CLINICAL RESEARCH STUDY

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Association Between Patient-Reported Medication Adherence and Anticoagulation Control

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ABSTRACT

BACKGROUND: The prevention of thromboembolism events remains challenging in cases of poor medication adherence. Unfortunately, clinical prediction of future adherence has been suboptimal. The objective of this study was to examine the correlation between 2 measures of real-time, self-reported adherence and anticoagulation control.

METHODS: The IN-RANGE2 cohort recruited patients initiating warfarin therapy in 3 urban anticoagulation clinics. At each study visit, participants reported adherence using a 100-point visual analogue scale (VAS, marking percentage of pills taken since prior visit on a linear scale) and 7-day recall of pill-taking behavior. Anticoagulation control was measured by between-visit percent time in international normalized ratio range (BVTR), dichotomized at the cohort median. The longitudinal association between adherence and anticoagulation control was estimated using generalized estimating equations, controlling for clinical and demographic characteristics, prior BVTR, and warfarin dose changes.

RESULTS: Among 598 participants with 3204 (median 4) visits, the median BVTR was 36.8% (interquartile range 0%-73.9%). Participants reported ≤80% adherence in 182 visits (5.7%) and missed pills in the past 7 days in 377 visits (11.8%). Multivariable regression analysis found poorer anticoagulation control (BVTR <36.8%) in those with a VAS ≤80% (odds ratio 1.89; 95% confidence interval, 1.12-3.18; $P = .02$) and self-reported change in adherence since last visit (odds ratio 1.55; 95% confidence interval, 1.20-2.01; $P = .001$).

CONCLUSION: Self-reported VAS medication adherence at a clinic visit and changes in reported adherence since the last visit are independently associated with BVTR. Clinicians may gain additional insight into patients' medication adherence by incorporating this information into patient management.

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KEYWORDS: Anticoagulation; Medication adherence; Self-report; Visual analogue scale; Warfarin

Warfarin is the oldest and most commonly used oral anticoagulant (OAC) for the prevention of thromboembolic events. Despite extensive clinical experience with this medication, appropriate dosing remains challenging owing to the influence of numerous patient factors, including medication nonadherence, on achieving and maintaining a therapeutic level.

Previous research using electronic pill monitoring has shown that up to 36% of patients taking warfarin miss more

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than 20% of their doses, and every 10% increase in nonadherence is associated with a 10% increase in the odds of having a nontherapeutic international normalized ratio (INR).[1] The INR is the strongest and most robust predictor of the risk of thromboembolic and hemorrhagic events.[2,3] Although the introduction of direct oral anticoagulants (DOACs) has offered patients new OAC therapeutic options that solve many of the challenges of warfarin use, adherence to DOACs has not been found to differ significantly from warfarin in practice.[4] Given the absence of clinically useful and accurate ways for clinicians to monitor adherence, medication nonadherence for patients on anticoagulation regimens remains a serious public health problem.

Although physicians understand the importance of discussing adherence with patients, many report difficulty engaging in these conversations, with time representing the greatest barrier.[5] Most importantly, patient reports and physician assessments of patient adherence in routine clinical practice do not reflect objective measures of adherence using electronic pill monitoring.[6] Unfortunately, electronic pill monitoring is impractical for routine clinical practice. Formal prediction models to predict future adherence have suboptimal performance with poor validation.[7] Therefore, there is a need for accurate self-reported adherence measures that can be obtained quickly and efficiently (see conceptual framework, **Figure**).

This study sought to characterize the association of 2 adherence measurements, the traditional 7-day recall and a visual analogue scale (VAS), with anticoagulation control in patients starting warfarin therapy at 3 urban anticoagulation clinics. The VAS has been found to correlate with objective adherence measurements[8-10] and clinical outcomes in other patient populations,[8,10,11] but it has never been adequately tested in an anticoagulation population.

