RISK FACTORS AFFECT LONG-TERM COMPLIANCE TO COUMADIN TREATMENT (SELF-REPORTING)

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Low compliance to a prescribed Coumadin treatment can result in negative health outcomes. In this study we aimed to evaluate risk factors affecting patient compliance to Coumadin. For this purpose, two study phases were performed: Phase 1: a retrospective eight-year follow-up of databases from health care services; and Phase 2: a cross-sectional study with telephone interviews. A Total Compliance Index was constructed using the number of Coumadin purchases (40%), international standardised ratio (INR) tests (40%), and average INR values (20%). Multiple models for the Total Compliance Index were constructed using socio-demographic, treatment-related, and health care utilisation variables, use of drugs, patient-physician relationships and patient's quality of life. $78.5 \pm 3.4\%$ of patients in the total population were non-compliant in the retrospective phase of the study, and 53.2% in the second, cross-sectional phase. Total Compliance Index was significantly associated with older age, number of doctor visits, and drugs from group C. We suggest that the Total Compliance Index for other drugs can be utilised as well.

Key words: Coumadin, anti-coagulant treatment, international standardised ratio (INR), compliance to treatment, Total Compliance Index.

INTRODUCTION

Coumadin (warfarin) is a vitamin K antagonist, which for many years was the sole oral anti-coagulant treatment. It is well established that Coumadin can aid in preventing primary and secondary venous and arterial thromboembolic events (Kimmel *et al.*, 2007). Effective treatment with Coumadin requires monitoring with repetitive blood tests for prothrombine time and determination of the international standardised ratio (INR). Although Coumadin is an important therapy, it remains a challenging drug since it has a narrow therapeutic range (Hylek and Singer, 1994; Hylek *et*

al., 1996) and requires frequent monitoring, the results of which can be influenced by genetic factors, drugs, food intake, nutritional supplements, and diseases states (Ansell *et al.*, 2008).

Compliance (adherence to treatment) is the extent to which patients take their prescribed medical treatment or the level of patient participation in an agreed-on medication regimen (Osterberg and Blaschke, 2005). Low compliance to a prescribed treatment can result in negative health outcomes. In a meta-analysis of 19 000 patients with acute or chronic diseases it was found that the proportion of patients achieving

a better outcome was 26% higher in adherent versus non-adherent patients (DiMatteo *et al.*, 2002). A meta-analysis that examined the time that patients spent in the therapeutic range of INR due to Coumadin treatment showed that patients from anticoagulant clinics were 66% more compliant to the treatment, while patients treated in usual care were only compliant in 57% of the cases (van Walraven *et al.*, 2006). Kimmel *et al.* (2007) demonstrated that 36% of patients defined as having low compliance to Coumadin were at a higher risk (OR = 2.10 95 %CI 1.48–2.96) to have INR levels below the target range. Low or non-compliance with Coumadin treatment may lead to a 16-fold increase in risk for thrombosis and bleeding (Osterberg and Blaschke, 2005). In another study that included 4188 patients with atrial fibrillation (AF) it was demonstrated that 26.3% of patients who were started on Coumadin treatment discontinued therapy within the first year of treatment (Fang *et al.*, 2010). In a study by Ganz *et al.* (2000) that investigated compliance to Coumadin treatment after vein thromboembolism (VTE) or pulmonary emboli events it was found that 25% of patients used oral anti-coagulation therapy for less than 90 days, the minimal recommended time for therapy (Ganz *et al.*, 2000). Another study that also investigated patients with VTE found that 63% of these patients had stopped Coumadin therapy within a one-year period, and among them 12% had discontinued therapy within three months after treatment initiation (Deitelzweig *et al.*, 2010). Finally, in a study investigating 8040 patients with high risk for recurrent VTE it was observed that 76.9% of them were non-compliant with Coumadin therapy and 51.5% had completely discontinued the therapy (Chen *et al.*, 2013).

