

# Preventing Medication Errors in Ambulatory Care: The Importance of Establishing Regimen Concordance

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**Objective:** Miscommunications between patients and providers can have serious consequences—especially where medications are concerned. Because oral anticoagulants are associated with preventable adverse events at disproportionately high rates, we used the model of anticoagulant care to examine the extent to which regimen discordance between patient and provider contributes to unsafe medication management. **Methods:** We performed a study among 220 long-term users of warfarin in an anticoagulation clinic to characterize the importance of two medication assessment components. We measured (1) adherence to warfarin by asking patients to report any missed doses during the prior 30 days, and (2) concordance between patients' and providers' reports of prescribed warfarin regimens. We categorized patients as having complete adherence if they missed no doses and regimen concordance if there was patient-provider agreement in the total weekly dosage. We examined the independent relationships between (a) adherence and anticoagulant outcomes, and (b) concordance and anticoagulant outcomes. We characterized anticoagulant outcomes as unsafe if international normalized ratio (INR) values either were  $< 2.0$  (at risk for thrombosis) or  $> 4.0$  (at risk for hemorrhage) over 90 days, using repeated measures analysis. **Results:** One hundred fifty-five patients (70.5 percent) reported no missed warfarin doses during the prior 30 days. In multivariate models, poor adherence was associated with under-anticoagulation (adjusted odds ratio [AOR] = 2.33; 95% confidence interval [CI] = 1.56–3.45;  $P < 0.001$ ), but not with over-anticoagulation (AOR = 1.36; 95% CI = 0.69–2.66;  $P = 0.38$ ). One hundred ten patients (50 percent) reported warfarin regimens that were discordant with respect to the clinicians' report. Among adherent patients, discordance was associated with both under-anticoagulation (AOR = 1.67; 95% CI = 1.00–2.78;  $P = 0.05$ ) and over-anticoagulation (AOR = 3.44; 95% CI = 1.32–9.09;  $P = 0.01$ ). There was no relationship between patients' reports of adherence and concordance (odds ratio [OR] = 1.14 95% CI = 0.64–2.04;  $P = 0.66$ ). **Conclusion:** Discordance between clinicians and patients regarding warfarin regimens is unsettlingly common and places patients at risk for thromboembolic and hemorrhagic events. To promote safe and effective care, clinicians should sequentially determine adherence (missed doses) and regimen concordance during routine medication assessments. Systems need to be developed to ensure patient-provider concordance in medication regimens.

## Report Documentation Page

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## **Introduction**

For patients with atrial fibrillation and other conditions associated with a risk of thromboembolic complications, anticoagulant care is the cornerstone of treatment. While warfarin therapy can markedly reduce the rate of thromboembolic events, not all treated patients receive the full benefits of warfarin therapy. Studies have demonstrated that, among treated patients, nearly one-half have international normalized ratios (INRs) outside the therapeutic range,<sup>1,2</sup> placing them at risk for serious, preventable complications such as stroke (if under-anticoagulated)<sup>3,4</sup> and bleeding (if over-anticoagulated).<sup>5</sup>

Among older patients, oral anticoagulants have been shown to be associated with as many as 10 percent of preventable adverse drug events.<sup>6</sup> Drugs that have a narrow therapeutic window and require long-term management with frequent dose adjustments, such as oral anticoagulants, require intensive communication. Effective communication regarding medications has been shown to promote medication adherence in the treatment of chronic diseases<sup>7</sup> and can help prevent medication-related errors.<sup>8,9</sup>

Numerous studies have documented the prevalence and consequences of patient non-adherence (e.g., pill-taking) in the chronic disease context,<sup>7,10</sup> including anticoagulant care.<sup>11</sup> Much less is known about rates of medication miscommunication, manifested as regimen discordance between patient and provider,<sup>9,12,13</sup> or the contribution of regimen discordance to chronic disease outcomes independent of adherence. While studies have demonstrated tremendous variability in the means used by clinicians to counsel their patients about medications,<sup>14,15</sup> there is little empirical evidence to support one practice over another. We used the model of anticoagulant care to examine the extent to which regimen discordance between patient and provider contributes to unsafe medication management. This research could influence adherence assessment and medication counseling in routine clinical practice,<sup>16,17</sup> and may inform interventions to reduce medication-related errors.<sup>18</sup>