CLINICAL SIGNIFICANCE

- Clinicians may gain additional insight into patients' medication adherence by incorporating information from the visual analogue scale and changes in 7-day recall into clinical decision making.
- The visual analogue scale represents a promising tool to monitor adherence to other medications, and might be useful in patients on DOACs because the association is independent of knowing prior anticoagulation control.

METHODS

Study Design

The INR Adherence and Genetics 2 (IN-RANGE2) cohort is an extension of the IN-RANGE cohort previously described.[1] Briefly, this is a large, multicenter, prospective cohort of patients initiating warfarin therapy between 2009 and 2013 at 3 urban anticoagulation clinics: the Hospital of the University of Pennsylvania, the Corporal Michael J. Crescenz Veterans Affairs Medical Center, and the Johns Hopkins Medical Institutions. Self-identified Caucasians and African Americans were included in the study, with minimal exclusion criteria including age <21 years, inability to give consent, or abnormal INR before initiating therapy. For this analysis, additional exclusion criteria included having <2 in-person visits or <2 adherence measurements.

Data Collection

Information on participant demographic and clinical characteristics as well as factors that can influence warfarin response, warfarin dose, and medication adherence were collected prospectively through in-person interviews by trained research nurses at baseline and at subsequent visits, using standardized questionnaires and data collection forms. Data collection occurred before the current INR was revealed to participants or interviewers. Clinicians were blinded to interview responses.

Adherence and Outcome Measures

Medication adherence was assessed at each study visit using 2 measurements: VAS and 7-day recall. The VAS tool presented participants with a continuous line anchored by 0% and 100% with 10% intervals and asked them to mark the line at their best guess about their adherence since their previous visit (Supplementary Figure, available online). The 7-day recall tool asked participants whether they had skipped or taken any extra pills in the past 7 days and, if so, how many pills. The INR was measured at each visit according to the clinics' standard procedures, using either point of care fingerstick or venous samples from phlebotomy. The primary outcome was between-visit time in therapeutic INR range (BVTR). Thus, for each visit with a patient-reported adherence measure, the BVTR was calculated using all INRs collected between the prior study visit and the current study visit, according to the Rosendaal linear interpolation method.[12] Patients could have multiple BVTRs throughout the study period, each corresponding to the interval in which they reported an adherence measurement.

Data Analysis

Descriptive statistics were calculated for the cohort using mean, median, standard deviation, and interquartile range. The VAS score was analyzed a priori as dichotomized into >80% versus ≤80%, a commonly used threshold for poor adherence.[1,13,14] Secondary analyses dichotomized the VAS score as 100% versus <100%. Patient-reported number of pills taken correctly was converted into a continuous variable of percentage pill adherence. The correlation between the 2 adherence measurements was

