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Quality of Life Assessment in the Randomized PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) Trial of Patients at Risk for Stroke With Nonvalvular Atrial Fibrillation

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Objectives This study sought to assess quality of life parameters in a subset of patients enrolled in the PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) trial.

Background The PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) trial demonstrated that in patients with nonvalvular atrial fibrillation (AF) and CHADS2 (congestive heart failure, hypertension, age, diabetes mellitus, and prior stroke, transient ischemic attack, or thromboembolism) score $\geq$1, a left atrial appendage closure device is noninferior to long-term warfarin for stroke prevention. Given this equivalency, quality of life (QOL) indicators are an important metric for evaluating these 2 different strategies.

Methods QOL using the Short-Form 12 Health Survey, version 2, measurement tool was obtained at baseline and 12 months in a subset of 547 patients in the PROTECT AF trial (361 device and 186 warfarin patients). The analysis cohort consisted of patients for whom either paired quality of life data were available after 12 months of follow-up or for patients who died.

Results With the device, the total physical score improved in 34.9% and was unchanged in 29.9% versus warfarin in whom 24.7% were improved and 31.7% were unchanged ($p = 0.01$). Mental health improvement occurred in 33.0% of the device group versus 22.6% in the warfarin group ($p = 0.06$). There was a significant improvement in QOL in patients randomized to device for total physical score, physical function, and in physical role limitation compared to control. There were significant differences in the change in total physical score among warfarin naive and not–warfarin naive subgroups in the device group compared to control, but larger gains were seen with the warfarin naive subgroup with a 12-month change of 1.3 ± 8.8 versus -3.6 ± 6.7 ($p = 0.0004$) device compared to warfarin.

Conclusions Patients with nonvalvular AF at risk for stroke treated with left atrial appendage closure have favorable QOL changes at 12 months versus patients treated with warfarin. (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation [WATCHMAN PROTECT]; NCT00129545) (J Am Coll Cardiol 2013;61:1790–8) © 2013 by the American College of Cardiology Foundation

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Stroke prevention is critical to the management of patients with nonvalvular atrial fibrillation (AF). Anticoagulation therapy with oral anticoagulants including warfarin has been the standard of care for effective stroke prevention on the basis of numerous randomized clinical trials in this arena (1–3). Despite its high efficacy, there are numerous downsides to the use of warfarin, and these have led to the development of nonpharmacological approaches to stroke prevention. The multicenter randomized PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) trial revealed that percutaneous left atrial appendage (LAA) closure with the WATCHMAN device (Atritech, a subsidiary of Boston Scientific, Plymouth, Minnesota) was noninferior to warfarin therapy for stroke prevention (4).

Health-related quality of life (HRQOL) measures are important clinical outcome measures of therapy in the treatment of chronic disease, and based on the equivalency of the PROTECT AF trial, quality of life (QOL) indicators are important for evaluating these strategies, particularly in elderly patient populations with multiple comorbidities. It is known that QOL improves when rate and rhythm control of AF is undertaken, irrespective of the mode of treatment (5,6–20), either pharmacologic or using ablation. In contrast, the uses of warfarin for stroke prevention in patients with AF has been shown to either have no impact on QOL or may potentially have a negative impact on QOL in these patients (7).

Currently, there are no QOL data on the patient population undergoing nonpharmacologic approaches to stroke prevention using LAA exclusion. The goal of this study was to assess the changes in QOL parameters over a 12-month period in a subset of patients enrolled in the PROTECT AF trial who underwent LAA closure with the WATCHMAN device versus medical therapy with warfarin anticoagulation therapy alone.

Methods

The prospective, randomized, controlled trial PROTECT AF was performed at 59 sites in the United States and Europe. Enrollment began in February 2005 and ended in June 2008. Patients who were age 18 years or older with paroxysmal, persistent, or permanent nonvalvular AF were eligible for enrollment if they had a CHADS2 (congestive heart failure, hypertension, age, diabetes mellitus, and prior stroke, transient ischemic attack, or thromboembolism) (21) risk score of 1 or more (i.e., at least 1 of the following: previous stroke or transient ischemic attack, congestive heart failure, diabetes mellitus, hypertension, or were 75 years of age or older). Exclusion criteria included contraindications to warfarin, comorbidities other than AF that required chronic warfarin use, LAA thrombus, a patent foramen ovale with atrial septal aneurysm and right-to-left shunt, mobile aortic atheroma, and symptomatic carotid artery disease. After baseline screening, patients were randomly assigned by a computer-generated randomization sequence to intervention group or control group in a 2:1 ratio.

Abbreviations and Acronyms

AF = atrial fibrillation
HRQOL = health-related quality of life
LAA = left atrial appendage
QOL = quality of life

A subset of 547 patients in the PROTECT trial (361 device and 186 control patients) are included in this analysis. Patients with complications and adverse events with the WATCHMAN device implant were included in the analysis. Randomized patients excluded from the analysis include the following: patients who did not provide a baseline QOL; patients who did not provide a 12-month QOL (exception made for patients who died before 12 months); and patients with an unsuccessful implant of the device as they were required by protocol to exit the study at 45 days post-implant attempt, therefore not providing a 12-month QOL. As shown in Figure 1, of the 361 patients enrolled in the device arm, 12 patients died before 12 months, and of the 186 patients enrolled in the control arm, 8 patients died before 12 months; therefore, 12-month QOL analyses were unavailable for these patients.

Procedure. Patients allocated to the intervention group received percutaneous closure of the LAA with the WATCHMAN device. This device is a self-expanding nickel titanium (nitinol) frame structure with fixation barbs and a permeable polyester fabric cover. It is implanted through a transseptal approach by use of a catheter-based delivery system to seal the ostium of the LAA. The implantation is guided by fluoroscopy and transesophageal echocardiography to verify proper positioning and stability. Patients in the device group were treated with acetylsalicylic acid and warfarin for 45 days after implant to facilitate device endothelialization. If the 45-day echocardiography documented satisfactory closure of the LAA (22,23), then the patient was switched to acetylsalicylic acid and clopidogrel for 4.5 months, after which acetylsalicylic acid alone was continued indefinitely. Patients in the control group received warfarin for the duration of the study, target international normalized ratio between 2.0 and 3.0. The patient's treating physician monitored the international normalized ratio at least every 2 weeks for 6 months and at least once a month thereafter.

