

# Factors Associated with Large Improvements in Health-Related Quality of Life in Patients with Atrial Fibrillation: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF)

**Running title:** *Steinberg et al.; Dramatic hrQoL Improvement in AF*

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## Abstract:

**Background** - Atrial fibrillation (AF) adversely impacts health-related quality of life (hrQoL). While some patients demonstrate improvements in hrQoL, the factors associated with large improvements in hrQoL are not well described.

**Methods** - We assessed factors associated with a 1-year increase in AFEQT of 1 standard deviation ( $\geq 18$  points; 3x clinically important difference), among outpatients in the ORBIT-AF I registry.

**Results** - Overall, 28% (181/636) of patients had such a hrQoL improvement. Compared with patients not showing large hrQoL improvement, they were of similar age (median 73 vs. 74,  $p=0.3$ ), equally likely to be female (44% vs. 48%,  $p=0.3$ ), but more likely to have newly-diagnosed AF at baseline (18% vs. 8%;  $p=0.0004$ ), prior antiarrhythmic drug use (52% vs. 40%,  $p=0.005$ ), baseline antiarrhythmic drug use (34.8% vs. 26.8%,  $p=0.045$ ), and more likely to undergo AF-related procedures during follow-up (AF ablation: 6.6% vs. 2.0%,  $p=0.003$ ; cardioversion: 12.2% vs. 5.9%  $p=0.008$ ). In multivariable analysis, a history of alcohol abuse (adjusted OR 2.41,  $p=0.01$ ) and increased baseline diastolic BP (adjusted OR 1.23 per 10-point increase and  $>65$  mm Hg,  $p=0.04$ ) were associated with large improvements in hrQoL at 1 year, whereas patients with prior stroke/TIA, COPD, and PAD were less likely to improve ( $p<0.05$  for each).

**Conclusions** - In this national registry of AF patients, potentially treatable AF risk factors are associated with large hrQoL improvement, whereas less reversible conditions appeared negatively associated with hrQoL improvement. Understanding which patients are most likely to have large hrQoL improvement may facilitate targeting interventions for high-value care that optimizes patient reported outcomes in AF.

**Clinical Trial Registration** - [clinicaltrials.gov.](https://clinicaltrials.gov/); Unique Identifier: NCT01165710

**Key words:** atrial fibrillation; patient reported outcome; quality of life; AFEQT; response

**Nonstandard Abbreviations and Acronyms:** ORBIT-AF: Outcomes Registry for Better Informed Treatment of Atrial Fibrillation; AFEQT: Atrial Fibrillation Effect on Quality-of-Life; AFFECTS: Atrial Fibrillation: Focus on Effective Clinical Treatment Strategies

## **Introduction**

Atrial fibrillation (AF) represents the most common sustained tachyarrhythmia in adults, and accounts for substantial health systems resources.<sup>1-3</sup> Additionally, patients with AF demonstrate reduced health-related quality of life (hrQoL), which is similar in magnitude to that experienced by patients who have had a myocardial infarction.<sup>4</sup> Certain interventions for AF may improve hrQoL.<sup>5-7</sup> However, there can be heterogeneity of responses in hrQoL: some patients may not improve at all while others appear to demonstrate marked improvement in symptom burden over time. Patients with heart rhythm disorders who exhibit large improvement of symptoms and/or hrQoL are often labeled as ‘super-responders’, as is the case for some patients treated with cardiac resynchronization therapy.<sup>8</sup>



However, the optimal identification of AF patients who are most likely to experience such large improvement in hrQoL, and how to tailor therapy to these patients, remains a challenge.<sup>6,7</sup> Patients’ health status is particularly important for highly symptomatic patients and is not reflected in traditional clinical outcomes of rehospitalization or death. Accordingly, we used data from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry to identify factors associated with large improvements in hrQoL for patients with AF. More specifically, the primary aims of this analysis are: (1) to identify patients who experience large improvements in hrQoL; (2) to understand patient factors associated with large improvements in hrQoL; and (3) to describe interval interventions and outcomes among these patients with large improvements in hrQoL.

## **Methods**

Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to Dr.

Jonathan P. Piccini, at Duke University. The ORBIT-AF registry is a national, US, prospective cohort study of outpatients with AF, enrolled by primary care physicians, cardiologists, and/or electrophysiologists from June 2010 to August 2011. The study was managed and coordinated by the Duke Clinical Research Institute. Sites enrolled consecutive patients with electrocardiographically-documented AF, age 18 years or older. Patients were followed up every 6 months for at least 2 years. Patients were excluded if life expectancy was less than 6 months or AF was felt to be due to a reversible cause.

Data were entered in a web-based case report form, derived primarily from the patient's medical record. Data elements included demographics, medical history, AF history (including symptoms), medical therapies, vital signs, laboratory and echocardiographic measures, and incident procedures and adverse events. Complete details of the ORBIT-AF design and rationale have been described previously.<sup>9</sup>

Approximately 20% of all enrolled patients participated in the pre-specified ORBIT-AF hrQoL substudy, as determined by the local site. Among these patients, disease-specific hrQoL was measured using the Atrial Fibrillation Effect on Quality-of-Life (AFEQT) Questionnaire.<sup>10</sup> This 20-item AF-specific patient-reported outcome (PRO) tool assesses AF-related hrQoL across four domains: symptoms, daily activities, treatment concern, and treatment satisfaction. Each domain is evaluated through 2-4 questions each with a 7-point Likert response ranging from the most severe limitation/symptoms (resulting in a minimum overall score of 0) to no limitation/symptoms (resulting in a maximum overall score of 100). The AFEQT score is calculated based on questions answered, and complete response to all questions is not required to calculate an overall score.