Several studies identified risk factors related to low compliance for different drugs. In general, predictors for low compliance to therapy include disease-related factors, such as treatment of chronic disease (Haynes *et al.*, 2002; Jackevicius *et al.*, 2002), treatment of asymptomatic disease (Sewitch *et al.*, 2003), side effects of medication (van Servellen *et al.*, 2002), complexity of treatment (Ammassari *et al.*, 2002); psychological factors (Ammassari *et al.*, 2002; Stille *et al.*, 2004), and cognitive impairment (Okuno *et al.*, 2001; Stille *et al.*, 2004). Another group of factors that can affect drug compliance are related to contact with medical staff, such as poor physician-patient relationship (Urquhart, 2002; van Servellen *et al.*, 2002), inadequate follow-up or discharge planning, and missed appointments (Lacro *et al.*, 2002). Factors that can improve compliance to Coumadin are increased patient education, availability and accessibility of the clinic (Haynes *et al.*, 2002), and improvement of physician-patient communication (Misdrahi *et al.*, 2002).

In this study we aimed to determine risk factors affecting patient compliance to Coumadin in a cohort of patients from the largest health maintenance organisation (HMO) in Israel for eight years of follow-up, and using additional personal interviews. We attempted to build a Total Compliance Index that explains patient behaviour regarding factors that can affect their compliance to Coumadin treatment.

METHODS

Study design and population. The aim of the study was to evaluate a maximum amount of factors that might affect compliance to Coumadin treatment. Partly these factors can be identified using information stored in databases of health services, but others, such as regarding patient-staff relationships, additional drug insurance of patient, or self-estimation of quality of life (QOL) of the patient can be investigated only by personal interviews. For this reason, the proposed study was composed of two phases:

Phase 1: Retrospective phase with follow-up during 1.01.02 till 31.12.09 — analysis of “Clalit” health care service (the largest HMO in Israel) datasets. The “Clalit” database includes 350 000 patients; of them 7109 (SD 1914) patients per year of study met inclusion criteria and were used in the analysis in Phase 1. All patients over 30 years of age receiving Coumadin treatment during the study period through “Clalit” health care services in the southern region of Israel were included in this phase of the study. In order to verify long-term Coumadin use (at least two years), we analysed the data of patients starting from 2002, even though the data was collected from 2000. Patients with malignancies, patients after accidents, and patients who required a short period of Coumadin treatment (less than three months) were excluded from the analysis.

Phase 2: A cross-sectional study during 1.1.09 to 31.12.09, in addition to the analysis of datasets, was conducted using telephone interviews. This phase of the study included participants that received Coumadin treatment for no less than two years before 2009, were over 30 years old, and had provided updated telephone numbers. We excluded patients who did not understand Hebrew, English, Arabic, or Russian languages. The study sample for the Phase 2 (phone interview) was 689 patients.

Ethical approval. The study was approved in 2002 by the Helsinki committee of Soroka University Medical Centre in Be'er-Sheva, Israel. For security reasons identification data for patients were recoded into a study identification number according to the Helsinki committee guidelines. For Phase 2 of the study, additionally verbal consent of the patient was received at the beginning of the conversation.

Data assessment. Data regarding patients characteristics (date of birth/death, gender, place of residence), purchasing Coumadin and different groups of drugs (type and dates), performing INR tests (dates, number of tests and results), and health care utilisation (number of doctor visits, hospitalisation days) was obtained from “Clalit” computerised database.

Data regarding socio-economic status according to residence of living was obtained from the central bureau of statistics. Missing data for socio-economic status was obtained via telephone interviews.

Phone interviews were conducted by interviewers (10 persons) who were medical students, trained by the research

coordinator after signing a confidentiality agreement. Interviewers received instruction about the questionnaires and study aims. The first five calls were made under supervision of the coordinator, which included checking the forms and listening to randomly selected tapes of interviews. If the patient was unreachable, one more attempt was made.