## **Methods**

### **Setting and study participants**

We enrolled patients from a cardiologist-supervised, pharmacist-staffed anticoagulation clinic at San Francisco General Hospital (SFGH), the University of California at San Francisco (UCSF)-affiliated public hospital of the City and County of San Francisco. The clinic serves ethnically diverse patients of low socioeconomic status. For non-English speakers, professional interpreter services generally are available.<sup>19</sup> The majority of decisions pertaining to anticoagulant care are made by anticoagulation clinic pharmacists, using a standard algorithm. Patients do not perform at-home International Normalized Ratio (INR) self-testing. INR tests are done by hospital phlebotomists prior to anticoagulation clinic visits; all values are entered into the hospital's electronic database. After

each visit, and subsequent to any changes made via telephone between visits, clinic pharmacists document the patient's updated regimen and indication for warfarin in the database, which also generates a paper template for the medical record.

Between March 2002 and June 2003, bilingual research assistants attempted to enroll all eligible patients who attended an anticoagulation clinic appointment. Patients were offered \$5.00 for their participation and consent was obtained from all patients prior to their enrollment. Patients were required to be age 18 or older, and fluent in English, Spanish, or Chinese (Cantonese) to be eligible. We initially determined the patients' language and diagnoses by querying the hospital's database. To isolate the impact of regimen concordance on anticoagulant outcomes from factors due to inexperience with warfarin or differences in practice style or setting,<sup>5</sup> we included only those patients who reported taking warfarin while under the care of the SFGH anticoagulation clinic for at least 3 months. We excluded patients with any International Classification of Diseases (ICD)-9 diagnosis of psychotic disorders, dementia, blindness, or aphasia, as well as those who were too ill to participate, or had corrected vision of 20/100 or worse, as these conditions could interfere with concordance measurements. We further excluded patients who were using warfarin preparations not on the SFGH or Medicaid formulary, and patients using medi-sets filled by health professionals. The study protocol was approved by the UCSF Human Subjects Committee and the SFGH Research Committee.

## **Measures**

Trained bilingual research assistants interviewed patients in the anticoagulation clinic prior to their appointment.

## **Predictor variables**

**Adherence:** Research assistants asked subjects to report their warfarin adherence using a well-established instrument similar to that used in other studies.<sup>20, 21</sup> Patients were asked to recall the number of times during the past 30 days when they did not take their medication (warfarin, in this case), based on their understanding of their regimen. We categorized patients as having complete adherence if they reported no missed days of warfarin use during the prior 30 days. For the purposes of this study, we used a 30-day adherence (rather than 3- or 7-day adherence measures), to better reflect the typical interval between anticoagulant appointments.<sup>1</sup>

**Concordance:** Research assistants then asked patients to verbalize their weekly warfarin regimen. Specifically, patients were asked, "Can you tell me exactly how you take your warfarin/Coumadin<sup>®</sup>?" All patients were prompted to indicate on which days of the week they take the medicine; the number of pills they take on these days; and the exact number of milligrams per pill on each day. To ensure that our assessment reflected the patient's report as accurately as possible, each of the 7-day reports was reviewed with the patient for his/her final agreement<sup>22</sup> and the total weekly dosage, in milligrams, was calculated. We

obtained the clinicians' regimen reports by recording the warfarin regimen from the most recent clinical interaction documented in the anticoagulation clinic database.

Patients were categorized as having *regimen concordance* if there was no patient-clinician discrepancy in the total weekly dosage of warfarin when the patient verbalized the regimen. Our method of collecting medication regimen reports and determining concordance is similar to the few published studies of drug regimen knowledge and discrepancy.<sup>12, 23–25</sup>

