



# Body Mass Index, Quality of Life, and Catheter Ablation in Patients with Atrial Fibrillation

Ethan R. Ellis, M.D.\*, Matthew R. Reynolds, M.D., M.Sc.‡

\* Beth Israel Deaconess Medical Center; and ‡Harvard Clinical Research Institute, Boston, Massachusetts, USA.

## Abstract

Atrial fibrillation and obesity are interlinked epidemics and both impair quality of life. As the prevalence of both conditions in the US continues to rise, so will the number of obese patients with atrial fibrillation referred for catheter ablation. Catheter ablation has already been shown to significantly improve quality of life in patients with atrial fibrillation. Until recently, there has been little attention to the effects of catheter ablation on quality of life specifically in obese patients with atrial fibrillation. This paper will review what is known about the effects of atrial fibrillation and obesity on quality of life and how quality of life is affected by catheter ablation for atrial fibrillation in obese patients.

## Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in the US, and it is expected to affect more than 12.1 million people by the year 2050.<sup>1</sup> Obesity has also become a major health problem in the US, with more than 70% of US adults classified as overweight or obese.<sup>2</sup> Obese patients have a 1.5 times higher risk of developing new onset AF compared to normal weight patients<sup>3,4</sup> and it has been speculated that obesity could be responsible for almost 60% of the increase in AF incidence.<sup>1,4</sup> Given that these epidemics appear to be interlinked, understanding their interplay is of increasing importance.

Both AF and obesity have been shown to negatively impact health related quality of life (QoL)<sup>5-8</sup> and catheter ablation for AF has been shown to improve QoL measures of AF patients to population norms.<sup>9-11</sup> As the prevalence of AF and obesity continue to rise, it is no surprise that a substantial proportion of patients referred for catheter ablation for AF are overweight or

obese.<sup>12-16</sup> In these patients, catheter ablation has been shown to be equally effective when compared to normal body weight patients.<sup>12,13</sup>

Although catheter ablation has been shown to improve QoL in multiple study populations, little is known about the effects of catheter ablation for AF on QoL specifically in obese patients. The aim of this review is to summarize what is known about the interaction between atrial fibrillation, obesity, and quality of life as well as specifically the effects of catheter ablation on quality of life in AF patients who are overweight and obese.

## Atrial Fibrillation, Obesity, and Quality of Life

Most patients with symptomatic AF report impaired QoL, at least prior to treatment. In a cross-sectional study, Dorian et al. assessed the effect of intermittent AF on QoL using the SF-36, Specific Activity Scale (SAS), and AF Symptom Checklist. The AF patients had significantly worse scores on all scales compared to healthy controls,

**Corresponding Address :** Matthew R. Reynolds, MD, MSc, Beth Israel Deaconess Medical Center, 185 Pilgrim Road, Baker 4 Boston, MA 02215.

and similar scores to patients with moderate heart failure or prior coronary events.<sup>6</sup> Reynolds et al.<sup>5</sup> published QoL outcomes for a large inception cohort of AF patients followed for up to 2.5 years in the FRACTAL registry. FRACTAL patients had SF-12 derived physical and mental summary scores below age-adjusted population norms, and AF Symptom Checklist scores were above historical healthy controls. In another large cross sectional study, Dagues et al.<sup>27</sup> reported low baseline QoL scores in AF patients as measured by the EuroQoL questionnaire with average EQ-5D scores of 0.73 and 0.85 and average EQ-VAS scores of 60 and 70 for women and men respectively.

Like atrial fibrillation, obesity also has a profound effect on patient outcomes. From 1990 to 2000 the number of deaths attributable to poor diet and physical inactivity has increased substantially.<sup>28</sup> Beyond its effects on mortality, obesity also impacts quality of life both directly and indirectly through association with other chronic health problems.<sup>29-31</sup> Sturm and Wells<sup>32</sup> examined health-related QoL in a US civilian population using the physical health scale of the SF-12 and the Mental Health Inventory from the Medical Outcomes Study. They found that obesity was consistently a significant predictor of poor physical health, but not mental health. After adjusting for a number of other chronic health conditions, they found that BMI $\geq$ 35 was associated with SF-12 physical scores that were 1.1 to 2 points lower in men and women, respectively, than scores from normal weight individuals (BMI 18.5 – 25).

