Pillbox Use and INR Stability in a Prospective Cohort of New Warfarin Users

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ABSTRACT

BACKGROUND: Warfarin, a frequently prescribed oral anticoagulant, is well known for its narrow therapeutic index. Adherence to warfarin may help to achieve a stable international normalized ratio (INR), but little data are available regarding the impact of using a pillbox as a potential adherence aid device.

OBJECTIVE: To evaluate the association between pillbox use and time in therapeutic range (TTR) <60% and INR instability pattern.

METHODS: This study was based on a prospective cohort of 1,069 new warfarin users who initiated warfarin between May 2010 and July 2013 within 17 hospitals in Quebec, Canada. Demographic, lifestyle, and clinical data were collected for 3 months to a year after warfarin initiation, and genetic factors were assessed. Patients using self-prepared and pharmacist-prepared pillboxes were compared with nonusers for the 3- to 12-month follow-up period. The primary outcome was a TTR <60%, which represents a low percentage of time in the INR therapeutic range or an unstable patient. The secondary outcome was the INR instability pattern (unstable below range; unstable over range; unstable with erratic pattern; and stable) to better describe patient INR profiles. A multivariate generalized linear mixed model was used for the primary outcome, along with a multivariate multinomial linear mixed model for the secondary outcome.

RESULTS: The cohort included patients with a mean age of 70.4 ± 11.7 years; 61.8% of patients were men; 76.3% had atrial fibrillation as warfarin's primary indication; and 35.6% had a previous history of myocardial infarction or angina. Self-prepared and pharmacist-prepared pillbox use was not associated with TTR <60% or a specific INR instability pattern. A sensitivity analysis showed that self-prepared pillbox users had a higher TTR than nonusers ($3.55\% \pm 1.69\%$; $P=0.036$). This effect was greater among patients aged <70 years ($5.48\% \pm 2.50\%$; $P=0.029$) than among older patients ($1.92\% \pm 2.31\%$; $P=0.406$).

CONCLUSIONS: Pillbox use was not associated with TTR <60% or a specific INR instability pattern. The impact of self-prepared pillbox use was greater among younger patients, but results were not clinically significant. Future studies adjusting for concomitant drug use are needed to clarify these results.

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What is already known about this subject

- Adherence to warfarin is a key factor involved in the achievement of a therapeutic and stable international normalized ratio (INR), but little is known about the potential benefits of pillbox use.
- Pillbox use has been proven to help patients achieve a higher level of adherence in other therapeutic areas.

What this study adds

- This study reported that pillbox use in a real clinical setting was not associated with INR stability.
- Patients aged <70 years who used a self-prepared pillbox achieved a greater INR stability than older users, but this finding was not clinically significant.

Despite the addition of new oral anticoagulants on the market, warfarin remains a frequently prescribed drug to prevent thromboembolic events.¹ However, warfarin's narrow therapeutic index is still an ongoing challenge for clinicians and patients. Multiple blood tests and dosage adjustments are required for patients to achieve an international normalized ratio (INR) within the targeted therapeutic range, defined according to a patient's indication. A subtle change in a patient's clinical profile and behaviors, such as adherence, can have a large impact on warfarin's effectiveness and safety.

As reported in the literature, patients who are taking warfarin and whose INR target range is between 2 and 3 have an increased risk of bleeding, if they are above the targeted range instead of within or below (odds ratio [OR] = 3.2; 95% confidence interval [CI] = 1.2-8.3). Inversely, patients with an INR below the targeted therapeutic range have an increased risk of having a thromboembolic event (OR = 5.1; 95% CI = 2.9-8.8).² In order to assess the quality of warfarin anticoagulation control, a linearly interpolated time in therapeutic range (TTR) is commonly used.³ A low TTR (<60%) is associated with higher rates of major bleeding and thromboembolic events, which indicates the importance of good INR monitoring strategies.^{4,5} Multiple INR monitoring programs do exist, as well as specialized anticoagulation clinics, but patients attending such clinics only have had a mean TTR of 65.4%.⁶