The questionnaire for the telephone interview included socio-demographic details, such as the level of education (elementary school — up to 8 years, high school — 12 years, and academic or professional education — more than 12 years), income, place of birth; questions regarding QOL SF12 (Anonymous, 1994) and the depression, anxiety, stress scale (DASS) adapted for the effect of anticoagulation treatment for Coumadin patients (Samsa *et al.*, 2004). Additional questions were added by the research team: ways of receiving INR results, reasons for not purchasing the drug, time of taking the drug, the extent of satisfaction from patient-physician and patient-staff relationships, and having additional health insurance. Before the pilot study, the developed questionnaire containing 50 questions in Hebrew was translated to Russian, English, and Arabic by two independent translators. This was adapted to 40 questions based on interviewer notes. Questions on SF-12 related to QOL were divided into physical and mental scores. The data was entered into an electronic database. Quality control was achieved by constant typing, reviewing a sample of cases and rechecking 5% of the patients by performing a second interview after obtaining consent.

Study variables

The following independent variables were used:

1. Socio-demographic variables: age, gender, socio-economic status, income, nationality, place of birth, language, immigration year, education, additional health insurance.
2. Coumadin treatment: duration of Coumadin treatment (in years), way of receiving INR results, INR results.
3. Health care utilisation: number of doctor visits during the study period, hospitalisation days.
4. Use of drugs: 22 groups of drugs (According to World Health Organization (WHO) classification). Of them: Group C (Cardiovascular System drugs category), Group O (no defined drugs), Group A (Alimentary Tract & Metabolism drugs), group B (Blood and Blood Forming Organs drugs), group D (Dermatological drugs), group G (Genitourinary System & Sex Hormones) and group H (Systemic Hormonal Preparations, Excluding Sex Hormones).
5. Patient-physician relationships: satisfaction from patient-physician relationship, satisfaction from patient-staff relationship.
6. Quality of Life: Mental and Physical QOL Scores according to the SF-12 questionnaire.

The following dependent variables were used:

The Total Compliance Index was defined using three variables (by a board-certified haematologist): number of Coumadin purchases (40%), compliance to perform INR tests (40%), and average INR value (20%).

The number of Coumadin purchases was calculated per month. Performing one or more purchases during one month was given a score of one, while non-purchasing — zero. The total number of purchases per year was divided by 12 to calculate the mean number of purchases per month. It should be noted that in Israel, Coumadin can be prescribed for a three-month period. Therefore, the minimum number of purchases made per year is 4 (received a value of one).

Compliance to perform an INR test was calculated as the number of tests performed during one month; performing at least one test a month received a value of one, and less — zero value. The total number of tests during a year was calculated, and then divided by 12 to estimate mean number of tests per month.

Average INR value. The targeted value of INR is 2 to 3 (Ansell *et al.*, 2008). The INR test result for the Compliance Index was calculated as dichotomous variable. If the mean INR of a patient was between 2 to 3, the patient received 1 point, if not — 0 points. The test result index was calculated for each patient by dividing the total number of points during one year, by the number of tests performed during the same year. Since the recommended INR testing period is four weeks after achieving a stable dose, the minimum number of INR tests performed during a year was eight (received a value of one).

For the purpose of this study we defined a “compliant patient” as scoring 73% or more on the Total Compliance Index scale (the 20th percentile of the calculated Total Compliance Index), and with less than 73% on the scale as non-compliant. The proportions of compliant and non-compliant patients did not change when this threshold was lowered or raised by 10% on the scale.

Statistical analysis. Descriptive statistics of study variables included means and standard deviations for normally distributed quantitative variables; for quantitative variables with non-normal distribution the median and range were presented. For qualitative variables the distribution (N, %) were presented. The univariate analysis of possible relations between dependent variables and each of the independent variables was performed using the Mann-Whitney test, or Chi-square (Exact Fisher test) for qualitative variables. Pearson correlation coefficients between Physical and Mental factors of the SF-12 questionnaire were determined. Variables that were significantly associated in the univariate analysis with the Total Compliance Index were included in multiple logistic regression, and *p* values of ≤ 0.05 were considered to be statistically significant. Statistical analysis was performed using the SPSS 18th version.

