

# Patient-Reported Outcomes in Relation to Continuously Monitored Rhythm Before and During 2 Years After Atrial Fibrillation Ablation Using a Disease-Specific and a Generic Instrument

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**Background**—Atrial fibrillation (AF) ablation improves patient-reported outcomes, irrespective of mode of intermittent rhythm monitoring. We evaluated the use of an AF-specific and a generic patient-reported outcomes instrument during continuous rhythm monitoring 2 years after AF ablation.

**Methods and Results**—Fifty-four patients completed the generic 36-Item Short-Form Health Survey and the AF-specific AF6 questionnaires before and 6, 12, and 24 months after AF ablation. All patients underwent continuous ECG monitoring via an implantable loop recorder. The generic patient-reported outcomes scores were compared with those of a Swedish age- and sex-matched population. After ablation, both summary scores reached normative levels at 24 months, while role-physical and vitality remained lower than norms. Responders to ablation (AF burden <0.5%) reached the norms in all individual 36-Item Short-Form Health Survey domains, while nonresponders (AF burden >0.5%) reached norms only in social functioning and mental component summary. All AF6 items and the sum score showed moderate to large improvement in both responders and nonresponders, although responders showed significantly greater improvement in all items except item 1 from before to 24 months after ablation. Higher AF burden was independently associated with poorer physical component summary and AF6 sum score.

**Conclusions**—The AF-specific AF6 questionnaire was more sensitive to changes related to AF burden than the generic 36-Item Short-Form Health Survey. Patients improved as documented by both instruments, but a higher AF burden after ablation was associated with poorer AF-specific patient-reported outcomes and poorer generic physical but not mental health. Our results support the use of an AF-specific instrument, alone or in combination with a generic instrument, to assess the effect of ablation.

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**Key Words:** atrial fibrillation • catheter ablation • quality of life

Atrial fibrillation (AF) frequently causes symptoms that have a negative impact on health-related quality of life (HRQoL).<sup>1,2</sup> In addition to symptoms, side effects of medications and comorbidities can reduce HRQoL in AF patients.<sup>3</sup>

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Catheter ablation of AF is an increasingly used treatment for patients with symptomatic paroxysmal and persistent AF who have failed antiarrhythmic drug therapy and in selected patients with paroxysmal AF as first-line therapy.<sup>4</sup> Success of AF ablation is primarily reported as freedom from AF based on intermittent rhythm monitoring,<sup>5</sup> although the main goal of AF intervention is a reduction of symptoms and improvement of HRQoL<sup>4,6</sup> (ie, improvement of patient-reported outcomes [PROs]). AF ablation has been shown to improve PROs in patients with AF, predominantly using generic instruments during intermittent rhythm monitoring.<sup>7</sup> Occasionally, the resulting HRQoL was compared with that of the general population.<sup>7,8</sup>

AF-specific instruments have been developed, variously well validated and used to different extents in order to increase the sensitivity to detect changes in PROs related to AF, but little is known about their performance in relation to long-term continuous rhythm monitoring.

## Clinical Perspective

### What Is New?

- Patients with a low atrial fibrillation (AF) burden (<0.5%) reached age- and sex-matched norms in all individual 36-Item Short-Form Health Survey domains, while patients with an AF burden (>0.5%) reached norms only in social functioning and mental component summary.
- The AF-specific AF6 showed moderate to large improvement in all patients, irrespective of AF burden, but the improvement was greater in patients with an AF burden <0.5%.
- Higher AF burden was independently associated with worse physical health and worse AF6 sum score.

### What Are the Clinical Implications?

- The AF6 was more sensitive to changes related to AF burden than the 36-Item Short-Form Health Survey, which supports the use of an AF-specific instrument to assess the effect of AF ablation.

The aim of this study was to (1) evaluate effects of AF ablation on AF-specific and generic PROs; and (2) assess the association between the AF-specific and the generic PROs and the AF burden estimated by continuous rhythm monitoring over a period of 2 years after ablation. The generic HRQoL of a Swedish age- and sex-matched population was used as reference.

## Methods

### Patients

Patients scheduled for AF ablation were enrolled at 2 Scandinavian university hospitals between April 2009 and January 2013. All patients gave their written informed consent, and the study protocol was approved by the Regional Ethical Review Board in Uppsala and the Regional Scientific Ethical Committees for Southern Denmark and complied with the Declaration of Helsinki. All patients completed the generic 36-Item Short-Form Health Survey (SF-36) questionnaire (version 1)<sup>9</sup> and the AF-specific AF6 questionnaire<sup>10</sup> before and 6, 12, and 24 months after ablation. After instruction, the patients completed the questionnaires before ECGs were recorded and without interaction from physicians or nurses.

The corresponding author has full access to all study data and takes responsibility for their integrity and the data analysis. The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Generic HRQoL Instrument and Norm Data

SF-36 consists of 36 items assessing 8 domains reflecting physical and mental health aspects: physical functioning, role-

physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Domain scores range from 0 to 100, with higher values indicating better HRQoL. The 8 domains generate 2 summary measures: the physical component summary (PCS) and the mental component summary (MCS) scores.<sup>11</sup> PCS and MCS are calculated using norm-based scoring with a mean of 50 and a value above 50 indicating better HRQoL than the general Swedish population. In the Swedish validation of SF-36, internal consistency reliability estimated (Cronbach  $\alpha$ ) for the 8 domains ranged between 0.79 (role-emotional) and 0.93 (bodily pain).<sup>9</sup>

The SF-36 profile was compared with a general population sample randomly selected from the Swedish SF-36 normative database (n=8930; response rate 68%).<sup>9</sup> The normative sample (validated in Sweden 1991–1992) was matched for sex and age and comprised 742 people (453 males) with a mean age of 56.9 years (9.3 SD).