Multiple studies have shown that adherence to warfarin is a key factor in the achievement of a therapeutic and stable INR.⁷⁻¹² Missing a warfarin dose at least 20% of the time significantly increases the odds of having a subtherapeutic INR of up to

2.8-fold ($P < 0.001$). Inversely, overadherence at least 10% of the time significantly increases the odds of having a supratherapeutic INR of up to 1.7-fold ($P = 0.02$).¹³ Patients can typically be overadherent to warfarin by taking an additional dose 1 day because they forgot that they had already taken their daily dose earlier the same day.

In order to improve adherence, and ultimately clinical outcomes, patients taking warfarin are often encouraged to use a pillbox—a container with compartments that correspond to a day or a period of the day into which the medication can be placed in advance. Pillbox use has already been linked to health improvements among HIV-infected patients taking anti-retroviral therapy and patients with uncontrolled hypertension who are taking at least 3 antihypertensive drugs.^{14,15} Therefore, there is an implicit belief that using a pillbox for warfarin improves adherence and ultimately clinical outcomes, but very limited data with a sufficient sample size are actually available to support this belief.¹⁶ Moreover, studying the link between adherence and pillbox use in a cohort of warfarin users is subject to bias, since pharmacy claims data are unreliable because of the multiple warfarin dose adjustments, and the use of electronic pillboxes (MEMs) would prevent the use of a comparison group. In order to assess the potential benefits from using a pillbox, the purpose of this study is to evaluate the association between pillbox use and 2 clinical outcomes: TTR < 60% and the INR instability pattern.

Methods

Patient Selection

Data were used from the Quebec Warfarin Cohort Study (QWCS), an ongoing prospective and multicentric cohort study that assesses the genetic, clinical, and environmental risk factors associated with the effectiveness and safety of warfarin. The ethics committees of the Montreal Heart Institute (MHI) and the 17 participating hospitals approved the study. All of the participating hospitals had cardiology departments where research nurses could screen patients in order to select potential eligible participants.

Study participants started using warfarin between May 1, 2010, and July 31, 2013. The primary indication for warfarin treatment was atrial fibrillation, mechanical valve replacement, or mitral stenosis. Participants had to be aged at least 18 years in order to participate. Patients excluded from the QWCS were those with a history of clinically important bleedings or a recent gastrointestinal bleeding or hemorrhagic stroke (< 3 months before warfarin initiation) and those with known coagulation factors deficiency, chronic thrombocytopenia, hematologic malignancy, cirrhosis, chronic hepatitis, jaundice, or cognitive impairment (unreliability).

Data Collection and Measurements

Sociodemographic data, comorbidities, previous history of cardiovascular disease, and lifestyle data were collected at baseline by a research nurse approximately 2 weeks after warfarin initiation. Lifestyle data (e.g., alcohol intake, diet, over-the-counter

drug use, and natural products use), with the exception of physical activity and smoking, were updated via 4 follow-up telephone interviews that took place 3, 6, 9, and 12 months after initiation of warfarin by research nurses and trained research assistants. Because of the noninterventional nature of this study, patients were asked whether they used a pillbox for warfarin at each of these interviews. If pillboxes were used, patients were asked to clarify whether the pillboxes were self-prepared or prepared by a pharmacist. Those lifestyle and pillbox use data defined patients' habits for the following 3 months to avoid temporality bias. Patients were asked whether they missed any of their warfarin doses or experienced any known deviations in dosage during the previous 3 months to evaluate self-reported adherence. Before the interview, patient-reported warfarin dose regimen for the last 7 days were collected, along with the prescribed warfarin dose regimen corresponding to this period. There was no significant difference between reported and prescribed warfarin dose (Pearson coefficient = 0.969), as described in a study using data from the same cohort.¹⁷

INRs were obtained from each patient's monitoring site. At the 12-month follow-up, 76.2% of patients were monitored at a hospital-based anticoagulation clinic; 13.9% were monitored by their physicians; 7.2% were monitored by a pharmacist; and 1.9% were monitored with other means, such as self-monitoring.