RESULTS

Phase 1. The mean total population size included in the analysis was 7109 (SD 1914) patients per year (range from 4311 in 2002 to 9745 in 2009). The mean proportion of males in the population was 46.8 (SD 0.4), and this proportion remained stable during all years of the study (range 46.3 to 47.3%). The median age of the study population was 70.3. The distributions of variables related to Coumadin treatment for Phase 1 are shown in Table 1. We observed a similar proportion of non-compliant patients for each Total Compliance Index-related variables during the study period. Division of the Total Compliance Index into dichotomous variables gave a mean proportion of $78.5 \pm \text{SD } 3.4\%$ non-compliant patients in the total population during the study period. The mean duration of Coumadin treatment was $4.49 \pm \text{SD } 1.36$ years (median 5, range 0–10). The median number of Coumadin purchase was 0.28 (range 0–1). Dur-

ing the study period, the number of doctor visits ranged 0 to 19, with the mean of $2.30 \pm \text{SD } 0.18$ for the total population (median 2.32). The mean days of hospitalisation among the total population was $5.09 \pm \text{SD } 0.75$.

The univariate analysis between Total Compliance Index (dichotomised) and patient characteristics for Phase 1 is presented in Table 2. There was a significant association between the Total Compliance Index and the variables age, number of doctor visits, days of hospitalisation, and amount of health service usage during all years of the study. The variable “duration of Coumadin treatment” was significantly associated with the Total Compliance Index in years 2003, 2004, 2005, 2008, and 2009.

The results of logistic regression are presented in Table 3. For all years of study, the Total Compliance Index for Coumadin patients was associated with age, number of doctor visits, and usage of drugs from C group.

Table 1

DISTRIBUTION OF VARIABLES RELATED TO TOTAL COMPLIANCE INDEX (PHASE 1)

Year	Average INR level (range 0;1)		Amount of INR tests (range 0;1)		Number of Coumadin purchase (range 0;1)	
	Total number of participants and % of non-compliant	Mean (SD), median	Total number of participants and % of non-compliant	Mean (SD), median	Total number of participants and % of non-compliant	Mean (SD), median
2002	3317 (53.9)	2.15 (0.63) 2.17	3853 (58.0)	0.49 (0.37) 0.50	4311 (41.5)	0.36 (0.32); 0.33
2003	3627 (56.5)	2.16 (0.66) 2.20	4398 (61.0)	0.46 (0.37) 0.42	5145 (46.8)	0.33 (0.33); 0.25
2004	3979 (55.1)	2.12 (0.65) 2.19	4858 (61.6)	0.44 (0.38) 0.42	5961 (57.7)	0.31 (0.33); 0.17
2005	4187 (57.0)	2.16 (0.67) 2.22	5262 (62.1)	0.44 (0.38) 0.42	6751 (54.3)	0.29 (0.33); 0.08
2006	4517 (56.4)	2.11 (0.64) 2.18	5673 (61.7)	0.44 (0.39) 0.42	7759 (56.8)	0.28 (0.34) 0.08
2007	4583 (55.4)	2.10 (0.67) 2.18	5959 (64.1)	0.41 (0.38) 0.33	8310 (59.6)	0.26 (0.33) 0
2008	4849 (56.2)	2.06 (0.67) 2.16	6242 (64.9)	0.42 (0.39) 0.33	9031 (62.5)	0.25 (0.34) 0
2009	4954 (59.6)	2.06 (0.66) 2.11	6533 (65.5)	0.41 (0.38) 0.33	9745 (64.4)	0.24 (0.33) 0