## **Study Population**


The present study included all patients for whom hrQoL improvement could be assessed. This required patients to have baseline and 1-year AFEQT scores, and a baseline AFEQT score low enough to provide an opportunity for significant improvement ( $\leq 82$ ). For the purpose of this analysis, we defined large hrQoL improvement as an increase in AFEQT of  $\geq 18$  points from baseline to one-year follow-up. This was based on one standard deviation above the mean change in AFEQT for this population, and also because it represents a 3-fold greater improvement compared with: (1) the clinically important difference for AFEQT,<sup>11, 12</sup> and (2) the improvement in hrQoL observed in recent major clinical trials of AF ablation.<sup>6, 7</sup>

### **Statistical Methods**

All baseline characteristics and univariate data are presented as frequencies and percentages for categorical variables and medians (25<sup>th</sup>, 75<sup>th</sup> percentiles) for continuous variables for those with large hrQoL improvement versus those without. The baseline characteristics were compared using the Chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables. Events occurring between baseline and the one-year AFEQT measure, by hrQoL improvement status, are described as frequencies and percentages. Statistical comparisons were based on a Chi-square test.

To determine which factors were associated with a large hrQoL improvement, backwards selection with an exclusion criterion of 0.05 was used to build a multivariable logistic regression model using the candidate variables in **Supplemental Material, Table S1**. All continuous variables were evaluated for non-linearity with the outcome, and linear splines were used for variable that did not meet the linear relationship criteria ( $p < 0.05$ ). Odds ratio (OR) with corresponding 95% confidence interval (CI) and p-value were presented from a multivariable GEE logistic regression model with constant correlation between patients within sites

(exchangeable working correlation structure). Missing data was handled with single imputation and imputed values were obtained by Markov chain Monte Carlo (MCMC) or regression methods. Specifically, MCMC was used to create a monotone missing data pattern and then the logistic regression method and regression method were used to impute binary/ordinal and continuous variables, respectively. Lastly, the discriminate function method was used to impute the remaining nominal variables with missing values. All variables on the candidate variable list had less than 5% missing except: LVEF type (16%), LA diameter type (20%), eGFR (8%) and hematocrit (10%).

Event rates per 100-person years are presented by hrQoL improvement status and compared using Poisson regression. Time zero for event ascertainment was the date of the one-year AFEQT survey date. 

All subjects provided written, informed consent, and each site received institutional review board (IRB) approval for this study, according to local regulations. The ORBIT-AF registry is approved by the Duke University IRB. All analyses of the aggregate, de-identified data were performed by the Duke Clinical Research Institute using SAS software (version 9.4, SAS Institute, Cary, North Carolina, USA) and a two-tailed p-value <0.05 was considered significant for all statistical tests.

### **Sensitivity Analyses**

Two sensitivity analyses of the model of large hrQoL improvement were calculated: a) including patients who died from baseline to 1 year as unimproved, and b) in the subset of patients who were diagnosed with AF > 1 year before entry into the study.

### **Results**

## Cohort Formation & Patient Characteristics

Among the overall ORBIT-AF population of 10,137 patients from 176 sites, 2,008 subjects participated in the ORBIT-AF hrQoL substudy (from 56% of sites) at baseline. Among these, 94% answered all AFEQT questions at baseline. After excluding patients without 1-year AFEQT assessments (n=661), and those with baseline AFEQT >82 (n=711), this yielded an analysis population of 636 patients. At baseline, these patients had a median overall AFEQT score of 67.6 (IQR 54.6, 75.9). Overall, 181 patients (28%) qualified as having a large improvement in hrQoL with AFEQT improvement of  $\geq 18$  points from baseline to 1 year (see **Figure 1**).

Baseline characteristics overall and stratified by hrQoL improvement status are shown in **Table 1**. Compared with those without an improvement in health status, patients experiencing large improvement in AFEQT were of similar age (median 73 vs. 74,  $p=0.3$ ), and frequency of female sex (44% vs. 48%,  $p=0.3$ ). However, those with marked improvements in hrQoL were more likely to have newly-diagnosed AF at baseline (18% vs. 8%) and less likely to be persistent/permanent AF (33.7% vs. 46.2%,  $p=0.0004$ ). Baseline use of rate control medications was not different between the groups, however, those with large hrQoL improvement were more likely to be on antiarrhythmic therapy at baseline (34.8% vs. 26.8%,  $p=0.045$ ). There was no difference in rates of sinus rhythm on most recent electrocardiogram, between those with or without large hrQoL improvement (32.0% vs. 29.2%,  $p=0.5$ ). Baseline symptom status, including specific AF symptoms and AFEQT subscales, are shown in the **Table 2**. Specific symptoms at baseline were generally balanced between the groups, except those with large hrQoL improvement were more likely to experience light-headedness/dizziness (40% vs. 29%,  $p=0.009$ ) and fatigue (45% vs. 35%,  $p=0.02$ ). However, patterns of AFEQT domain change at 1

year differed between the groups (**Figure 2**); patients with large overall improvement in hrQoL at 1 year appeared to demonstrate more improvement in daily activities and treatment concerns.

### **hrQoL Response & Interval Events**

Interval interventions and adverse events between baseline and one-year follow-up in these patients are shown in **Supplemental Material, Table S2**, stratified by hrQoL response status.

Overall, patients that experienced large improvement in hrQoL at one year, were more likely to have had interval procedures related to AF, including catheter ablation of AF (6.6% vs. 2.0%,  $p=0.003$ ), surgical AF ablation (1.1 % vs. 0,  $p=0.02$ ), and cardioversion (12.2% vs. 5.9%,  $p=0.008$ ). There were no significant differences in interim adverse clinical events between the two groups, including major bleeding, thromboembolic events, new heart failure, or hospitalization, though event rates were low.