Quality of life assessment. HRQOL was assessed using the generic validated questionnaire Short-Form 12 Health Survey, version 2 (SF-12v2), which offers a short, precise, statistically

tego, CSI, CVRx, EndoCross, EndoTex, Epitek, ev3, FlowCardia, Gore, Guidant, Guided Delivery Systems, InSeal Medical, Lumen Biomedical, HLT, Kensey Nash, Kyoto Medical, Lifetech, Lutonix, Maya Medical, Medinol, Medtronic, NDC, NMT, OAS, Occlutech, Osprey, Ovalis, Pathway, PendraCare, Percardia, pfm Medical, Recor, ResMed, Rox Medical, Sadra, Sorin, Spectranetics, SquareOne, Trireme, Trivascular, Velocimed, Veryan, and Vessix. Dr. Mullin is a paid consultant for NAMSA. Dr. Swarup has research relationships with Biosense Webster, St. Jude Medical, Boston Scientific, Medtronic, and Biotronik. Dr. Whisenant is a consultant to and has equity in Coherex. Dr. Alli has reported he has no relationships relevant to the contents of this paper to disclose.

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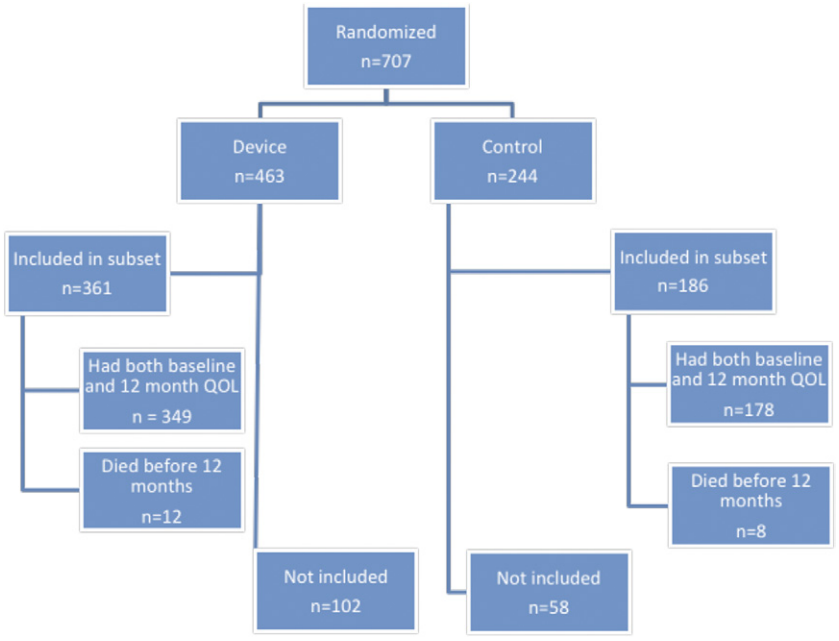

Figure 1 **Flow of Patients Enrolled in the Study**

Details of the flow of the device patients and control patients enrolled in the study. QOL = quality of life.

valid tool for health risk assessment and health outcomes monitoring. The SF12v2 is a multipurpose short-form survey with 12 questions, all selected from the Short-Form 36 Health Survey (24–26). The questions were combined, scored, and weighted to create 2 scales that provide an evaluation of mental and physical functioning and overall health-related-QOL. In the assessment of HRQOL by the SF-12v2, 8 dimensions are used, and these include physical functioning, physical role limitation, bodily pain, general health, vitality, social functioning, emotional role limitation, and mental health. Responses were acquired at baseline and at the end of 12 months in both the treatment group and the control group. Physical and mental health composite scores were then computed using the scores of the different dimensions and a score range from 0 to 100, where a zero score indicates the lowest level of health measured by the scales and 100 indicates the highest level of health.

Statistical analysis. Analyses were performed on randomized subjects for those with a paired mental and physical component score at baseline and 12 months, or in subjects who died before 1 year of follow-up irrespective of actual treatment received, following the intention-to-treat principle. Of the 463 subjects randomly assigned to the device group, 29 did not have baseline QOL data collected, and 101 did not have 12-month QOL data (not mutually exclusive). Of the 244 randomly allocated to the control group, 20 subjects did not have a baseline QOL and 58 did not have 12-month QOL data (not mutually exclusive). Of the 463 randomized device subjects, 361 (78%) were included in this analysis, and among the 244 randomized control subjects, 186 (76%) were included in this analysis ($p = 0.5991$, indicating no evidence of a different inclusion rate between groups).

Patients who had complications/adverse events with the WATCHMAN device were included with the analysis if they had baseline and 12-month QOL data available, including those with procedure-related complications. Subjects were not in the analysis if they withdrew from the study before 1 year or did not have 12-month QOL data available and did not die within 1 year. Figure 1 details the flow of the device and control patients enrolled into the study.

Of the 244 randomized control group subjects, 15 (6.2%) experienced an adverse event before 12 months and did not complete a 12-month QOL assessment, whereas of the 463 randomized device subjects, 50 (10.8%) experienced an adverse event before 12 months and did not complete a 12-month QOL assessment ($p = 0.937$, comparing the randomized groups for the fraction of subjects experiencing an adverse event who did not complete a 12-month QOL assessment). Thus, while the device group expectedly experienced more adverse events in the first year, largely due to the acute procedure, a similar fraction of subjects who experienced an adverse event had missing QOL data between the randomized groups.

