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Exploring The Obesity Paradox In Atrial Fibrillation. AFBAR (Atrial Fibrillation Barbanza Area) Registry Results

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Abstract

Introduction and Objectives: Previous studies have described an inverse relationship between obesity and adverse events in a variety of conditions. Our aim was to investigate the relationship between obesity and prognosis in patients with atrial fibrillation.

Methods: We studied 746 patients who were prospectively included, between January and April 2008, in the AFBAR (Atrial Fibrillation in BARbanza area) registry. Patients were categorized into 3 body mass index groups using baseline measurements: normal (< 25 kg/m2), overweight (25-30 kg/m2), and obese (≥30 kg/m2). Survival free from the composite endpoint hospitalization for cardiovascular causes or all-cause mortality was compared across the 3 body mass index groups. A multivariable Cox proportional hazard regression was also performed to determine the independent effect of obesity as well as overweight, with respect to normal body mass index as a reference category, regarding the study endpoint. Median follow-up time was 36 (28-36) months.

Results: 49.3% were obese and 38.2% had overweight. The composite endpoint rate was 70.9%, 67.5%, and 57.6% for obese, overweight, and normal weight patients, respectively (log rank test; p=0.02). An inverse association of obesity with a favorable prognosis persisted even after multivariable adjustment: hazard ratio 0.668; 95% confidence interval 0.449-0.995; p=0.047. Hazard ratio of overweight, however, was 0.741; 95% confidence interval: 0.500-1.098; p=0.096.

Conclusions: Obesity, defined as a body mass index ≥ 30 kg/m2, is associated with better prognosis in a community-based cohort of patients with atrial fibrillation.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice. It is estimated that currently affects more than 6 million Europeans, and its prevalence is expected to double in the upcoming years.[1] Furthermore, AF leads to a higher mortality rate and hospital admissions,[1-2] as well as to a major economic burden.[3] On the other hand, obesity is a well established risk factor for developing AF,[5-9] like many other cardiovascular diseases.

However, once cardiovascular disease was expressed, their prognosis and relationship with obesity becomes more complex.[10] Several studies have shown that subjects with established cardiovascular disease, overweight or obese have better prognosis than patients with normal or low weight.[10-23]

The aim of this study was to explore the obesity paradox in a community-based cohort of patients with AF.

Key Words:

Atrial Fibrillation, Body Mass Index, Prognosis, Mortality.

Disclosures:
None

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Methods

Patients

The AFBAR (Atrial Fibrillation in the BARbanza area) was a prospective study that has been described in detail previously.[24]

Briefly, AFBAR registry was carried out by a team of primary care physicians in a single health-service of Galicia, north-western of Spain. AFBAR had aimed to describe the natural history of AF in an unselected population attending by primary care services, and treated at the discretion of their attending physicians. Each doctor had enrolled all his/her patients with AF, aged >18 years, during a 3 month period (from January-2008 to April-2008). All patients had signed a consent form. Patients demographic and clinical data, such as previous cardiovascular events and comorbidities, treatment, and AF complications during follow-up, were ascertained from the patients clinical interview and hospital records. At the time of inclusion, anthropometric measurements were recorded for each patient. Body mass index [BMI] (calculated as weight [in kilograms] divided by the square of height [in meters]) was evaluated as a categorical variable according to World Heart Organization criteria.[25] Thus, study patients were classified into 3 groups: normal weight, BMI <25 kg/m2, overweight, BMI 25-30 kg/m2, and obesity as BMI ≥30 kg/m2. AFBAR study included a total of 798 patients with FA diagnosed. Patients without data on baseline BMI (n=2), those with BMI <18.5 kg/m2 (underweight) or ≥40 kg/m2 (morbidly obese) (n=18) and prosthetic valves (n=27) were excluded from the analysis in this study. Five patients without valid data on vital status and hospitalizations during follow-up were also excluded. Thus, the final study cohort was made of 746 patients.

The primary endpoint was cardiovascular hospitalization (heart failure, ischemic heart disease, AF, thromboembolic complications [stroke, transient ischemic attack or peripheral embolism], non-AF arrhythmic events or pulmonary embolism) or all-cause mortality. Median follow-up was 36 (interquartile range 28-36) months.