### **Factors Associated with Large Improvements in hrQoL**

Complete results of multivariable analysis to identify factors associated with large improvements in hrQoL are shown in **Figure 3**. Patients with worse hrQoL at baseline have more opportunity for improvement; in our adjusted analyses, compared to those with baseline score  $<50$ , patients with a baseline score  $>50$  had lower odds of AFEQT improvement, and rate of improvement decreased as baseline AFEQT increased (adjusted OR 0.69 per 5-point increase, 95% CI 0.63-0.76; see **Supplemental Material, Figure S1**). Additionally, patients most likely to experience large hrQoL improvement were those with a history of alcohol abuse (adjusted OR 2.41, 95% CI 1.23-4.70) and patients with elevated diastolic blood pressure at baseline (adjusted OR 1.23 per 10-point increase  $>65$ , 95% CI 1.01-1.49). In contrast, patients with prior stroke/TIA (adjusted OR 0.48, 95% CI 0.29-0.8), COPD (adjusted OR 0.67, 95% CI 0.47-0.95), or peripheral arterial



disease (PAD; adjusted OR 0.53, 95% CI 0.30-0.93) were less likely to experience a large improvement in hrQoL.

### **Clinical Events & Sensitivity Analyses**

During follow-up *after* 1 year, there was no difference in rates of major bleeding, thromboembolic events, new heart failure, or hospitalization between those with and without significant hrQoL improvement (**Supplemental Material, Table S3**). In the primary analysis, patients who died during follow-up were excluded as not having the opportunity to improve hrQoL. In a sensitivity analysis including these patients as not improved, multivariate models yielded similar factors associated with large hrQoL improvement (**Supplemental Material, Table S4**).



After excluding patients with recent AF diagnosis (<1 year of enrollment), the resulting sensitivity analysis population yielded 448 patients of which 113 experienced a large improvement in hrQoL (25%). Baseline characteristics of these subgroups did not differ dramatically from the primary analytic cohort. Multivariate analysis of factors associated with a large improvement in hrQoL in this subset consistently included baseline AFEQT score, prior stroke/TIA, and PAD; instead of COPD, history of anemia was associated with increased odds of experiencing a large improvement in hrQoL (adjusted OR 2.11, 95% CI 1.25-3.55;

**Supplemental Material, Table S5**).

### **Discussion**

In this analysis of symptomatic patients with AF, there are several important conclusions. First, there is a substantial subgroup of AF patients who will demonstrate large improvement in AF hrQoL over one-year follow up, and these changes appear driven by improvements in activities

of daily living and treatment concerns. Second, patients who experienced a large improvement in hrQoL at 1 year had higher rates of rhythm control interventions, including baseline antiarrhythmic drug therapy (34.8% vs, 26.8%,  $p=0.045$ ) and interim AF ablation (6.6% vs. 2.0%,  $p=0.003$ ). Nevertheless, after adjustment baseline rhythm control therapy (i.e., antiarrhythmic drug use) was not associated with having large hrQoL improvement at one year, whereas potentially modifiable risk factors, including alcohol abuse and elevated diastolic blood pressure, were associated with large symptomatic improvement. Lastly, chronic, difficult-to-treat comorbidities appear to make large hrQoL improvement less likely. These data highlight the potential for significant improvement in symptom status for a condition that is typically associated with poor hrQoL, and further studies are needed to evaluate interventions in the patients most likely to improve.

There are several likely contributors to the symptomatic improvement in these patients with large improvements with hrQoL. Our multivariable model demonstrated both baseline alcohol abuse and elevated diastolic blood pressure were significantly associated with large hrQoL improvement at one year; these are both potentially-modifiable risk factors for AF, which can be effectively treated and may have led to improvement in hrQoL. We acknowledge, however, that we cannot definitely demonstrate a causal relationship between treatment of these conditions and hrQoL response. Additionally, patients with large hrQoL improvement were more likely to have new-onset AF and more recent-diagnosis date – while this may have meant more aggressive rhythm control interventions to improve symptoms, we cannot exclude an element of ‘hedonic adaptation’ leading to improvement in *reported* hrQoL. The Atrial Fibrillation: Focus on Effective Clinical Treatment Strategies (AFFECTS) registry previously demonstrated differing symptom profiles among patients with paroxysmal versus persistent AF.<sup>13</sup> Lastly, while

we observed that patients with large hrQoL were more likely to have received medications for rhythm control (prior and baseline antiarrhythmic drug therapy), this was not associated with hrQoL improvement at follow-up.

In contrast, several significant, difficult-to-treat comorbidities were associated with not having significant improvement in hrQoL: COPD, prior stroke/TIA, and PAD. It is well-known that concomitant COPD impacts outcomes, including hrQoL, among AF patients.<sup>14</sup> Those with prior cerebrovascular events may have permanent, residual deficits limiting their hrQoL, and patients with PAD may have life-altering symptoms that are difficult to treat, and less likely to be impacted by interventions for AF.

Furthermore, our data on the domains of the AFEQT show more frequent improvement in daily activities and treatment concerns, compared with symptoms and treatment satisfaction – in fact, significant proportions of our patients had no improvement, or worsening, in the later metrics. These findings may underscore the above model, demonstrating that the primary factors associated with large hrQoL improvement (or not) were geared towards risk factors (e.g., hypertension, alcohol) and co-morbidities (e.g., PAD, COPD), and not specific AF interventions. However, the domains also suggest opportunities for further improvement in the hrQoL of these patients – relatively few underwent catheter ablation during follow-up, an intervention proven to improve disease-specific symptoms across AF cohorts.<sup>6, 7, 15, 16</sup>

These data have important implications for the management of patients with symptomatic AF. Among the primary objectives is to improve hrQoL, and as we have observed, this response is heterogeneous. Understanding factors associated with improvement and decline, and particularly among components of hrQoL, is vital to the appropriate implementation of therapies for both AF and concomitant comorbidities. While rhythm control therapies, primarily

antiarrhythmic drugs and catheter ablation, are generally safe and effective, they are not without risk and would ideally target patients most likely to benefit. Ultimately, targeting the appropriate intervention, at the appropriate disease state, and in the appropriate patient, will provide the best opportunities for more consistently, and comprehensively, improving hrQoL in these patients.

