Patient Satisfaction With Warfarin- and Non–Warfarin-Containing Thromboprophylaxis Regimens for Atrial Fibrillation

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Objective: To compare patient-reported limitations, concerns, and burdens in those receiving and not receiving warfarin for thromboprophylaxis in atrial fibrillation (AF).

Methods: We conducted a cross-sectional survey study of patients with AF receiving thromboprophylaxis for stroke prevention. Patients were administered the validated Anti-Clot Treatment Scale (ACTS). Mean scores of patients receiving and not receiving warfarin were compared for each ACTS item, and for the Burden and Benefit subscales.

Results: From July 2010 to August 2011, 80 patients with AF were administered the survey, with 65 patients receiving a regimen containing warfarin and 15 patients not receiving a regimen containing warfarin. Six of the 17 individual questions depicting patient- perceived limitations in physical activity due to bleeding, limitations on diet, feelings of inconvenience of occasional aspects of thromboprophylaxis therapy, and frustration, and burden had less favorable scores in the warfarin-managed patients compared with the patients not receiving warfarin ($P < 0.05$ for all). Mean ACTS Burden scores were more favorable in the no-warfarin group (44.5 ± 6.4) compared with the warfarin group (39.8 ± 8.0; $P = 0.003$). No difference was seen between the 2 groups on the ACTS Benefits score (11.1 ± 3.4 vs 10.4 ± 3.7; $P = 0.38$).

Conclusion: Patients with AF receiving warfarin may have less favorable feelings regarding thromboprophylaxis versus those receiving non-warfarin thromboprophylaxis. Patients report having more limitations and having greater feelings of burden on warfarin.

Key Words: atrial fibrillation, anticoagulation, patient-reported outcomes, patient satisfaction

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Multiple randomized controlled trials have demonstrated that the use of long-term anticlot therapy with warfarin reduces the relative risk of stroke in atrial fibrillation (AF) by approximately 65%.[1,2] Unfortunately, there are significant disadvantages to warfarin therapy, including complex dosing regimens, inconvenient regular blood monitoring, dangerous food and drug interactions, and as high as a 3% annual risk of major bleeding. Antiplatelet agents (aspirin alone or with clopidogrel) have been found to be somewhat efficacious in lowering stroke risk in patients with AF,[1] and newer oral anticoagulants including rivaroxaban, dabigatran, and apixaban bring the promise of at least similar efficacy to warfarin but with enhanced safety and ease of use.[1] Although it might be assumed that these disadvantages associated with warfarin would intuitively reduce patient satisfaction versus other choices, this has not been evaluated adequately to date. Given the long-standing experience with warfarin and its relatively low cost versus other antithrombotic choices, research in this area is needed. As such, we report the results of our comparison of patient-reported feelings of limitation, concern, and burden when receiving a warfarin- and non–warfarin-containing thromboprophylaxis regimen.

MATERIALS AND METHODS

We conducted a cross-sectional survey study of patients with AF from 3 arrhythmia clinics associated with a large urban teaching hospital receiving thromboprophylaxis for stroke prevention. The study was institutional review board approved, and all patients provided written informed consent. Eligible patients had to have a diagnosis of AF, be receiving thromboprophylaxis to prevent stroke (warfarin, dabigatran, and antiplatelet or combination therapy), and live in the community (not living in an assisted living or a skilled nursing facility). Eligible patients were asked to participate at check-in to a scheduled arrhythmia clinic follow-up visit. Patients self-administered the validated Anti-Clot Treatment Scale (ACTS).[3,4] The ACTS was chosen because it has been recently used in 2 large randomized controlled trials[4,5] and is included as an outcome in both the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation and the Global Anticoagulant Registry in the FIELD prospective, longitudinal AF patient registries.[6,7] The scale contains 17 questions about the impact of thromboprophylaxis treatment scored on a 5-point Likert scale (1, "not at all", to 5, "extremely"). For the first 13 questions, higher scores represented less favorable perceptions of thromboprophylaxis treatment. For questions 14 to 17, higher scores represented more favorable perceptions. The ACTS questions were also separated into 2 domains, "Burden" and "Benefit", each with their own scores. The Burden score was calculated as the sum of questions 1 to 12 subtracted from 60, with a higher score suggesting greater satisfaction with treatment. The Benefit subscale was calculated as the sum of questions 14 to 16, again with a higher score suggesting greater satisfaction. The 2 domains also showed good internal consistency with Cronbach alpha (a measure of the reliability of a psychometric test) ranging from 0.90 to 0.93 (scores ≥0.70 are typically considered desirable). Questions 13 and 17 were intended to stand alone and assess

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patients' global perception of negative and positive aspects of anticoagulation.

