist with a master's degree in pharmacy, three researchers with a Ph.D. in pharmacy and a Ph.D. candidate in pharmacy. The panel ensured equivalence and local adaptation of the two language versions in terms of content, wording, and cognitive level. The two language versions had been pilot-tested in a small group of patients on warfarin ($n = 8$) prior to the survey to ensure the questions' clarity and readability. In addition, patients' INR records, i.e. the percentage of INRs within the therapeutic range and the percentage of time within the therapeutic range (TTR) during the past 2 weeks and 3 months, were retrieved from the hospital electronic database. The study was approved by the Singhealth Institution Review Board.

Medication adherence measures

The 8-item MMAS was originally used to assess adherence to antihypertensive medications in the US [10]. The underlying theory of the scale was that medication non-adherence could be due to patients' behavioral and attitudinal problems, and, therefore, the scale measured several factors that could cause failure to medication adherence, including forgetting to take medications, forgetting to bring along medications when travelling, not taking medications when feeling worse or better, and feeling hassled about sticking to medication treatment plans etc. The wording of seven questions was reversed to avoid the "yes-saying" bias. Seven items used dichotomous item responses (i.e. "yes" or "no"), and one item adopted a 5-point Likert-type item response (i.e. "never", "rarely", "sometimes", "often" or "always"). The scale scores ranged from 0 to 8, with higher scores indicating better medication adherence.

The 100-point VAS was a vertical percentile scale anchored by 100 and 0 at the high and low ends of the scale, respectively. Participants were instructed to draw an arrow beside the scale to indicate the extent to which they were able to take their warfarin as prescribed in the 2 weeks prior to the survey. A point of "100" indicated that the patient was able to follow the prescribed warfarin regimen perfectly whereas a point of "0" indicated that the patient was not able to adhere to the prescribed warfarin regimen at all.

Warfarin refill records were retrieved for each patient from the hospital electronic pharmacy databases in order to calculate the MRA value, which was equal to the total days of supply divided by the number of evaluated days during the observation period and multiplied by 100 [11]. The observation period was 3 months to ensure that every patient had at least one warfarin refill record.

Statistical analysis

Descriptive statistics were used to describe the respondents' characteristics. Associations among the three measures were examined by the Spearman correlation, while the three measures' associations with patients' INR values were examined by the Spearman correlation and the Mann–Whitney U test where appropriate. In the analysis, the respondents were divided into two groups based on their percentage of INRs in the therapeutic range (≥80 % and <80 %). All analyses were performed using SPSS version 19.0. The level of significance was set at probability (p) < 0.05.

Results

Among the 202 patients approached, 174 patients or their proxies agreed to participate in the survey, giving a response rate of 86.1 %. Respondents' characteristics are shown in Table 1. Respondents were evenly distributed between the two language versions (55.2 % English) and the two genders (50.0 % male), with the mean (SD) age of 58.7 (15.4) years. Approximately two-thirds of the participants were Chinese (72.4 %) and more than half of the participants had completed secondary education (55.1 %). The major indications for warfarin were atrial fibrillation and deep vein thrombosis (28.7 % and 43.1 %, respectively). Non-respondents were older than the respondents ($p = 0.02$); other socio-demographics, clinical characteristics, and INR and MRA values between the two groups were comparable.

The English and Chinese versions of the questionnaire were combined in the analyses, as they were comparable in distributions of responses and scale scores. The mean (SD) of the MMAS scores, the VAS scores and the MRA values were 7.0 (1.1), 91.9 (10.8) and 93.6 % (13.7 %), respectively. The distributions of the three measures were trended towards the high end, indicating high adherence to warfarin. Approximately one-third (34.5 %) of the respondents had an MMAS score of 8, while 46.6 % of the respondents had a VAS score of 100 and 63.2 % of the respondents had a MRA value of 100 % (Fig. 1). With a VAS score of 80 serving as a cut-off point, 89.1 % of the respondents were considered to have good adherence to their warfarin therapies; with an 80 % warfarin refill rate serving as a cut-off point, 85.1 % of the respondents were considered adherent.

The MMAS scores were associated with both the VAS scores and the MRA values ($r_s = 0.23$ and 0.18; $p = 0.002$ and 0.02, respectively) whereas no association was found between the VAS scores and the MRA values ($r_s = 0.08$; $p = 0.32$). In the analysis of the associations between the three adherence measures and four INR measures, the MRA values were associated with the percentage of TTR in the past 3 months and past 2 weeks ($r_s = 0.21$ and 0.16; $p = 0.01$ and 0.045, respectively) as well as with the percentage of INRs within the therapeutic range in the past 2 weeks ($p = 0.03$). The MMAS scores were only associated with the percentage of INRs within the therapeutic range in the past 2 weeks ($p = 0.02$). The VAS scores were not associated with any INR measures.