### **Limitations**

The data utilized in this analysis are derived from an observational, real-world dataset, and therefore may be subject to sampling bias. Additionally, the analytic cohort was relatively small, with a lower power to detect differences in rarer events between the two groups. There were few events per variable included in the candidate variable list for the factors associated with large improvement in hrQoL model, which may have led to overfitting in the model. The assessments of hrQoL were not timed to specific interventions or changes in therapy. Residual measured and unmeasured confounding may account in part for the observed associations, and we cannot ascribe a direct causal effect for factors associated with hrQoL improvement; additionally, there may be some aspect of regression to the mean that contributed to our findings. Lastly, the definition of large improvement in hrQoL was empirically based on both the population distribution and other studies of observed hrQoL changes, and results may vary with different hrQoL change thresholds or in different AF cohorts.

### **Conclusions**

Large improvement in hrQoL occurs in a significant proportion of AF patients at one year, however, we observed heterogeneity in improvement across domains of hrQoL. In addition to lower hrQoL at baseline, additional factors associated with large improvement at one year include potentially reversible risk factors (alcohol, elevated diastolic BP) and less likely among patients with difficult-to-treat comorbidities (prior stroke, COPD, PAD). Understanding the

impact of comorbidities and therapeutic interventions on AF hrQoL can facilitate appropriate implementation to optimize these outcomes.

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**Appendix:** The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Investigators and Patients members include the following: R. Mendelson, A. Nahhas, J. Neutel, B. Padanilam, D. Pan, J. Poock, J. Raffetto, R. Greengold, P. Roan, F. Saba, M. Sackett, R. Schneider, Z. Seymour, J. Shanes, J. Shoemaker, V. Simms, N. Smiley, D. Smith, C. Snipes, R. Sotolongo, C. Staniloae, S. Stoltz, D.P. Suresh, T. Tak, A. Tannenbaum, S. Turk, K. Vora, P. Randhawa, J. Zebrack, E. Silva, E. Riley, D. Weinstein, T. Vasiliauskas, S. Goldberg, D. Hayward, C. Yarlagadda, D. Laurion, A. Osunkoya, R. Burns, T. Castor, D. Spiller, C. Luttman, S. Anton, J. McGarvey, R. Guthrie, G. Deriso, R. Flood, L. Fleischer, J.S. Fierstein, R. Aggarwal, G. Jacobs, N. Adjei, A. Akyea-Djamson, A. Alfieri, J. Bacon, N. Bedwell, P. Berger, J. Berry, R. Bhagwat, S. Bloom, F. Boccalandro, J. Capo, S. Kapadia, R. Casanova, J.E. Morriss III, T. Christensen, J. Elsen, R. Farsad, D. Fox, B. Frandsen, M. Gelernt, S. Gill, S. Grubb, C. Hall, H. Harris, D. Hotchkiss, J. Ip, N. Jaffrani, A. Jones, J. Kazmierski, F. Waxman, G.L. Kneller, A. Labroo, B. Jaffe, M. Lebenthal, D. Lee, M. Lillestol, K. LeClerc, P. Maccaro, N. Mayer, J. Kozlowski, S. Benjamin, R. Detweiler, P. Igic, T. Jackson, J. Pappas, R. Littlefield, A. Frey, R. Vranian, W. Long, P. Grena, A. Arouni, J. Quinn, K. Browne, S. Forman, M. Ebinger, R. Blonder, H. Snyder, S. Slabic, D. Williams, R. Stein, S. Kirkland, K. Cohen, W. Walthall, K. Davis, B. Snoddy, O. Alvarado, C. Leach, S. Rothman, A. Sharma, A. Olatidoye, S. AlMahameed, S. Rosenthal, G. Sutter, W. Reiter, T. Thompson, S. Thew, J. Kobayashi, M. Williams, J. Kramer, S.A. Latif, B. Rhee, A. Adler, D. Ruiz-Serrano, S. Stringam, K. Wolok, A. Focil, S. Butman, H. Ingersoll, R. Borge, Y. Al-Saghir, P. Coats, N. Farris, K. Shore, M.B. Schwartz, C. Gornick, P. Eilat, E. Quinlan, Y. Paliwal, R. Mitra, A. Jingo, A.A. Aslam, L. Allen,

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# Circulation: Arrhythmia and Electrophysiology

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**Table 1.** Baseline characteristics by hrQoL improvement status