### AF-Specific Instrument

AF6 is a validated AF-specific PRO instrument<sup>10</sup> tested for clinical responsiveness,<sup>12</sup> with a recall period of 7 days. This 6-item questionnaire includes item 1 “breathing difficulties at rest,” item 2 “breathing difficulties upon exertion,” item 3 “limitations in day-to-day life due to AF,” item 4 “feeling of discomfort due to AF,” item 5 “tiredness due to AF,” and item 6 “worry/anxiety due to AF.” A score of 0 (no symptoms) to 10 (severe symptoms) is recorded for each item, and all scores are added to give a single sum score of 0 to 60, with higher values reflecting more severe AF-related symptoms. The internal consistency of the 6 items measured using Cronbach  $\alpha$  was 0.82, 0.88, 0.19, 0.04, 0.39, and 0.93, respectively.<sup>10</sup>

### Implantable Loop Recorder and Catheter Ablation

Patients were implanted with an implantable loop recorder (Reveal<sup>®</sup> XT; Medtronic Inc, Minneapolis, MN) at least 2 weeks before the ablation. This remained active for a minimum of 24 months after ablation. The AF detection algorithm classifies the heart rhythm as AF when the R-R intervals within a 2-minute interval show uncorrelated irregularity.<sup>13</sup> The AF burden was calculated as the percentage of time in AF between each follow-up visit based on manually adjudicated AF episodes.<sup>14</sup> In addition, we used the only published AF burden cut-off limit after AF ablation of <0.5% at each scheduled visit in order to classify patients as responders or nonresponders.<sup>14,15</sup> The catheter ablation consisted of circumferential radiofrequency lines around each pair of pulmonary veins.<sup>14</sup> Reablation was permitted at the investigator’s discretion.

### Statistical Analyses

Categorical variables are presented as percentages and continuous variables as mean $\pm$ SD or median and interquartile

range where appropriate. Unpaired *t* tests were used for comparison of SF-36 domains between patients versus norms. The linear mixed model for repeated measurement with unstructured covariance was used to compare SF-36 and AF6 mean scores over time: at baseline, 6, 12, and 24 months after ablation, in all patients and in responders and nonresponders. Linear regression was used to evaluate potential prognostic variables for the PCS, MCS, and AF6 sum score at 24 months. The potential prognostic variables were age, sex, persistent AF, AF burden 3 to 24 months after ablation, hypertension, previous stroke/transient ischemic attack, left ventricular ejection fraction, left atrial diameter, antiarrhythmic drugs before ablation, and body mass index. The AF burden was evaluated on a log linear scale, and age, left ventricular ejection fraction, and left atrial diameter were evaluated on a continuous scale, while the remaining variables were categorical. Body mass index was categorized as normal weight (<25 kg/m<sup>2</sup>), overweight (25 to <30 kg/m<sup>2</sup>), and obese (≥30 kg/m<sup>2</sup>) using the World Health Organization standard, and age was evaluated both as continuous and categorical variables as ≤65 or >65 years. All regression analyses were adjusted for age and sex as it has been shown that HRQoL is associated with age and sex,<sup>16</sup> which could be confounders in the study. All potential prognostic variables were further included in a multiple linear regression to identify independent prognostic variables for the PROs. In the same way, linear regression was used to evaluate the change in PRO scores from baseline to 24 months adjusted for the baseline score of the outcome. The magnitude of differences between patients and norms and patients before and after ablation was determined by calculation of effect sizes (ESs). ES was estimated by calculating the mean difference, divided by the pooled SD (Cohen's *d*). ES was interpreted according to standard criteria: trivial (<0.20), small (0.20–0.49), moderate (0.50–0.79), and large (≥0.80).<sup>17</sup> A *P* value of <0.05 was considered statistically significant. To account for multiple testing, Bonferroni correction was performed for the number of tests applied in each analysis. Statistical analyses were done using SPSS version 22 (IBM, Armonk, NY); some graphical presentations used Excel 2010 (Microsoft Corporation, Redmond, WA).

## Results

### Baseline Demographics

Clinical characteristics are shown in Table 1. The mean age was 57±9 years, and there was a majority of men (60%). Fifty-four patients completed the 24-month follow-up. All answered questionnaires were fully completed, and the response rate was 100% before ablation and 98%, 89%, and 98% at 6, 12, and 24 months after ablation, respectively.

**Table 1.** Baseline Patient Characteristics

	n=57
Male sex	34 (60%)
Age, y (mean±SD)	57±9
BMI (mean±SD)	29±5
Paroxysmal AF	50 (88%)
Months from first AF episode (median [IQR])	57 (IQR 36–120)
Concomitant cardiovascular disease	
Heart failure	2 (4%)
Hypertension	24 (42%)
Diabetes mellitus	2 (4%)
Coronary artery disease	1 (2%)
Valvular heart disease	1 (2%)
Stroke/TIA	8 (14%)
CHA <sub>2</sub> DS <sub>2</sub> -VAsc scores	
0	15 (26%)
1	20 (35%)
≥2	22 (39%)
Medications	
β-Blockers	37 (65%)
Class I AAD	16 (28%)
Class III AAD	16 (28%)

Values are n (%), mean±SD, or median (IQR). AAD indicates antiarrhythmic drugs; AF, atrial fibrillation; BMI, body mass index; CHA<sub>2</sub>DS<sub>2</sub>-VAsc, congestive heart failure, hypertension, age ≥65 or 75 years, diabetes mellitus, prior stroke/transient ischemic attack, vascular disease, female sex; IQR, interquartile range; TIA, transient ischemic attack.