In a cross-sectional study, Jia et al.<sup>8</sup> assessed QoL in obese patients without other chronic medical conditions using the SF-12 and EuroQoL (EQ-5D) and found that scores on both measures decreased with increasing levels of obesity. Compared to normal weight persons, the greatest decrement in both measures was seen in the most obese group (class II, BMI  $\geq$  35) but even overweight patients (BMI 25 to  $<$ 30) and moderately obese patients (BMI 30 to  $<$ 35) had significantly lower QoL scores than patients with normal BMI. In the class II obesity group, decrements in QoL measures were similar to the impact of asthma, hypertension, and diabetes. For example, SF-12 physical summary scores for class II obesity were 4 points lower compared with normal BMI after multivariate adjustment, while

the adjusted effects of asthma, hypertension, and diabetes were 2.0, 2.7, and 2.8 points respectively. The impact of overweight (BMI 25-30) and class I obesity (BMI 30-35) were considerably smaller. Sach et al.<sup>7</sup> similarly reported decrements in QoL measures in obese patients compared to normal BMI patients after controlling for patient characteristics and co-morbidities using the EQ-5D, SF-6D, and EuroQoL visual analogue scale (EQ-VAS). It is worth noting that not all population studies have found impaired QoL in AF patients. "Elderly" patients with AF have been shown to have no differences in QoL measured by SF-36 when compared to age-matched controls. However, this is likely a different population than obese patients with AF being treated with catheter ablation as these patients tend to present at younger ages.<sup>13,14,15,16</sup> Cha et al. found that their most obese group of patients was significantly younger than their lower BMI groups.<sup>12</sup>

The precise interaction between AF, obesity, and other associated medical problems on QoL is dif-

**Table 1** | Impact of Obesity on SF-36 Scores in AF Patients Prior to Catheter Ablation

Measure	US Norm	BMI <25	BMI 25-29.9	BMI $\geq$ 30
General Health	70.8	68 $\pm$ 18	66 $\pm$ 19	55 $\pm$ 21
General Health	70.8	70.3	60.3	
Mental Health	75.0	79 $\pm$ 16	76 $\pm$ 15	71 $\pm$ 18
Mental Health	75.0	75.8	76.5	
Physical Function	83.3	73 $\pm$ 21	76 $\pm$ 21	64 $\pm$ 26
Physical Function	83.3	76.9	66.6	
Social Function	84.3	74 $\pm$ 23	74 $\pm$ 24	67 $\pm$ 26
Social Function	84.3	80.1	77.3	
Physical Role	82.5	46 $\pm$ 43	47 $\pm$ 44	40 $\pm$ 42
Physical Role	82.5	73.4	52.8	
Emotional Role	87.4	78 $\pm$ 34	81 $\pm$ 35	70 $\pm$ 40
Emotional Role	87.4	83.3	69.8	
Pain	71.3	80 $\pm$ 22	75 $\pm$ 23	71 $\pm$ 22
Pain	71.3	80.4	78.3	
Vitality	58.3	50 $\pm$ 23	47 $\pm$ 23	41 $\pm$ 22
Vitality	58.3	56.9	50.7	

SF-36 sub-scale scores are shown across BMI categories from Cha et al.<sup>12</sup> in the non-shaded rows and Mohanty et al.<sup>13</sup> in the shaded rows. Normal values for the US adult population<sup>26</sup> are also shown

difficult to specify. We are not aware of studies evaluating the QoL impacts of obesity while adjusted for the presence or absence of AF. In Table 1, taken from 2 cohorts of AF ablation patients,<sup>12,13</sup> the baseline impact of AF on SF-36 sub-scales across categories of BMI is shown. Generally speaking, SF-36 scales pertaining to physical health and functioning (e.g. physical function, role physical, vitality) are below normal even in patients with BMI <25, but in AF patients, all scales tend to decline as BMI increases, particularly when BMI is  $\geq 30$ .