### **Additional co-variates**

Research assistants obtained the subjects' demographic characteristics, including primary language and English proficiency. Patients who reported speaking English fluently were categorized as English-speakers, regardless of their primary language. We measured health literacy for English and Spanish speakers using the abbreviated version of the Test of Functional Health Literacy in Adults (s-TOFHLA, English and Spanish versions), a reliable and validated measure of health-related literacy.<sup>26–29</sup> Using established convention, we categorized patients as having *inadequate* FHL if the s-TOFHLA score was 0 to 16, *marginal* FHL if the score was 17 to 22, and *adequate* FHL if it was 23 to 36.<sup>30</sup> Because health literacy and patient recall may be influenced by unmeasured or undiagnosed cognitive deficits,<sup>31–33</sup> we measured cognitive ability using the shortened version of the Cognitive Abilities Screening Instrument (s-CASI).<sup>34</sup> The s-CASI has been validated in international dementia studies, does not require literacy,<sup>35</sup> and has been shown to provide an accurate measure of cognition across cultural groups, including those who speak Asian languages.<sup>36</sup> We used an established cutoff of  $\leq 19$  points to categorize patients with cognitive impairment. We obtained patients' indications for chronic anticoagulation from the anticoagulation clinic charts. Because studies have demonstrated that medication adherence and/or knowledge varies with the number of medications in the regimen,<sup>9</sup> and because anticoagulant outcomes may be compromised in patients with 3 or more co-morbidities,<sup>5</sup> we categorized patients as having significant co-morbid conditions and/or at risk for poly-pharmacy if they had 2 or more chronic conditions (e.g., congestive heart failure, diabetes, hypertension, etc.) beyond the indication for warfarin noted in the electronic database. Finally, we classified each regimen as "complex" if the prescribed warfarin regimen deviated beyond the same daily pill dosage.

### **Outcome measures**

We queried the hospital's clinical database to obtain the patients' INR serum results for the three months prior to the interview date. We then categorized the INR results as either unsafe/low (INR < 2.0), unsafe/high (INR > 4), or safe (INR  $\leq 2$  but  $\geq 4$ ), based on cutoff values associated with increased risks of adverse events,<sup>4, 37</sup> such as thrombotic events (under-treatment) or bleeding (over-treatment).

## Statistical analyses

We started by examining the proportion of patients who reported perfect 30-day adherence versus non-adherence, and the proportion of patients who reported warfarin regimen concordance versus discordance. We then examined the relationship between adherence and concordance using the chi-square test.

We then calculated the percentage of INR tests over the prior 90 days that were categorized as unsafe/low, unsafe/high, and safe (in-range). To examine the relationship between adherence and anticoagulant outcomes, we first compared the probability of having an unsafe/low INR value ( $< 2.0$ ) for those who reported perfect 30-day adherence, with those who reported non-adherence. We then compared the probability of having an unsafe/ high INR value ( $> 4.0$ ) for those who reported perfect 30-day adherence, with those who reported non-adherence. We further generated adjusted odds ratios (AORs) using logistic regression, adjusting for patient age (less than or equal to the median age vs. greater than median age), race/ethnicity, gender, language, health literacy level, cognitive score ( $s\text{-CASI} \leq 19$ ), co-morbidity (3 or more co-existing co-morbid conditions), and complexity of the warfarin regimen (complex vs. straightforward).

Because we were interested in isolating the effects of concordance on INR from the effects of poor self-reported adherence on INR, we performed subsequent analyses with only those patients who reported complete 30-day adherence. To examine the relationship between concordance and anticoagulant outcomes, we first compared the probability of having a low INR value ( $< 2.0$ ) for those who reported a regimen *lower* in strength than what the clinician reported, with those whose regimen reports were concordant with the clinician. We then compared the probability of having a high INR value ( $> 4$ ) for those who reported a regimen *greater* in strength than what the clinician reported, with those whose regimen reports were concordant with the clinician. We also generated adjusted odds ratios using logistic regression, as described above.

Because all patients had more than one prior INR value in the prior 3 months, we used repeated measures analyses. Specifically, standard errors for all model coefficients were adjusted for the clustering of INR tests within patient, using Generalized Estimating Equations.<sup>38</sup>

We predicted a 10 percent difference in anticoagulant outcomes between those patients who reported regimens that were concordant with their clinician, and those patients who reported regimen discordance. Using this assumption, we calculated that a sample of 194 patients would have 80 percent power to detect this difference at  $P < 0.05$ .