Table 2

SIGNIFICANCE OF UNIVARIATE ASSOCIATIONS BETWEEN THE TOTAL COMPLIANCE INDEX AND SOCIO-DEMOGRAPHIC AND HEALTH CARE UTILISATION, BY YEARS (PHASE 1)

Year	Gender* χ^2 (p)	Age Z (p)	Duration of Coumadin treatment Z (p)	Number of doctor visits Z (p)	Amount of hospitalisation days Z (p)	Amount of health service usage Z (p)
2002	0.36 (0.57)	-5.26 (< 0.001)	0.01 (0.99)	-9.43 (< 0.001)	-1.72 (0.08)	-1.25 (0.21)
2003	3.59 (0.06)	-4.79 (< 0.001)	-5.15 (< 0.001)	-14.2 (< 0.001)	-2.7 (0.01)	-3.06 (0.01)
2004	4.13 (0.04)	-6.11 (< 0.001)	-4.09 (< 0.001)	-16.5 (< 0.001)	-3.11 (0.01)	-3.11 (0.01)
2005	2.07 (0.16)	-7.19 (< 0.001)	-2.52 (0.01)	-21.8 (< 0.001)	-5.88 (< 0.001)	-5.96 (< 0.001)
2006	6.62 (0.01)	-7.20 (< 0.001)	-0.09 (0.92)	-23.8 (< 0.001)	-6.74 (< 0.001)	-7.06 (< 0.001)
2007	1.87 (0.17)	-8.45 (< 0.001)	-1.59 (0.11)	-27.0 (< 0.001)	-7.55 (< 0.001)	-8.03 (< 0.001)
2008	1.13 (0.29)	-8.84 (< 0.001)	-3.22 (0.01)	-28.5 (< 0.001)	-8.59 (< 0.001)	-8.92 (< 0.001)
2009	3.15 (0.08)	-8.73 (< 0.001)	-4.68 (< 0.001)	-32.1 (< 0.001)	-10.0 (< 0.001)	-10.3 (< 0.001)

* Analysis performed using χ^2 test

All other analyses are performed using Mann-Whitney test

Table 3

MULTIVARIATE ANALYSIS OF FACTORS AFFECTING COMPLIANCE PATIENTS (PHASE 1)

Variable*	OR								Study sample
	2002	2003	2004	2005	2006	2007	2008	2009	
Age	1.015	1.01	1.01	1.01	1.01	1.01	1.01	1.01	1.32
Number of doctor visits	1.07	1.10	1.10	1.13	1.10	1.12	1.08	1.09	1.13
Group C drugs	1.44	1.05	1.06	1.05	1.06	1.06	1.05	1.06	1.04

*Only variables significant at 0.05 level are presented

Phase 2. Socio-demographic data of the studied sample is presented in Table 4. Most participants were non Bedouin (90.7%), females (55.3%), with medium socio-economic status (79.0%), income below average (41.3%), Hebrew speakers (70%), with academic education (36.4%) and with additional health insurance (69.4%). No significant differences at 0.05 significance level were found between the studied sample and total population for the following variables: age, gender, socio-economic status, and the duration of Coumadin treatment (in years) (Table 4). Among 689 patients, 219 had missing data for one or two of the three components of the Total Compliance Index. The Total Compliance Index was calculated for 470 patients (68.2%); 53.2% ($n = 250$) of them were non-complaint. The mean duration of Coumadin treatment was 5.54 (SD 3.42) years. The median of number of Coumadin purchases was 0.5 (range 0–1). During the study period, the number of doctor visits ranged 0 to 19, with mean 3.52 (SD 2.71). From patients with Phase 2 data, 146 were hospitalised during the year. Of those, 69 were compliant, total hospitalisation days was 557 days with mean 8.07 hospitalisation days of per admission. Among the non-compliant group ($n = 77$), the total hospitalisation days of the group was 1035 days with mean 13.4 days per admission ($p = 0.086$). INR results were received directly from the primary care physician (161 persons, 23.5%); by telephone (403 persons; 59.8%), checking the results on the Internet (44 persons; 6.4%), and all above ways (65 persons; 9.8%). Four patients (0.6%) had equipment for INR tests at home, and five patients (0.7%) did not inquire about the results of their tests. High, moderate, and low levels of satisfaction from patient-physician relationships were found in 85.8% ($n = 599$), 12.9% ($n = 90$), and 1.3 % ($n = 9$) patients, respectively. The satisfaction of patient-staff relationship was high for 605 (86.7%), medium for 85 (12.1%), and low for 8 (1.1%) of respondents. The mean values for the Physical score of SF12 questionnaire were $37.2 \pm \text{SD } 11.24$ with range 13.2 to 58.5. For the Mental score of the SF12 questionnaire, the mean value was 46.6 (SD 11.2) with range 13.4 to 67.3. Weak correlation between Physical and Mental scores was found ($r_{\text{Pearson}} = 0.380$, $p < 0.001$). No significant differences were found between compliant and non-compliant patients regarding the following variables: socio-economic status, additional health insurance, days of hospitalisation, patient-staff satisfaction, and QOL. The results of univariate analysis of variables related to Total Compliance Index of Phase 2 are presented in Table 5. Univariate analysis showed similar Mental and Physical SF12 scores ($p = 0.63$ and $p = 0.87$, re-