Table 1 Socio-demographic and clinical characteristics ($n = 174$)

Characteristics	n (%)[a]
Language version	
English	96 (55.2)
Chinese	78 (44.8)
Interview's role	
Patient	151 (86.8)
Next of kin	23 (13.2)
Gender	
Male	87 (50.0)
Female	87 (50.0)
Ethnicity	
Chinese	126 (72.4)
Malay	25 (14.4)
Indian	14 (8.0)
Others	9 (5.2)
Educational level	
No school	37 (21.3)
Primary	39 (22.4)
Secondary	46 (26.4)
Post-secondary	50 (28.7)
Indication(s) for warfarin	
AF	50 (28.7)
DVT	75 (43.1)
PE	18 (10.3)
Others	27 (15.5)
Percentage of INRs in the therapeutic range in the past 3 months	
<80 %	94 (54.0)
≥80 %	68 (39.1)
Percentage of INRs in the therapeutic range in the past 2 weeks	
<80 %	63 (36.2)
≥80 %	94 (54.0)
	Mean ± SD
Age (year)	58.7 ± 15.4
Percentage of TTR in the past 3 months	64.5 ± 33.8
Percentage of TTR in the past 2 weeks	65.3 ± 39.4
MRA (%)	93.6 ± 13.7

AF atrial fibrillation, *DVT* deep vein thrombosis, *INR* International Normalized Ratio, *MRA* medication refill adherence, *PE* pulmonary embolism, *TTR* time in the therapeutic range

[a] Percentage may not add up to 100 % due to missing values

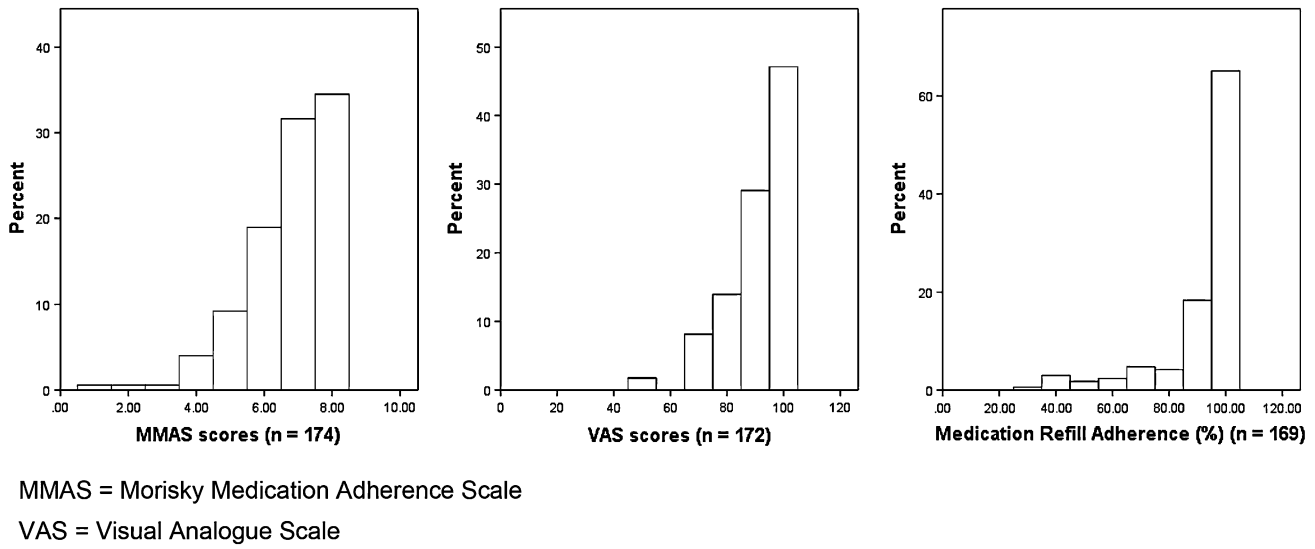

Fig. 1 Distributions of responses to the medication adherence measures

Discussion

The primary objective of the study was to compare the 8-item MMAS, the VAS and the MRA in patients taking warfarin. To the best of our knowledge, this is one of the few studies that compared pharmacy refill data-based and patient-reported medication adherence measures, and is the first study that compared the three adherence measures in a multi-ethnic Asian population.