Mean scores with accompanying standard deviations and medians with minimum and maximum values of patients receiving and not receiving warfarin were compared for each of the 17 items and for the Burden and Benefit subscales. Mann-Whitney U tests were used, with $P \leq 0.05$ considered significant. Analysis was performed using SPSS version 17.0 (SPSS Inc, Chicago, IL).

RESULTS

Patients were recruited between July 2010 and August 2011. During this time, 103 patients were approached before an office visit at one of the arrhythmia clinics, of which 23 refused participation. Characteristics of the 80 AF respondents are in Table 1. Of them, 65 respondents were receiving a regimen containing warfarin (n = 39, warfarin; and n = 26, warfarin plus antiplatelet agent/s) and 15 were not (n= 11, aspirin; n = 2, aspirin plus clopidogrel; and n = 2, dabigatran). Patients receiving warfarin spent 63% of the time in the therapeutic international normalized ratio range of 2 to 3 (calculated using the Rosendaal method).[8] Of the 15 patients not receiving a regimen containing warfarin, 4 patients had a CHADS2 (congestive heart failure, hypertension, advanced age, diabetes and prior stroke/transient ischemic attack) score of 0 to 1, 4 patients were 80 years or older (3 patients were 85 years or older), 2 patients were receiving dabigatran, and 2 were receiving dual antiplatelet therapy (owing to the presence of coronary stents).

Six of the 17 individual questions (1, 5, 7, and 11–13) had higher mean scores in the patients receiving warfarin compared with the patients not receiving warfarin ($P < 0.05$ for all; Table 2). No difference was seen between the 2 groups with regard to the ACTS Benefits score (11.1 ± 3.4 vs 10.4 ± 3.7; $P = 0.38$). The mean ACTS Burden scores were higher (more favorable) in the no-warfarin group (44.5 ± 6.4) compared with the warfarin group (39.8 ± 8.0; $P = 0.003$). Within the warfarin group, no difference in the ACTS Burden or Benefits scores were observed when comparing those receiving or not receiving aspirin ($P > 0.05$ for both). However, the ACTS Burden scores were significantly associated with time spent in the therapeutic international normalized ratio range (a small and positive correlation; Pearson $r = 0.248$; $P = 0.046$).

DISCUSSION

Our assessment of the patients with AF receiving thromboprophylaxis suggests that those taking warfarin may have less favorable feelings about their treatment compared to other available agents. The patients' responses suggested that the respondents believe they suffer significant burden owing to receiving warfarin but receive no incremental benefit compared to other thromboprophylaxis agents. Specifically, the patients perceived they had limitations on both the physical activity they could engage in and regarding their diet. The patients taking warfarin also reported feeling more hassled and frustrated by their thromboprophylaxis.