Statistical Analysis

Quantitative variables were expressed as mean ± standard deviation and were compared by Student t test and ANOVA variance analysis. Categorical variables were compared using Pearson's $\chi 2$ test and were described as value and percentage. Event-free survival curves were constructed using Kaplan-Meier method. The groups according to BMI were compared using log-rank test. The relationship between baseline characteristics and the occurrence of the primary endpoint of this study was determined using a Cox univariate analysis. The independent effect on prognosis of Obesity and overweight, respect to normal weight (i.e., reference category), was determined by a multivariate Cox model, which was constructed with the following variables: age, sex, BMI groups, type of AF at baseline study, smoking, dyslipidemia, hypertension, diabetes mellitus, peripheral arterial disease, thromboembolic complications history (stroke, transient ischemic attack or peripheral embolism), heart failure, ischemic heart disease, chronic obstructive pulmonary disease, baseline creatinine, hemoglobin and baseline drug treatment.

We confirmed the assumption of proportional risks for the overall Cox model by Grambsch and Therneau test .[26] Statistical significance was set with bilateral p value at <0.05. Analysis were performed using SPSS programm v. 18.0 and R v. 2.14.1.

Results

In the total of 746 patients, BMI was 30.1±4.9 kg/m2. The vast majority of patients (87.5%) had BMI ≥25 kg/m2 and 49.3% were obese (BMI ≥30 kg/m2). Mean age was 75.0±9.2 years and 47.8% were women. At study entry, 68.5% of patients were on permanent AF. Table 1 shows 3 groups baseline characteristics according to BMI. Obese patients (73.9±9 years) and those overweighted (75.8±8.4) were significantly lower than age in those with normal weight (76.9±11.6) (p<0,05). The rate of hypertension, diabetes mellitus and dyslipidemia proportion was significantly higher in obese compared to normal weight patients (Table 1). In contrast, peripheral arteriopathy prevalence was significantly higher in patients with normal weight (18.5%) as compared to obese (10.1%) and those with overweight (9.8%).

In addition, baseline hemoglobin values were significantly lower in normal weight patients. Thromboembolic risk estimated by CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age≥75 years [double], Diabetes, Stroke [doubled], Vascular disease and

Table 1: Clinical characteristics of subgroups according to BMI

	BMI <25 (n=92; 12.3%)	BMI 25-30 (n=286; 38.2%)	BMI ≥30 (n=368; 49.3%)
Age (years)	76.9±11.6*†	75.8±8.4	73.9±9¶
Weight (kg)	60.0±8.3*†	71.2±8.6	87.5±13.1¶
Size (meters)	1.61±0.93	1.60±0.86	1.61±0.89
Women,%	44 (47.8)	124 (43.3)	185 (50.3)
AF class,%			
First episode	10 (10.9)	29 (10.1)	49 (13.3)
Recurrent	14 (15.2)	61 (21.3)	72 (19.5)
Permanent	68 (73.9)	196 (68.5)	247 (67.1)
Smoking,%			
No	57 (62)	182 (63.6)	245 (66.6)
Former smoker	31 (33.7)	83 (29)	103 (28)
Present	4 (4.3)	21 (7.3)	20 (5.4)
COPD,%	14 (15.2)	46 (16.1)	78 (21.2)
Hypertension,%	56 (60.9)†	208 (72.7)	316 (85.9)¶
Diabetes mellitus,%	15 (16.3)†	62 (21.7)	111 (30.2)¶
Dyslipidemia,%	36 (39.1)†	153 (53.5)	233 (63.3)¶
Ischemic heart disease,%	18 (19.6)	51 (17.8)	66 (17.9)
Heart failure,%	13 (14.1)	45 (15.7)	44 (12)
Peripheral arteriopathy,%	17 (18.5)*†	28 (9.8)	37 (10.1)
Stroke, TIA or previous peripheral embolism,%	7 (7.6)	27 (9.4)	32 (8.7)
Creatinine (mg/dl)	1.03±0.25	1.07±0.25	1.05±0.3
Haemoglobin (gr/dl)	13.4±1.6*†	14±1.5	13.8±1.6
CHA2DS2-VASc	3.36±1.68	3.42±1.59	3.43±1.59
Oral anticoagulation,%	67 (72.8)	227 (79.4)	303 (82.3)
Antiplatelet,%	20 (21.7)	55 (19.2)	61 (16.6)
ACE o AAR II,%	49 (53.3)†	196 (68.5)	278 (75.5)
B-bloquers,%	22 (23.9)	85 (29.7)	130 (35.3)
Statin,%	36 (39.1)†	146 (51)	190 (51.6)
Other hypolipidemics,%	3 (3.2)	12 (4.2)	31 (8.4)¶
Dyuretics,%	47 (51.1)†	155 (54.2)	234 (63.6)¶
Calcium bloquers,%	19 (20.7)†	91 (31.8)	142 (38.6)
Digoxin,%	32 (34.8)	97 (33.9)	123 (33.4)
Anti aldosterone,%	9 (9.8)	14 (4.9)	32 (8.7)
Antiarrythmics,%§	10 (10.9)	36 (12.6)	49 (13.3)