Table 4

SOCIO-DEMOGRAPHIC AND TREATMENT-RELATED DATA OF THE STUDIED SAMPLE IN PHASE 2 ($n = 689$)

Variable	Categories	N (%)	p value**
Age (years)*	30–39	14 (3.0)	0.12
	40–49	19 (4.0)	
	50–59	58 (12.3)	
	60–69	93 (19.8)	
	70–79	914 (41.3)	
	80–89	89 (18.9)	
	90+	3 (0.6)	
Gender*	Male	302 (44.7)	0.12
	Female	374 (55.3)	
Socio-economic status*	Low	75 (11.3)	0.98
	Medium	526 (79.0)	
	High	65 (9.8)	
Income	Welfare subsidy	201 (30.4)	
	Below average	285 (43.1)	
	Average	102 (15.4)	
	Above average	73 (11.0)	
Nationality	Bedouin	62 (9.3)	< 0.01
	Not Bedouin	604 (90.7)	
Place of birth	Israel	160 (23.7)	
	USSR (former)	172 (25.5)	
	Europe/America	126 (18.7)	
	Asia/Africa	217 (32.1)	
Speaking language	Hebrew	490 (70.0)	
	Russian	136 (19.4)	
	Arabic	74 (10.6)	
Immigration year	Before 1990	372 (71.3)	
	After 1990	150 (28.7)	
Education	Elementary school (up to 8 years)	216 (32.5)	
	High school (up to 12 years)	206 (31.0)	
	Academic	142 (36.4)	
Additional Health Insurance	No	213 (30.6)	
	Additional	484 (69.4)	

*No significant differences between the sample and all the study population were found

**Only for variables received both for total population and studied sample

spectively) between compliant and non-compliant patients. Multiple analysis indicated that the way of receiving INR results was related to non-compliance, i.e. patients who checked their results from the clinic had better compliance. The strongest predictors of Total Compliance Index to Coumadin usage were age ($\text{OR} = 1.32$ $p < 0.05$), and the number of doctor visits ($\text{OR} = 1.13$ $p < 0.05$), i.e. more visits resulted in better compliance.