### Generic HRQoL Before Ablation in Relation to the General Population

Seven of the 8 SF-36 domains and summary scores showed statistically significantly lower values as compared with sex- and age-matched population norms (Table 2 and Figure). The mean difference in summary scores between patients and norms corresponded to moderate ESs (PCS 0.64 and MCS 0.65). The effect sizes for the domains varied between small (general health 0.41) and large (role-physical 1.1) and were interpreted as small to moderate in most domains but large in vitality and role-physical.

### Change in Generic HRQoL After Ablation

Four of the 8 SF-36 domains and the summary scores improved significantly 2 years after ablation (Table 3). The effect sizes were moderate for the domains role-physical and social functioning but were otherwise small. The improvement occurred mainly during the first 6 months after ablation. The mean of the summary scores, physical functioning, general

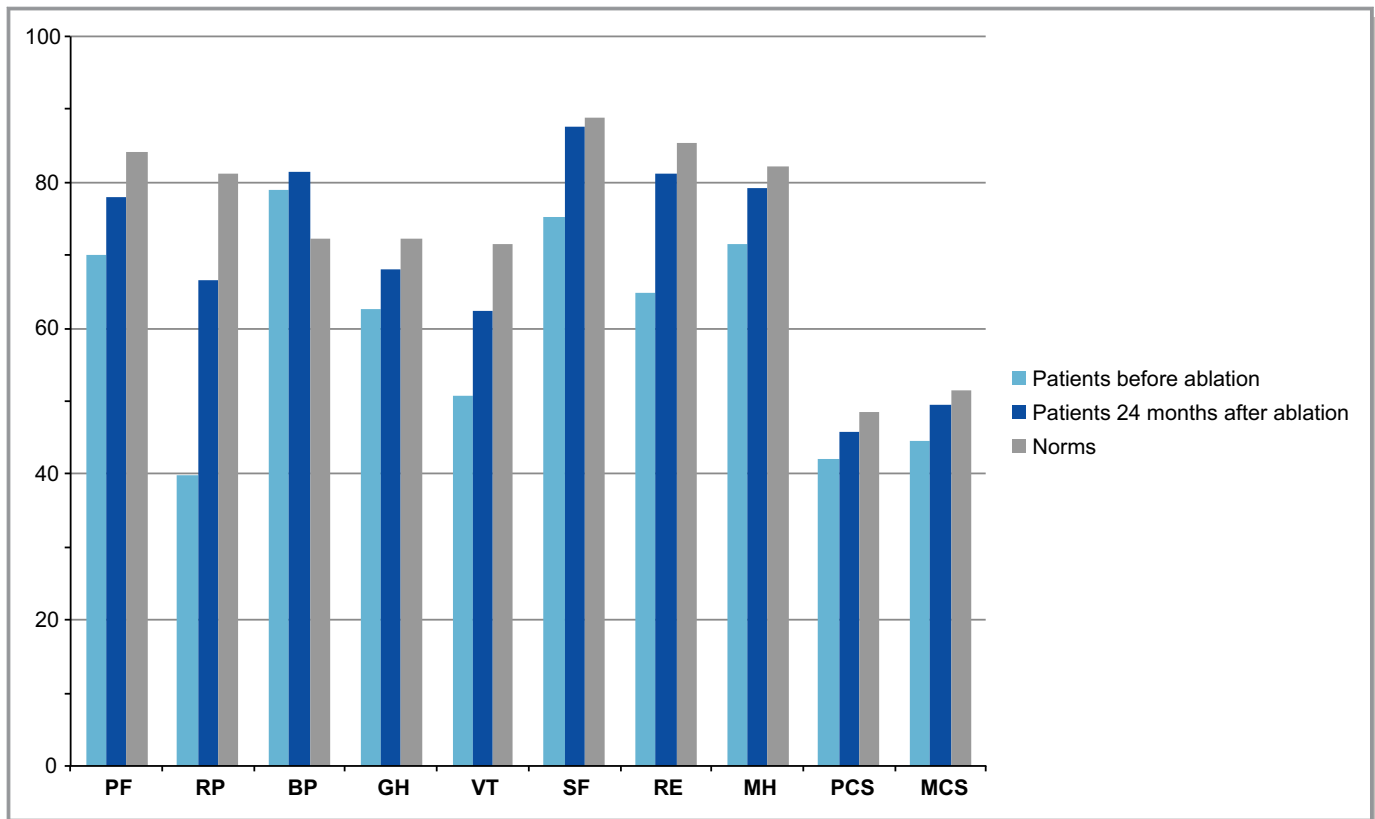
**Table 2.** SF-36 Mean Scores in Patients at Baseline and 6, 12, and 24 Months After AF Ablation Compared With General Swedish Population Norms