TIA: transient ischemic attack; AARII: angiotensin II receptor antagonist; CHA2DS2-VASc: heart failure, hypertension, age ≥75years (double), diabetes, stroke (double), vascular disease and female; COPD: chronic obstructive pulmonary disease; AF: atrial fibrillation; HR: hazard ratio; HF: heart failure; 95% CI: 95% confident interval; ACE: angiotensin converting inhibitor enzime; INR: international normalized ratio. *p<0.05 to compare <25 kg/m2 vs. BMI 25-30 kg/m2; †p<0.05 to compare BMI < 25 kg/m2 vs BMI ≥ 30 kg/m2; ¶p<0.05 to compare BMI 25-30 kg/m2 vs BMI ≥ 30 kg/m2. § Refered to flecainide, disopyramide, propaphenone, amiodarone or sotalol.

Table 2: Cardiovascular event or mortality cox univariate analysis at 36 months follow-up.

	HR	95% CI	P
Age, years	1.025	1.009-1.040	0.002
Sex,			
Men	1.0 (Reference)		
Women	0.912	0.707-1.177	0.48
AF class,	1.0 (Reference)		
First episode	1.869	1.120-3.118	0.02
Recurrent	1.477	0.928-2.349	0.10
Permanent			
Smoking			
No	1.0 (Reference)		
Former smoker	0.741	0.449-1.225	0.24
Present	0.873	0.516-1.478	0.61
COPD	1.347	0.995-1.824	0.054
Hypertension	0.903	0.670-1.215	0.50
Diabetes mellitus	1.580	1.209-2.069	0.001
Dyslipidemia	0.747	0.580-0.963	0.024
Ischemic heart disease	1.908	1.431-2.545	<0.001
Heart failure	2.695	2.007-3.620	<0.001
Peripheral arteriopathy	1.586	1.112-2.260	0.01
Stroke, TIA or previous peripheral embolism	1.183	0.965-1.450	0.11
Creatinine (for each 1 mg/dl increase)	2.780	1.959-3.946	<0.001
Haemoglobina (for each 1 gr/dl increase)	0.830	0.765-0.899	<0.001
Antiplatelet or anticoagulation			
None	1.0 (Reference)		
Antiaplatelet	0.623	9.320-1.215	0.17
Anticoagulation	0.651	0.354-1.195	0.17
ACE or AAR II	1.069	0.809-1.417	0.64
B-bloquers	1.049	0.800-1.378	0.73
Statin	0.925	0.718-1.192	0.55
Other hypolipidemics	0.864	0.494-1.511	0.61
Dyuretics	1.210	0.932-1.571	0.15
Calcium bloquers	1.007	0.771-1.315	0.96
Digoxin	1.064	0.816-1.388	0.65
Anti aldosterone	2.257	1.547-3.293	<0.001
Antiarritmics,%*	0.995	0.682-1.451	0.98