## Results

We approached 299 consecutive patients identified by the electronic database as meeting the eligibility criteria. Of these, 30 were excluded because they reported being on non-formulary warfarin ( $n = 3$ ), having their medications filled

by a medi-set service or other health professional ( $n = 10$ ), had visual acuity worse than 20/50 ( $n=5$ ), or being too ill to participate in the study ( $n = 12$ ). Twenty-six patients declined to participate in the study and 23 patients consented but did not complete the interview. The remaining 220 patients comprised our final sample. Patients who declined to participate or did not complete the interview were not statistically different from the study subjects in terms of their age, gender, language, or race/ethnicity.

Fifty-seven percent of the patients spoke English, 24 percent spoke Spanish, and 19 percent spoke Cantonese. Among the English and Spanish-speakers ( $n = 178$ ), 86 (48 percent) were found to have inadequate health literacy, while 23 (13 percent) had marginal health literacy, and 69 (39 percent) had adequate health literacy. Most patients were taking warfarin for atrial fibrillation (62 percent) and/or valvular heart disease (26 percent) (Table 1).

One hundred fifty-five patients (70.5 percent) reported perfect 30-day adherence to their warfarin regimen. One hundred ten patients (50 percent) reported warfarin regimens that were discordant with that of the clinicians (Figure 1). Patients who reported discordance were as likely to report perfect adherence as patients who were concordant (51 percent versus 49 percent, OR = 1.14; 95% CI = 0.64–2.04;  $P = 0.66$ ).

Among the 856 INR values obtained during the 90 days prior to the patients' enrollment date, 375 (43.8 percent) were unsafe, including 321 (37.5 percent) INR values  $< 2.0$  (under-anticoagulation) and 54 (6.3 percent) INR values  $> 4.0$  (over-anticoagulation). Self-reported non-adherence in the past 30 days among all patients ( $n = 220$ ) was associated with a greater risk of under-anticoagulation, when compared with complete adherence (OR = 2.38; 95% CI = 1.61–3.45;  $P < 0.001$ ; AOR = 2.33; 95% CI = 1.56–3.45;  $P < 0.001$ ). Self-reported non-adherence in the past 30 days was not associated with a greater risk of over-anticoagulation when compared with complete adherence (OR = 1.17; 95% CI = 0.65–2.12;  $P = 0.60$ ; AOR = 1.36; 95% CI = 0.69–2.66;  $P = 38$ ).

Among those patients who reported perfect 30-day adherence, a comparison of patients who reported a regimen *lower* in strength than that reported by the clinician ( $n = 58$ ) to those whose regimen reports were concordant with the clinician ( $n = 76$ ) revealed that discordance associated with under-anticoagulation (OR = 1.75; 95% CI = 1.12–2.70;  $P = 0.01$ ; AOR = 1.67; 95% CI = 1.00–2.78;  $P = 0.05$ ), but not over-anticoagulation (OR = 0.83; 95% CI = 0.41–1.67;  $P = 0.60$ ; AOR = 0.99; 95% CI = 0.43–2.33;  $P = 0.98$ ). Comparing patients who reported a regimen *greater* in strength than that reported by the clinician ( $n = 21$ ) to those whose regimen reports were concordant with the clinician ( $n = 76$ ) revealed a discordance associated with over-anticoagulation (OR = 2.32; 95% CI = 0.94–5.89;  $P = 0.07$ ; AOR = 3.44; 95% CI = 1.32–9.09;  $P = 0.01$ ), but not under-anticoagulation (OR = 0.68; 95% CI = 0.37–1.25;  $P = 0.22$ ; AOR = 0.76; 95% CI = 0.41–1.41;  $P = 0.39$ ).