SF-36 Domains	Norm Data Mean±SD (n=742)	Baseline			6 Mo			12 Mo			24 Mo		
		Mean Difference (95% CI) (n=54) to -8.1)	P Value*	ES	Mean Difference (95% CI) (n=53) to -3.7)	P Value*	ES	Mean Difference (95% CI) (n=48) to 13.6)	P Value*	ES	Mean Difference (95% CI) (n=53) to 16.7)	P Value*	ES
PF	84.1±20.9	-14.0 (-19.9 to -8.1)	<0.001 <sup>†</sup>	0.61	-6.5 (-12.5 to -0.56)	0.03	0.29	-7.4 (-13.6 to -1.3)	0.02	0.34	-6.1 (-11.9 to -0.23)	0.04	0.29
RP	81.3±33.0	-41.5 (-50.7 to -32.2)	<0.001 <sup>†</sup>	1.1	-13.0 (-22.3 to -3.7)	0.006 <sup>†</sup>	0.39	-5.7 (-15.4 to 3.9)	0.25	0.17	-14.8 (-24.1 to -5.4)	0.002 <sup>†</sup>	0.40
BP	72.3±27.4	6.6 (-0.89 to 14.1)	0.08	0.26	2.7 (-5.0 to 10.4)	0.48	0.10	5.7 (-2.3 to 13.6)	0.16	0.22	9.1 (1.5 to 16.7)	0.02	0.35
GH	71.6±22.7	-9.8 (-16.1 to -3.5)	0.002 <sup>†</sup>	0.41	-4.2 (-10.6 to 2.1)	0.19	0.19	-5.0 (-11.6 to 1.5)	0.13	0.24	-4.2 (-10.5 to 2.1)	0.19	0.19
VT	71.6±23.4	-20.7 (-27.2 to -14.3)	<0.001 <sup>†</sup>	0.90	-11.7 (-18.3 to -5.0)	0.001 <sup>†</sup>	0.47	-10.0 (-16.9 to -3.1)	0.004 <sup>†</sup>	0.41	-9.2 (-15.8 to -2.6)	0.006 <sup>†</sup>	0.36
SF	88.9±21.1	-13.7 (-19.6 to -7.7)	<0.001 <sup>†</sup>	0.56	-6.2 (-12.2 to -0.24)	0.04	0.29	-1.4 (-7.5 to 4.7)	0.66	0.01	-1.4 (-7.3 to 4.5)	0.64	0.07
RE	85.3±29.2	-20.5 (-28.9 to -12.1)	<0.001 <sup>†</sup>	0.57	-7.7 (-16.1 to 0.59)	0.07	0.24	-2.7 (-11.2 to 5.9)	0.54	0.09	-4.2 (-12.5 to 4.1)	0.32	0.13
MH	82.3±19.2	-10.6 (-16.0 to -5.3)	<0.001 <sup>†</sup>	0.57	-6.4 (-11.9 to -1.0)	0.02	0.33	-5.4 (-11.0 to 0.15)	0.06	0.29	-3.0 (-8.3 to 2.4)	0.28	0.16
PCS	48.4±9.9	-6.4 (-3.7 to -9.2)	<0.001 <sup>†</sup>	0.64	-2.6 (-5.5 to 0.19)	0.07	0.25	-2.2 (-5.1 to 0.7)	0.14	0.21	-2.6 (-5.4 to 0.23)	0.07	0.25
MCS	51.5±9.7	-7.0 (-4.3 to -9.8)	<0.001 <sup>†</sup>	0.65	-4.0 (-6.7 to -1.2)	0.005 <sup>†</sup>	0.38	-2.4 (-5.3 to 0.5)	0.10	0.25	-1.8 (-4.6 to 0.90)	0.19	0.18

SF-36 scores ranging between 0 and 100, where higher scores indicate better health. Negative mean differences calculated with unpaired *t* test indicate lower mean in patients than norms. AF indicates atrial fibrillation; BP, bodily pain; CI, confidence interval; ES, effect size; GH, general health; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical functioning; RE, role-emotional; RP, role-physical; SF, social functioning; SF-36, 36-item Short-Form Health Survey; VT, vitality.

\*Uncorrected *P* values are stated.

<sup>†</sup>Significant results after Bonferroni correction for multiple testing of the 8 SF-36 domains.



**Figure.** Thirty-six-Item Short-Form Health Survey domain and summary scores before and 24\* months after AF ablation compared with Swedish age- and sex-matched population norms (n=742). BP indicates bodily pain; GH, general health; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical functioning; RE, role-emotional; RP, role-physical; SF, social functioning; VT, vitality. \*Data from 1 patient are missing.

health, social functioning, role-emotional, and mental health did not differ significantly from that of the general population at 24 months after ablation (Table 2), but the patients scored slightly but significantly lower than norms on role-physical and vitality.

### Change in Generic HRQoL in Responders and Nonresponders

There were no significant differences in the SF-36 domains between subsequent responders and nonresponders before ablation. Responders showed statistically significantly improved scores 2 years after ablation in physical functioning, role-physical, and PCS. The effect sizes were large in physical functioning (0.86), role-physical (0.83), and role-emotional (0.90), and moderate in general health (0.55), vitality (0.54), social functioning (0.63), mental health (0.53), and both summary scores (PCS 0.63 and MCS 0.64). The responders reached the HRQoL of general population norms in all domains and both summary scores. The nonresponders showed significant improvement in role-physical and social functioning, in particular role-physical, where the ES was moderate (0.58). However, nonresponders did not reach the

HRQoL of general population norms except in social functioning and MCS. Responders showed significantly greater improvement in physical functioning and PCS than nonresponders from before to 2 years after ablation (Table 3).