### Catheter Ablation for AF and Quality of Life

A variety of treatment strategies, including rate control alone, have been shown to improve symptoms and QoL in patients with AF.<sup>33</sup> Catheter ablation has become an important option for patients with AF whose symptoms are not well controlled despite other therapies. Multiple nonrandomized and randomized studies assessing the effects of catheter ablation for both paroxysmal and persistent AF have included QoL or symptom assessment among their endpoints, often using the SF-36 and/or some type of symptom checklist. Although, these studies involved a variety of ablation techniques and included patients with both paroxysmal and persistent forms of atrial fibrillation, all studies reported large positive changes in all or nearly all SF-36 subscales in patients following ablation with varying follow up between 6 months and up to 3 years.<sup>33</sup>

Several studies have described the effect of sinus rhythm maintenance following catheter ablation on QoL outcomes, with mixed results. Reynolds et al.<sup>9</sup> analyzed SF-36 QoL data from the Thermocool AF trial, a prospective, randomized, multicenter study comparing RFA catheter ablation with antiarrhythmic drug therapy. Three months after, ablation group scores on all 8 subscales of the SF-36 as well as the physical and mental summary scores had statistically significant increases, approximating or exceeding general US population means. With mixed linear regression modeling, documentation of atrial arrhythmia on monitoring within 30 days of the QoL measurement was strongly associated with reduced QoL scores. Cha et al.<sup>12</sup> found a similar association between QoL improvement and maintenance of sinus rhythm. Mohanty et al.<sup>13</sup> also found that patients with suc-

cessful ablation experienced a significantly higher improvement in SF-36 physical summary scores compared with those with recurrent arrhythmia. On the other hand, Wokhlu et al.<sup>34</sup> did not find a statistically significant difference in QoL improvement based on ablative efficacy although the recurrence free group did show a trend toward greater improvement in physical and mental summary scores than those who had a recurrence. In contrast, changes in AF specific symptoms measured using the Mayo AF-Specific Symptom Inventory (MAFSI) more consistently reflected ablation efficacy suggesting important differences between generic and disease-specific QoL measures following catheter ablation. Purerfellner et al.<sup>35</sup> also reported differences in QoL measures based on ablation efficacy in disease-specific but not generic QoL measures following ablation. In their study, symptom checklist frequency and severity scores as well as SF-36 physical and mental summary scores improved significantly following ablation. However, when correlating both measures to atrial tachyarrhythmia burden as measured by pacemaker interrogation, symptom checklist frequency and severity but not SF-36 composite scores was significantly associated with atrial tachyarrhythmia burden.

### Catheter Ablation and Quality of Life in Obese Patients

Recently, several groups of investigators have reported the effects of catheter ablation in patients with atrial fibrillation based on BMI – with inconsistent results. Cha et al.<sup>12</sup> prospectively studied 523 patients with highly symptomatic AF who underwent catheter ablation at a single center. In this cohort, 18% of patients were lean (BMI <25), 44% were overweight (BMI 25 to <30), and 38% were obese (BMI  $\geq 30$ ). There was no statistical difference in AF recurrence rates among BMI groups. As expected, significant differences in baseline SF-36 QoL scores were seen across the 3 BMI groups. In particular, baseline scores appeared to be poorer in the obese patients (BMI  $\geq 30$ ) compared with the lean (BMI <25) and overweight (BMI 25 to <30) groups in all SF-36 domains. After 12 months of follow up, improvement was seen in nearly all SF-36 functional domains compared with baseline and the magnitude of increase for each SF-36 scale was similar for all BMI groups. Therefore, in this population, generic QoL as measured by the SF-



36 improved to a similar degree one year after AF ablation, regardless of BMI grouping.

In contrast, Wokhlu et al.<sup>34</sup> reported that obese patients experienced smaller long-term improvement in QoL following ablation than non-obese patients. They prospectively followed 502 symptomatic AF patients undergoing AF ablation at a single center and reported a significant increase in SF-36 scores after ablation at 12 and 24 months for their cohort as a whole. On univariate analysis, obese patients (BMI $\geq$ 30) enjoyed smaller improvements in SF-36 physical summary scores at 2 years than non-obese patients (BMI $<$ 30), with gains of roughly 12 points and 16 points, respectively, in the two groups (using 0-100 scoring). After multivariate adjustment, the improvement in SF-36 physical scores 2 years after ablation was found to be 6.8 points smaller in obese compared with non-obese patients ( $p=0.0002$ ). Based on Wokhlu's data, obese patients undergoing AF ablation still reported improved SF-36 physical scores at 2 years, but the improvement was less robust than in non-obese patients.

