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Factors Associated with Non-adherence to Therapy with Warfarin in a Population of Chronic Heart Failure Patients

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Summary

Background: Adherence to heart failure therapy is important in reducing morbidity and mortality over the course of the disease process. The aim of this study was to examine factors associated with non-adherence to warfarin in chronic heart failure patients.

Methods: Eighty patients receiving warfarin therapy in 2002 were included. Adherence was defined as maintenance of international normalized ratio (INR) between 2 and 3.5 and keeping scheduled appointments for INR checks at least 75% of the time. Clinical variables examined included age, gender, race, insurance, left ventricular ejection fraction (LVEF), etiology, New York heart association (NYHA) class, comorbidities, smoking, and alcohol use.

Results: Of 80 patients studied, 59 were male with mean age (± standard deviation) 52 ± 13 years, 24 had ischemic etiology with mean LVEF of $24\% \pm 9\%$. Non-adherence was associated with tobacco use, odds ratio of 6.5 ($p < 0.01$). Ischemic etiology was associated with adherence, odds ratio of 4.5 ($p < 0.01$). Non-adherent patients were more likely to be insured with Medicare/Medicaid ($p = 0.04$) and have better NYHA class ($p = 0.04$). Adherence positively correlated with older age and lower LVEF, and negatively correlated with number of hospitalizations ($p<0.01$ for all). In a multiple regression model, patients with improvement in LVEF had decreased adherence over the year ($p<0.01$).

Conclusions: The profile of heart failure patients who demonstrated non-adherence to warfarin therapy included younger age, nonischemic etiology, better NYHA class, smoking, insurance with Medicare/Medicaid and improved LVEF over the study. Measures targeting these patients may result in improved adherence to other pharmacologic treatments of heart failure.

Key words: heart failure, cardiac transplantation, cardiomyopathy, myocarditis

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Introduction

Chronic heart failure currently affects approximately 4.7 million U.S. adults with an estimated 350,000 to 450,000 new cases diagnosed yearly.[1] Although the prognosis of this disease has improved with advances in medical and surgical therapy, 1 in 5 affected individuals will die within a year of diagnosis. [2] In the current era of heart failure management, standard medical management consists of a complex regimen including combinations of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, diuretics, digoxin, spironolactone, in addition to other drugs that the patient may be taking to manage commonly associated comorbid conditions. Individually, these drugs may be dosed once to three times daily, therefore, after accounting for each drug class, a patient could conceivable be taking multiple medications 3, 4, or more times per day.

Adherence is defined as the extent to which a person's medication taking behavior coincides with medical advice.[3] Clearly an association has been described

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between the complexity of medical regimens and patient's ability to adhere to them.[4,5]

Non-adherence to prescribed medical regimens has been shown to be associated with increased hospitalization rates and emergency room visits.[6–8] Standard drug therapies for heart failure, such as angiotensin-converting enzyme inhibitors, beta-blockers and spironolactone, have been demonstrated to decrease both morbidity and mortality[9–11] but can only be effective to the extent to which patients actually follow the prescribed regimen.

Variables associated with non-adherence to medical therapy can generally be classified as demographic, medical, medication-related, economic, related to physician–patient interaction and related to patients' health knowledge and beliefs.[12] Some of these factors are challenging to define, and even more elusive to measure. It could be postulated that aiming interventions to improve adherence (which themselves may be costly and labor intensive) toward patients identified to be at highest risk of non-adherence using common clinical variables, could translate into improved clinical outcomes, as improved adherence has been shown to be associated with improved clinical outcomes.[13,14]

Standard management of patients on warfarin therapy includes ongoing clinical monitoring with international normalized ratio (INR) measurement, which is performed under the direction of a health care provider. Although not equivalent to direct measurement of the drug in serum, the INR does provide evidence of the presence of drugs and may be reflective of the patient's ability to follow the prescribed regimen; albeit, with the caveat that factors other than compliance may influence the INR. Because the medication is adjusted based on objective levels, warfarin therapy lends itself to the study of adherence. The aim of this investigation was to examine factors that may be associated with non-adherence to warfarin in a sample of chronic heart failure patients treated in a specialized heart failure program.