Table 5

UNIVARIATE ASSOCIATIONS BETWEEN COMPLIANCE INDEX AND PATIENT CHARACTERISTICS (PHASE 2)

Variable	<i>p</i> value	Variable	<i>p</i> value
Language	0.01	Place of birth	0.01
Age (grouped)	< 0.01	Income	0.06
Number of doctor visits	< 0.01	Drugs form 0 group	0.03
Morbidities	0.01	Drugs form A group	< 0.01
How much the treatment limits your life	0.04	Drugs form B group	< 0.01
How much the treatment frustrates	0.03	Drugs form C group	< 0.01
Timing of medicine consumption	0.01	Drugs form D group	< 0.01
Way of receiving INR results	0.02	Drugs form G group	0.02
Total amount of drugs used	< 0.01	Drugs form H group	0.01

Use of drugs. Both for Phase 1 and Phase 2, the majority of drugs were from group C (mean 12.25 ± 7.55 per year). Other groups of drugs used were: 0 group (mean 0.87 ± 1.32); A group (mean 6.34 ± 5.38); B group (mean 5.44 ± 3.46); D group (mean 2.25 ± 3.11); G group (mean 1.22 ± 2.29), and H group (mean 1.23 ± 2.29). The total median number of drugs that one patient used simultaneously without mention of drug categories was 41 (range 0 to 132).

DISCUSSION

Coumadin is an essential lifesaving drug which necessitates full compliance from patients; however, our eight-year follow-up prospective study showed that more than 50% patients were non-compliant. In this study we developed a Coumadin Total Compliance Index and found that good compliance was related to older age, frequent doctor visits, patients involved in their own care, and patients taking cardiovascular medication. As newer anti-coagulation drugs are increasingly used, there is a need to investigate the components of the compliance index.

During the study from 2002 to 2009, the compliance for Coumadin-treated patients was related with age, which was found to be the strongest predictor of non-compliance to Coumadin usage. Age was evaluated in various prior studies. In contrast to our results, most studies showed statistically significant reduction in Coumadin use with advanced age. Coumadin usage decreased sharply after 75 years of age (DeWilde *et al.*, 2006). The reason for that difference might be because younger AF patients do not receive Coumadin as commonly as older patients. Older age (≥ 85 years), as well as younger age (< 55 years) decrease the use of warfarin (Johnston *et al.*, 2003). Therefore, the association between age and Coumadin is nonlinear. In our study, the majority of patients were aged 55–80 (70%), and conse-

quently we did not examine the population group for which age in which the Coumadin-age relationship has opposite nature.

Our results are similar to previous studies that showed primary care in a giver-patient relationship to be a major interventional point for treatment enhancement. Previous studies have showed that inadequate follow-up (Sewitch *et al.*, 2003), poor physician-patient relationship (Lacro *et al.*, 2002; Urquhart, 2002) and missed appointments (Stilley *et al.*, 2004) are all related to low medical treatment compliance. Studies that focused on Coumadin compliance have found that improving physician-patient communication (Misdrahi *et al.*, 2002) results in improved compliance to Coumadin treatment. All these findings are in line with ours.

Another important predictor for Coumadin compliance that was demonstrated in our study was the level of patient involvement in their own care. Patients who received INR results from the clinic had better compliance. These results support past studies that showed low compliance in patients who had lack of belief in the benefit of the treatment (Okuno *et al.*, 2001; Lacro *et al.*, 2002), or a lack of insight into the illness (Lacro *et al.*, 2002). In contrast, greater understanding of why medication was prescribed and anticipated side effects was found as a predictor for enhanced compliance (Bushnell *et al.*, 2011).

In our study, receiving drugs from Group C (Cardiovascular System drugs category) in addition to Coumadin was found to improve medical compliance. Data on the association between cardiovascular diseases as congestive heart failure and ischemic heart disease with Coumadin compliance was demonstrated in various studies and supports these findings. It is assumed that having increased risk of stroke due to other cardiovascular morbidities increases both patient and care-giver focus on stroke prevention with anti-coagulation treatment (Johnston *et al.*, 2003). Although we did not observe significant differences between compliant and non-compliant patients regarding hospitalisation days, in Phase 2 of the study non-compliant patients were hospitalised almost twice as long (at average) as were compliant patients, and they used the health care services approximately twice as much as compliant patients.