TIA: transient ischemic attack; AARII: angiotensin II receptor antagonist; CHA2DS2-VASc: heart failure, hypertension, age ≥ 75years (double), diabetes, stroke (double), vascular disease and female; COPD: chronic obstructive pulmonary disease; AF: atrial fibrillation; HR: hazard ratio; HF: heart failure; 95% CI: 95% confident interval; ACE: angiotensin converting inhibitor enzime; INR: international normalized ratio. *p<0.05 to compare <25 kg/m2 vs. BMI 25-30 kg/m2; †p<0.05 to compare BMI < 25 kg/m2 vs BMI ≥ 30 kg/m2; ¶p<0.05 to compare BMI 25-30 kg/m2 vs BMI ≥ 30 kg/m2. § Refered to flecainide, disopyramide, propaphenone, amiodarone or sotalol.

female Sex) risk score was similar among 3 BMI groups. There was a higher rate usage of oral anticoagulants in obese group in contrast to the higher rate usage of antiplatelet drugs in normal weight patients, although no significant differences were seen.

Events During Tracing

There were 239 (32%) events during follow-up: 91 (12.2%) patients died and 148 (19.8%) required hospitalization. All-cause mortality by BMI subgroup was 20.7% (n=19), 12.2% (n = 35) and 10.1% (n=37) in normal weight, overweight and obese patients, respectively. Cardiovascular hospitalization occurred in 21.7% (n=20) in patients with normal weight, 20.3% (n=58) in those overweighed and 19% (n=70) in obese patients. Survival free from cardiovascular hospitalization or mortality is shown in Figure 1. Among obese and overweighed patients, the combined endpoint occurred in 29.1% (n=107) and 32.5% (n=93), respectively, in contrast to the 42.4% (n=39) in normal weight patients (log-rank test, p=0,03).

In patients with BMI ≥ 25 kg/m2, the incidence of the composite endpoint was 30.6% (n=200) in contrast to 42.4% (n=39), in those patients with BMI <25 kg/m2 (log-rank test, p=0,01). Table 2 shows the relationship between baseline patient characteristics and the composite endpoint of all-cause mortality and cardiovascular hospitalization. Crude and adjusted effect of obesity and overweight, with respect to normal weight subgroup, is presented in Table 3. Although overweight and obesity compared to normal weight were associated with reduced risk of mortality and cardiovascular hospitalization, after adjusting for various clinical factors that association was maintained only for obesity.

Obese patients showed a rate of cardiovascular hospitalizations and all-cause mortality 33.2% lower than those patients with normal weight (Hazard Ratio 0.668, 95% Confidence Interval: 0.449 to 0.995, p=0.047).

Discussion

The main finding of the present study is that in a community-based population of patients with AF, obesity (defined as BMI ≥30 kg/m2) is associated with a reduction of the mortality and risk of cardiovascular hospitalization, despite the fact of having those patients with a higher rate of diabetes mellitus and hypertension.

Despite the well established association of overweightness and obesity with cardiovascular heart disease (CHD), numerous studies have reported that patients with established CHD have a better clinical prognosis than those with normal weight. This phenomenon has been termed "the obesity paradox", and it has been demonstrated in many cardiovascular diseases such as heart failure,[11-15] ischemic cardiopathy,[16-18] peripheral artery disease[19] and, recently in cerebrovascular disease.[20] Likewise, the paradox of the obesity was described in other non-cardiovascular diseases as chronic obstructive pulmonary disease.[27]

In a sub-analysis of the AFFIRM study[21-22] (Atrial Fibrillation Follow-up Investigation of Rhythm Management), an inverse relationship between obesity and prognosis was also described. Accordingly, rate of all-cause death was higher in the normal BMI group (5.8 per 100 patient-years) than in the overweight and obese groups (3.9 and 3.7, respectively). In that study, cardiovascular death rate was also highest in the normal BMI group (3.1 per 100 patient-years), lowest in the overweight group (1.5 per 100 patient-years), and intermediate in the obese group (2.1 per 100 patient-years), being overweight associated with a lower risk of cardiovascular death

Table 3: Overweight and obesity crude and adjusted effect (Hazard Ratio) in the occurrence of cardiovascular events or all-mortality causes over the 36 month follow-up.

	Crude		Adjusted	
BMI cathegories	HR (95%CI)	P	HR (95%CI)	P
Normal weight: BMI <25 kg/m2	1.0 (Reference)		1.0 (Reference)	
Overweight: BMI 25-30 kg/m2	0.665 (0.446-0.964)	0.036	0.741 (0.500-1.098)	0.096
Obesity: BMI ≥30 kg/m2	0.615 (0.426-0.888)	0.009	0.668 (0.449-0.995)	0.047

HR: hazard ratio; 95% CI: 95% confidence interval; BMI: body mass index.