For analysis of continuous changes in QOL, only observed results were used. For analyses based on a classification of improved/no change/worsened, subjects who died before 1 year without a follow-up QOL measure were included in the "worsened" category. Standard summary statistics (mean, standard deviation, median, range) were calculated for continuous variables. Categorical variables

were summarized using counts and percentages. Baseline characteristics were compared between randomized arms using *t* tests and chi-square tests. Quality of life scores were based on the SF-12 U.S. general population *t* scores.

Changes in QOL scores (month 12 from baseline) were compared between randomized groups using linear regression models, adjusted for by the baseline value. Subjects were classified as "worsened/death," "no change," and "improved" using the change in QOL. Subjects with a change of ≥3 were classified as improved; changes ≤−3 or subjects who died were classified as worsened/death. Otherwise subjects were classified as having no change in QOL status. The change within each limb and the magnitude of change between the 2 were compared with a linear model for the change in QOL adjusted for baseline. Changes are reported as the mean change ± SD. For the analysis of improved/no change/worsened, subjects who died were treated as worsened and the randomized groups were compared by Mantel-Haenszel chi-square tests. The analysis was not blinded to the treatment group, and there was no pre-defined endpoint for QOL. In addition, subsequent analysis was performed on the control group based on duration on warfarin; patients were divided into 2 subgroups: warfarin naive and not warfarin naive. Nominal p values were reported with no adjustments for multiple comparisons. Statistical analyses were conducted in SAS version 9.2 (SAS Institute, Cary, North Carolina).

Results

As discussed, 361 patients randomly assigned to the treatment arm and 186 patients in the control arm are included in this analysis (Table 1). Regarding patients excluded from this analysis based on the previously discussed reasons, it is important to state that there were very few differences between the group included in this analysis and the group excluded from this analysis in terms of their baseline differences and clinical outcomes (Table 2).

The baseline characteristics between the 2 groups included in this analysis were similar, with no clinically relevant differences between the 2 groups except for a higher prevalence of coronary artery disease in the control group compared to the device group ($p < 0.01$) (Table 1).

Table 3 summarizes the mean follow-up score and the mean change from baseline in the HRQOL assessment of all subjects. The baseline mean total physical score for the entire study population was 42.7 and 42.8 for device and control groups, respectively, which is below the norm for this population (norm = 50). The baseline total mental score of 53.1 and 53.9 for the device and control groups, respectively, was slightly above average for this population. As seen in Table 3 and Figure 2A, there was a significant difference in the change in the total physical score in the device treatment arm compared to the control arm ($p = 0.0015$), with most of the change being a decrease in total physical score in patients on warfarin therapy. On an individual basis, the total physical score improved in 34.9% of subjects and was unchanged in 29.9% compared to control subjects, of whom 24.7% were improved and 31.7% were unchanged ($p = 0.01$) (Fig. 2B). Comparing the device and control groups, there was no difference in the change in total mental score (Table 3); however, a more detailed assessment revealed that mental health improvement occurred in 33.0% of the device group versus 22.6% in the control group ($p = 0.06$). There were also differences in the change in HRQOL in the areas of physical functioning and physical role limitation in favor of the device group ($p = 0.0005$ and $p = 0.002$, respectively). As there was a significant difference between the groups for history of cardiovascular disease (Table 1), we performed adjusted analyses to account for possible confounding; results (not shown) were generally consistent after adjustment.

Subgroup comparisons. Within the device and control groups, patients were further divided into warfarin naive and

Table 1 Patient Characteristics

Characteristic	WATCHMAN (n = 361)	Control (n = 186)	p Value
Age, yrs	71.7 ± 8.8 72 (46–95)	72.9 ± 9.3 73.5 (41–95)	0.1609
Height, inches	68.4 ± 4.2 69 (54–82)	68.5 ± 4.2 69 (59–78)	0.7685
Weight, lbs	196.6 ± 44.0 193 (85–376)	198.0 ± 44.9 190 (110–312)	0.7276
Sex			0.8487
Female	102/361 (28.3)	54/186 (29.0)	
Male	259/361 (71.7)	132/186 (71.0)	
Race/ethnicity			0.5045
Asian	2/361 (0.6)	0/186 (0)	
Black/African American	3/361 (0.8)	2/186 (1.1)	
Caucasian	333/361 (92.2)	174/186 (93.6)	
Hispanic/Latino	21/361 (5.8)	9/186 (4.8)	
Hawaiian/Pacific Islander	0/361 (0)	1/186 (0.5)	
Other	2/361 (0.6)	0/186 (0)	
CHADS score	2.2 ± 1.1 2.0 (1–6)	2.4 ± 1.2 2.0 (1–6)	0.0517
CHADS score			
1	120/361 (33.2)	48/186 (25.8)	
2	127/361 (35.2)	68/186 (36.6)	
3	66/361 (18.3)	40/186 (21.5)	
4	32/361 (8.9)	17/186 (9.1)	
5	14/361 (3.9)	9/186 (4.8)	
6	2/361 (0.6)	4/186 (2.2)	0.3000
Warfarin naive			0.3325
Yes	75/361 (20.8)	32/185 (17.3)	
No	286/361 (79.2)	153/185 (82.7)	
>90 days warfarin experience	241/361 (66.8)	133/185 (71.9)	0.2217
>1 yr warfarin experience	178/361 (49.3)	90/185 (48.7)	0.8841
History of CAD	143/361 (39.6)	92/186 (49.5)	0.0275
History of diabetes mellitus	90/361 (24.9)	57/186 (30.6)	0.1532
History of hypertension	328/361 (90.9)	168/186 (90.3)	0.8381

Values are mean ± SD, median (range), or n (%).

CAD = coronary artery disease; CHADS = congestive heart failure, hypertension, age, diabetes mellitus, and stroke, transient ischemic attack, or thromboembolism.