	Overall N=636	No large improvement in hrQoL ( $<18$ point improvement) N=455	Large improvement in hrQoL ( $\geq 18$ point improvement) N=181	P-Value
Age (year)	74.0 (67.0, 81.0)	74.0 (67.0, 81.0)	73.0 (66.0, 80.0)	0.2966
Female	300 (47.2%)	220 (48.4%)	80 (44.2%)	0.3442
Race				0.4318
White	577 (90.7%)	409 (89.9%)	168 (92.8%)	
Black or African American	26 (4.1%)	19 (4.2%)	7 (3.9%)	
Hispanic	20 (3.1%)	17 (3.7%)	3 (1.7%)	
Other	12 (1.9%)	10 (2.2%)	2 (1.1%)	
Hypertension	544 (85.5%)	389 (85.5%)	155 (85.6%)	0.9637
Hyperlipidemia	476 (74.8%)	349 (76.7%)	127 (70.2%)	0.0867
Diabetes	182 (28.6%)	137 (30.1%)	45 (24.9%)	0.1867
Anemia	105 (16.5%)	71 (15.6%)	34 (18.8%)	0.3301
Chronic kidney disease (using MDRD)	236 (37.1%)	171 (37.6%)	65 (35.9%)	0.8588
COPD	134 (21.1%)	105 (23.1%)	29 (16.0%)	0.0492
Peripheral arterial disease	87 (13.7%)	72 (15.8%)	15 (8.3%)	0.0126
Obstructive sleep apnea	160 (25.2%)	118 (25.9%)	42 (23.2%)	0.4744
Frailty	49 (7.7%)	38 (8.4%)	11 (6.1%)	0.3322
Alcohol abuse	26 (4.1%)	15 (3.3%)	11 (6.1%)	0.1103
GI bleed	59 (9.3%)	46 (10.1%)	13 (7.2%)	0.2512
Sinus node dysfunction/sick sinus syndrome	134 (21.1%)	109 (24.0%)	25 (13.8%)	0.0047
Cardiac implantable device	207 (32.5%)	156 (34.3%)	51 (28.2%)	0.1382
Congestive heart failure	198 (31.1%)	151 (33.2%)	47 (26.0%)	0.0762
Ischemic cardiomyopathy etiology	71 (35.9%)	54 (35.8%)	17 (36.2%)	0.8828
Functional status				0.9210
NYHA Class I	44 (22.2%)	34 (22.5%)	10 (21.3%)	
NYHA Class II	93 (47.0%)	70 (46.4%)	23 (48.9%)	
NYHA Class III	55 (27.8%)	43 (28.5%)	12 (25.5%)	
NYHA Class IV	6 (3.0%)	4 (2.6%)	2 (4.3%)	
Prior cerebrovascular events	95 (14.9%)	78 (17.1%)	17 (9.4%)	0.0134
Significant valvular disease	173 (27.2%)	129 (28.4%)	44 (24.3%)	0.3017
Moderate/severe mitral stenosis	11 (1.7%)	11 (2.4%)	0 (0.0%)	0.0350
Prior valve replacement/repair	55 (8.6%)	40 (8.8%)	15 (8.3%)	0.8385
History of CAD	202 (31.8%)	143 (31.4%)	59 (32.6%)	0.7754
CHA <sub>2</sub> DS <sub>2</sub> VASc score	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)	4.0 (3.0, 4.0)	0.0039
CHA <sub>2</sub> DS <sub>2</sub> VASc score				0.1942
Low: 0	11 (1.7%)	8 (1.8%)	3 (1.7%)	
Medium: 1	35 (5.5%)	21 (4.6%)	14 (7.7%)	
High: 2+	590 (92.8%)	426 (93.6%)	164 (90.6%)	
ORBIT bleeding score	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	0.8919
BMI (kg/m <sup>2</sup> )	29.7 (25.9, 34.5)	29.6 (25.8, 34.5)	30.2 (26.3, 34.4)	0.3950
Heart rate (bpm)	70.0 (64.0, 80.0)	70.0 (64.0, 80.0)	72.0 (62.0, 80.0)	0.3851
Systolic blood pressure (mm Hg)	126.0 (118.0, 138.0)	126.0 (118.0, 138.0)	128.0 (120.0, 139.0)	0.3238
Diastolic blood pressure (mm Hg)	72.0 (68.0, 80.0)	72.0 (67.0, 80.0)	74.0 (70.0, 80.0)	0.0216
LVEF (%)	55.0 (50.0, 60.0)	55.0 (50.0, 60.0)	55.0 (50.0, 60.0)	0.7107



	Overall N=636	No large improvement in hrQoL (<18 point improvement) N=455	Large improvement in hrQoL (≥18 point improvement) N=181	P-Value
<b>Most recent 12-lead electrocardiogram</b>				
Sinus rhythm	191 (30.0%)	133 (29.2%)	58 (32.0%)	0.4853
Atrial fibrillation	347 (54.6%)	250 (54.9%)	97 (53.6%)	0.7572
Atrial Flutter	11 (1.7%)	7 (1.5%)	4 (2.2%)	0.5581
Paced	122 (19.2%)	95 (20.9%)	27 (14.9%)	0.0851
Serum creatinine	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	1.1 (0.8, 1.3)	0.8398
Estimated creatinine clearance (mL/min)*	70.7 (50.3, 96.9)	70.6 (50.7, 96.0)	71.0 (49.2, 97.1)	0.7118
Hematocrit (%)	40.1 (37.1, 42.8)	40.0 (37.1, 42.9)	40.4 (37.1, 42.6)	0.7035
<b>Type of AF</b>				
First Detected / New Onset	69 (10.8%)	37 (8.1%)	32 (17.7%)	
Paroxysmal AF	296 (46.5%)	208 (45.7%)	88 (48.6%)	
Persistent/permanent AF	271 (42.6%)	210 (46.2%)	61 (33.7%)	
Time to diagnosis from screening (months)	36.0 (9.0, 79.5)	40.0 (11.0, 83.0)	28.0 (3.0, 69.0)	0.0015
Time from AF diagnosis to enrollment > 12 months	448 (70.4%)	335 (73.6%)	113 (62.4%)	0.0053
<b>Current AF management strategy</b>				
Rate Control	447 (70.3%)	325 (71.4%)	122 (67.4%)	0.3166
Rhythm Control	189 (29.7%)	130 (28.6%)	59 (32.6%)	
Prior cardioversions	174 (27.4%)	129 (28.4%)	45 (24.9%)	0.3734
Treated with antiarrhythmic drug in the past	275 (43.2%)	181 (39.8%)	94 (51.9%)	0.0053
Prior catheter ablation of AF	47 (7.4%)	31 (6.8%)	16 (8.8%)	0.3784
Prior atrial flutter ablation	23 (3.6%)	11 (2.4%)	12 (6.6%)	0.0103
Prior AV Node/HIS bundle ablation	15 (2.4%)	11 (2.4%)	4 (2.2%)	0.8764
<b>Current Medications at baseline</b>				
Angiotensin Receptor Blocker	137 (21.5%)	98 (21.5%)	39 (21.5%)	0.9981
Beta Blockers	422 (66.4%)	307 (67.5%)	115 (63.5%)	0.3435
Nondihydropyridine CCBs	116 (18.2%)	81 (17.8%)	35 (19.3%)	0.6513
Digoxin	167 (26.3%)	127 (27.9%)	40 (22.1%)	0.1331
Statin	339 (53.3%)	238 (52.3%)	101 (55.8%)	0.4259
Diuretic	336 (52.8%)	247 (54.3%)	89 (49.2%)	0.2440
<b>Currently on antiarrhythmic drug therapy at baseline</b>				
Amiodarone	48 (7.5%)	28 (6.2%)	20 (11.0%)	0.0351
Dronedarone	37 (5.8%)	25 (5.5%)	12 (6.6%)	0.5813
Dofetilide	5 (0.8%)	3 (0.7%)	2 (1.1%)	0.5661
Flecainide	17 (2.7%)	9 (2.0%)	8 (4.4%)	0.0852
Propafenone	24 (3.8%)	17 (3.7%)	7 (3.9%)	0.9376
Sotalol	43 (6.8%)	32 (7.0%)	11 (6.1%)	0.6652
Other antiarrhythmic drug	10 (1.6%)	7 (1.5%)	3 (1.7%)	0.9134
OAC (warfarin or dabigatran) †	534 (84.0%)	379 (83.3%)	155 (85.6%)	0.4687