Methods

Patients

Patients treated by the Rush Heart Failure Program who were on chronic anticoagulation therapy with warfarin, and were monitored by the anticoagulation nurse (under supervision of the heart failure physician) were eligible. Patients with four or more INR measurement during the calendar year 2002 were included. Eighty such patients were identified. This protocol was approved by the Institutional Review Board of Rush Medical Center.

Data

For the 80 patients identified, data collected included the number of INR measurements scheduled, the number of INR measurements actually obtained, and the INR reading itself. A designated anticoagulation nurse scheduled INR measurements and adjusted warfarin dosage based on the INR with the aid of a commercially available software program (CoumaCare, Bristol-Myers Squibb, Princeton, N.J., USA). All adjustments in warfarin regimen were reviewed and approved by a heart failure physician. In addition to the information regarding warfarin, clinical data were collected. These included demographics such as race (self reported), age, gender, insurance status, etiology of heart failure, New York heart association (NYHA) class, serial ejection fraction measured over the year 2002 as estimated by transthoracic echocardiography, number of hospitalizations, history of or current alcohol use, and history of or current tobacco use.

Definition of Non-adherence

Two definitions for non-adherence were used. The first involved the number of out-of-range INR measurements. For the purposes of the study, the target INR range was defined as 2–3.5 for all patients, regardless of indication for warfarin. The reason for this was twofold: to include patients with mechanical valves and to avoid unduly penalizing patients with a target INR of 2–3 who may have had a slightly higher INR, such as 3.2, which was considered to be a better clinical scenario than having a slightly subtherapeutic INR, such as 1.8. The number of INR measurements out of range was divided by the total number of measurements obtained. If this total was greater than 25%, the patient was classified as non-adherent with regards to maintaining target INR. For example, if a patient had a total of five INR measurements and one was out of range, the percentage would be 20%, and the patient would be considered adherent.

The second definition utilized the number of scheduled lab appointments for INR measurement. The number of appointments the patient missed was divided by the total number of appointments scheduled. Again, a cutoff of 25% missed appointments was used to define non-adherence. For example, if 10 appointments were scheduled and the patient only attended 7 of these, the percentage would be 30%, and the patient would be considered non-adherent.

Statistical Analysis

Student's *t*-test was used to compare baseline characteristics between groups. Statistical comparisons for categorical data were performed by chi-square test. Non-adherence and adherence were categorized using cutoff points as outlined above, and to be classified as non-adherent, the individual had to meet the criteria for both definitions. For example, if an individual was classified as non-adherent with regards to INR targets, but

was adherent to scheduled appointments for INR testing, these were classified as adherent in the chi-square analysis. Pearson correlation coefficient was used to measure the strength of the linear relationship between adherence and clinical variables of interest. Multivariable regression, with percent adherence to appointments as the dependent variable, was also performed. Different combinations of predictor variables as well as interaction variables were included, and the "best" model was presented. The variable "African-American race" was left in the model to demonstrate its effect. For all analyses conducted, a p-value of 0.05 was considered to be statistically significant. Analyses were performed using SAS software (Cary, N.C., USA).

Results

Of the entire cohort of 80 patients, 59 were male and 34 were African-American. Mean age at the start of the study was 52.8 ± 13.1 years for the entire cohort. Mean left ventricular ejection fraction (LVEF) was $24\% \pm 9\%$ at the start of the study and $30\% \pm 15\%$ at the end of the study. Five patients had diastolic heart failure with left ventricular ejection fraction of $\geq 40\%$ at the start of the study. Participants had a mean of 1.6 ± 0.9 comorbidities with 0.96 ± 1.4 hospitalizations during the study year. Indications for anticoagulation included left ventricular (LV) thrombosis treatment or prophylaxis in 34, secondary prevention poststoke in 19, treatment of deep venous thrombosis in 3, atrial fibrillation in 28 and mechanical valve in 5.