**Table 1. Characteristics of patients**

		(n=220)
		No. (%)
Age (median=59)		
	≤59	113 (51)
	≥60	107 (49)
Sex		
	Female	110 (50)
	Male	110 (50)
Language		
	English	126 (57)
	Cantonese	42 (19)
	Spanish	52 (24)
Race/Ethnicity		
	Asian	87 (39)
	Black	31 (14)
	Latino	61 (28)
	White	41 (19)
Health Literacy* (n=178)		
	Inadequate	86 (39)
	Marginal	23 (11)
	Adequate	69 (31)
Complex Regimen		
	Yes	84 (38)
	No	136 (62)
Cognitive Score		
	>19	168 (76)
	≤19	52 (24)
Indication for Warfarin**		
	Atrial Fibrillation	137 (62)
	Prosthetic Valve	57 (26)
	Prior Stroke/Transient Ischemic Attack	31 (14)
	Deep-Vein Thrombosis/Pulmonary Embolism	29 (13)
	Other	10 (5)
Additional Comorbidities		
	2 or more	143 (65)
	less than 2	77 (35)

\*Sample is limited as health literacy cannot currently be measured among Cantonese-speaking individuals

\*\*Totals sum to >100% as patients may have more than one indication

**Figure 1. Adherence and concordance status of patients (n = 220)**

	Concordant	Discordant	Total:
Adherent	<b>A</b>  76 Patients	<b>B</b>  79 Patients	155
Non-Adherent	<b>C</b>  34 Patients	<b>D</b>  31 Patients	65
Total:	110	110	220

**Box A** = Numbers of patients who reported perfect 30 day adherence (based on their perceived regimen) and reported warfarin regimens concordant with their clinician's report.

**Box B** = Numbers of patients who reported perfect 30 day adherence (based on their perceived regimen) but reported warfarin regimens discordant with their clinician's report.

**Box C** = Numbers of patients who reported 30 day non-adherence (based on their perceived regimen) but reported warfarin regimens concordant with their clinician's report.

**Box D** = Numbers of patients who reported 30 day non-adherence (based on their perceived regimen) and reported warfarin regimens discordant with their clinician's report.

## Discussion

While studies have identified medication non-adherence and medication-related discordance as quantifiable problems,<sup>9, 10, 12, 23, 25, 39</sup> we attempted to disentangle the constructs of adherence (patient reports of following regimen) and concordance (clinician-patient agreement regarding regimen), to better inform efforts aimed at promoting safe medication management in ambulatory care settings. Specifically, we assessed rates of adherence and regimen concordance among a sample of long-term warfarin users and explored separately the associations between poor adherence, discordance, and anticoagulant outcomes. We demonstrated that while nearly one-third of the patients reported missing at least one day of warfarin during the previous 30 days, one half of all patients reported a warfarin regimen that deviated from that recommended by the clinician. While poor adherence was predictably associated with under-anticoagulation, the fact that patients who were discordant with their clinician were as likely as patients who were concordant to report perfect 30-day adherence suggests that the additional step of assessing regimen concordance can uncover

important errors in communication. Among patients who reported perfect adherence, regimen discordance was independently associated with under- and over-anticoagulation, each of which has been shown to be related to adverse outcomes such as stroke and bleeding, respectively.<sup>3-5</sup>

Our study has implications for reducing medication-related errors.<sup>40</sup> In the chronic disease context, effective medication-related communication requires, at a minimum, an accurate assessment of what the patient is taking as well as an explanation to the patient regarding modifications in the regimen. In anticoagulant care, the components most critical to decision-making are (1) results of patients' blood tests and (2) the assessment of the medications the patient has been taking. Clinicians frequently make management decisions by first assessing adherence with the prescribed warfarin regimen through patients' verbal reports. Inaccuracy in patients' reports—or failure on the part of the clinician to verify these reports—could place patients at risk for poor outcomes. Our findings, like previous reports, highlights patient difficulties with instructions printed on medication bottles<sup>17</sup> and/or the processing of technical information, such as verbally conveyed medication instructions.<sup>22, 41</sup>