\*As calculated by the Cockcroft-Gault formula.

†No other anticoagulants were used in this cohort.

Values are presented as n (%) or median (25<sup>th</sup>, 75<sup>th</sup> percentiles), unless noted otherwise.

COPD: chronic obstructive pulmonary disease; BMI: body mass index; OAC: oral anticoagulant.

**Table 2.** Baseline symptom status, by hrQoL improvement

	<b>Overall N=636</b>	<b>No large improvement in hrQoL N=455</b>	<b>Large improvement in hrQoL N=181</b>	<b>P-Value</b>
<b>AF Symptoms at Baseline</b>				
Palpitations	251 (39.5%)	173 (38.0%)	78 (43.1%)	0.2380
Syncope/fainting	41 (6.4%)	28 (6.2%)	13 (7.2%)	0.6339
Dyspnea at exertion	281 (44.2%)	197 (43.3%)	84 (46.4%)	0.4761
Exercise Intolerance	118 (18.6%)	80 (17.6%)	38 (21.0%)	0.3183
Lightheadedness/dizziness	204 (32.1%)	132 (29.0%)	72 (39.8%)	0.0087
Dyspnea at Rest	81 (12.7%)	52 (11.4%)	29 (16.0%)	0.1172
Fatigue	243 (38.2%)	161 (35.4%)	82 (45.3%)	0.0203
Chest Tightness/discomfort	90 (14.2%)	64 (14.1%)	26 (14.4%)	0.9224
<b>AFEQT Score - Baseline</b>				
AFEQT overall score at baseline	67.6 (54.6, 75.9)	70.4 (58.3, 76.9)	57.4 (44.4, 67.6)	<.0001
AFEQT symptoms subscale at baseline	79.2 (62.5, 91.7)	83.3 (66.7, 91.7)	70.8 (54.2, 87.5)	<.0001
AFEQT daily activities subscale at baseline	54.2 (33.3, 66.7)	58.3 (37.5, 70.8)	41.7 (27.1, 58.3)	<.0001
AFEQT treatment concern subscale at baseline	75.0 (61.1, 86.1)	77.8 (63.9, 88.9)	66.7 (50.0, 77.8)	<.0001
AFEQT treatment satisfaction subscale at baseline	83.3 (66.7, 91.7)	83.3 (66.7, 91.7)	83.3 (58.3, 91.7)	0.0173
<b>AFEQT Score - 1 Year</b>				
AFEQT overall score at 1 year	74.1 (60.2, 85.2)	68.5 (54.8, 78.7)	90.7 (79.4, 98.1)	<.0001
AFEQT symptoms subscale at 1 year	87.5 (75.0, 100.0)	83.3 (70.8, 95.8)	100.0 (87.5, 100.0)	<.0001
AFEQT daily activities subscale at 1 year	62.5 (41.7, 83.3)	54.2 (33.3, 72.9)	89.6 (66.7, 100.0)	<.0001
AFEQT treatment concern subscale at 1 year	83.3 (66.7, 94.4)	77.8 (63.9, 91.7)	94.4 (83.3, 100.0)	<.0001
AFEQT treatment satisfaction subscale at 1 year	83.3 (75.0, 100.0)	83.3 (66.7, 91.7)	100.0 (83.3, 100.0)	<.0001

hrQoL: health-related quality of life; AFEQT: Atrial Fibrillation Effect on QualiTy-of-Life

## Figure Legends

**Figure 1.** Waterfall plot of all patients in the analytic cohort, by absolute change in overall AFEQT score at 1 year, stratified by presence of large hrQoL improvement during follow-up.  
AFEQT: Atrial Fibrillation Effect on QualiTy-of-Life

**Figure 2.** Waterfall plots of AFEQT domain scores, for all analyzed patients, by absolute change in subdomain scores, stratified by presence of large hrQoL improvement at 1 year.