Conversely, Mohanty et al.<sup>13</sup> reported the results of 660 prospectively enrolled patients undergoing catheter ablation for AF. They divided patients into two groups based on baseline BMI with 21% of patients in the normal BMI group (BMI $<$ 25) and 79% of patients in the overweight or obese group (BMI $\geq$ 25). Once again, baseline QoL scores – assessed using the SF-36 and several depression and anxiety scales – were generally higher among the patients with normal BMI. In fact, most of the SF-36 scales were at or close to population norms in the normal BMI group. In this group, no significant improvement in SF-36 scores was observed after 12 months of follow up. In the overweight/obese group, the 12-month post-ablation QoL scores improved significantly in all measures except physical functioning and bodily pain. However, given the differences between groups at baseline, almost all SF-36 scores were higher at 12 months in the normal versus the overweight/obese group. On multivariate analysis, “high” BMI (BMI $\geq$ 25) was found to be an independent predictor of QoL improvement, however the magnitude of this effect, while statistically significant, was small (3.5 points on the physical summary score, using the 0-100 scale), after adjustment for baseline scores.

The three recent studies which assessed the impact of BMI on QoL improvement (using the SF-36 questionnaire) after AF ablation therefore each reported a different result. Cha et al. observed similar degrees of QoL improvement following ablation among three different BMI groups. Wokhlu et al. reported a lower degree of QoL improvement at 2 years in patients with obesity (BMI $\geq$ 30) compared with lean and overweight patients combined. Mohanty et al. reported no improvement in QoL in lean patients (BMI $<$ 25) at one year, but significant QoL gains in overweight and obese patients combined (BMI $\geq$ 25).

Several possibilities for these discrepancies exist, however, comparison between the studies is limited by the fact that each study reported results using different BMI cut-points, and all 3 described the relationship between obesity and QoL improvement after ablation only using the generic SF-36 scale. More importantly, none of the 3 reported results specifically for patients with stage 2-3 obesity (BMI $\geq$ 35), so results to date generally pertain to ablated patients who are overweight or have stage 1 obesity. The impact of AF ablation on more severely obese patients is therefore presently unknown.

In the study by Mohanty et al., no improvement was seen in QoL in the normal BMI group, which is contrary to the results of most published literature on AF ablation. The most likely explanation for this finding is that the normal BMI group in this study had relatively normal SF-36 scores at baseline. This is evident by comparing the baseline QoL scores of normal BMI patients in the Mohanty study to the normal BMI group in the Cha study, which were lower in almost every sub-scale (Table 1). It remains quite possible that improvements in AF symptoms and AF-related QoL might have been observed in this group had they been assessed with a disease specific questionnaire having greater sensitivity to change in AF status, as suggested by others.<sup>36</sup> This would be especially true in a population of obese patients with multiple medical problems affecting their QoL. Reynolds et al. reported that noncardiac comorbid illness correlated with diminished scores on QoL scales reflecting general health and functional status, whereas cardiac conditions correlated with both reduced general physical function and higher AF symptom scores.<sup>42</sup> Wokhlu et al., did find a greater sensitiv-

ity to AF status with the AF-specific MAFSI score, which was reflective of AF ablation efficacy unlike generic SF-36 scores.<sup>34</sup>

Recognizing that most studies have shown a correlation between ablation success and QoL improvement, one might expect obese patients to have lower rates of QoL improvement related to more technically challenging and, therefore, less successful ablations. There is also a strong association between obesity and obstructive sleep apnea, which has been correlated with AF recurrence post-ablation independent of its association with BMI.<sup>16</sup> Surprisingly, although obesity has been reported to be an independent predictor of catheter ablation failure in at least one study,<sup>14</sup> multiple other studies have shown catheter ablation to be equally efficacious in obese patients with AF when compared to patients with normal BMIs.<sup>12,13,16</sup>