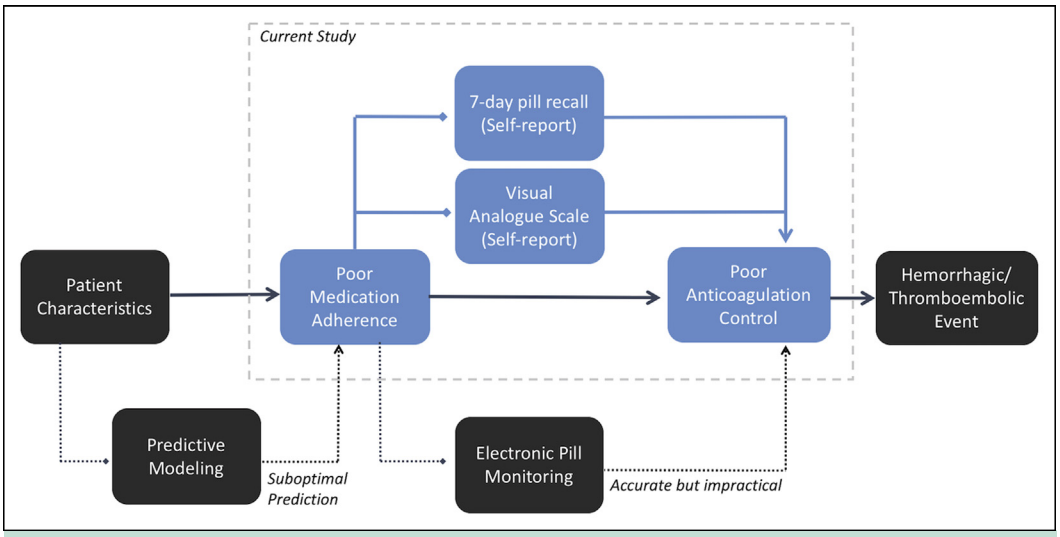

Figure Conceptual framework. Poor medication adherence is strongly associated with poor anticoagulation control, which places patients at increased risk of hemorrhagic and thromboembolic events. A challenge in addressing poor medication adherence has been to readily identify patients with poor adherence, to provide them with additional resources and targeted interventions. Previous studies have found prediction models of future adherence to be suboptimal, and objective measurement, through electronic pill monitoring, to be accurate but impractical in routine clinical practice. Our study's aim (dashed box) was to analyze the association between 2 quick and easily implemented self-reported adherence measurements, a visual analogue scale and change in 7-day pill recall, and anticoagulation control.

assessed using Pearson correlation coefficient and κ statistic. The BVTR was dichotomized at the median value to maximize power.

Three measurements of adherence were analyzed for each tool: adherence at current visit, adherence at prior visit, and change in adherence between visits. Univariable analysis was used to calculate the association of each adherence measure and each covariate with BVTR utilizing generalized estimating equations, based on an independent correlation matrix to account for longitudinal observations within participant. Adherence measurements that were not found to have a statistically significant association with BVTR were not included in subsequent adjusted models.

Three types of potential confounders were assessed in our adjusted analysis: demographics, clinical factors, and baseline medication-taking practices (specific questions in Supplementary Table, available online). These covariates were considered to be confounders and included in multivariate models if they were associated with BVTR with a univariate P value $<.20$. The final models were adjusted for these confounders, BVTR during prior interval, and having a warfarin dose change since the prior visit.

All statistics were performed with SAS (version 9.1; SAS Institute, Cary, NC) and STATA (version 13.1; StataCorp, College Station, Tex). The institutional review boards at all participating hospitals approved the study, and all participants provided informed, signed consent.

RESULTS

The IN-RANGE2 cohort comprised 687 participants, with 89 participants excluded from this analysis for having <2 in-person visits or adherence measurements, leaving a final population of 598 (87%) participants and 3204 total in-person visits, with a median follow-up of 4 visits (interquartile range [IQR], 2-7). Of these, 447 (75%) reached maintenance dose, 78 (13%) stopped warfarin before reaching the primary endpoint, 57 (9.6%) were lost to follow-up, 15 (2.5%) did not reach the primary endpoint before the end of the study, and 1 (0.2%) withdrew consent. Baseline characteristics of our study population are shown in **Table 1**. Participants excluded from this analysis were more likely to be Caucasian, current smokers, to have been hospitalized in the past 12 months, and to score higher on the Cognitive Capacity Screening Examination (data not shown).

The mean (median) number of INR measurements per BVTR measurement was 3.0 (2.0), with a median BVTR of 36.8% (IQR, 0%-73.9%). The median number of visits to reach maintenance dose was 5 (IQR, 2-7).

Participants had a median of 4 (IQR, 3-7) VAS and 7-day recall measurements. Mean adherence by VAS was 96.6% (standard deviation 5.8%), with participants reporting less than 100% adherence in 729 visits (28%) and ≤80% adherence in 182 visits (5.7%). Mean adherence by 7-day recall was 97.4% (standard deviation 10.4%), with participants reporting incorrect pill taking in 408 (13%) visits. The 2 adherence measures were moderately correlated with a