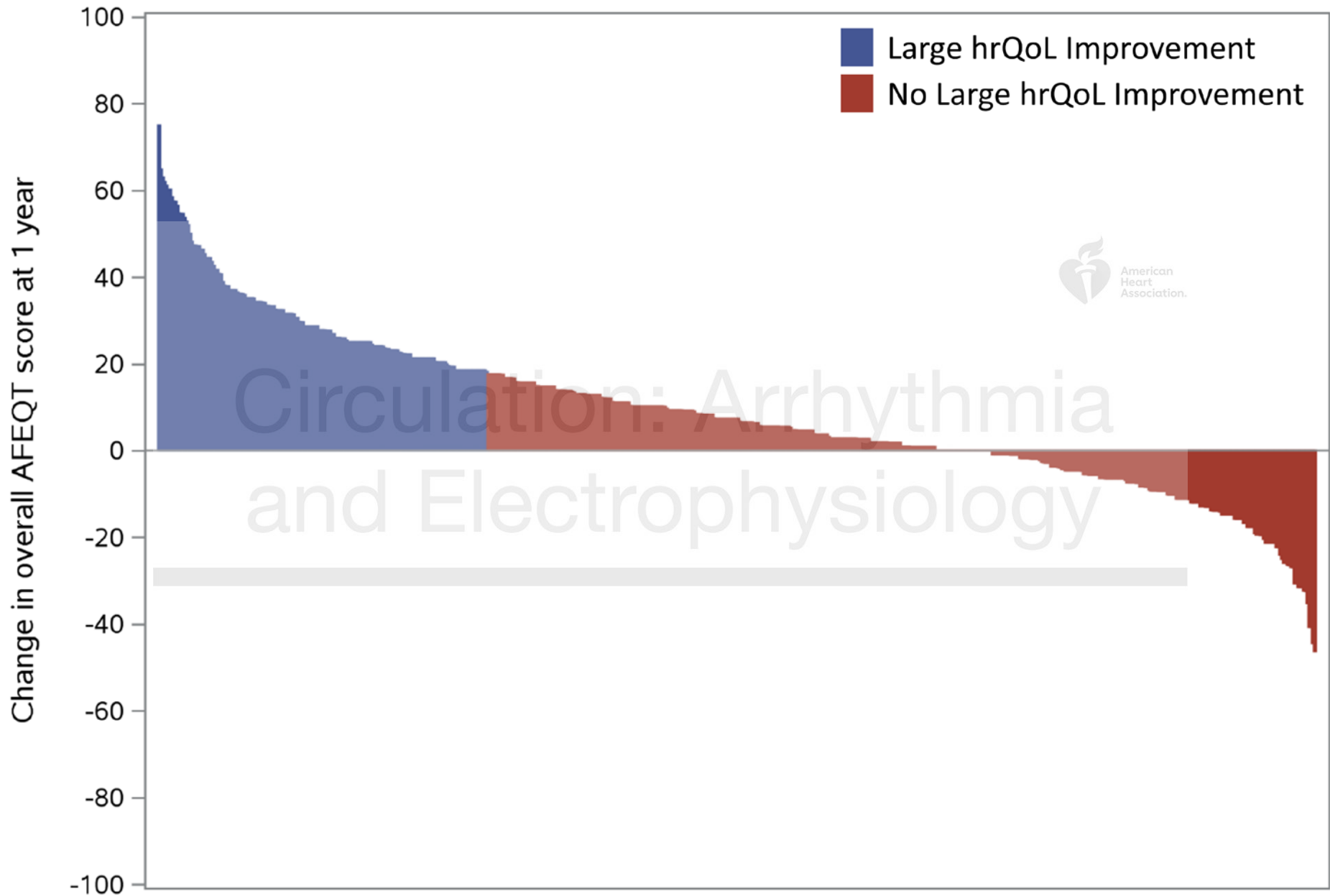
AF: atrial fibrillation; EHRA: European Heart Rhythm Association.