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Table 2 Comparison of Baseline Characteristics of Patients Included and Excluded in the Analysis

Characteristic	Included (n = 547)	Not Included (n = 160)	p Value
Age, yrs	72.1 ± 9.0	71.8 ± 8.8	0.7286
Height, inches	68.5 ± 4.2	67.7 ± 4.3	0.0508
Weight, lbs	197.1 ± 44.3	188.2 ± 42.0	0.0251
Sex			
Female	156/547 (28.5)	54/160 (33.8)	0.2028
Male	391/547 (71.5)	106/160 (66.3)	
Race/ethnicity			
Asian	2/547 (0.4)	3/160 (1.9)	0.0307
Black/African American	5/547 (0.9)	6/160 (3.8)	
Caucasian	507/547 (92.7)	140/160 (87.5)	
Hispanic/Latino	30/547 (5.5)	10/160 (6.3)	
Hawaiian/Pacific Islander	1/547 (0.2)	1/160 (0.6)	
Other	2/547 (0.4)	0/160 (0.0)	
CHADS score	2.2 ± 1.2	2.2 ± 1.2	0.7346
CHADS score			
1	168/547 (30.7)	55/160 (34.4)	0.8370
2	195/547 (35.7)	51/160 (31.9)	
3	106/547 (19.4)	33/160 (20.6)	
4	49/547 (9.0)	12/160 (7.5)	
5	23/547 (4.2)	6/160 (3.8)	
6	6/547 (1.1)	3/160 (1.9)	
Warfarin naive			
Yes	107/546 (19.6)	30/152 (19.7)	0.9694
No	439/546 (80.4)	122/152 (80.3)	
>90 days warfarin experience	374/546 (68.5)	107/152 (70.4)	0.6550
>1 yr warfarin experience	268/546 (49.1)	74/152 (48.7)	0.9305
History of CAD	235/547 (43.0)	74/160 (46.3)	0.4608
History of diabetes mellitus	147/547 (26.9)	38/160 (23.8)	0.4291
History of hypertension	496/547 (90.7)	137/160 (85.6)	0.0664

Values are mean ± SD or n/N (%).
Abbreviations as in Table 1.

not warfarin naive subgroups. There were significant differences in the change in total physical score in warfarin naive patients in the device group compared to control (Fig. 3A), with a 12-month change of 1.3 ± 8.8 in the device group compared to −3.6 ± 6.7 in the control group (p = 0.0004) (Table 4). Specifically, in the device group, total physical score improved in 37.3%, unchanged in 32.0%, and worsened/death in 30.7% compared to the control group, in whom 15.6% improved, 34.4% were unchanged, and 50.0% worsened/death (p = 0.01) (Table 4, Fig. 3B). Significant improvement was also observed in the area of physical role limitation (p = 0.02) in the device group compared to control. There was no difference between the device group and the control group with regard to the change in total mental score.

Among the patients who had already been on warfarin, a similar difference in the change in total physical score was observed in the device group compared to control, with a 12-month change from baseline of 0.1 ± 9.0 for the device group compared to −1.7 ± 8.8 for the control group (p = 0.04) (Table 5, Fig. 4). Specifically, in the device group, total physical score improved in 34.3%, unchanged in 29.4%, and worsened/death in 36.4% compared to control, of whom 26.8% improved, 31.4% were unchanged, and 41.8% worsened/death (Table 5). There were also differences in the change in physical functioning and physical role limitation in the device group compared to the control group ($p < 0.05$). There was no significant difference between the device group and control group with regard to the change in the total mental score.

Analysis of mortality outcomes shows that among the entire randomized cohort of 707 subjects there was a higher proportion of deaths in the control group (26 of 244, 10.7%) compared to the device group (34 of 463, 7.3%). Of patients included in this analysis, there were 8 of 186 deaths within 1 year in the control group and 12 of 361 deaths within 1 year in the device group. That corresponds to 4.3% and 3.3% of patients in this analysis in the control group and the device group, respectively—again, proportionally fewer deaths in the device group.

Discussion

The main finding in this study is that patients with nonvalvular AF at risk for stroke treated with LAA closure have favorable QOL at 12 months compared to patients treated with warfarin. The improvements were mainly in the area of physical functioning and were seen in both warfarin naive and not warfarin naive patients treated with LAA closure. We also found a decrease in overall HRQOL in patients receiving chronic warfarin anticoagulation therapy compared to device therapy, and in subgroup comparisons, the decrease in overall HRQOL was more evident in subjects naive to warfarin compared to subjects' not naive to warfarin.

The PROTECT AF trial is the first randomized clinical trial that showed that LAA closure with the WATCHMAN device was noninferior to chronic warfarin therapy in stroke prevention in patients with nonvalvular AF. In addition, subsequent analysis revealed that the initial concerns about safety events in the PROTECT AF trial were largely procedure-related and that these events decreased in frequency with improvements in the learning curve and the rates of events, with the result that significant disability or death were statistically lower for LAA closure compared to warfarin therapy. We have also shown that, in addition to its efficacy and safety, there are significant improvements in HRQOL with device therapy in this population of elderly patients with multiple comorbidities.