Table 1 Participant Demographic and Baseline Clinical Characteristics*

Characteristic	Value
Participants (N)	598
Age (y), mean (SD)	55.5 (14.9)
Gender	
Male	368 (61.5)
Female	228 (38.1)
Race	
African American	429 (71.7)
Caucasian	157 (26.3)
Education	
High school or less	262 (43.8)
More than high school	335 (56.0)
Marital status	
Married	174 (29.1)
Separated	159 (26.6)
Widowed	59 (9.9)
Not married	196 (32.8)
Insurance status	
Medicare	209 (34.9)
Medicaid	58 (9.7)
Private	186 (31.1)
VA	80 (13.4)
Other	33 (5.4)
None	28 (4.7)
Site	
Hospital of the University of Pennsylvania	241 (40.3)
Corporal Michael J. Crescenz Veterans Affairs Medical Center	173 (28.9)
Johns Hopkins Medical Institutions	184 (30.8)
Indication	
Atrial fibrillation/flutter	189 (31.6)
Venous thromboembolism	311 (52.0)
Other	95 (15.9)
History of prior warfarin use	184 (30.8)
Doctor visits in past 12 mo	
0-3 visits	110 (18.4)
4-12 visits	259 (43.3)
13+ visits	225 (37.6)
Alcohol use with warfarin	
Yes	211 (35.3)
No	380 (63.5)
Smoking status	
Ever smoker	339 (56.7)
Never smoker	256 (42.8)
Poor kidney function	
GFR <30 mL/min/1.73 m^2	36 (6.0)
30< GFR <60 mL/min/1.73 m^2	107 (17.9)
GFR >60 mL/min/1.73 m^2	411 (68.7)
$CHADS_2$ score	
0	133 (22.2)
1	172 (28.8)
2+	282 (47.2)
Standardized General Health Perception, mean (SD)	54.8 (23.3)
Statins at baseline	
Yes	263 (44.0)
No	334 (55.9)
Amiodarone at baseline	
Yes	35 (5.9)
No	563 (94.1)

Values are number (percentage) unless otherwise noted.
GFR = glomerular filtration rate; SD = standard deviation.
*Some percentages are based on fewer than 598 participants because of missing data.

Pearson's correlation coefficient of 0.62 (P <.001). When dichotomized they had fair agreement, with a κ statistic of 0.40 (P <.001).

Adherence and Anticoagulation Control

Univariable analysis demonstrated a VAS score of ≤80% at the current visit to be associated with 2.36 (95% confidence interval [CI], 1.71-3.25) times greater odds of poor anticoagulation control (**Table 2**). This association remained significant when modeling the VAS score continuously but not when dichotomized at 100%. Incorrect pill taking by 7-day recall was associated with a 63% (95% CI, 1.32-2.02) increase in the odds of poor anticoagulation control, with the association remaining when modeling percentage of pill adherence continuously. Adherence measurements at the prior visit, change in reported adherence, BVTR at the prior visit, and dosage changes since the last visit were found to have a significant association with anticoagulation control at the current visit (**Table 2**).

Covariates and Anticoagulation Control

Demographic covariates, including age, sex, race, education, marital status, insurance status, and anticoagulation clinic site, were found to be associated with BVTR, with a P value <.20, and were included in subsequent models. Clinical factors, including anticoagulation indication, varying dosing regimen, general health self-assessment, number of doctor visits in the past 12 months, smoking status, alcohol use, poor kidney function, use of statins at baseline, use of amiodarone at baseline, health care encounter since prior visit, and having warfarin stopped since last visit, were also associated with BVTR, with a P value <.20. Of 17 medication-taking practice questions in the survey, 9 were associated with BVTR, with a P value <.20 (Supplementary Table, available online).