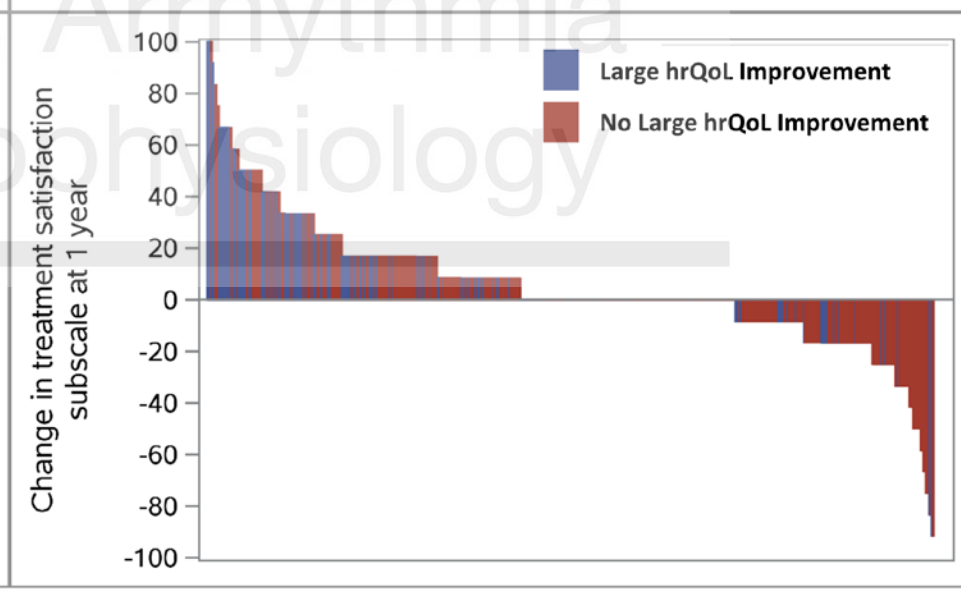
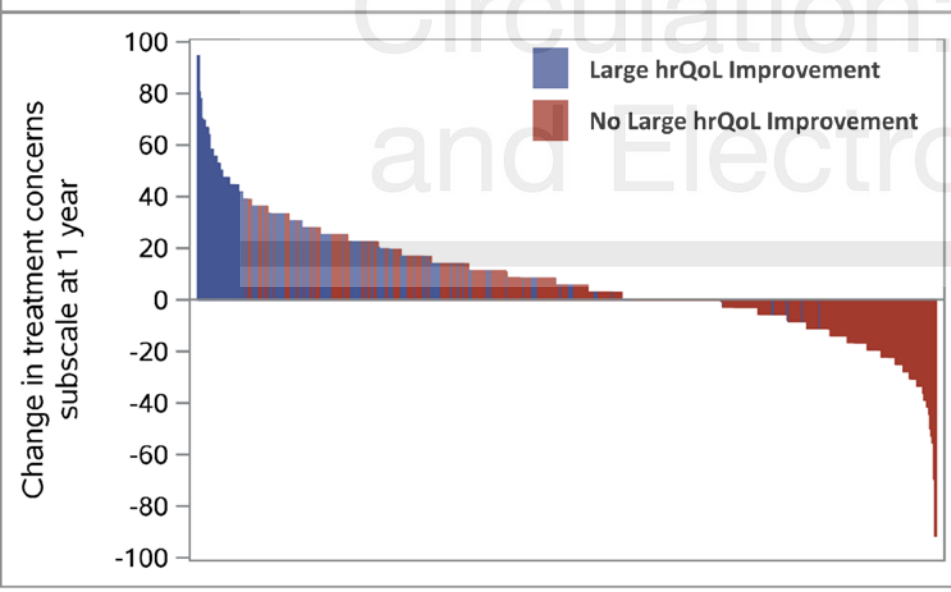
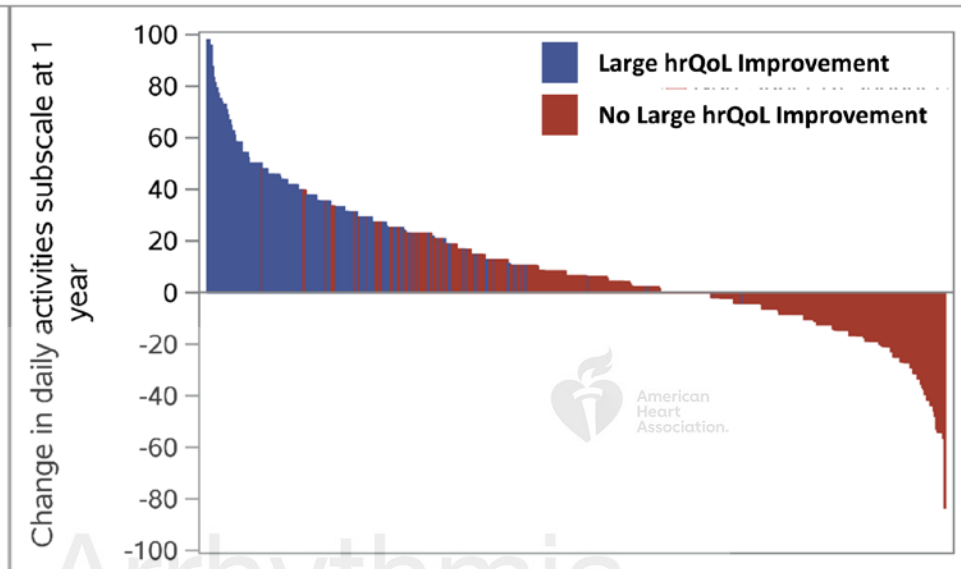
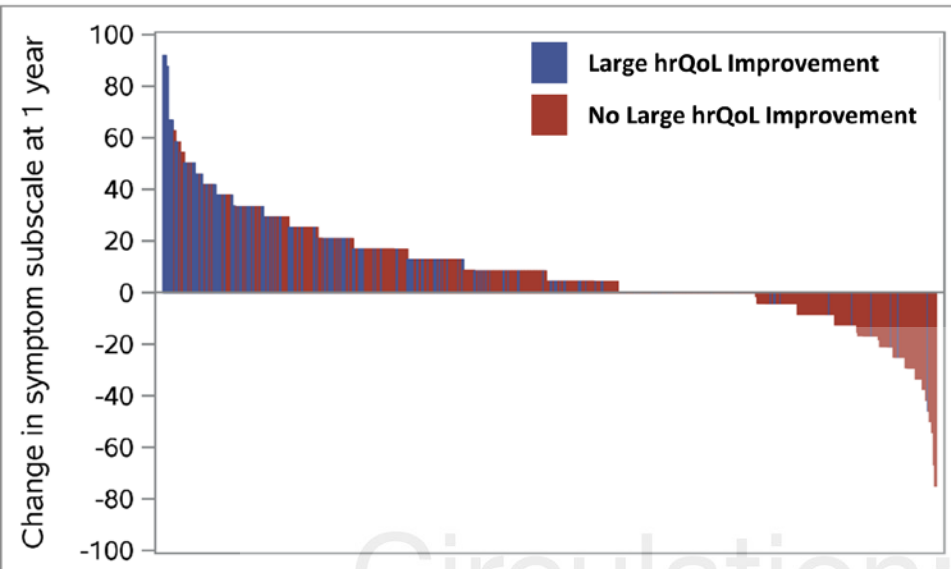


**Figure 3.** Factors associated with large improvement in hrQoL (n=636) based on the multivariable model.

hrQoL: health-related quality of life; AFEQT: Atrial Fibrillation Effect on QualiTy-of-Life.

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OR (95% CI)

P-Value

Baseline AFEQT increase per 5, >50

0.69 (0.63-0.76)



<.0001

Prior Stroke/TIA

0.48 (0.29-0.80)



0.0045

History of alcohol abuse

2.41 (1.23-4.70)



0.0103

COPD

0.67 (0.47-0.95)



0.0255

PAD

0.53 (0.30-0.93)



0.0257

Diastolic BP increase per 10, >65

1.23 (1.01-1.49)



0.0375

0.5 1 1.5 2 3 4.5

Adjusted Odds Ratio



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## AF Patients with and without Large hrQoL Improvement at 1 Year