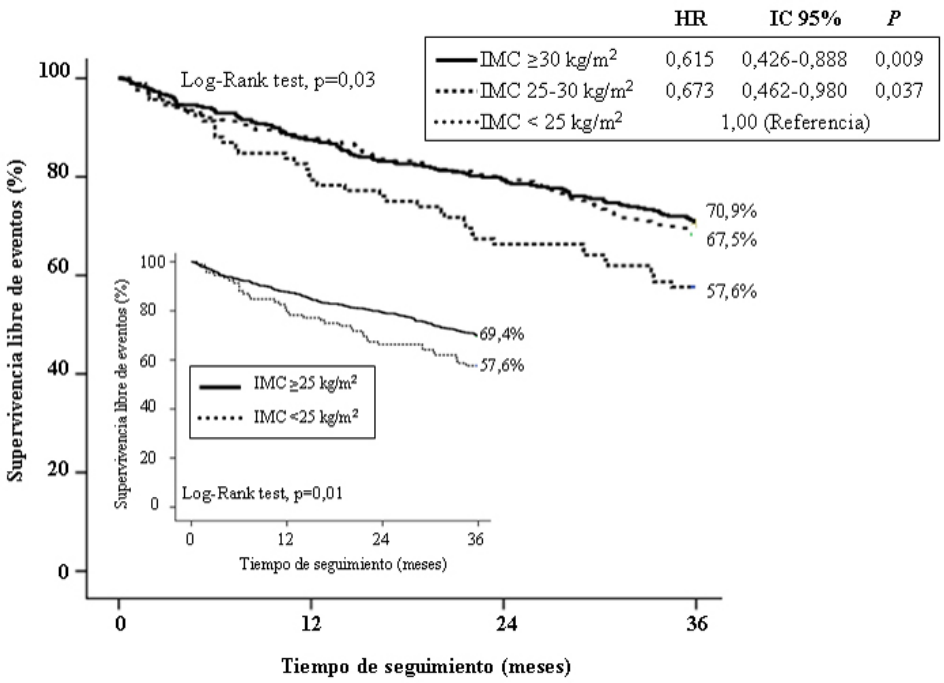

Figure 1: **Event-free survival and follow-up time relationship, according to BMI**

(hazard ratio 0.47, p = 0.002).

Although the potential mechanism of obesity paradox has not been fully elucidated , several hypotheses had been proposed in this regard. It seems that TNF alpha can increase the pulmonary vein arrhythmogenicity, thereby causing inflammation-related AF.[28,29] Another potential explanation could be lipoproteins higher levels in obese people, which could remove proinflamatory toxins, with the subsequent inflammatory state reduction.[30] Low circulating natriuretic peptide levels could be related with more favourable outcomes.[31] As may occur during a cardiovascular event or a major interventional procedure, adipose tissue may respond with enhanced function, which may improve cardiovascular and other clinical outcomes.

Higher body fat and especially higher lean mass index (LMI) may be associated with muscular strength, linked to better prognosis and survival. Many epidemiological studies were unable to show a higher risk for adverse events in overweight (BMI 25–29kg/m^2) compared to normal weight patients. This could be explained by the limited ability of BMI to differentiate body fat from lean mass.[32-36]

Based on the present study characteristics, we cannot relate some of the abovementioned theories with the presented results, but in our opinion it deserves further investigation in order to explain the mechanism why this particular subgroup of patients, despite the higher rate of diabetes mellitus and hypertension, presented a better outcome. These results made create doubts about whether current recommendations for cardiovascular prevention should be extrapolated to populations with established cardiovascular disease.

The results of our study should be considered in light of its potential limitations. First of all, conclusions are based in the BMI, which as it is known, does not differentiate body fat from lean mass. Second, we were unable to account for fat distribution (peripheral versus abdominal obesity) and other measures of adiposity such as body fat percentage. Third, a small but potentially significant number of patients (5) were excluded from the sample due to missing BMI data, and it is unlike that this fact could bias the results.