CYP2C9 and VKORC1 Genotyping

Patients provided a blood sample at the beginning of the follow-up for DNA extraction. Genotyping was performed at the Beaulieu-Saucier Pharmacogenomics Centre of the MHI. The Sequenom iPLEX ADME CYP2C9/VKORC1 Panel v1.0 (Sequenom, San Diego, CA) was used to genotype samples from QWCS patients. The mass array was analyzed using Sequenom MassArray Typer software (version 4.0.25.73). Genotypes were subjected to data quality check procedures that ensured single nucleotide polymorphism (SNP) and sample completion rates of 98% or more, absence of plate bias effects, absence of sample duplicates, and related individuals based on identical by descent estimates and Hardy-Weinberg equilibrium ($P < 0.05$). Two SNPs from the gene CYP2C9 (rs1799853 or CYP2C9*2; rs1057910 or CYP2C9*3) and 1 SNP from the gene VKORC1 (rs9934438) were used in this study.

Outcomes Measures

The TTR was calculated using linear interpolation between available INR measures for each of the follow-up periods (3-6, 6-9, and 9-12 months).¹⁸ Interview dates were used as delimiters between follow-ups to consider the time-dependant nature of pillbox use. The TTR was also calculated for the entire study period (3-12 months). A TTR was not calculated for the first 3 months of warfarin therapy to discriminate the potential impact of a patient's stabilization period and inexperience with warfarin. A TTR was excluded from the analysis for the corresponding follow-up period if (a) there were more than 70 days (10 weeks) between 2 INR measures and (b) if the patient temporarily

FIGURE 1 Periods of Data Collection, Study Design, and Losses to Follow-up and Exclusions from the Analyses for Each Follow-up Period

stopped taking warfarin for more than 7 days. The distribution of the TTR calculated for each segmented follow-up period (3-6, 6-9, and 9-12 months) suggested a lack of normality, which was confirmed by a Shapiro-Wilk (W) test. The TTR calculated for the overall follow-up period (3-12 months) was distributed normally (W=0.96). We opted to categorize TTRs to obtain an indicator for INR instability (TTR<60%), which represents the primary outcome. This indicator was previously associated with a higher rate of thrombosis and bleeding events.^{4,5}

The secondary outcome was the INR instability pattern, which categorizes patients according to the pattern of their out-of-range INRs.¹⁹ Patients with TTR<60% and ≥75% of the out-of-range time below the therapeutic range were categorized as *unstable below range*. Patients with TTR<60% and ≥75% of the out-of-range time above the therapeutic range were categorized as *unstable above range*. Patients were categorized as *unstable with an erratic pattern* when they did not fit the first 2 definitions. Patients with TTR≥60% were the reference group.

Covariates

Covariates included age at initiation of warfarin, sex, level of education, and body mass index. The following lifestyle variables were also considered: alcohol intake, green vegetable intake, smoking status, and level of physical activity. Physical activity was evaluated according to the Stanford Brief Activity Survey, a validated questionnaire for cardiac patients.²⁰ History of hypertension, diabetes, dyslipidemia, myocardial infarction (MI) or angina, and stroke were also covariates, along with the genotype based on the presence of ≥1 SNP on either the CYP2C9 and VKORC1 gene.

Statistical Analysis

Users with self-prepared and pharmacist-prepared pillboxes were compared with nonusers for the primary and secondary outcomes between 3 and 12 months of warfarin therapy. The primary outcome (TTR<60%) was tested with a multivariate generalized linear mixed model. As a sensitivity analysis, this outcome was tested using a different threshold (TTR<45%).²¹

FIGURE 2 Distribution of Each Patient's Percentage of TTR for Each Subgroup of Pillbox Use at Each Follow-up Period and Overall

TTR=time in therapeutic range.