There was no association between gender and adherence. Non-adherent individuals were more often NYHA class I or II at the start of the study compared with adherent individuals, who were more often NYHA class III or IV ($p = 0.04$). The odds ratio for adherence in patients with ischemic etiology was 4.8 compared with patients with nonischemic cardiomyopathy ($p = 0.04$). The odds of adherence were 6.5 times greater for nonsmokers compared to smokers ($p = 0.006$). There was an association between insurance type and non-adherence (Table 1) and a trend toward an association between race and non-adherence (Table 2). There was no association between the number of comorbid conditions and adherence.

TABLE 1 Association between insurance type and non-adherence

Insurance type	Adherent (n = 61)	Nonadherent (n = 19)
Medicare	35 (57%)	12 (63%)
Medicaid	7 (11%)	6 (31%)
Private	18 (30%)	1 (6%)
Indemnity	1 (2%)	0

p = 0.04

TABLE 2 Association between race and non-adherence

Race	Adherent (n = 61)	Non-adherent (n = 19)
African-American	22 (36%)	12 (63%)
Caucasian	33 (54%)	7 (37%)
Other	6 (10%)	0

p = 0.09

TABLE 3 Pearson correlation coefficients for adherence to appointments and adherence to international normalized ratio

Clinical variable	Target INR	p-value	Appointments	p-value
Age	0.16	0.16	0.32	0.004
LVEF at start of study	0.22	0.07	−0.28	0.03
LVEF at end of study	0.16	0.30	−0.45	0.002
Number of hospital admissions	−0.36	0.001	0.12	0.29
Number of comorbidities	−0.15	0.17	0.08	0.48
Tobacco use	−0.17	0.13	−0.13	0.23

Abbreviations: INR = international normalized ratio; LVEF = left ventricular ejection fraction

For calculation of Pearson correlation coefficients, adherence was divided into adherence with INR appointments and adherence with maintaining therapeutic INR. There results are summarized in Table 3. There was a positive correlation between age (at the start of the study) and keeping appointments. Left ventricular ejection fraction at both the start and end of the study period were negatively correlated with keeping appointments. In other words, worse cardiac function was correlated with better adherence to keeping scheduled appointments. Number of hospitalizations over the course of the study year was negatively correlated with maintenance of a therapeutic INR.

A multiple regression model was developed to examine the relationship between the dependent variable, percent compliance with appointments, and the independent variables. Table 4 summaries the model including parameter estimates and p-values. This particular model explained 45% of the observed variability.

Discussion

This study of chronic heart failure patients identified characteristics that may be associated with non-adherence with warfarin therapy. These variables included younger age, positive smoking history, nonischemic

TABLE 4 Multiple linear regression model

Variable	Parameter estimate	Standard error	p-value
Intercept	51.6	12.6	0.0002
Age at start	0.57	0.17	0.003
African-American race	−4.66	4.76	0.33
LVEF at end of study	−0.50	0.17	0.005
NYHA class	5.67	3.24	0.09

Abbreviations: LVEF = left ventricular ejection fraction; NYHA = new york heart association; $r^2 = 0.45$

etiology, insurance with Medicare and Medicaid, number of hospitalizations and improved LV function. These factors are easily identifiable, which may allow resources at improving adherence to be more efficiently focused on individuals at risk.

Adherence can be measured by direct methods including measurement of drug metabolite levels, measurement of biologic markers in blood and observation of patients taking therapy. Disadvantages of these methods include impracticality, cost, and variations in metabolism, which may affect measured blood levels. Indirect measurements of adherence include patient self-reports, pill counts, electronic medication monitors, rates of prescription refills and measurement of physiologic responses, such as decrease in heart rate with beta-blocker therapy. Again, these methods have significant limitations including expense, patient alteration of data (for example pill dumping), and biologic factors that may affect clinical response.[15] Direct measures are preferred, but no gold standard exists. In our study, we used direct methodology to define adherence. Because warfarin therapy requires intensive monitoring, direct measurement of both appointment keeping and therapeutic drug levels collected as routine clinical practice lends itself to further analysis of adherence. Our definition of non-adherence based on a combination of less than 75% appointment-keeping and therapeutic INR measurements may be considered a liberal one, as patients who were adherent in either category were considered to be adherent overall. However, this definition did not unduly penalize patients who may have had difficulty achieving therapeutic INR because of biologic factors, but attended scheduled appointments regularly in an effort to regulate their INR. Likewise, patients who maintained a therapeutic INR, but missed occasional appointments, were not likely to be at increased risk of an adverse clinical event, and therefore were not classified as non-adherent.