Assessment of HRQOL is becoming an increasingly important metric in the evaluation of strategies with similar outcomes, or strategies with no distinct survival benefit. Improvement in QOL is a major goal in the management of chronic illnesses. Important issues addressed with HRQOL include the potential burdens and side effects of any treatment that leads to symptom improvement but may have a deleterious effect on general well-being. HRQOL is an

Table 3 SF12v2 Quality of Life Summary in All Patients (Device and Control) Comparing Baseline and 12-Month Change

	Treatment			Control			p Value*
	Baseline	12 Month	Change (12–BL)	Baseline	12 Month	Change (12–BL)	
Total physical score	42.7 ± 10.2 (360) 43.1 (17.6–64.3)	43.3 ± 11.0 (349) 45.0 (12.3–64.2)	0.4 ± 9.0 (349) 0.0 (−27.0 to 24.4)	42.8 ± 9.8 (183) 43.3 (11.6 to 59.6)	40.8 ± 10.3 (178) 41.4 (16.7 to 61.8)	−2.0 ± 8.5 (178) −1.2 (−24.7 to 23.4)	0.0015
Total mental score	53.1 ± 9.2 (360) 55.3 (20.0 to 70.9)	53.1 ± 8.7 (349) 55.0 (25.8, 73.0)	0.0 ± 10.3 (349) 0.1 (−31.0 to 45.2)	53.9 ± 8.9 (183) 55.8 (22.8, 70.6)	53.1 ± 9.7 (178) 54.9 (25.5, 70.9)	−0.9 ± 9.2 (178) −0.3 (−25.9 to 42.1)	0.6400
Physical functioning	43.3 ± 11.6 (360) 47.9 (22.1–56.5)	43.6 ± 12.0 (349) 47.9 (22.1, 56.5)	0.1 ± 11.7 (349) 0.0 (−34.4 to 34.4)	43.1 ± 11.2 (184) 43.6 (22.1, 56.5)	40.3 ± 11.3 (178) 39.3 (22.1, 56.5)	−3.0 ± 10.9 (178) 0.0 (−34.4 to 34.4)	0.0005
Physical role limitation	44.6 ± 10.3 (360) 43.4 (20.3–57.2)	45.2 ± 10.6 (349) 48.0 (20.3, 57.2)	0.4 ± 10.0 (349) 0.0 (−36.9 to 36.9)	45.2 ± 10.8 (185) 48.0 (20.3, 57.2)	43.0 ± 10.8 (178) 43.4 (20.3, 57.2)	−2.5 ± 10.1 (178) 0.0 (−36.9 to 32.2)	0.0021
Pain	47.9 ± 10.9 (360) 47.3 (16.7–57.4)	48.0 ± 11.4 (349) 47.3 (16.7, 57.4)	−0.1 ± 11.6 (349) 0.0 (−40.8 to 30.6)	48.6 ± 11.3 (185) 57.4 (16.7, 57.4)	47.8 ± 11.8 (178) 57.4 (16.7, 57.4)	−1.0 ± 10.4 (178) 0.0 (−30.6 to 30.6)	0.5668
General health	43.3 ± 9.7 (360) 40.4 (18.9, 62.0)	44.2 ± 10.2 (349) 40.4 (18.9, 62.0)	0.8 ± 8.8 (349) 0.0 (−21.6 to 32.3)	42.4 ± 10.2 (185) 40.4 (18.9, 62.0)	42.2 ± 9.7 (178) 40.4 (18.9, 62.0)	−0.2 ± 9.7 (178) 0.0 (−43.1 to 32.3)	0.0606
Vitality	50.3 ± 9.8 (360) 47.7 (27.6, 67.9)	50.7 ± 10.1 (349) 47.7 (27.6, 67.9)	0.2 ± 10.9 (349) 0.0 (−40.3 to 40.3)	51.0 ± 10.4 (185) 47.7 (27.6, 67.9)	49.8 ± 10.7 (178) 47.7 (27.6, 67.9)	−1.4 ± 10.8 (178) 0.0 (−30.2 to 40.3)	0.1614
Social functioning	49.9 ± 9.6 (360) 56.6 (16.2, 56.6)	50.4 ± 9.4 (349) 56.6 (16.2, 56.6)	0.5 ± 10.5 (349) 0.0 (−30.3 to 30.3)	50.9 ± 9.5 (185) 56.6 (16.2, 56.6)	49.3 ± 10.1 (178) 56.6 (16.2, 56.6)	−1.6 ± 10.2 (178) 0.0 (−30.3 to 40.4)	0.0650
Emotional role limitation	48.2 ± 10.7 (360) 56.1 (11.3, 56.1)	48.1 ± 10.8 (349) 56.1 (11.3, 56.1)	−0.3 ± 11.9 (349) 0.0 (−44.7 to 44.7)	48.3 ± 10.5 (185) 56.1 (11.3, 56.1)	46.6 ± 11.5 (178) 50.5 (11.3, 56.1)	−1.8 ± 11.7 (178) 0.0 (−44.7 to 44.7)	0.1115
Mental health	52.6 ± 9.8 (360) 52.3 (21.9–64.5)	52.8 ± 9.1 (349) 52.3 (21.9–64.5)	0.0 ± 10.5 (349) 0.0 (−36.6 to 42.7)	53.7 ± 9.1 (184) 58.4 (15.8–64.5)	52.9 ± 9.4 (178) 52.3 (28.0–64.5)	−0.9 ± 9.6 (178) 0.0 (−24.4 to 42.7)	0.6780

Values are mean ± SD (N), and median (range). *The p values compare the randomized groups for the change in quality of life component adjusted for the baseline value.
BL = baseline.

outcome assessment that reflects subjective impairment in general well-being caused by individual aspects of pain and psychological, emotional, and physical disturbances.

The minimally important difference in the SF-12v2 summary scales is approximately 2 to 2.5 points (27,28). Examination of the randomized groups revealed modest improvements in HRQOL with LAA closure, but a significant decrease in HRQOL with warfarin therapy. When the analysis was performed looking at individual subjects, a larger fraction of patients had significant improvements in HRQOL with device therapy compared to control. In our study population, 34.9% of device subjects improved on the total physical score by 3 or more points compared to 24.7% of control subjects; furthermore, 35.2% of device subjects worsened compared to 43.5% of control subjects. Similar changes were also seen in the subgroups as mentioned earlier. The clinical significance of these changes is that a larger proportion of patients who underwent LAA closure had an improvement in their health status compared to control subjects. Our data also suggest that the benefits may be more pronounced in patients who are naive to warfarin compared to patients who were already receiving warfarin, but these are not conclusive data as this was a subgroup analysis and head-to-head comparisons of both groups were not performed.