An obesity paradox has been described in congestive heart failure, hypertension, peripheral vascular disease, and coronary artery disease with obese patients having better long term outcomes than non-obese patients.<sup>37-40</sup> Badeka et al.<sup>41</sup> showed that among AFFIRM trial patients, overweight and obese patients were at significantly less risk of suffering death, cardiovascular death, and the combined end points of the original AFFIRM trial (ventricular tachycardia, ventricular fibrillation, cardiac arrest, ischemic stroke, major bleeding, systemic embolism, pulmonary embolism, and myocardial infarction) compared to normal BMI patients. It remains unclear as to whether such an obesity paradox exists for obese patients undergoing catheter ablation. From a quality of life perspective, such an obesity paradox could be explained by regression to the mean, given that obese patients are known to have lower baseline QoL scores than nonobese patients. In general, obese patients tend to present to physicians at younger ages, tend to be younger in cohort studies, and may be on more beneficial medical regimens from earlier ages, which could contribute to effects seen.

It seems clear that the relationship between BMI and quality of life following catheter ablation for AF is neither linear nor simple. Future research will need improved standardization in order to answer the question of how quality of life of obese patients is affected following catheter ablation. Standardization should focus not only on how

BMI is analyzed but also what type of QoL measures are utilized. Patients with multiple comorbidities in addition to AF, such as obese patients, are less likely to have large changes in generic QoL measures even if AF is well controlled<sup>42</sup> suggesting that a disease-specific QoL measure might be more applicable to obese patients. Though, if overall quality of life is unlikely to be improved following catheter ablation, one could question the utility of the procedure for obese patients from a clinical and cost effectiveness perspective.

## Disclosures

No disclosures relevant to this article were made by the authors.

## References

1. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang, TSM. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006 Jul. 11;114(2):119–125.
2. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999–2008. *JAMA*. 2010 Jan. 20;303(3):235–241.
3. Wang TJ, Parise H, Levy D, D'Agostino RB, Wolf PA, Vasani RS, Benjamin, EJ. Obesity and the risk of new-onset atrial fibrillation. *JAMA*. 2004 Nov. 24;292(20):2471–2477.
4. Dublin S, French B, Glazer NL, Wiggins KL, Lumley T, Psaty BM, Smith NL, Heckbert SR. Risk of new-onset atrial fibrillation in relation to body mass index. *Arch Intern Med*. 2006 Nov. 27;166(21):2322–2328.
5. Reynolds MR, Lavelle T, Essebag V, Cohen DJ, Zimetbaum P. Influence of age, sex, and atrial fibrillation recurrence on quality of life outcomes in a population of patients with new-onset atrial fibrillation: the Fibrillation Registry Assessing Costs, Therapies, Adverse events and Lifestyle (FRACTAL) study. *Am Heart J*. 2006 Dec.;152(6):1097–1103.
6. Dorian P, Jung W, Newman D, Paquette M, Wood K, Ayers GM, Camm J, Akhtar M, Luderitz B. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. *J Am Coll Cardio*. 2000 Oct.;36(4):1303–1309.
7. Sach TH, Barton GR, Doherty M, Muir KR, Jenkinson C, Avery AJ. The relationship between body mass index and health-related quality of life: comparing the EQ-5D, EuroQol VAS and SF-6D. *Int J Obes Relat Metab Disord*. 2006 May 9;31(1):189–196.
8. Jia H, Lubetkin EI. The impact of obesity on health-related quality-of-life in the general adult US population. *J Public Health*. 2005 Jun. 1;27(2):156–164.
9. Reynolds MR, Walczak J, White SA, Cohen DJ, Wilber DJ. Im-