The secondary outcome (INR instability pattern) was tested with a multinomial mixed linear model. Primary and secondary models were implemented with the GLIMMIX procedure in SAS to allow for the time-dependant nature of pillbox use and potential confounders. They could account for up to 3 outcome measures per patient (3-6, 6-9, and 9-12 months of warfarin therapy).

The multivariate models with the lowest Bayesian information criteria were selected.²² The final models were adjusted for age, sex, warfarin's indication, history of hypertension, dyslipidemia, diabetes, MI or angina, stroke, green vegetable intake, and genotype. Statistical analyses were conducted with SAS version 9.3 (SAS Institute, Cary, NC).

Sensitivity Analyses

The overall TTR (3-12 months) was tested as a continuous variable, since it was distributed normally. A multivariate generalized linear regression model was used that was implemented with a GLM procedure in SAS. Since this model cannot account for time-dependent variables, only patients who did not change their habits in terms of pillbox use or nonuse were included (n = 817, 76.4%). Using this model, the potential age-associated differential association between pillbox use and TTR was also explored by stratifying the population based on the cohort mean age at the initiation of warfarin (< 70 years; ≥ 70 years).

Pillbox Use and INR Stability in a Prospective Cohort of New Warfarin Users

TABLE 1 Patient Characteristics by Type of Pillbox Use 3 Months After the Initiation of Warfarin Therapy

Characteristics	Nonusers (N = 519) n (%)	Self-Prepared Pillbox Users (N = 342)		Pharmacist-Prepared Pillbox Users (N = 112)		
		n (%)	P Value ^{a,b}	n (%)	P Value ^{b,c}	
Demographic						
Age, mean (SD)	70.4 (11.5)	68.5 (11.9)	0.022	76.9 (10.9)	<0.001	
Sex (male)	335 (64.6)	208 (60.8)	0.280	54 (48.2)	0.002	
Education						
University or college	188 (36.2)	128 (37.4)	0.116	22 (19.6)	<0.001	
High school	142 (27.4)	111 (32.5)		14 (12.5)		
No degree	189 (36.4)	103 (30.1)		76 (67.9)		
Body mass index ≥ 30	171 (33.0)	119 (34.8)	0.606	39 (34.8)	0.740	
Lifestyle						
Alcohol intake						
Nondrinker	168 (32.4)	111 (32.5)	0.846	55 (49.1)	0.006	
Occasional drinker	175 (33.7)	122 (35.7)		33 (29.5)		
Regular drinker ^d	132 (25.4)	85 (24.9)		18 (16.1)		
Heavy drinker ^e	44 (8.5)	24 (7.0)		6 (5.4)		
Regular intake of green vegetables ^f	221 (42.7)	163 (47.8)	0.142	33 (30.0)	0.014	
Smoking status						
Never smoker	159 (30.6)	119 (34.8)	0.322	36 (32.4)	0.793	
Former smoker > 5 years	252 (48.6)	163 (47.7)		55 (49.6)		
Former smoker ≤ 5 years or current smoker	108 (20.8)	60 (17.5)		20 (18.0)		
Moderate, high, or very high level of physical activity ^g	144 (27.8)	91 (26.6)	0.755	16 (14.3)	0.003	
Indication for warfarin treatment						
Atrial fibrillation	390 (75.1)	246 (71.9)	0.304	89 (76.5)	0.394	
Mechanic valve replacement	80 (15.4)	58 (17.0)	0.570	7 (6.3)	0.010	
Flutter	53 (10.2)	38 (11.1)	0.734	14 (12.5)	0.499	
Stenosis	5 (1.0)	6 (1.8)	0.360	1 (0.9)	1.000	
Other	3 (0.6)	3 (0.9)	0.687	2 (1.8)	0.217	
INR therapeutic range						
2.0-3.0	452 (87.1)	295 (86.3)	0.758	107 (95.5)	0.008	
2.5-3.5	67 (12.9)	47 (13.7)		5 (4.5)		
Clinical comorbidity						
Hypertension	360 (69.9)	220 (64.7)	0.117	86 (76.8)	0.168	
Diabetes	127 (24.5)	92 (27.0)	0.425	47 (42.0)	<0.001	
Dyslipidemia	309 (60.1)	216 (63.7)	0.314	71 (64.6)	0.451	
Prior history of cardiovascular disease						
History of myocardial infraction or angina	176 (34.5)	121 (36.5)	0.606	56 (51.4)	0.002	
History of stroke	39 (7.6)	23 (6.8)	0.688	9 (8.1)	0.845	
Genotype						
No SNP on CYP2C9/No SNP on VKORC1	118 (22.7)	90 (26.3)	0.256	24 (21.4)	0.384	
No SNP on CYP2C9/≥ 1 SNP on VKORC1	212 (40.8)	118 (34.5)		43 (38.4)		
≥ 1 SNP on CYP2C9/No SNP on VKORC1	66 (12.7)	45 (13.2)		21 (18.8)		
≥ 1 SNP on CYP2C9/≥ 1 SNP on VKORC1	118 (22.7)	88 (25.7)		22 (19.6)		