Besides, information regarding proinflamatory and nutritional status were not collected. We did not consider potential changes in BMI over the study follow-up.

Finally, it should be remark that this sample was drawn from rural medical centres, and may not be generalizable to urban areas.

Conclusions:

Obesity, defined as a body mass index ≥30 kg/m^2, is associated with lower cardiovascular hospitalization and global mortality risk, independent of other clinical features, in a community-based cohort of patients with AF. These results must be analyzed under the BMI parameter limitations. Also, future research should aim to understand the mechanisms underlying the obesity paradox.

References:

1. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et-al. Management of Atrial Fibrillation Guidelines. European Heart Journal (2010) 31, 2369–2429.
2. Mensah GA, Croft JB. Increasing trends in hospitalization for atrial fibrillation in the United States, 1985 through 1999: implications for primary prevention. Circulation. 2003;108:711-63.
3. Costs of atrial fibrillation in five European countries: results from the Euro Heart Survey on atrial fibrillation. Ringborg A, Nieuwlaat R, Lindgren P, Jönsson B, Fidan D, Maggioni AP, López-Sendón J, Stepinska J, Cokkinos DV, Crijns HJ. Europace. 2008;10:403-11.
4. Aranceta J, Foz M, Gil B, Jover E, Mantilla J, Millan J, et-al. Consensus document: obesity and cardiovascular Risk. Clin Invest Arterioscl 2003; 15:196-233.
5. Menezes AR, Lavie CJ, DiNicolantonio JJ, O´Keefe J, Morin DP, Khatib S, Milani RV. Atrial Fibrillation in the 21st Century: A Currrent Understanding of Risk Factors and Primary Prevention Strategies. Mayo Clinic Proc. 2013; 88(4):394-409.
6. Salas-Salvadó J, Rubio MA, Barbany M, Moreno B; SEEDO Collaborative group. SEEDO 2007. Consensus for the evaluation of overweight and obesity