Previous studies have employed various adherence measures and found that patients generally have good adherence to warfarin therapy. For example, Orensky and Holdford [12]. found that 80 % patients were deemed adherent to warfarin, using a cut-off level of an 80 % warfarin refill rate. Platt et al. [13]. reported that patients were adherent to warfarin in 78.7 % of patient-days observed in a study using an electronic pill cap opening monitoring system. As in the previous studies, the distributions of the MMAS scores, the VAS scores and the MRA values in this study were skewed to the high end, indicating that most patients were adherent to their warfarin therapies. The high warfarin adherence could be due to the use of a pill box, as mentioned by the majority of the respondents. Another explanation could be the critical nature of warfarin, which frequently subjects patients to severe complications and even death and, therefore, discourages patients from being nonadherent [1–4]. In addition, strong family support may have enhanced patients' adherence to warfarin, as a few patients were looked after by their next of kin.

In this study, the 8-item MMAS scores were found to be associated with both the VAS scores and the MRA values. Similar findings have been reported by other studies. Krousel-Wood et al. [14] found that the 8-item MMAS was associated with three pharmacy refill adherence measures in elderly patients with hypertension. Another study that assessed patients' adherence to diabetes medications found that patients with higher 8-item MMAS scores were more likely to have higher VAS scores [15]. Nevertheless, the associations between MMAS and the other two measures found in our study were small, and no significant association was found between the VAS scores and the MRA values. This could be due to the different observation periods of the three measures. The MRA assessed patients' adherence over the past 3 months, whereas the VAS evaluated patient adherence over the past 2 weeks and the MMAS, which was composed of questions with specified (from yesterday to the past 2 weeks) and non-specified observation periods, assessed the most recent warfarin-taking behavior. Another explanation could be that the three measures assessed different aspects of medication adherence. The MRA assessed the patient's behavior regarding warfarin refills, assuming that the patient took warfarin every day as prescribed if the refill was collected on time. In the two self-reported measures, the MMAS evaluated the patient's behavioral and attitudinal problems related to medication adherence, whereas the VAS assessed the patient's perceived adherence and allowed for the patient's own interpretation and evaluation of his or her warfarin-taking behavior, which may have caused additional variability in the scale scores. Moreover, a few elderly respondents with low literacy indicated cognitive problems with the VAS, which may have adversely affected the accuracy of their responses and thus their VAS scores.

Despite the a priori expectation that patients with better medication adherence would be more likely to have better

INR control, the associations between the MMAS scores and the INR control measures were not conclusive in this study. One explanation could be that the MMAS is a generic measure of medication adherence and does not cover all dimensions of warfarin-specific adherence. For example, regular timing of daily warfarin doses was found to be associated with percentage of TTR [16]. Moreover, the MMAS may include questions that are not sensitive to different levels of warfarin adherence. For example, although a number of the respondents indicated that they felt it was troublesome to stick to their warfarin regimen plans, they remained adherent in order to reduce the risk of complications. In addition, the dichotomous item responses of the MMAS may make the scale difficult to differentiate among patients with higher levels of adherence and, as a result, diminish potential associations between the scale scores and the INR values. Moreover, a number of factors (e.g. diet and lifestyle) other than medication adherence can also affect patients' INR control.

Among the various medication adherence measures, the 8-item MMAS, the VAS and the MRA have a number of advantages and have been used in patients with a variety of diseases. The 8-item MMAS is a reliable measure with good validity, and is simple to understand and easy to administer [10]. It has been used to assess medication adherence in patients with diseases such as hypertension [10, 14], diabetes mellitus [15, 17] and epilepsy [18]. The VAS is another self-report measure that features its brevity, low response burden and easy incorporation into a medical visit, and it has been used to in patients with diseases such as diabetes mellitus [19], asthma [20] and HIV [21]. The MRA is an objective method based on refill data and, therefore, it is not susceptible to social desirability and recall bias. In addition, it requires the fewest calculations and the least amount of data compared to other measures that use pharmacy administrative data [11]. In this study, it was found that the MRA had a significant correlation with most of the INR measures, and, therefore, may be incorporated into clinical practice to help identify patients with poor INR control. Moreover, MRA can assess medication adherence in patients who refuse to report their medication adherence or often miss their clinic visits, who are likely to be in the greatest need of targeted interventions to improve their medication adherence. Future research is needed to compare the MRA or TTR with other medication adherence measures such as the electronic monitoring system that has been used as a gold standard in several studies [22, 23]. However, the electronic monitoring system is expensive and, therefore, its application may be limited. Moreover, a longitudinal study is needed to evaluate the changes in MRA over time to get a better understanding of patients' long-term medication adherence.

There are a few limitations to this study. Patients were recruited from an outpatient ACC, so the findings may not be generalizable to inpatients or other ambulatory patients not cared for by ACCs, such as those managed by their primary care providers, who may have poorer INR control. Another limitation is that the actual adherence to warfarin may have been inflated, as the convenience sampling procedure of the survey may have rendered the study sample liable to selection bias. Patients who were non-adherent to their warfarin therapies were more likely to have missed their clinic appointments and to have subjected themselves to non-adherence-induced fatal complications prior to the survey. In addition, the actual medication adherence may have been overestimated because of the social desirability and recall bias of patient-reported measures and the assumption of the MRA that patients took warfarin as prescribed.