### Change in AF-Specific AF6 in Responders and Nonresponders

All items and the sum score showed statistically significant improvement at 24 months after ablation, with moderate to large ESs (Table 3). Before ablation, item 1, “breathing difficulties at rest,” scored significantly lower in subsequent responders than nonresponders ( $P=0.01$ ), while there were no significant differences in the other items or the AF6 sum score. In responders, 5 items and the AF6 sum score showed statistically significant improvement, all with large ESs (ES 1.0–1.7). The only item not to reach statistical significance, item 1, still had a moderate ES of 0.58. All items and the AF6 sum score improved significantly in nonresponders; item 2, “breathing difficulties upon exertion,” showed a large ES (0.84), and all others moderate ESs (ES 0.50–0.75). Responders showed significantly greater improvement in all items

**Table 3.** Patient-Reported Outcomes at Baseline and 24 Months After Ablation in Responders and Nonresponders

	All (n=54)			Responders (n=22)			Nonresponders (n=32)			Responders vs Nonresponders	
	Baseline (Mean±SD)	24 Mo* (Mean±SD)	Mean Difference (95% CI)	P Value †	ES	Baseline (Mean±SD)	24 Mo (Mean±SD)	Baseline (Mean±SD)	24 Mo* (Mean±SD)	Mean Difference 24 Mo* (95% CI)	P Value ‡
<b>SF-36</b>											
PF	70.1±25.3	78.0±20.6	8.1 (2.1 to 14.0)	0.009	0.35	67.0±29.8	86.8±16.2	71.9±22.5	72.7±21.3	15.9 (7.3 to 24.6)	0.001 ‡§
RP	39.8±39.3	66.5±40.4	26.7 (15.5 to 38.0)	<0.001 ‡§	0.67	41.3±44.6	76.3±40.1	39.0±36.5	60.6±40.0	14.7 (-5.7 to 35.1)	0.15
BP	78.9±23.8	81.4±25.1	2.6 (-5.9 to 11.1)	0.55	0.10	79.6±27.2	83.4±23.3	78.5±22.0	80.2±26.4	2.3 (-12.2 to 16.9)	0.75
GH	62.5±21.2	68.0±20.6	5.7 (-0.6 to 12.1)	0.08	0.26	63.7±25.3	75.9±18.8	61.7±18.7	63.3±20.4	11.2 (0.6 to 21.8)	0.04
VT	50.8±23.0	62.4±27.1	11.4 (5.2 to 17.6)	0.001 ‡§	0.46	52.5±27.9	67.3±27.3	49.9±20.0	59.4±27.0	6.4 (-6 to 18.7)	0.31
SF	75.2±27.1	87.5±20.4	12.5 (5.8 to 19.3)	<0.001 ‡§	0.51	72.5±32.8	88.8±19.0	76.8±23.5	86.7±21.4	3.2 (-7.0 to 13.4)	0.53
RE	64.8±41.7	81.1±35.5	16.6 (3.0 to 30.3)	0.02	0.42	58.3±45.7	90.0±24.4	68.6±39.3	75.8±40.2	15.8 (-3.9 to 35.5)	0.11
MH	71.6±18.1	79.3±18.2	7.7 (2.9 to 12.5)	0.002 ‡§	0.42	70.8±20.8	81.2±18.8	72.1±16.7	78.2±18.1	3.7 (-5.1 to 12.6)	0.40
PCS	42.0±10.1	45.9±10.6	3.9 (1.2 to 6.6)	0.005 ‡§	0.38	42.3±12.2	49.3±10.2	41.9±8.8	43.8±10.4	5.2 (0.3 to 10.0)	0.04 ‡§
MCS	44.5±11.7	49.6±10.5	5.2 (2.0 to 8.5)	0.002 ‡§	0.46	43.4±14.0	50.5±8.5	45.1±10.4	49.1±11.7	5.0 (-0.5 to 10.5)	0.07
<b>AF6</b>											
Item 1	2.0±2.6	0.8±1.5	-1.2 (-2.0 to -0.6)	<0.001 ‡§	0.57	0.90±1.7	0.20±0.7	2.7±2.8	1.1±1.8	-0.5 (-1.4 to 0.3)	0.22
Item 2	4.9±3.3	2.9±3.1	-2.0 (-2.9 to -1.1)	<0.001 ‡§	0.62	4.0±3.5	1.1±2.3	5.5±3.1	4.0±3.1	-2.2 (-3.7 to -0.7)	0.005 ‡§
Item 3	4.8±3.2	2.1±2.5	-2.8 (-3.9 to -1.8)	<0.001 ‡§	0.94	5.0±3.7	0.7±1.8	4.9±3.0	3.0±2.5	-2.4 (-3.6 to -1.0)	0.001 ‡§
Item 4	5.5±3.0	2.7±3.3	-2.8 (-3.9 to -1.7)	<0.001 ‡§	0.89	5.0±3.4	0.7±1.7	5.9±2.7	3.9±3.4	-3.1 (-4.7 to -1.5)	<0.001 ‡§
Item 5	5.9±3.2	3.2±3.5	-2.7 (-3.7 to -1.6)	<0.001 ‡§	0.81	5.1±4.0	1.1±2.3	6.4±2.5	4.5±3.5	-3.0 (-4.7 to -1.2)	0.001 ‡§
Item 6	4.3±3.0	2.1±2.8	-2.2 (-3.1 to -1.3)	<0.001 ‡§	0.76	4.1±3.3	0.9±1.3	4.4±2.8	2.9±3.2	-1.9 (-3.3 to -0.5)	0.01
Sum score	29.5±13.9	13.6±14.3	-13.8 (-18.3 to -9.0)	<0.001 ‡§	0.99	24.1±15.3	4.6±9.1	29.7±12.7	19.3±14.1	-13.0 (-20.1 to -6.0)	0.001 ‡§