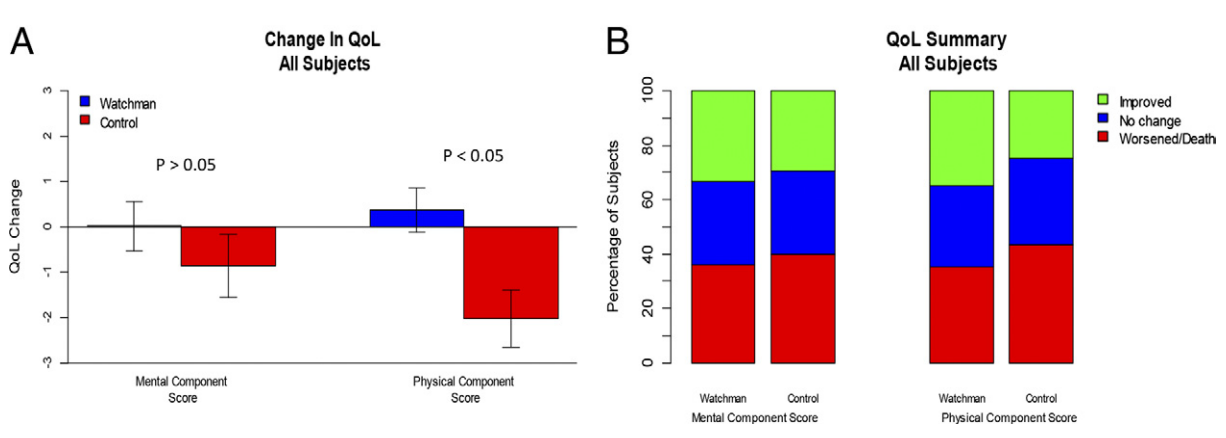

Figure 2 Change in QOL in All Subjects, Device Versus Control

(A) The change in quality of life (QOL) in all patients for the mental and physical component scores, device **(blue bars)** compared to warfarin **(red bars)**, is shown. **(B)** The relative change in QOL among individual patients within each group is depicted. **Green areas** = improved; **blue areas** = no change; **red areas** = worsened/death.

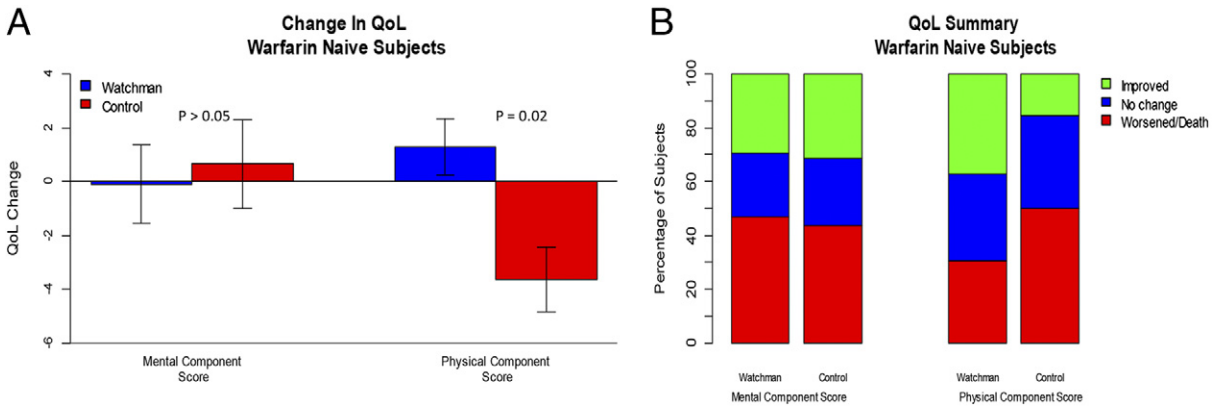

Figure 3 Change in QOL in Warfarin Naive Subjects, Device Versus Control

(A) The change in quality of life (QOL) is shown in warfarin naive patients for the mental and physical component scores, device **(blue bars)** compared to warfarin **(red bars)**. **(B)** The relative change in QOL among individual patients within each group. **Green areas** = improved; **blue areas** = no change; **red areas** = worsened/death.

This is the first study examining the impact of LAA closure on HRQOL in patients with chronic AF at a high risk of stroke. We have found a modest improvement in HRQOL with LAA closure, with a concomitant decrease in HRQOL with warfarin therapy. There are several potential reasons for the findings. We believe that perhaps the most plausible is based on the following information: 1) patients are told at length about the risks of stroke with AF; 2) they are told that the stroke typically, although not 100%, comes from the LAA; 3) they are told that this trial is aimed at testing whether a mechanical solution can be as effective as long-term warfarin therapy in reducing stroke but without the need for the issues of long-term warfarin therapy; and 4) they are given information on the risks of the device and the risks of warfarin. With that information background, patients who receive the device, and are reassured during follow-up that the device is working, are reassured and empowered in a sense to be more active and to behave in that way. The patients on warfarin, conversely, continue to have the blood tests and the dietary issues that we talk to them about and the bleeding hazard, and so they may restrict their activities more. More importantly, among the warfarin naive patients, avoiding those issues with anticoagulation therapy with warfarin may lead to improved QOL in these patients.