TABLE 1. Patients' and Thromboprophylaxis Treatment Characteristics

Characteristic	No Warfarin N = 15 n (%)	Warfarin N = 65 n (%)	*P*
Age, mean ± SD, yrs	73.1 ± 12.0	74.4 ± 9.1	0.63
$CHADS_2$ score, mean ± SD	2.2 ± 1.4	2.1 ± 1.2	0.66
Congestive heart failure	7 (46.7)	25 (38.5)	0.56
Hypertension	8 (53.3)	45 (69.2)	0.24
Age ≥75 yrs	10 (66.7)	39 (60.0)	0.63
Diabetes	5 (33.3)	13 (20.0)	0.27
Stroke	2 (13.3)	8 (12.3)	0.91
Number of thromboprophylaxis agents, mean ± SD	1.1 ± 0.4	1.5 ± 0.7	0.05
Sex, % male	10 (66.7)	38 (58.5)	0.56
Race, % white	14 (93.3)	63 (96.9)	0.61
Married	12 (80.0)	54 (83.1)	0.72
Health and prescription insurance	15 (100)	65 (100)	>0.99
Renal impairment	0 (0)	10 (15.4)	0.20
Liver impairment	0 (0)	2 (3.1)	>0.99
History of GI bleeding	0 (0)	8 (12.3)	0.34
History of myocardial infarction	6 (40.0)	15 (23.1)	0.18
Anemia	0 (0)	7 (10.8)	0.34
Taking current thromboprophylaxis agent for ≥ 6 months	14 (93.3)	63 (96.9)	0.47
Number of office visits in the past 3 months, mean ± SD	1.5 ± 1.0	2.4 ± 1.7	0.01
Number of laboratory visits in the past 3 months, mean ± SD	0.3 ± 0.6	6.3 ± 3.6	<0.001
Number of hospitalizations in the past 3 months, mean ± SD	0.1 ± 0.4	0.3 ± 0.5	0.26
Number of warfarin strengths, mean ± SD	NA	1.2 ± 0.5	NA
Number of warfarin dose changes in the past 3 months, mean ± SD	NA	2.6 ± 3.0	NA
Number of tablets per week, mean ± SD	NA	9.2 ± 3.9	NA
Percentage time in therapeutic INR range, mean ± SD	NA	63.1 ± 29.5	NA

INR indicates international normalized ratio; NA, not applicable; SD, standard deviation.

TABLE 2. Responses to the ACTS According to Warfarin Use

ACTS Question*	No Warfarin Mean ± SD Median (Range)	Warfarin Mean ± SD Median (Range)	*P*†
1. How much does the possibility of *bleeding* as a result of your anticlot treatment limit you from taking part in *vigorous physical activities* (eg, exercise, sports, dancing, etc.)?	1.0 ± 0.0 1 (1–1)	1.6 ± 1.0 1 (1–5)	0.01
2. How much does the possibility of *bleeding* as a result of your anticlot treatment limit you from taking part in your *usual activities* (eg, work, shopping, housework, etc.)?	1.2 ± 0.6 1 (1–3)	1.3 ± 0.7 1 (1–5)	0.44
3. How bothered are you by the possibility of *bruising* as a result of your anticlot treatment?	1.7 ± 1.1 1 (1–4)	2.2 ± 1.3 2 (1–5)	0.09
4. How bothered are you by having to *avoid other medicines* (eg, aspirin) as a result of your anticlot treatment?	1.5 ± 0.9 1 (1–4)	1.7 ± 1.1 1 (1–5)	0.38
5. How much does your anticlot treatment *limit what you eat and drink* (including alcohol)?	1.3 ± 0.5 1 (1–2)	1.7 ± 1.1 2 (1–5)	0.04
6. How much of a hassle (inconvenience) are the *daily* aspects of your anticlot treatment (eg, remembering to take your medicine at a certain time, taking the correct dose of your medicine, limiting what you eat and drink (including alcohol, etc.)?	1.4 ± 0.5 1 (1–2)	1.8 ± 1.0 1 (1–5)	0.30
7. How much of a hassle (inconvenience) are the *occasional* aspects of your anticlot treatment (eg, the need for blood tests, going to or contacting the hospital/doctor, making arrangements for treatment while traveling, etc.)?	1.4 ± 0.9 1 (1–4)	1.8 ± 1.0 2 (1–4)	0.05
8. How *difficult is it to follow* your anticlot treatment?	1.1 ± 0.5 1 (1–3)	1.4 ± 0.7 1 (1–4)	0.07
9. How *time-consuming* is your anticlot treatment?	1.1 ± 0.5 1 (1–3)	1.4 ± 0.7 1 (1–4)	0.06
10. How much do you *worry* about your anticlot treatment?	1.5 ± 1.1 1 (1–4)	1.7 ± 1.0 1 (1–5)	0.19
11. How *frustrating* is your anticlot treatment?	1.2 ± 0.8 1 (1–4)	1.8 ± 1.1 1 (1–5)	0.02
12. How much of a *burden* is your anticlot treatment?	1.1 ± 0.5 1 (1–3)	1.7 ± 1.0 1 (1–4)	0.03
13. Overall, how much of a *negative impact* has your anticlot treatment had on your life?	1.2 ± 0.6 1 (1–3)	1.9 ± 1.0 2 (1–4)	0.003
14. How *confident* are you that your anticlot treatment will protect your health (eg, prevent blood clots, stroke, heart attack, DVT, embolism)?	3.5 ± 1.2 4 (1–5)	3.5 ± 1.3 4 (1–5)	>0.99
15. How *reassured* do you feel because of your anticlot treatment?	3.8 ± 1.2 4 (1–5)	3.5 ± 1.2 4 (1–5)	0.34
16. How *satisfied* are you with your anticlot treatment?	3.8 ± 1.3 4 (1–5)	3.5 ± 1.3 4 (1–5)	0.30
17. Overall, how much of a *positive impact* has your anticlot treatment had on your life?	3.7 ± 1.5 4 (1–5)	3.2 ± 1.4 3 (1–5)	0.18
ACTS Burden score‡ (Cronbach α = 0.90) (questions 1–12, each reverse coded)	44.5 ± 6.4 47 (24–48)	39.8 ± 8.0 42 (12–48)	0.003
ACTS Benefits score§ (Cronbach α = 0.93) (questions 14–16)	11.1 ± 3.4 12 (3–15)	10.4 ± 3.7 11 (3–15)	0.38