SF-36 scores ranging between 0 and 100, where higher scores indicate better health. Positive mean differences calculated with the linear mixed model indicate improvement at 24 months compared with baseline or greater improvement for responders compared with nonresponders from baseline to 24 months. AF6 item 1 “breathing difficulties at rest,” item 2 “breathing difficulties upon exertion,” item 3 “limitations in day-to-day life due to AF,” item 4 “feeling of discomfort due to AF,” item 5 “tiredness due to AF,” and item 6 “worry/anxiety due to AF.” A score of 0 (no symptoms) is reported for each item, and all scores are added to give a single AF6 sum score of 0 to 60. Negative mean differences calculated with the linear mixed model indicate improvement at 24 months compared with baseline or greater improvement for responders compared with nonresponders from baseline to 24 months. BP indicates bodily pain; CI, confidence interval; ES, effect size; GH, general health; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical functioning; RE, role-emotional; RP, role-physical; SF, social functioning; SF-36, 36-Item Short-Form Health Survey; VT, vitality.

\*Data from 1 patient missing.

†Uncorrected P values are stated.

‡Significant results after Bonferroni correction for multiple testing of the 8 SF-36 domains.

§Significant results after Bonferroni correction for multiple testing of the 6 AF6 items.

**Table 4.** Linear Regression With Outcome AF6 Sum Score at 24 Months and Outcome AF6 Sum Change From Baseline to 24 Months by Demographic and Clinical Characteristics in 53 Patients

	AF6 Sum Score at 24 Mo				Change in AF6 Sum Score Baseline to 24 Mo			
	Adjusted for Age and Sex		Adjusted for All Variables		Adjusted for Age and Sex		Adjusted for All Variables	
	$\beta$ (95% CI)	P Value	$\beta$ (95% CI)	P Value	$\beta$ (95% CI)	P Value	$\beta$ (95% CI)	P Value
AF burden 3–24 mo, log scale per unit	10.7 (4.7–16.6)	0.001*	11.5 (4.3–18.7)	0.003*	10.5 (4.7–16.3)	0.001*	11.4 (4.3–18.5)	0.002*
Sex, female	2.2 (–6.3 to 10.8)	0.60	–0.2 (–8.9 to 8.6)	0.97	0.6 (–7.8 to 9.1)	0.88	–1.0 (–9.7 to 7.6)	0.81
Age (per y)	0.2 (–0.2 to 0.6)	0.38	0.1 (–0.4 to 0.6)	0.66	0.2 (–0.2 to 0.6)	0.35	0.1 (–0.3 to 0.6)	0.54
Age >65 y	1.3 (–8.3 to 10.9)	0.79			3.6 (–6.0 to 13.2)	0.45		
<b>BMI</b>								
<25	Ref.		Ref.		Ref.		Ref.	
25 to <30	–5.1 (–16.8 to 6.6)	0.38	–1.4 (–14.0 to 11.2)	0.82	–8.7 (–20.5 to 3.2)	0.15	–3.6 (–16.4 to 9.1)	0.56
$\geq 30$	2.7 (–9.3 to 14.6)	0.66	3.4 (–10.0 to 16.8)	0.61	–1.7 (–14.0 to 10.6)	0.79	1.1 (–12.5 to 14.6)	0.87
Persistent AF	1.0 (–11.6 to 13.6)	0.88	5.6 (–7.2 to 18.4)	0.38	0.9 (–11.3 to 13.2)	0.88	5.5 (–7.1 to 18.1)	0.38
Hypertension	0.1 (–8.7 to 9.0)	0.97	2.2 (–6.5 to 10.9)	0.61	–0.5 (–9.2 to 8.1)	0.90	1.2 (–7.4 to 9.9)	0.77
Previous stroke/TIA	–0.9 (–12.4 to 10.6)	0.88	–5.7 (–17.5 to 6.1)	0.34	–0.3 (–11.5 to 10.9)	0.96	–5.7 (–17.3 to 6.0)	0.33
AAD	–5.2 (–13.3 to 2.8)	0.20	–4.9 (–13.1 to 3.3)	0.24	–2.5 (–11.2 to 6.2)	0.57	–1.7 (–10.8 to 7.3)	0.70
LVEF, per %	0.0 (–0.8 to 0.7)	0.95	–0.2 (–0.9 to 0.6)	0.63	0.0 (–0.7 to 0.7)	0.97	–0.1 (–0.9 to 0.6)	0.72
Left atrial diameter, per mm	2.6 (–3.3 to 8.6)	0.38	–1.0 (–7.7 to 5.6)	0.76	1.4 (–4.6 to 7.4)	0.64	–1.8 (–8.4 to 4.9)	0.60

Positive regression coefficient  $\beta$  indicates higher (worse) AF6 sum score in exposed category compared with reference or per 1 unit increase in continuous variables log AF burden, age per year, LVEF, and left atrial diameter. AF6 sum score of 0 to 60. AAD indicates antiarrhythmic drugs; AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack.

\*Significant results ( $P < 0.05$ ).

except items 1 and 6 than nonresponders from before to 2 years after ablation (Table 3).