Since medication-related adverse events are common<sup>18</sup> and warfarin is involved in preventable adverse drug events at rates disproportionate to its use,<sup>6</sup> routinely identifying discordance and developing interventions to reduce it may reduce medication-related errors in anticoagulant care and other settings.<sup>42</sup> While all instances of discordance are the exclusive result of poor clinician-patient communication; previous studies suggest that clinicians, while consistently inquiring about patients' adherence (e.g., pill-taking), are largely inconsistent and/or ineffective in their assessments of prescribed regimen concordance.<sup>14, 15, 22</sup> As such, our findings have implications for medication adherence assessment in the clinical and research contexts. While there is no gold standard for measuring adherence,<sup>16, 43</sup> most experts agree that self-reporting is the most efficient means for collecting adherence data, in routine clinical work<sup>43</sup> and in research.<sup>15, 23, 44</sup> Our work suggests that the accuracy of patients' reporting of adherence may be compromised by unrecognized discordance, inasmuch as patients may report perfect adherence to an erroneous medication regimen. This provides empirical support to a view among some researchers that adherence assessment requires measures of medication-taking behavior,<sup>16, 23, 25</sup> as well as regimen concordance (i.e., regimen knowledge).

Reducing medication-related communication errors will likely involve rigorous reviews of medication regimens during the assessment phase of a patient visit. The use of a visual aid may improve the accuracy of patient reports<sup>41</sup> and, with time, could lead to greater regimen concordance between the clinician and the patient. Results of studies in other contexts<sup>45-48</sup> suggest that visual aids can be used to augment verbal communication, particularly for those patients with communication barriers. Our work in the anticoagulation setting suggests that visual aids reduce discordance rates<sup>41</sup> and may ameliorate the negative consequences of regimen discordance on anticoagulant outcomes.<sup>49</sup>

Our study has a number of limitations. Subjects were recruited from one anticoagulation clinic in a public hospital, which limits generalizability. The selection of one clinic that uses standard algorithms for medication management, with the sole purpose of managing one medication, permitted us to eliminate much of the influence that system- and provider-related factors may have had on variations in regimen concordance and anticoagulant outcomes. The clinic serves a diverse, low-income population; however, its performance with regard to anticoagulant outcomes is similar to that of other anticoagulation clinics described in the literature,<sup>1, 50</sup> and the self-reported medication adherence rates are similar to those in other chronic disease studies.<sup>7, 42, 44</sup> Moreover, the concordance rates for the clinic are similar to those reported in the few studies of regimen discordance that create a composite knowledge score.<sup>12, 23, 24</sup> Prior studies have demonstrated that clinicians in specialty settings are more likely to perform intensive medication assessment and counseling with regard to disease-specific medications,<sup>20</sup> so our results may underestimate the prevalence and effects of discordance in primary care settings.

Second, our method of determining regimen concordance, while similar to those in the few published studies,<sup>12, 23-25</sup> does not allow us to determine (a) whether discordance occurred because of miscommunication, poor recall, undocumented changes in regimen, or because the clinician was misinformed as to what the actual prescribed regimen should be, or (b) what the patient was actually taking at home. The inability to include pharmacy dispense data is unlikely to have a significant effect on our results, as combining such data sources does not appear to alter the results of models predicting appropriate medication use.<sup>51</sup>

Third, the fact that bilingual research assistants obtained patients' reports raises the possibility that we overestimated concordance rates for patients with limited English proficiency, insofar as providers' limited language proficiency may lead to lower "real-life" concordance. As such, we may have underestimated the relationship between discordance and poor anticoagulant outcomes. Further, because the study was observational, we cannot rule out the possibility that our findings were a consequence of unmeasured confounding. While we attempted to include relevant co-variates in models, some of our measures were indirect and, therefore, imprecise (e.g. co-morbidities as a proxy for poly-pharmacy). It is also possible that the observed relationship between discordance and poor anticoagulant outcomes is a result of reverse causation; that is, patients with out-of-range INR results are more likely to be confused about any resultant changes in medication. We recently demonstrated in a smaller prospective study, however, that regimen discordance is associated with poor anticoagulant outcomes,<sup>49</sup> and a prospective study in HIV disease had similar findings.<sup>24</sup>

Given the prevalence of chronic diseases,<sup>52</sup> the challenge of managing multiple medications, and the incidence of adverse drug events (particularly among the elderly),<sup>6</sup> there is a need for providers to communicate with patients about medications more safely and effectively. We found that in a sample of diverse, older patients undergoing chronic anticoagulation, clinician-patient

discordance in warfarin regimen was common and unrelated to patients reports of adherence. To promote safe and effective care, clinicians should sequentially determine adherence (missed doses) and regimen concordance during routine medication assessment.

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