Multivariable Models

Visual analogue scale scores at both current and prior visits were independently associated with anticoagulation control, when including only VAS adherence measurements, after adjustment for the above confounders, prior BVTR, and dose changes since the prior visit (**Table 3**). Models including only 7-day recall measurements found change in

Table 2 Univariable Analysis

Factor	Poor Anticoagulant Control, OR (95% CI)	*P* Value
VAS (%)		
>80	Ref	
≤80	2.36 (1.71-3.25)	<.001
100	Ref	
<100	1.15 (0.98-1.34)	.08
Prior VAS (%)		
>80	Ref	
≤80	2.20 (1.59-3.05)	<.001
100	Ref	
<100	1.15 (0.97-1.35)	.1
Change in VAS		
No	Ref	
Yes	1.63 (1.42-1.88)	<.001
7-day recall		
No incorrect pill	Ref	
Incorrect pill	1.63 (1.32-2.02)	<.001
Prior 7-day recall		
No incorrect pill	Ref	
Incorrect pill	2.09 (1.66-2.63)	<.001
Change in 7-day recall		
No	Ref	
Yes	1.38 (1.14-1.66)	<.001
Prior BVTR		
10% decrease	1.23 (1.20-1.26)	<.001
Dosage change		
No	Ref	
Yes	3.52 (3.04-4.07)	<.001

AC = anticoagulation; BVTR = between-visit percent time in international normalized ratio range; CI = confidence interval; OR = odds ratio; VAS = visual analogue scale.

adherence since last visit to have a significant association with anticoagulation control, whereas the current 7-day recall value was not significant. Models using both VAS and 7-day recall measurements found an independent association between poor anticoagulation control and both a VAS score ≤80% at the current visit and a reported change in adherence since last visit using 7-day recall. Importantly, no other self-reported measurements of adherence were found to be independently associated with anticoagulation control. The association remained when using VAS score as a continuous measurement, with a 10% decrease in adherence being associated with a 14% increase in the odds of having poor anticoagulation control (OR 1.14; 95% CI, 1.00-1.29; $P = .04$).

DISCUSSION

In this prospective study, we found that patient self-reported adherence using 2 quick and simple tools for the assessment of adherence at each patient visit—a VAS and changes in adherence using 7-day pill recall—were independently associated with anticoagulation control. Our results are consistent with previous studies in human immunodeficiency virus patients[8,10] and women taking aromatase inhibitors.[11] The only previous study comparing VAS with anticoagulation control in warfarin-treated patients found no association; however, it was a small, cross-sectional study using a convenience sample.[15]

We found only a moderate correlation between 7-day recall and VAS, despite the fact that they were administered in succession. We found that participants reported imperfect adherence more often with the VAS than with the 7-day recall. Although this might reflect that the tools ask about adherence over different periods of time, it is possible that the VAS is more accurate and less prone to desirability bias because patients can report imperfect adherence across a range of adherence on a scale without having to report their incorrect pill taking directly to a clinician.

Association Between Self-Reported Adherence and Anticoagulation Control

In our final combined model, the only measurements that had a significant association with anticoagulation control were adherence at the current visit reported using VAS and a change in adherence from the previous visit reported with

Table 3 Multivariable Analysis

	VAS Only Model*		7-Day Recall Only Model*		Final Combined Model*	
Model	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Current VAS score (≤80%)	1.88 (1.12-3.18)	.02	Not included		1.90 (1.13-3.20)	.02
Prior VAS score (≤80%)	1.94 (1.27-2.97)	.002	Not included		†	
Change in 7-day recall (yes)	Not included		1.61 (1.24-2.08)	<.001	1.56 (1.20-2.01)	.001
Prior BVTR (10% decrease)	1.18 (1.15-1.22)	<.001	1.19 (1.15-1.22)	<.001	1.19 (1.15-1.22)	<.001
Dosage change since prior visit (Yes)	4.11 (3.36-5.04)	<.001	4.09 (3.34-5.02)	<.001	4.10 (3.35-5.03)	<.001

AC = anticoagulation; BVTR = between-visit percent time in international normalized ratio range; CI = confidence interval; OR = odds ratio; VAS = visual analogue scale.

*Covariates included in models: gender, age, race, education, insurance status, marital status, AC clinic site, AC indication, varying dosing regimen, general health perception, number of doctor visits in past 12 months, smoking status, alcohol use, poor kidney function, use of statins at baseline, use of amiodarone at baseline, health encounter since prior visit, warfarin stopped since last visit, medication taking practice (questions 2, 3, 4, 7, 12, 13, 16, 17, and 18).