Conclusion

Measure selection is essential to assessing patient adherence to medication regimens. In this study, most of the patients on warfarin were adherent as indicated by three adherence measures. In addition, the pharmacy refill data-based MRA was found to be significantly associated with INR control and self-reported MMAS but not VAS. The findings provided insight into the correlations and differences among three medication adherence measures and their associations with INR control, which may assist healthcare providers to select the most suitable measure for the assessment of warfarin adherence. Future research is needed to verify the findings in different patient populations and clinical settings.

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Conflict of interest Nothing to declare.

References

1. Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E (2004) The pharmacology and management of the vitamin K antagonists: the seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 126:204S–233S
2. Levine MN, Raskob G, Beyth RJ, Kearon C, Schulman S (2004) Hemorrhagic complications of anticoagulant treatment: the seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 126:287S–310S

3. Merli GJ, Tzanis G (2009) Warfarin: what are the clinical implications of an out-of-range-therapeutic International Normalized Ratio? J Thromb Thrombolysis 27:293–299
4. Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV, Singer DE (2003) Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med 349:1019–1026
5. Wittkowsky AK, Devine EB (2004) Frequency and causes of overanticoagulation and underanticoagulation in patients treated with warfarin. Pharmacotherapy 24:1311–1316
6. Waterman AD, Milligan PE, Bayer L, Banet GA, Gatchel SK, Gage BF (2004) Effect of warfarin nonadherence on control of the International Normalized Ratio. Am J Health Syst Pharm 61:1258–1264
7. Hixson-Wallace JA, Dotson JB, Blakey SA (2001) Effect of regimen complexity on patient satisfaction and compliance with warfarin therapy. Clin Appl Thromb Hemost 7:33–37
8. Osterberg L, Blaschke T (2005) Adherence to medication. N Engl J Med 353:487–497
9. Vermeire E, Hearnshaw H, Van Royen P, Denekens J (2001) Patient adherence to treatment: three decades of research. a comprehensive review. J Clin Pharm Ther 26:331–342
10. Morisky DE, Ang A, Krousel-Wood M, Ward HJ (2008) Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens (Greenwich) 10:348–354
11. Hess LM, Raebel MA, Conner DA, Malone DC (2006) Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. Ann Pharmacother 40:1280–1288
12. Orensky IA, Holdford DA (2005) Predictors of noncompliance with warfarin therapy in an outpatient anticoagulation clinic. Pharmacotherapy 25:1801–1808
13. Platt AB, Localio AR, Brensinger CM et al (2010) Can we predict daily adherence to warfarin?: results from the International Normalized Ratio adherence and genetics (IN-RANGE) study. Chest 137:883–889
14. Krousel-Wood M, Islam T, Webber LS, Re RN, Morisky DE, Muntner P (2009) New medication adherence scale versus pharmacy fill rates in seniors with hypertension. Am J Manag Care 15:59–66
15. Sakthong P, Chabunthom R, Charoenvisuthiwongs R (2009) Psychometric properties of the thai version of the 8-item Morisky medication adherence scale in patients with type 2 diabetes. Ann Pharmacother 43:950–957
16. Palareti G, Legnani C, Guazzaloca G et al (2005) Risks factors for highly unstable response to oral anticoagulation: a case-control study. Br J Haematol 129:72–78
17. Al-Qazaz H, Hassali MA, Shafie AA, Sulaiman SA, Sundram S, Morisky DE (2010) The eight-item Morisky medication adherence scale MMAS: translation and validation of the Malaysian version. Diabetes Res Clin Pract 90:216–221
18. Sweileh WM, Ihbesheh MS, Jarar IS et al (2011) Self-reported medication adherence and treatment satisfaction in patients with epilepsy. Epilepsy Behav 21:301–305
19. Nau DP, Steinke DT, Williams LK, Austin R, Lafata JE, Divine G, Pladevall M (2007) Adherence analysis using visual analog scale versus claims-based estimation. Ann Pharmacother 41:1792–1797
20. Bozek A, Jarzab J (2010) Adherence to asthma therapy in elderly patients. J Asthma 47:162–165
21. Berg KM, Wilson IB, Li X, Arnsten JH (2012) Comparison of antiretroviral adherence questions. AIDS Behav 16:461–468
22. Choo PW, Rańd CS, Inui TS et al (1999) Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. Med Care 37:846–857
23. Zeller A, Ramseier E, Teagtmeyer A, Battegay E (2008) Patients' self-reported adherence to cardiovascular medication using electronic monitors as comparators. Hypertens Res 31:2037–2043