^aSelf-prepared pillbox users compared with nonusers.

^bT test for continuous variables and Fisher's exact test for binary and categorical variables.

^cPharmacist-prepared pillbox users compared with nonusers.

^d<15 drinks per week for men and <8 drinks per week for women.

^e ≥ 15 drinks per week for men and ≥ 8 drinks per week for women.

^f ≥ 4 times per week.

^gSBAS score ≥ 3 .

INR = international normalized ratio; SBAS = Stanford Brief Activity Survey; SD = standard deviation; SNP = single nucleotide polymorphism.

TABLE 2 Multivariate Generalized Linear Mixed Model on Association Between Pillbox Use and TTR <60% Between 3 and 12 Months of Warfarin Therapy (All Patients, N = 1,069)

Independent Variable	3-6 Months		6-9 Months		9-12 Months		Adjusted OR ^a	95% CI	P Value
	n (%)	TTR <60% n (%)	n (%)	TTR <60% n (%)	n (%)	TTR <60% n (%)			
Self-prepared pillbox	342 (32.0)	104 (30.4)	358 (33.5)	92 (25.7)	354 (33.1)	97 (27.4)	0.86	0.70-1.05	0.129
Pharmacist-prepared pillbox	112 (10.5)	41 (36.6)	116 (10.9)	28 (24.1)	111 (10.4)	31 (27.9)	1.15	0.85-1.56	0.357
No pillbox	519 (48.6)	158 (30.4)	431 (40.3)	118 (27.4)	382 (35.7)	109 (28.5)		reference	

^aAdjusted with pillbox use, age, sex, warfarin's indication, hypertension, dyslipidemia, diabetes, myocardial infarction or angina history, stroke history, green vegetable intake, and genotype.

CI = confidence interval; OR = odds ratio; TTR = time in therapeutic range.

Results

Demographic and Clinical Data

As of July 31, 2013, 1,069 participants were enrolled in the QWCS to complete a 1-year follow-up. Of those participants, 836, 771, and 721 were included in the analyses for the follow-up periods at 3-6, 6-9, and 9-12 months, respectively (Figure 1). The major reason for sample size reduction was related to warfarin cessation. At each of the follow-up periods, approximately 43% of patients were using a pillbox that included warfarin, of which about 75% self-prepared their pillboxes. An increase of the mean TTR was observed across the follow-up periods, as well as a high variability among all subgroups of patients (Figure 2).