### Prognostic Variables for AF6 Sum Score, PCS, and MCS 24 Months After Ablation

Higher AF burden 3 to 24 months after ablation was significantly associated with a higher AF6 sum score, indicating more severe AF-related symptoms, and a larger increase in the AF6 sum score from baseline (Table 4), both adjusted for age and sex as well as for all variables. Moreover, the AF6 sum score increased 11.5 (95% confidence interval, 4.3%–18.7%) points with every log unit increase in AF burden, adjusted for all variables.

Higher AF burden after ablation and obesity, adjusted for age and sex, were significantly associated with lower PCS (Table 5). The AF burden was still associated with lower PCS when adjusted for all variables. Higher AF burden was also significantly associated with a negative change in PCS from baseline adjusted for all variables. Persistent AF before

ablation was significantly associated with lower MCS 24 months after ablation, adjusted for age and sex as well as adjusted for all variables. Persistent AF was significantly associated with a negative change in MCS from baseline when adjusted for all variables (Table 5). Higher age was associated with higher MCS when adjusted for all variables.

## Discussion

### Main Findings

The generic HRQoL improved during the 2-year follow-up after AF ablation with the greatest improvement during the first 6 months after ablation. The physical and mental summary scores reached normative levels 24 months after ablation. The AF-specific instrument AF6 was more sensitive to changes in PROs than the generic SF-36 as the AF6 detected improvement in both responders and nonresponders to AF ablation, although the improvement was greater in responders. A higher AF burden was associated with poorer generic physical and AF-specific PROs.

**Table 5.** Linear Regression With Outcome PCS and MCS Scores at 24 Months and Outcome PCS and MCS Change From Baseline to 24 Months by Demographic and Clinical Characteristics in 53 Patients

	PCS/MCS at 24 Mo				Change in PCS/MCS From Baseline to 24 Mo			
	Adjusted for Age and Sex		Adjusted for All Variables		Adjusted for Age and Sex		Adjusted for All Variables	
	β (95% CI)	P Value	β (95% CI)	P Value	β (95% CI)	P Value	β (95% CI)	P Value
<b>PCS</b>								
AF burden 3–24 mo, log scale per unit	−5.0 (−9.7 to −0.3)	0.04*	−7.0 (−12.2 to −1.7)	0.01*	−5.9 (−9.8 to −2.0)	0.004*	−6.7 (−11.4 to −2.0)	0.006*
Age (per y)	−0.1 (−0.5 to 0.2)	0.45	0.0 (−0.3 to 0.4)	0.78	0.0 (−0.3 to 0.2)	0.75	0.1 (−0.3 to 0.4)	0.72
Age >65 y	−2.9 (−9.9 to 4.1)	0.41			−2.1 (−8.1 to 3.9)	0.49		
Persistent AF	−5.7 (−14.9 to 3.4)	0.21	−5.9 (−15.3 to 3.4)	0.21	−4.1 (−12.0 to 3.8)	0.30	−5.3 (−13.6 to 3.1)	0.21
<b>MCS</b>								
AF burden 3–24 mo, log scale per unit	−3.4 (−8.3 to 1.5)	0.17	−2.3 (−7.8 to 3.2)	0.41	−3.8 (−8.3 to 0.6)	0.09	−3.0 (−8.3 to 2.3)	0.26
Age (per y)	0.1 (−0.2 to 0.5)	0.39	0.4 (0.0 to 0.8)	0.03*	0.0 (−0.4 to 0.3)	0.78	0.2 (−0.2 to 0.6)	0.37
Age >65 y	0.6 (−6.5 to 7.7)	0.87			−2.8 (−9.5 to 4.0)	0.41		
Persistent AF	−9.8 (−18.7 to 0.9)	0.03*	−10.1 (−20.0 to −0.3)	0.04*	−7.8 (−16.2 to 0.5)	0.06	−9.4 (−18.8 to −0.1)	0.048*

Negative regression coefficient β indicates lower (worse) PCS/MCS scores in exposed category compared with reference, or per 1 unit increase in continuous variables log AF burden, age, LVEF, and left atrial diameter. AF indicates atrial fibrillation; CI, confidence interval; LVEF, left ventricular ejection fraction; MCS, mental component summary; PCS, physical component summary.

\*Significant results (P<0.05).

### Improvement of PROs Following AF Ablation

The greatest impairment in HRQoL before ablation measured by SF-36 was seen in the role-physical and vitality domains, which indicates that patients experienced problems with daily activities as well as energy and fatigue, which is in line with a study by Wokhlu et al in 323 patients undergoing AF ablation.<sup>18</sup> The same domains also showed the greatest improvement from before ablation to 24 months after ablation but were still lower in patients than in norms at the end of follow-up. This is in contrast to the study of Wokhlu et al in which all SF-36 domains reached norm values, but their norms were not matched for age and sex and they used the same mean score for every domain for norms, which may have affected their results. Nevertheless, in both studies both the physical and mental summary scores and domains representing mental health and social aspects of life reached normative levels after ablation. This is consistent with a recent meta-analysis that also showed that AF ablation is associated with a significant increase in both PCS and MCS.<sup>19</sup>

All items in the AF-specific instrument AF6 improved after ablation, with large ESs in items corresponding to limitations in day-to-day life, feelings of discomfort and tiredness because of AF, as did the AF6 sum score, which is consistent with previous studies. Wokhlu et al used the not yet validated Mayo AF-Specific Symptom Inventory and showed significant

improvement in 10 of 12 symptoms 2 years after ablation.<sup>18</sup> Raine et al used a validated AF-specific instrument, the Atrial Fibrillation Effect on Quality-of-Life, before and 3 months after AF ablation and found a significant improvement only in patients without AF recurrence.<sup>20</sup>