*All ACT questions were answered on a 5-point Likert scale of 1, "not at all", to 5, "extremely".

†Calculated using Mann-Whitney *U* test.

‡Calculated as the sum of questions 1 to 12 subtracted from 60 per Bamber 2011 (higher score equals greater satisfaction with treatment).

§Calculated as the sum of questions 14 to 16 per Bamber 2011 (higher score equals greater satisfaction with treatment).

Currently, there is no published guidance as to what constitutes a minimally important clinical difference on the ACTS scale. However, many researchers have suggested that a change of 0.5 SD units or more on a patient-reported outcomes measure often estimates this value.[9] The SD on the ACTS Burden score in our overall population was 7.9, suggesting a minimally important clinical difference of approximately 4 points on the ACTS burden domain. Because we observed a 4.7-point difference between the warfarin and no-warfarin groups in our analysis, it seems reasonable to suggest that the difference is not only statistically significant but also clinically relevant.

Of note, 2 recent randomized trials[10,11] evaluating the use of thromboprophylaxis agents in patients with AF deemed "unsuitable" for warfarin suggest that up to 38% of patients refuse to use warfarin. A number of patient-preference studies demonstrated that if the decision was left to patients, far fewer patients would opt to receive warfarin compared to what is suggested by national treatment guidelines.[12–14] Countless observational studies have found that only a fraction of patients with AF indicated to receive warfarin are actually receiving it.[12,13] The results of these studies may be explained by our trial. In the patients who were taking warfarin therapy, many for prolonged periods of time, they felt burdened by the lifestyle limitations and the variable nature of the regimen and blood monitoring versus non–warfarin-based regimens.

It has been suggested that greater patient involvement in health care decision-making processes may lead to increased satisfaction with the decision-making process, improved adherence

to treatment modalities, and ultimately, prolongation of quality-adjusted survival. Consequently, at least one set of national AF clinical practice guidelines[14] has recommended that patient preferences be incorporated into clinical decision making and selection of optimal thromboprophylaxis for individual patients. Factors such as efficacy, safety, cost, and convenience matter to a different extent in different individuals; and extrapolating the values of the caregiver onto the patient may not be as optimal as providing information to the patient and engaging in shared decision making.