As shown in Table 1, the demographic and clinical characteristics are quite similar between nonusers and self-prepared pillbox users (except for age). On the other hand, pharmacist-prepared pillbox users were older, disproportionally female, less educated, differed in their alcohol and green vegetable intake, were less active, more diabetic, had a greater history of MI or angina, and were less prone to have a mechanic valve replacement as a main indication for warfarin than nonusers.

Instability Indicator (TTR <60%)

Self-prepared pillbox use showed a nonsignificant trend towards a lower risk of TTR <60% (OR = 0.86; 95% CI = 0.70-1.05; *P* = 0.129). Pharmacist-prepared pillbox use was not associated with a TTR <60% (OR = 1.15; 95% CI = 0.85-1.56; *P* = 0.357; Table 2). Age was protective against TTR <60% (OR = 0.98; 95% CI = 0.97-0.98; *P* = 0.001). History of hypertension (OR = 1.33; 95% CI = 1.07-1.66; *P* = 0.012) and history of MI or angina (OR = 1.24; 95% CI = 1.00-1.53; *P* = 0.047) were risk factors for TTR <60%.

When changing the threshold to define INR instability to TTR <45% and using the same confounders, results were similar. Patient-prepared pillbox users (OR = 0.81; 95% CI = 0.64-1.03; *P* = 0.087) and pharmacist-prepared pillbox users (OR = 1.04; 95% CI = 0.72-1.50; *P* = 0.851) were still comparable with nonusers (data not shown).

INR Instability Patterns

The majority of unstable patients were below range between 3 and 6 months of warfarin therapy, but this proportion decreased until the end of the follow-up period (58.1%-41.0%). On the other hand, there was a growing proportion of patients who were unstable above therapeutic range or with an erratic pattern (24.4%-35.8% and 17.8%-23.2%, respectively).

Self-prepared pillbox users tended to be less at risk of being unstable above range (OR = 0.78; 95% CI = 0.57-1.07; *P* = 0.123) and below range (OR = 0.84; 95% CI = 0.65-1.08; *P* = 0.174) when compared with nonusers, but results were not significant (Table 3).

Sensitivity Analyses

Using the overall TTR as a continuous variable, self-prepared pillbox users had a significantly higher adjusted TTR than nonusers (3.55 ± 1.69 ; *P* = 0.036; Table 4). Using the same model, but subgrouping for age, the impact of self-prepared pillbox use seemed greater among patients aged <70 years (5.48 ± 2.50 ; *P* = 0.029) than older patients (1.92 ± 2.31 ; *P* = 0.406). Finally, women had a significantly lower TTR than men (3.70 ± 1.67 ; *P* = 0.027), and patients with an INR target between 2.5 and 3.5 had a lower TTR than patients with an INR target between 2.0 and 3.0 (-7.35 ± 2.62 ; *P* = 0.005).

Discussion

The impact of pillbox use on INR instability among new users of warfarin was assessed by testing the association of pillbox use with a TTR <60% indicator and the INR instability pattern. Results were not significant with regards to the primary and secondary outcomes. In the sensitivity analysis, patients using a self-prepared pillbox had a significantly, but not clinically, higher TTR than nonusers. Patients aged <70 years seemed to derive more benefit from self-prepared pillbox use than older patients.

According to this study's results, patients aged ≥ 70 years had a more stable INR profile during the follow-up period than younger patients. Previous studies have reported an association between younger age and warfarin nonadherence and INR instability.^{11,23,24} This association could support this

TABLE 3 Multivariate Model of INR Instability Pattern Between 3 and 12 Months of Warfarin Therapy (N=1,069)^a