- provements in Symptoms and Quality of Life in Patients With Paroxysmal Atrial Fibrillation Treated With Radiofrequency Catheter Ablation Versus Antiarrhythmic Drugs. *Circ Cardiovasc Qual Outcomes*. 2010 Nov. 16;3(6):615–623.
10. Pappone C, Rosanio S, Augello G, Gallus G, Vicedomini G, Mazzone P, Gulletta S, Gugliotta F, Pappone A, Santinelli V, Tortoriello V, Sala S, Zangrillo A, Crescenzi G, Benusi S, Alfieri O. Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation. *J Am Coll Cardio*. 2003 Jul.;42(2):185–197.
11. Weerasooriya R, Jais P, Hocini M, Scavée C, MacLe L, Hsu LF, Sandars P, Garrigue S, Clementy J, Haissaguerre M. Effect of catheter ablation on quality of life of patients with paroxysmal atrial fibrillation. *Heart Rhythm*. 2005 Jun.;2(6):619–623.
12. Cha YM, Friedman PA, Asirvatham SJ, Shen WK, Munger TM, Rea RF, Brady P, Jahangir A, Monahan KH, Hodge DO, Meverden RA, Gersh BJ, Hammill SC, Packer DL. Catheter Ablation for Atrial Fibrillation in Patients With Obesity. *Circulation*. 2008 May 19;117(20):2583–2590.
13. Mohanty S, Mohanty P, Di Biase L, Bai R, Dixon A, Burkhardt D, Gallinghouse JG, Horton R, Sanchez JE, Bailey S, Zagrodzky J, Natale A. Influence of body mass index on quality of life in atrial fibrillation patients undergoing catheter ablation. *Heart Rhythm*. In press. doi:10.1016/j.hrthm.2011.07.005
14. Chilukuri K, Dalal D, Gadrey S, Marine JE, Macpherson E, Henrikson CA, Cheng A, Nazarian S, Sinha S, Spragg D, Berger R, Calkins H. A Prospective Study Evaluating the Role of Obesity and Obstructive Sleep Apnea for Outcomes After Catheter Ablation of Atrial Fibrillation. *J Cardiovasc Electrophysiol*. 2010 May;21(5):521–525.
15. Ector J, Dragusin O, Adriaenssens B, Huybrechts W, Willems R, Ector H, Heidbuchel H. Obesity is a major determinant of radiation dose in patients undergoing pulmonary vein isolation for atrial fibrillation. *J Am Coll Cardio*. 2007 Jul. 17;50(3):234–242.
16. Jongnarangsin K, Chugh A, Good E, Mukerji S, Dey S, Crawford T, Sarrazin J, Kuhne M, Chalfoun N, Wells D, Boonyapisit W, Pelosi F, Bogun F, Morady F, Oral H. Body Mass Index, Obstructive Sleep Apnea, and Outcomes of Catheter Ablation of Atrial Fibrillation. *J Cardiovasc Electrophysiol*. 2008 Jul.;19(7):668–672.
17. Gami AS, Pressman G, Caples SM, Kanagala R, Gard JJ, Davison DE, Malouf JF, Ammash NM, Friedman PA, Somers VK. Association of atrial fibrillation and obstructive sleep apnea. *Circulation*. 2004 Jul. 27;110(4):364–367.
18. Gami AS, Caples SM, Somers VK. Obesity and obstructive sleep apnea. *Endocrinol Metab Clin North Am*. 2003 Dec.;32(4):869–894.
19. Gami AS, Hodge DO, Herges RM, Olson EJ, Nykodym J, Kara T, Somers VK. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardio*. 2007 Feb. 6;49(5):565–571.
20. Gersh BJ, Tsang TSM, Seward JB. The changing epidemiology and natural history of nonvalvular atrial fibrillation: clinical implications. *Trans. Am Clin Climatol Assoc*. 2004;115:149–59; discussion 159–60.
21. Rexrode KM, Pradhan A, Manson JE, Buring JE, Ridker PM. Relationship of total and abdominal adiposity with CRP and IL-6 in women. *Ann Epidemiol*. 2003 Nov.;13(10):674–682.
22. Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, Kronmal RA, Tracy RP, Van Wagoner DR, Psaty BM, Lauer MS, Chung MK. Inflammation as a risk factor for atrial fibrillation. *Circulation*. 2003 Dec. 16;108(24):3006–3010.
23. Vincent HK, Powers SK, Stewart DJ, Shanely RA, Demirel H, Naito H. Obesity is associated with increased myocardial oxidative stress. *Int J Obes Relat Metab Disord*. 1999 Jan.;23(1):67–74.
24. Engeli S, Sharma AM. The renin-angiotensin system and natriuretic peptides in obesity-associated hypertension. *J Mol Med*. 2001;79(1):21–9.
25. Pelat M, Verwaerde P, Merial C, Galitzky J, Berlan M, Montastruc JL, Senard, JM. Impaired atrial M(2)-cholinoceptor function in obesity-related hypertension. *Hypertension*. 1999 Nov.;34(5):1066–1072.
26. Ware JE Jr, Kosinski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME. *User's Manual for the SF-36v2 Health Survey*. 2nd ed. Lincoln, RI: QualityMetric Incorporated; 2007.
27. Dages N, Nieuwlaat R, Vardas PE, Andresen D, Lévy S, Cobbe S, Kremastinos DTh, Breithardt G, Cokkinos D, Crijns HJCM. Gender-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Heart Survey on Atrial Fibrillation. *J Am Coll Cardio*. 2007 Feb. 6;49(5):572–577.
28. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. *JAMA*. 2004 Mar. 10;291(10):1238–1245.
29. Kolotkin RL, Crosby RD, Williams GR. Health-related quality of life varies among obese subgroups. *Obes Res*. 2002 Aug;10(8):748–756.
30. Ford ES, Moriarty DG, Zack MM, Mokdad AH, Chapman DP. Self-reported body mass index and health-related quality of life: findings from the Behavioral Risk Factor Surveillance System. *Obes Res*. 2001 Jan.;9(1):21–31.
31. Hassan MK, Joshi AV, Madhavan SS, Amonkar MM. Obesity and health-related quality of life: a cross-sectional analysis of the US population. *Int J Obes Relat Metab Disord*. 2003 Oct.;27(10):1227–1232.
32. Sturm R, Wells KB. Does obesity contribute as much to morbidity as poverty or smoking? *Public Health*. 2001 May;115(3):229–235.
33. Reynolds MR, Ellis E, Zimetbaum P. Quality of Life in Atrial Fibrillation: Measurement Tools and Impact of Interventions. *J Cardiovasc Electrophysiol*. 2008 Jul.;19(7):762–768.
34. Wokhlu A, Monahan KH, Hodge DO, Asirvatham SJ, Friedman PA, Munger TM, Bradley DJ, Bluhm CM, Haroldson JM, Packer DL. Long-Term Quality of Life After Ablation of Atrial Fibrillation. *J Am Coll Cardio*. 2010 May;55(21):2308–2316.
35. Pürerfellner H, Aichinger J, Martinek M, Nesser HJ, Ziegler P, Koehler J, Warman E, Hettrick D. Quantification of atrial tachyarrhythmia burden with an implantable pacemaker before and after pulmonary vein isolation. *Pacing Clin Electrophysiol*. 2004 Sep.;27(9):1277–1283.
36. Spertus J, Dorian P, Bubien R, Lewis S, Godejohn D, Reynolds MR, Lakkireddy DR, Wimmer AP, Bhandari A, Burk C. Development and validation of the Atrial Fibrillation Effect on Quality-of-Life (AFEQT) questionnaire in patients with atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2011;4:15–25.