and the establishment of therapeutic intervention criteria. Med Clin (Barc). 2007; 128:184-96.
7. Dublin S, French B, Glazer NL, Wiggins KL, Lumley T, Psaty BM, et-al. Risk of new-onset atrial fibrillation in relation to body mass index. Arch Intern Med. 2006; 166:2322-8.
8. Frost L, Hune LJ, Vestergaard P. Overweight and obesity as risk factors for atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. Am J Med. 2005; 118:489-95.
9. Wang TJ, Parise H, Levy D, D'Agostino RB Sr, Wolf PA, Vasan RS, et-al. Obesity and the risk of new-onset atrial fibrillation. JAMA. 2004; 292:2471-7.
10. Morse SA, Gulati R, Reisin E. The obesity paradox and cardiovascular disease. Curr Hypertens Rep. 2010; 12:120-126.
11. Horwich TB, Fonaraow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH, et-al. The relationship between obesity and mortality in patients with heart failure. J Am Coll Cardiol. 2001; 38:789-795.
12. Curtis JP, Selter JG, Wang Y, Rathore SS, Jovin IS, Jadbabaie F, et-al. The obesity paradox: body mass index and outcomes in patients with heart failure. Arch Intern Med. 2005;165:55-61.
13. Fonarow GC, Srikanthan P, Costanzo MR, Cintron GB. An obesity paradox in acute heart failure: analysis of body mass index and in-hospital mortality for 108,927 patients in the Acute Decompensated Heart Failure National Registry. Am Heart J. 2007; 153:74-81.
14. Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of Obesity and the Obesity Paradox on Prevalence and Prognosis in Heart Failure. JACC/HF 2013; 1:93-102.
15. Clark AL, Fonarow GC, Horwich TB. Obesity and the Obesity Paradox in Heart Failure. Progress in Cardiovascular Diseases. 56 (2014) 409-414.
16. Bucholz EM, Rathore SS, Reid KJ, Jones PG, Chan PS, Rich MW, et-al. Body mass index and mortality in acute myocardial infarction patients. Am J Med. 2012; 125:796-803.
17. Uretsky S, Messerli FH, Bangalore S, Champion A, Cooper-Dehoff RM, Zhou Q, et-al. Obesity paradox in patients with hypertension and coronary artery disease. Am J Med. 2007; 120:863-70.
18. Lavie CJ, De Schutter A, Patel DA, Romero-Corral A, Artham SM, Milani RV. Body composition and survival in stable coronary heart disease: impact of lean mass index and body fat in the "obesity paradox". J Am Coll Cardiol. 2012; 60:1374-80.
19. Galal W, van Gestel YR, Hoeks SE, Sin DD, Winkel TA, Bax JJ, et-al. The obesity paradox in patients with peripheral arterial disease. Chest. 2008; 134:925-30.
20. Doehner W, Schenkel J, Anker DS, Springer J, Audebert HJ. Overweight and obesity are associated with improved survival, functional outcome, and stroke recurrence after acute stroke or transient ischaemic attack: observations from the TEMPIS trial. Eu Heart J.; 34(4):268-77.
21. Badheka AO, Rathod A, Kizilbash MA, Garg N, Mohamad T, Afonso L, et-al. Influence of obesity on outcomes in atrial fibrillation: yet another obesity paradox. Am J Med. 2011; 123:646-651.
22. Ardestani A, Hoffman HJ, Cooper HA. Obesity and outcomes among patients with established atrial fibrillation. Am J Cardiol. 2010; 106:369-73.
23. Badheka AO, Rathod A, Bharadwaj A, Afonso L, Jacob S. Obesity paradox in outcomes of atrial fibrillation. Am J Cardiol. 2011;108:474-746.
24. García-Castelo A, García-Seara J, Otero-Raviña F, Lado M, Vizcaya A, Vidal JM, et-al; Barbanza Group Investigators. Prognostic impact of atrial fibrillation progression in a community study: AFBAR Study (Atrial Fibrillation in the Barbanza Area Study). Int J Cardiol. 2011; 153:68-73.
25. WHO. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. 1995 Technical Report Series No. 854. Available in: http://www.who.int/childgrowth/publications/physical_status/en/index.html.
26. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika.1994; 81:515-526.
27. Blum A, Simsolo C, Sirchan R. "Obesity paradox" in chronic obstructive pulmonary disease. Isr Med Assoc J. 2011; 13:672-5.
28. Mohamed-Ali V, Goodrick S, Bulmer K, Holly JM, Yudkin JS, Coppack SW. Production of soluble tumor necrosis factor receptors by human subcutaneous adipose tissue in vivo. Am J Physiol. 1999; 277:971-975.
29. Issac TT, Dokainish H, Lakkis NM. Role of inflammation in initiation and perpetuation of atrial fibrillation: a systematic review of published data. J Am Cardiol. 2007; 50: 2021-2028.
30. Lee SH, Chen YC, Chen YJ, Chang SL, Tai CT, Wongcharoen W, et-al. Tumor necrosis factor-alpha alters calcium handling and increases arrhythmogenesis of pulmonary vein cardiomyocytes. Life Sci. 2007; 80:1806-1815.
31. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Wilson PW, et-al. Impact of obesity on plasma natriuretic peptide levels. Circulation. 2004; 109:594-600.
32. Okorodudu DO, Jumean MF, Montori VM, Romero-Corral A, Somers VK, Erwin J, et-al. Diagnosis performance of body mass index to identify obesity as defined by body adiposity: a systematic review and meta-analysis. Int J Obes (Lond). 2010; 34:791-9.
33. Lauretani F, Russo CR, Bandinelli S, Bartali B, Cavazzini C, Di Iorio A, et-al. Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. J Appl Physiol. 2003; 95:1851-60.
34. E.G. Artero, D.C. Lee, C.J. Lavie et al. Effects of muscular strength on cardiovascular risk factors and prognosis. J Cardiopulm Rehabil Prev. 2012.
35. Fadl YY, Krumholz HM, Kosiborod M, et al. Predictors of weight change in overweight patients with myocardial infarction. Am Heart J. 2007;154(4):711-717.
36. Schutter AS, Lavie CJ, Patel A, Artham SM, Milani RV. Relation of Body Fat Categories by Galagher Classification and by Continuous Variables to Mortality in Patients with Coronary Heart Disease. Am J Cardiol. 2013; 111:657-660.