Independent Variable	INR Instability Pattern	3-6 Months		6-9 Months		9-12 Months		Adjusted OR ^c	95% CI	P Value
		N	n (%)	N	n (%)	N	n (%)			
Self-prepared pillbox	Stable (TTR ≥ 60%)	342	205 (59.9)	358	212 (59.2)	354	203 (57.3)		reference	
	Unstable below range ^b		57 (16.7)		45 (12.6)		36 (10.2)	0.84	0.65-1.08	0.174
	Unstable above range ^c		23 (6.7)		30 (8.4)		36 (10.2)	0.78	0.57-1.07	0.123
	Erratic pattern ^d		14 (4.1)		12 (3.4)		25 (7.1)	0.99	0.66-1.49	0.975
Pharmacist-prepared pillbox	Stable (TTR ≥ 60%)	112	42 (48.2)	116	70 (60.3)	111	63 (56.8)		reference	
	Unstable below range ^b		34 (20.5)		13 (11.2)		13 (11.7)	1.27	0.87-1.86	0.219
	Unstable above range ^c		10 (8.9)		9 (7.8)		10 (9.0)	0.95	0.59-1.53	0.837
	Erratic pattern ^d		7 (6.3)		6 (5.2)		6 (5.4)	1.29	0.72-2.30	0.395
No pillbox	Stable (TTR ≥ 60%)	519	291 (56.1)	431	258 (59.9)	382	222 (58.1)		reference	
	Unstable below range ^b		84 (16.2)		48 (11.1)		47 (12.3)		reference	
	Unstable above range ^c		36 (6.9)		49 (11.4)		50 (13.1)		reference	
	Erratic pattern ^d		32 (6.2)		19 (4.4)		10 (2.6)		reference	

^aMultivariate multinomial generalized linear mixed model.

^bTTR < 60% and ≥ 75% of time out of range below therapeutic range.

^cTTR < 60% and ≥ 75% of time out of range above therapeutic range.

^dTTR < 60% and no specific pattern below or above range.

^eAdjusted with age, hypertension, myocardial infarction or angina history, and genotype.

CI = confidence interval; INR = international normalized ratio; OR = odds ratio; TTR = time in therapeutic range.

study's finding of a greater impact from self-prepared pillbox use among young patients taking warfarin. MI or angina history was associated with an increased INR instability, which could be an indicator of decreased adherence because of its link with depression and anxiety or co-medication use.²⁵⁻²⁷ Previous work conducted with the QWCS found that MI history was associated with a lower concordance between self-reported and prescribed warfarin doses.¹⁷ Hypertension was associated with an increased odds of having TTR < 60% but not with a lower TTR. History of MI or angina and hypertension could be indicators of an increased number of concomitant drugs and thus an increased risk of drug interactions with warfarin. Previous studies reported that various comorbidities were linked to a lower TTR and lower adherence, which reinforced this hypothesis.²⁸⁻³⁰ Finally, female sex and an INR target range of 2.5-3.5 were risk factors for a low TTR, which is concordant with results from previous studies.^{24,29}

This study is the first prospective cohort study that reports the impact of pillbox use on INR instability among warfarin users. It is also the first study to evaluate the impact of self-prepared pillbox use on this outcome in a real clinical setting. Results are generalizable to other populations of new warfarin users who have access to an anticoagulation monitoring program. A previous study did show an improved TTR from the use of clinician-prepared pillboxes, but the sample size was small (n=13). Moreover, the data were compared with pre-enrollment data, which suggests that the results might actually reflect a change in patients' behaviors in this 3-month study (i.e., Hawthorne effect).¹⁴ An observational study, such as the present study, is indeed an adequate study setting for these

research objectives, since a randomized controlled trial may raise ethical concerns. Pillbox use is recommended by guidelines on warfarin management and is already part of the day-to-day life of 53.1% of patients taking warfarin.³¹⁻³³

A particular strength of this study is the ability to discriminate between self-prepared and pharmacist-prepared pillbox users. In addition, the use of an incident-user cohort has allowed consideration of the time-dependent nature of pillbox use and other covariables in a mixed regression model. Also, the use of the INR instability pattern as a secondary outcome allows for greater precision in the evaluation of the impact of interventions among warfarin users.