37. Uretsky S, Messerli FH, Bangalore S, Champion A, Cooper-DeHoff R, Zhou Q, Pepine C. Obesity Paradox in Patients with Hypertension and Coronary Artery Disease. *Am J Med.* 2007 Oct.;120(10):863–870.
38. Arena R, Lavie CJ. The obesity paradox and outcome in heart failure: is excess bodyweight truly protective? *Future Cardiol.* 2010 Jan.;6(1):1–6.
39. Galal W, van Gestel YRBM, Hoeks SE, Sin DD, Winkel TA, Bax JJ, Verhagen H, Awara AMM, Klein J, van Domburg RT, Poldermans D. The obesity paradox in patients with peripheral arterial disease. *Chest.* 2008 Nov.;134(5):925–930.
40. Lavie CJ, Milani RV, Ventura HO. Obesity, heart disease, and favorable prognosis--truth or paradox? *Am J Med.* 2007 Oct.;120(10):825–826.
41. Badheka AO, Rathod A, Kizilbash MA, Garg N, Mohamad T, Afonso L, Jacob S. Influence of Obesity on Outcomes in Atrial Fibrillation: Yet Another Obesity Paradox. *Am J Med.* 2010 Jul. 1;123(7):646–651.
42. Reynolds M, Lavelle T, Essebag V, Cohen D, Zimetbaum P. Influence of age, sex, and atrial fibrillation recurrence on quality of life outcomes in a population of patients with new-onset atrial fibrillation: The Fibrillation Registry Assessing Costs, Therapies, Adverse events and Lifestyle (FRACTAL) study. *Am Heart J.* 2006 Dec.;152(6):1097–1103.