### Relationship Between AF Burden and PROs After Ablation

Responders improved to the level of general population norms in all SF-36 domains while nonresponders only reached norm level in social functioning and MCS. When using the AF-specific instrument AF6, both responders and nonresponders showed moderate to large improvement 24 months after ablation, even though the improvement was significantly larger in all AF6 items except items 1 and 6 in responders. Furthermore, a higher AF burden after ablation was independently associated with poorer physical health and more severe AF-related symptoms. There are several possible explanations for these findings, the most likely one being that reduction of the AF burden brought improvement in PROs in nonresponders even though AF was not entirely eliminated. Mantovan et al found an improvement of generic HRQoL with SF-36 both in patients with and without arrhythmia recurrence at 12 months after ablation, even though arrhythmia recurrence caused less improvement of the summary scores.<sup>7</sup> A



subgroup analysis showed that patients with AF up to 1.3 hours per month measured by intermittent rhythm monitoring improved in all SF-36 domains, while patients with AF 4.8 to 720 hours per month did not or had deteriorated at 12 months after ablation.

The improvement in nonresponders may, at least in part, be because of diminished perception of the AF episodes after ablation, and this may have reduced symptoms enough to give meaningful relief, both in generic and particularly in AF-specific PROs.<sup>21</sup> Furthermore, preprocedural anxiety may have caused lower scores before the ablation and may have overestimated the changes in PROs, but since the questionnaires were completed at least 1 month before the procedure, this is less likely. Patients undergoing AF ablation are often highly symptomatic, and improvement may also be the result of an expectancy effect. However, in our study, the improvement in PROs at 6 months after ablation was maintained at 24 months, rendering an expectancy effect unlikely. Moreover, it is also possible that the closer follow-up in a clinical study per se could reduce anxiety and increase psychological well-being.

The implantable loop recorder continuously monitored and detected both symptomatic and asymptomatic AF episodes that were then manually adjudicated before being entered into the AF burden. This full knowledge of the AF burden is the greatest strength of our study, as previous studies investigating PROs in relation to rhythm after AF ablation have used intermittent monitoring of different intensity to determine ablation success. We believe that rhythm monitoring is an important additional aspect in order to correctly understand the effects on PROs. Intermittent monitoring may have contributed to the conflicting results reported by these studies, with some reporting improvement in generic PROs regardless of AF recurrences<sup>7,18,22</sup> and others improvement only in patients who are classified as free of AF recurrences.<sup>8,20</sup> The recently published 5-year follow-up of MANTRA-PAF (The Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation) trial showed that the improvement in generic HRQoL measured by SF-36 seen at 2 years after ablation remained and was similar in patients who underwent AF ablation and pharmacological rhythm control in spite of more AF recurrences in the latter group.<sup>23,24</sup> However, previous studies that did include AF-specific instruments (Mayo AF-Specific Symptom Inventory, Atrial Fibrillation Effect on Quality-of-Life, and University of Toronto atrial fibrillation severity scale) showed that ablation outcome is most often correlated with AF-specific PROs.<sup>18,20,22</sup>

Interestingly, we found no significant association between AF burden and mental health after ablation, but persistent AF and younger age before ablation were both independently associated with poorer mental health. This is in line with a previous study reporting that younger patients had poorer

mental health than older patients and may benefit more from treatment.<sup>3</sup>

## Generic and AF-Specific PROs: Similarities and Differences

Generic instruments measure general health and functioning and are influenced by patient demographics and comorbidity, while AF-specific questionnaires were developed specifically to measure AF-related PROs. Our results suggest that the AF6 is more sensitive than SF-36 in capturing more components of AF, which is in line with previous studies using other AF-specific PRO instruments.<sup>18,20,22</sup> The potential for comorbidities to impact PRO scores further points to the need for AF-specific instruments when studying AF interventions. We believe that assessment of PROs after AF ablation should always include an AF-specific instrument. The main advantages of the AF6 instrument are that it is validated for AF patients and straightforward and simple to use and can easily be included in a routine clinical visit. The AF6 item 1 “breathing difficulties at rest” was lower in responders than nonresponders even before ablation, implying that this is an important symptom that could possibly indicate a more severe disease with lower success rates after ablation.

## Limitations

The study population was small and did not have a randomized control group but was followed in great detail for 2 years after ablation. Because of the low power, we have likely failed to detect some existing associations, but the significant predictors we have found are probably valid. The AF6 and the SF-36 had different recall periods, which may have influenced the results. The latest available national norm data, used in our study, were validated in 1991–1992, and the HRQoL of the general population may have changed since then. The AF6 was validated in symptomatic patients undergoing direct-current cardioversion for short-lasting persistent AF, while patients in the present study had paroxysmal and persistent AF.

## Conclusions

Patients improved after AF ablation as documented by a generic and an AF-specific instrument, but the AF6 was more sensitive to changes in PROs related to AF burden. However, a higher AF burden after ablation was associated with poorer generic physical health and worse AF-specific PRO, but not with mental health. The arbitrary AF burden cut-off limit of 0.5% was not a clinically meaningful efficacy end point, when the effect on PROs was taken into consideration. Focusing on AF-specific symptoms and their impact on HRQoL, both in

selection of ablation candidates and as an outcome measure after AF ablation, is reasonable: as symptoms and impaired HRQoL are what bring the patients to the physician and are currently the main indications for AF ablation.

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## Disclosures

None.

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