There are limitations to this study that should be considered when evaluating our results. We enrolled only a small population into this exploratory study. The small sample size and large proportion of patients taking warfarin may have resulted in a failure to show significant differences on individual survey questions when one truly exists (owing to underpowering). Also of import, the patients with AF were recruited from arrhythmia clinics affiliated with a single urban teaching hospital in the northeastern United States. All patients had health care insurance, the average patient CHADS2 score was 2.1, and the mean number of thromboprophylaxis agents used by patients was 1.4. Because these characteristics may not be representative of all patients with AF, caution should be used in generalizing our results to other practices or settings. Finally, we would have liked to compare warfarin patients' responses to ACTS with those receiving other agents individually; however, there were too few receiving any one specific alternative thromboprophylaxis regimen. Most of the patients not receiving warfarin were taking aspirin alone, with only a handful receiving dabigatran or clopidogrel plus aspirin. This is likely a result of these other regimens being new to the US market and only recently being included in national AF treatment guidelines.[1] As such, a study like ours should be repeated in the future on a larger scale when there is greater permeation of other antithrombotic agents in clinical use. The CHADS2 score was very similar in the 2 groups, and we do not believe that the underlying burden of stroke risk would explain our findings and is a strength of our study.

CONCLUSION

Patients with AF receiving warfarin may have less favorable feelings about their thromboprophylaxis compared to non–warfarin-based regimens. Patients may perceive greater burden owing to their warfarin, while not perceiving any incremental benefit, versus non–warfarin-based regimens.

REFERENCES

1. ACCF/AHA Task Force Members. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;123:104–123. Available at: http://circ.ahajournals.org/content/123/1/104.long. Accessed May 22, 2012.
2. Granger CB, Armaganijan LV. Newer oral anticoagulants should be used as first-line agents to prevent thromboembolism in patients with atrial fibrillation and risk factors for stroke or thromboembolism. *Circulation*. 2012;125:159–164.
3. Bamber L, Cano SJ, Lamping DL, et al. Patient-reported treatment satisfaction with oral rivaroxaban versus standard therapy in the treatment of symptomatic deep vein thrombosis Abstract P-TH-284 presented at the XXIII Congress of the International Society on Thrombosis and Haemostasis , Kyoto, Japan, 23–28 July 2011.
4. Cano S, Bamber L, Lamping D, et al. Comparing oral rivaroxaban versus standard treatment in the treatment of symptomatic deep vein thrombosis: a patient-reported treatment satisfaction study. *Eur J Hosp Pharm*. 2012;19:244.
5. National Institute for Health and Clinical Excellence. Single technology appraisal of rivaroxaban (Xarelto®), August 2011. Available at: http://www.nice.org.uk/nicemedia/live/13308/57753/57753.pdf. Last accessed on June 13, 2012).
6. Kakkar AK, Mueller I, Bassand JP, et al. International longitudinal registry of patients with atrial fibrillation at risk of stroke: Global Anticoagulant Registry in the FIELD (GARFIELD). *Am Heart J*. 2012;163(1):13–19.e1.
7. Piccini JP, Fraulo ES, Ansell JE, et al. Outcomes registry for better informed treatment of atrial fibrillation: rationale and design of ORBIT-AF. *Am Heart J*. 2011;162(4):606–612.e1.
8. Azar AJ, Deckers JW, Rosendaal FR, et al. Assessment of therapeutic quality control in a long-term anticoagulant trial in post-myocardial infarction patients. *Thromb Haemost*. 1994;72(3):347–351.
9. Guyatt GH, Osoba D, Wu AW, et al; Clinical Significance Consensus Meeting Group. Methods to explain the clinical significance of health status measures. *Mayo Clin Proc*. 2002;77(4):371–383.
10. ACTIVE Investigators, Connolly SJ, Pogue J, Hart RG, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med*. 2009;360:2066–2078.
11. Connolly SJ, Eikelboom J, Joyner C, et al; AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364(9):806–817.
12. Bungard TJ, Ghali WA, Teo KK, et al. Why do patients with atrial fibrillation not receive warfarin? *Arch Intern Med*. 2000;160:41–46.
13. Man-Son-Hing M, Gage BF, Montgomery AA, et al. Preference-based antithrombotic therapy in atrial fibrillation: implications for clinical decision making. *Med Decis Making*. 2005;25:548–559.
14. You JJ, Singer DE, Howard PA, et al; American College of Chest Physicians. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 suppl):e531S–e575S.