Limitations

Some of the limitations of this study should be mentioned. In particular, it was not possible to directly measure the impact of pillbox use on adherence. Pharmacy claims data can be unreliable because of the multiple warfarin dose adjustments, and the use of electronic pillboxes (MEMs) would create a bias in this particular study. However, no significant difference was found between reported and prescribed warfarin dose (Pearson coefficient=0.969), suggesting a good compliance from the QWCS participants to prescriber recommendations.¹⁵ Indeed, it was possible to test for self-reported adherence at each interview, with some reservation, since this variable could be biased. When asked, pillbox users tend to recall missed doses better than nonusers, since the latter do not have any visual clue of their omissions and are therefore more quick to perceive themselves as perfectly adherent. This recall bias could result in falsely considering pillbox use as a risk factor for

TABLE 4 Multivariate Generalized Linear Regression Model on Association Between Pillbox Use and TTR Between 3 and 12 Months of Warfarin Therapy (N=817)^a

Independent Variable	Age Subgroup	n	Mean TTR (SD)	Adjusted Coefficient ^b	SE	P Value
Self-prepared pillbox	< 70 years	159	69.3 (31.0)	5.48	2.50	0.029
	≥ 70 years	145	73.4 (27.0)	1.92	2.31	0.406
	All patients	304	71.3 (29.4)	3.55	1.69	0.036
Pharmacist-prepared pillbox	< 70 years	18	62.3 (25.9)	-3.21	5.67	0.572
	≥ 70 years	79	69.4 (28.6)	-1.89	2.93	0.520
	All patients	97	68.0 (28.0)	-2.75	2.57	0.285
No pillbox	< 70 years	161	66.6 (21.8)	reference		
	≥ 70 years	251	71.8 (21.1)	reference		
	All patients	412	69.8 (32.1)	reference		

^aExcluding patients whose pillbox use changed during follow-up (n=817) and excluding time-dependent predictors.

^bAdjusted with pillbox use, sex, INR target range, hypertension, myocardial infarction or angina history, level of education, and genotype.

INR = international normalized ratio; SD = standard deviation; SE = standard error; TTR = time in therapeutic range.

nonadherence. Using an age-adjusted logistic regression, it was demonstrated that there was indeed a tendency to a higher risk of reporting nonadherence among self-prepared pillbox users when compared with nonusers (OR = 1.22; 95% CI = 0.90-1.65). Similar but significant results were also seen among pharmacist-prepared pillbox users (OR = 2.36; 95% CI = 1.55-3.59).

The absence of concomitant drug information could explain the inability to detect an association with primary and secondary outcomes. Pillbox users could use a greater number of medications than nonusers and be more subject to drug interactions and an increase in INR instability. Therefore, it is possible that true association was overestimated in these analyses. In addition, data on pillbox use was only collected every 3 months during the first year of warfarin therapy, so the exact date of any change in pillbox use or nonuse was not captured. To prevent any temporality bias, the pillbox use data reported at the interview before the follow-up period analysed was considered, not the interview following. Moreover, 76.4% of patients did not change their pillbox use habits during the follow-up, which minimized the issue.

Another limitation of this study was the growing number of losses to follow-up and exclusions from analysis by the time of the 12-month follow-up interview. The main cause was the discontinuation or temporary cessation of warfarin, which was an inevitable event in this observational study. Finally, a healthy user bias may have been present in this study. Pillbox users could have had generally healthier behaviors than nonusers.

Conclusions

This study suggests that pillbox use was not associated with TTR <60% or INR instability, but these results may be biased by unmeasured confounders such as concomitant drug use. Self-prepared pillbox users had a slightly higher TTR than nonusers, which was more apparent in younger patients. Although further

research is still needed in this area, the promotion of pillbox use among warfarin users may help achieve therapeutic goals more quickly and safely, which would reduce the need for frequent monitoring visits.

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