There have been several studies looking at the HRQOL with warfarin therapy among patients with chronic AF. In a study by Lancaster et al. (7) for the Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators, the effect of long-term warfarin therapy was examined in a

Table 4 SF12v2 Quality of Life Summary in Warfarin Naive Patients (Device and Control) Comparing Baseline and 12-Month Change

	Treatment			Control			p
	Baseline	12 Month	Change (12–BL)	Baseline	12 Month	Change (12–BL)	Value*
Total physical score	41.1 ± 10.3 (75) 42.6 (17.7–58.6)	42.5 ± 9.1 (72) 43.4 (19.8–56.7)	1.3 ± 8.8 (72) 0.7 (–19.9 to 24.4)	38.9 ± 10.6 (32) 39.4 (11.6–58.1)	35.6 ± 11.1 (31) 37.0 (16.7–55.1)	–3.6 ± 6.7 (31) –3.0 (–15.0 to 10.6)	0.0004
Total mental score	52.0 ± 10.2 (75) 54.8 (20.0–68.3)	52.1 ± 9.0 (72) 53.7 (29.4–70.1)	–0.1 ± 12.3 (72) –0.9 (–26.1 to 40.3)	50.9 ± 10.2 (32) 53.2 (30.9–67.4)	52.0 ± 10.7 (31) 54.6 (27.3–70.9)	0.7 ± 9.2 (31) –1.6 (–11.9 to 29.3)	0.9230
Physical functioning	42.3 ± 12.2 (75) 47.9 (22.1–56.5)	43.0 ± 11.0 (72) 39.3 (22.1–56.5)	1.0 ± 10.5 (72) 0.0 (–17.2 to 25.8)	37.9 ± 11.4 (32) 39.3 (22.1–56.5)	35.7 ± 11.3 (31) 39.3 (22.1–56.5)	–2.8 ± 10.0 (31) 0.0 (–25.8 to 17.2)	0.0067
Physical role limitation	43.3 ± 10.1 (75) 43.4 (20.3–57.2)	44.1 ± 9.1 (72) 43.4 (20.3–57.2)	0.5 ± 10.4 (72) 0.0 (–23.0 to 36.9)	43.2 ± 10.0 (32) 43.4 (20.3–57.2)	38.7 ± 11.4 (31) 38.7 (20.3–57.2)	–4.9 ± 9.9 (31) –4.6 (–36.9 to 13.8)	0.0049
Pain	46.3 ± 11.4 (75) 47.3 (16.7–57.4)	48.1 ± 9.6 (72) 47.3 (26.9–57.4)	1.7 ± 10.8 (72) 0.0 (–20.4 to 20.4)	45.3 ± 13.8 (32) 47.3 (16.7–57.4)	43.0 ± 12.6 (31) 47.3 (16.7–57.4)	–2.6 ± 10.8 (31) 0.0 (–30.6 to 20.4)	0.0144

	Worse/Death†	No Change	Improved‡	Worse/Death†	No Change	Improved‡
Mental health improvement	41.3% (31/75)	28.0% (21/75)	30.7% (23/75)	40.6% (13/32)	28.1% (9/32)	31.3% (10/32)
Total physical score improvement	30.7% (23/75)	32.0% (24/75)	37.3% (28/75)	50.0% (16/32)	34.4% (11/32)	15.6% (5/32)
Total mental score improvement	46.7% (35/75)	24.0% (18/75)	29.3% (22/75)	43.8% (14/32)	25.0% (8/32)	31.3% (10/32)
Physical functioning improvement	30.7% (23/75)	38.7% (29/75)	30.7% (23/75)	37.5% (12/32)	46.9% (15/32)	15.6% (5/32)
Physical role limitation improvement	36.0% (27/75)	28.0% (21/75)	36.0% (27/75)	62.5% (20/32)	15.6% (5/32)	21.9% (7/32)

Values are mean ± SD, (N), median (range), and % (n/N). *p Values compare the randomized groups for the change in QoL component, adjusted for the baseline value. †Worsensing of 3 or more, or death prior to 12 months. ‡Improvement of 3 or more.
BL = baseline.

Table 5 SF12v2 Quality of Life Summary in Not Warfarin Naive Patients (Device and Control) Comparing Baseline and 12-Month Change

	Treatment			Control			p
	Baseline	12 Month	Change (12–BL)	Baseline	12 Month	Change (12–BL)	Value*
Total physical score	43.1 ± 10.1 (285) 43.2 (17.6–64.3)	43.5 ± 1.4 (277) 45.3 (12.3–64.2)	0.1 ± 9.0 (277) 0.0 (−27.0 to 23.9)	43.6 ± 9.5 (150) 45.0 (15.1–59.6)	41.9 ± 9.8 (147) 42.3 (16.9–61.8)	−1.7 ± 8.8 (147) −0.5 (−24.7 to 23.4)	0.0432
Total mental score	53.3 ± 8.9 (285) 55.4 (27.8–70.9)	53.4 ± 8.6 (277) 55.8 (25.8–73.0)	0.0 ± 9.7 (277) 0.2 (−31.0 to 45.2)	54.5 ± 8.5 (150) 56.8 (22.8–70.6)	53.3 ± 9.5 (147) 55.0 (25.5–70.3)	−1.2 ± 9.2 (147) 0.0 (−25.9 to 42.1)	0.5032
Physical functioning	43.6 ± 11.4 (285) 47.9 (22.1–56.5)	43.8 ± 12.3 (277) 47.9 (22.1–56.5)	−0.1 ± 12.0 (277) 0.0 (−34.4 to 34.4)	44.1 ± 10.9 (151) 47.9 (22.1–56.5)	41.2 ± 11.1 (147) 39.3 (22.1–56.5)	−3.1 ± 11.1 (147) 0.0 (−34.4 to 34.4)	0.0091
Physical role limitation	44.9 ± 10.4 (285) 48.0 (20.3–57.2)	45.5 ± 11.0 (277) 48.0 (20.3–57.2)	0.3 ± 9.9 (277) 0.0 (–36.9 to 27.6)	45.6 ± 11.0 (152) 48.0 (20.3–57.2)	44.0 ± 10.4 (147) 48.0 (20.3–57.2)	−2.0 ± 10.0 (147) 0.0 (–32.2 to 32.2)	0.0311
Pain	48.3 ± 10.7 (285) 47.3 (16.7–57.4)	47.9 ± 11.8 (277) 57.4 (16.7–57.4)	−0.6 ± 11.8 (277) 0.0 (–40.8 to 30.6)	49.3 ± 10.7 (152) 57.4 (16.7–57.4)	48.8 ± 11.4 (147) 57.4 (16.7–57.4)	−0.7 ± 10.3 (147) 0.0 (–30.6 to 30.6)	0.7071