Limitations of the study

Total Compliance Index. The Total Compliance Index was computed using three different variables: number of purchases of Coumadin, compliance to perform INR tests, and average INR values. For a part of the patients we had missing data for one or two of these variables, and thus it was impossible to calculate the index for these patients. This resulted in a difference between the number of patients that used Coumadin and were eligible for the study, and the number of patients with calculated Total Compliance Index. However, we did not observe differences in individual and treatment-related characteristics between patients with and without missing data.

We could not perform validation of calculated Total Compliance Index, as this was a completely new measure of Coumadin-related patient behaviour. On the other side, we divided a dataset onto two different groups: full population from Phase 1 of the study, and a study sample from the Phase 2. In both cases we obtained similar results in multivariate analysis. Thus, we can refer to Phase 2 of the study as a type of validation for the Total Compliance Index.

Socio-economic status. The city of residence was obtained for all patients. The socio-economic status was estimated using the Central Bureau of Statistics codes. Thus, the socio-economic status of the patients was estimated and was not specific to the patient. In the case of missing data for the place of patient residence, obtained data during the phone interview for the study sample of Phase 2, but we had no possibility to do this for the entire population.

Strengths of the study. The first strength of the study was that the study population included patients who used Coumadin for a period of at least for two years; hence we included only patients who were familiar to Coumadin treatment. This improves the validity of our study. Another important strength of this study was the use of questionnaires in addition to the medical records. This allowed to extract data that were not available in medical records, and allowed to demonstrate that variables such as distance to the clinic, QOL, medical side effects and patient-doctor relationship had no statistical effect on compliance.

CONCLUSIONS

In this study we developed a Coumadin Total Compliance Index. We offer this Total Compliance Index to be utilised for other drugs as well. Although Coumadin is a lifesaving drug, non-compliance rates were higher than 50% of the studied group of patients. Use of the compliance model showed that older age, doctor visits, INR check-up in the clinic and cardiovascular medication usage were associated with better Coumadin compliance.

DECLARATION OF INTEREST

The authors report no conflicts of interest. Authors declare no financial, consulting, and personal relationships with other people or organisations that could influence (bias) this work. No scientific writing assistances and grant supports were obtained for this study.

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RISKA FAKTORI, SAISTĪTI AR ILGSTOŠO LĪDZESTĪBU KUMODĪNA LIETOŠANAI (PAŠNOVĒRTĒTS)

Zema līdzestība izrakstītajai kumodīna ārstēšanai var radīt pazeminātus veselības parametrus. Šī pētījuma mērķis bija novērtēt riska faktorus, kuri saistīti ar pacientu līdzestību ilgstošai ārstēšanai ar kumodīnu. Šim nolūkam tika izveidotas divas atsevišķas pētījuma fāzes: retrospektīva astoņus gadus ilga pēcsekošana, izmantojot veselības aprūpes datu bāzes, un šķērsgrīzuma pētījums ar telefona aptauju. Globālais Līdzestības Indekss tika izveidots, izmantojot kumodīna pirkšanas skaitu (40%), Starptautisko standartu attiecības analīzes (INR) veikšanu (40%) un vidējos INR rezultātus (20%). Daudzdimensiju modeļi Globālā Līdzestības Indeksa pārbaudei tika veidoti, ņemot vērā sociālos un demogrāfiskos parametrus, mainīgos, kas saistīti ar ārstēšanas procesu un veselības sistēmas izmantošanu, citu zāļu lietošanu, attiecības starp pacientu un ārstu un pacientu dzīves kvalitāti. Vidēji $78,5 \pm 3,4\%$ no ģenerālkopas pacientiem un $53,2\%$ pacientiem šķērsgrīzuma pētījumā bija zema līdzestība kumodīna lietošanai. Globālais Līdzestības Indekss bija statistiski nozīmīgi saistīts ar lielāku vecumu, ārsta apmeklēšanas skaitu un zālēm no C grupas. Mēs piedāvājam izmantot Globālo Līdzestības Indeksu arī citu zāļu novērtējumam.