†Prior VAS score was not significant in combined models and was removed from final combined model.

7-day recall. Interestingly, our models did not show a change in VAS score from the previous visit, or 7-day recall at the current visit to be significantly associated with anticoagulation control. As noted above, it is likely that 7-day recall measurements are less accurate and therefore correlated poorly with anticoagulation control. This suggests that more comprehensive adherence information may be uncovered by combining these tools and considering not only adherence reported at a current visit, but also assessing changes in reported behavior over time. However, given the logistical challenges of implementing 2 distinct adherence measurements in clinical practice, given that the VAS is easier to measure and has a stronger association with BVTR, clinicians should choose the VAS over 7-day recall if they are able to measure only 1 parameter.

These findings are particularly relevant after the introduction of DOACs, because anticoagulation management is moving away from specialty anticoagulation clinics that are designed to spend time discussing adherence with patients to general practice clinics. At the same time, poor adherence to DOACs cannot be inferred as it can with warfarin because of the absence of a laboratory test (eg, INR) for monitoring DOAC response. Further, the short half-lives of DOACs (compared with the very long half-life of warfarin) place patients at increased risk of a thromboembolic event after missing just 1 or 2 doses.[16] This study identifies the VAS as a promising tool that might help identify poor adherence to DOACs, given that its association with anticoagulation control was found to be independent of both changes in warfarin dosing and knowledge of a patient's current INR. The simplicity of this tool would allow it to be administered during patient visits, flagging patients who report $\leq$80% adherence as being at risk of poor anticoagulation control. In these patients, clinicians should consider using visit time to discuss barriers to adherence, as well as consideration of treatment changes.

Study Limitations

Our study had several limitations. First, we had no objective adherence measurement to validate patient self-reported measurements. Although studies have found the VAS to correlate with objective measurements of medication adherence—including electronic monitoring,[9] pill counts,[8] and claims-based data[17]—it is possible that participants in our study were more likely to overestimate their adherence owing to recall and social desirability bias. This might be reflected in the high VAS score (which is slightly higher, yet consistent, with those reported in the literature).[8,9,11] This would bias our results toward the null. Second, VAS was measured before 7-day recall, and it is possible that the order affected participants' recall; however, the measurements could be easily implemented in this order in a clinical setting to replicate our findings. Third, we defined anticoagulation control using BVTR, a short-term measure specifically designed to detect effects between visit questionnaires; this measure should not be compared with the traditionally reported time in therapeutic INR range, which is a single measure over a patient's entire course of therapy. Fourth, although our study identified the VAS as a promising tool for use in patients taking DOACs, additional research is necessary to ensure that our findings apply in populations taking anticoagulants other than warfarin. Fifth, the study was underpowered to detect clinical events such as thromboembolisms and bleeding; however, anticoagulation control is a well-established predictor of these outcomes.[2,3] Fifth, warfarin metabolism and, subsequently, BVTR are known to be affected by a wide variety of factors besides medication adherence; although we adjusted for many of these factors, there may be unmeasured confounding from other important factors, such as variability in dietary vitamin K. Finally, this cohort only included participants initiating anticoagulation therapy, which may limit generalizability to patients already receiving stable warfarin dosing.

CONCLUSION

Medication nonadherence is an important public health issue, especially for patients taking OACs. Clinicians are currently ill-equipped to address these challenges, with few simple tools to accurately identify patients with poor adherence. The VAS is a promising tool to help clinicians assess patient adherence that is quick, inexpensive, and easily implemented. Future studies are needed to validate our findings and determine whether self-reported medication adherence can predict outcomes for patients taking anticoagulation and improve their safety.