	Worse/Death†	No Change	Improved‡	Worse/Death†	No Change	Improved‡
Mental health improvement	34.3% (98/286)	32.2% (92/286)	33.6% (96/286)	38.6% (59/153)	40.5% (62/153)	20.9% (32/153)
Total physical score Improvement	36.4% (104/286)	29.4% (84/286)	34.3% (98/286)	41.8% (64/153)	31.4% (48/153)	26.8% (41/153)
Total mental score improvement	33.2% (95/286)	32.5% (93/286)	34.3% (98/286)	38.6% (59/153)	32.0% (49/153)	29.4% (45/153)
Physical functioning improvement	32.5% (93/286)	42.7% (122/286)	24.8% (71/286)	42.5% (65/153)	43.1% (66/153)	14.4% (22/153)
Physical role limitation improvement	33.2% (95/286)	32.9% (94/286)	33.9% (97/286)	46.4% (71/153)	28.8% (44/153)	24.8% (38/153)

Values are mean ± SD (N), median (range), and % (n/N). *p Values compare the randomized groups for the change in QoL component, adjusted for the baseline value. †Worsening of 3 or more, or death prior to 12 months. ‡Improvement of 3 or more.
BL = baseline.

cohort of 333 patients enrolled in a randomized, controlled trial of warfarin for the prevention of stroke for nonrheumatic AF. They found no significant differences in HRQOL between warfarin-treated patients and control patients. However, significant differences were found in HRQOL among patients on warfarin who had a bleeding event, with a significant decrease in perceived health.

A more recent study examined HRQOL in patients with chronic AF just starting warfarin therapy (29). This was an observational study that had a cohort of 110 patients with chronic AF. In this study, the SF-12v2 questionnaire was also used for QOL assessment, and there was no significant difference in HRQOL in patients on warfarin after 6 months.

In a study by Wokhlu et al. (30), HRQOL in patients undergoing AF ablation was examined; 323 patients undergoing AF had HRQOL analysis using the SF-36 questionnaire. These investigators found that there was sustained improvement in HRQOL in these patients at 2 years even if they had recurrence of AF. Their analysis also looked at the impact of warfarin; they concluded that in their study cohort of post-ablation patients, the QOL benefit of AF ablation is decreased in patients receiving long-term anticoagulation therapy.

The potential advantage of device closure of the LAA over chronic warfarin therapy for patients with nonvalvular AF includes the reduction in bleeding complications, which includes serious bleeds and nuisance bleeds, and the elimination of the inconvenience of anticoagulation monitoring. Other benefits include elimination of dietary and potential drug interactions with warfarin that may affect the interna-

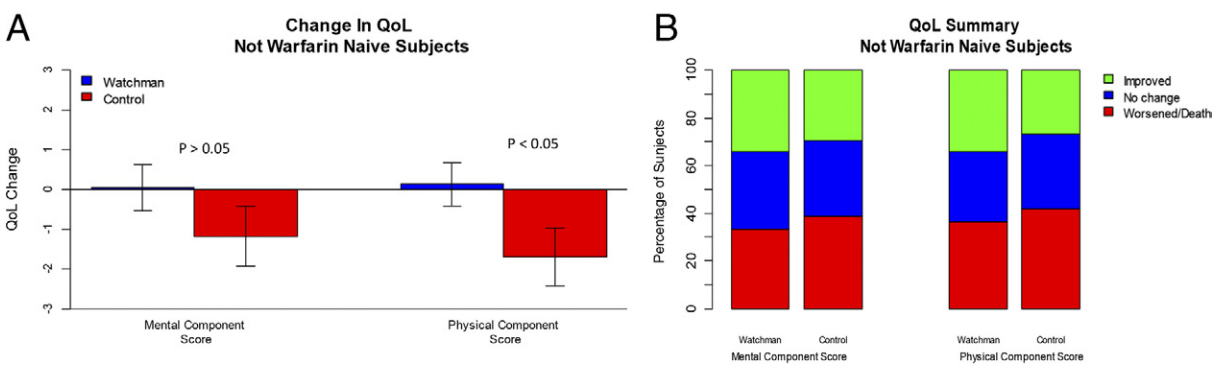

Figure 4 Change in QOL in Not Warfarin Naive Subjects, Device Versus Control

(A) Change in quality of life (QOL) in not warfarin naive patients for the mental and physical component scores, device **(blue bars)** compared to warfarin **(red bars)**, is depicted. **(B)** Relative change in QOL among individual patients within each group is shown. **Green areas** = improved; **blue areas** = no change; **red areas** = worsened/death.

tional normalized ratio levels and the potential benefit of using dual antiplatelet agents where necessary.

Study limitations. The small sample size of the study population and the relatively short follow-up period are limitations of this study. Patients were also unblended in this study. Subjects included in this analysis differed significantly from subjects not included in the analysis on several baseline factors, including weight and race/ethnicity (both $p < 0.05$); subjects included in the analysis tended to have a higher weight and were more likely to be Caucasian. It is possible that the cohort reported here suffers from selection bias and that the results could be different if there was complete follow-up on all randomized subjects. We leveraged the randomized comparison and covariate analysis to adjust for differences among the included randomized subjects to help control bias.

Conclusions

For patients with chronic AF treated with LAA closure with the WATCHMAN device versus chronic anticoagulation therapy with warfarin, there was improvement in HRQOL at 12 months among patients treated with device therapy, and a decrease in HRQOL among patients receiving warfarin therapy.

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Key Words: atrial fibrillation ■ health-related quality of life ■ left atrial appendage occlusion ■ stroke prevention ■ warfarin.