Demographic and socioeconomic factors have been inconsistently associated with medical adherence. In our study, younger age was associated with non-adherence. Waterman et al. found age younger than 65 and older than 80 years to be associated with non-adherence with warfarin therapy defined by INR below 1.8 or greater than 3.4.[16] Similarly, Arnsten and colleagues found cases of warfarin noncompliance to be younger than controls.[17] Evangelista et al. examined compliance behaviors in a population of elderly advanced heart failure patients and found older age (≥65 years) to be associated with compliance with diet and exercise, but not with medical appointments or taking medication.[18] In contrast, others have found younger individuals more likely to take prescribed medications.[19]

The relationship between insurance status and compliance has not been specifically addressed in studies involving chronic cardiovascular diseases to date, however, other measures of socioeconomic status have again been inconsistent in identifying non-adherence in other diseases, such as Acquired Immuno-deficiency Syndrome.[20]

Race has been shown to be associated with non-adherence in some studies of cardiovascular disease.[21,22] In our relatively small cohort, race was of borderline significance by univariate but not multivariable analysis which would imply either, (i) its effect is not significant when controlled for, or (ii) the study was too small to detect a significant effect of race. The relationship of demographic variables to adherence may be inconsistent amongst various studies because of differences between the severity and tempo of diseases in the patient population under study, as well as differences in the tolerability of disease-specific therapies. For example, even though hypertension and heart failure are both chronic cardiovascular diseases treated with the same classes of drugs, patients with hypertension are likely to be asymptomatic at the time of diagnosis whilst heart failure patients are likely to be very symptomatic, which may impact upon the patient's adherence to medical recommendations.

In our study, smoking was associated with increased odds of non-adherence. Adverse patient behaviors, such as smoking, may be a marker of non-adherence to good health practices in general; however this has not been reported in studies published to date. Other associations with non-adherence found in our study including improvement in LVEF over time and nonischemic etiology have also not been previously reported. Several explanations may be postulated for these observations. For example, with improvements in cardiac function, patients may feel better, and perhaps this leads to a feeling of decreased urgency to follow medical advice. Non-ischemic etiology was more likely in younger patients, who were found to be less adherent in our study. Any hypothesized explanations regarding these associations require further study.

Because the same group of specialized heart failure physicians and a single anticoagulation nurse followed all patients, the influence of provider–patient interaction was controlled for to a great extent. In addition, a software-based management program was used, which standardized the recommendations for monitoring of warfarin dosing and frequency of INR determinations.

Limitations

This was a retrospective study, with its inherent limitations. Detailed information regarding socioeconomic and educational status was not available; therefore, insurance status was used as a surrogate measure, with the presumption that patients with Medicare and Medicaid were of lower financial means. Information on patient factors that may influence adherence, such as depression and neurocognitive function was not collected. Data on prior to the year 2002 were not collected; therefore duration of illness was unknown. Four or more data points were required for entry into the study. This was to allow for meaningful calculation of percentage adherence but may have excluded individuals who were noncompliant. Data on the affect of other medications such as amiodarone and antibiotics on the INR was not available. Finally, the mean age of our study was relatively young for a heart failure study, and therefore may not be generalizable to other heart failure populations.

Conclusions

Adherence is a behavioral process, resulting from a convergence of influences upon an individual including knowledge, motivation, skills and resources in combination with healthcare practices and systems.[23] Although interventions to improve adherence may translate into improved clinical outcomes, a major deficit of most published approaches has been the uniform application of these interventions, rather than targeted efforts. In the economic constraints of the current healthcare environment, costly interventions must be directed to the highest risk individuals. Our study identifies a patient profile associated with non-adherence, who may be at increased risk. Further prospective study is required to further delineate who these "at-risk" individuals are, and what the consequences their non-adherence might be, before directed interventions can be evaluated.

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