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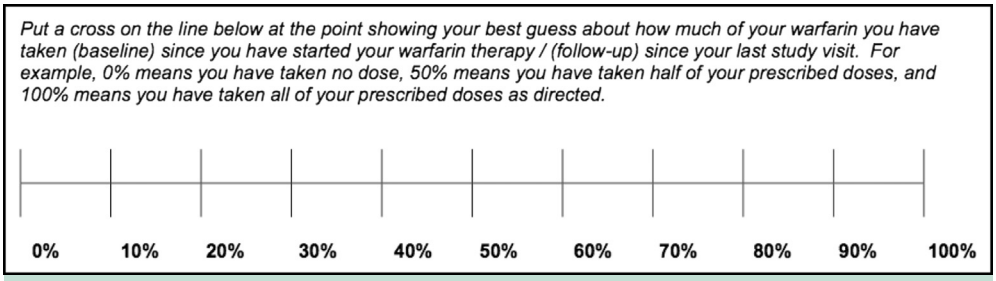
SUPPLEMENTARY DATA

Supplementary figure and table accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.amjmed.2017.03.038.

APPENDIX



Supplementary Figure Visual analogue scale.

Supplementary Table Medication-Taking Practice Questionnaire

Number	Question	Answer
1	Does anyone else lay out your medications for you to take each day or week?	Yes, No
	a If yes, who?	Spouse, Child, Parent, Sibling, Caretaker, Friend, Other
2*	Does anyone else make sure you take medicines as directed?	Yes, No
	a If yes, who?	Spouse, Child, Parent, Sibling, Caretaker, Friend, Other
3*	Do you use a reminder system for taking your pills?	Yes, No
	a If yes, what is it? (check all that apply)	7-day pillbox, Alarm, With a meal, Calendar, Other
4*	Since you started taking warfarin, did you experience difficulty obtaining an appointment with your usual prescriber of warfarin?	Yes, No
5	Since you started taking warfarin, did you experience difficulty in transportation to your usual prescriber of warfarin?	Yes, No
6	Since you started taking warfarin, did you experience difficulty in contacting your usual prescriber of warfarin over the telephone?	Yes, No
7*	Since you started taking warfarin, did you experience your usual prescriber of warfarin asked about medications from other physicians?	Yes, No
8	How do you get your warfarin? (Check all that apply)	Pharmacy, Mail order, Internet, Doctor's office, In-hospital, Other
9	Do you have a written explanation of how to take your warfarin?	Yes, No, Don't know
10	Did your doctor or healthcare provider tell you how often to take your warfarin?	Yes, No, Don't know
11	Did your doctor or healthcare provider tell you what time of day to take your warfarin?	Yes, No, Don't know
12*	Do you take your warfarin the same time every day?	Always, Most of the time (>1/2), Half of the time, Less than half, Never
13*	Over the past 7 days, how often do you cut or split your warfarin?	Always(7 days/week), Often (5-6 days/week), Sometimes(2-4 days/week), Rarely (1 day a week or less), Never
	a Why do you cut or spit your medication?	It makes it last longer, You feel better if you take less, Your healthcare provider told you to, Other reason
	b How do you split or cut your medication?	A special pill cutter, A knife, Scissors, Your teeth, By hand, Other way
14	How many pills did you skip taking in the past 7 days?	# of pills
15	In the past week, on how many days did you take an extra warfarin pill?	# of days
16*	Were you off schedule, that is, late or early by one hour or more in taking your warfarin medication over the past 7 days?	Yes, No, I have no strict schedule, Don't know
	a If yes, the number of times in the past 7 days?	# of days
17*	Did you skip any of your warfarin medication last weekend (last Saturday or Sunday) or on a holiday celebrated during the past 7 days?	Yes, No, Don't know
18*	Do you have any problems such as:	Pharmacy gave you the wrong dose, Pharmacy didn't fill the prescription, Lost medication, Had no money to fill the prescription, Other
19	Do you think you had any side effects of warfarin?	Yes, No, Don't know
	a Have you missed any pills because of it?	Yes, No, Don't know

*Variables associated with BVTR (between-visit percent time in international normalized ratio range) with a univariate P value $<.20$ included in multivariable models.