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Relation of Nonvalvular Atrial Fibrillation to Body Mass Index (from the SPORTIF Trials)

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Obesity is well-established as a major cardiovascular (CV) risk factor. Obesity confers a greater risk for developing atrial fibrillation (AF), but the relation between obesity and established nonvalvular AF for stroke and all-cause death is still unclear. To ascertain the prevalence of overweight and obesity in patients with nonvalvular AF, their influence on adverse events, and the relation with anticoagulation control, we performed this post hoc analysis of the pooled Stroke Prevention using an Oral Thrombin Inhibitor in patients with atrial Fibrillation (SPORTIF) III and V data sets. For this study, we analyzed all patients assigned to the warfarin arm with data on body mass index (BMI). Time in therapeutic range was used as an index of the quality of anticoagulation control. The 3,630 patients eligible for this analysis were categorized as follows: (1) BMI 18.5 to 24.9 ("normal weight") in 24.1%; (2) BMI 25.0 to 29.9 ("overweight") in 39.8%; and BMI ≥30 ("obese") in 36.1%. Both overweight (hazard ratio [HR] 0.70) and obese (HR 0.59) categories were inversely associated with the composite outcome of stroke/all-cause death. A similar inverse association was seen for the end point of stroke (HR 0.61 and 0.47, respectively). Good anticoagulation control also attenuated the association between BMI categories and outcomes. In patients with time in therapeutic range >70%, BMI category was not significantly associated with the composite outcome of stroke/death and stroke. Stroke and all-cause death progressively reduced in overweight and obese anticoagulated patients with AF. The inverse relation of BMI categories to the risk of stroke and all-cause death was mitigated by good anticoagulation control. **(Am J Cardiol 2016;■:■−■)**

Obesity represents one of the most prevalent cardiovascular (CV) risk factors in the general population.[1] Data released from the USA Center for Disease Control (*http://www.cdc.gov/obesity/index.html*) show that in the past 20 years, the prevalence of obesity has rapidly increased, up to 25% of the population. Obesity has been associated with a higher incidence of both CV and cerebrovascular events in the general population.[1−4] Indeed, obesity has been identified as one of the most important risk factors to be controlled in both primary and secondary preventions.[5,6] The relation between obesity and atrial fibrillation (AF) is robust, with evidence documenting how obesity could be a trigger and major risk factor in determining AF occurrence, with a direct causal relation.[2,7,8] Indeed, some recent data have shown how interventions to reduce weight in obese patients could lead to a reduction in the risk of developing AF.[9,10] However, data on the influence of obesity on adverse outcomes in AF patients have been conflicting. Although some data suggest that obese and overweight AF patients had a lower risk for both CV and all-cause death,[11] other evidence indicates that both overweight and obese patients with AF are at greater risk for the composite outcome of ischemic stroke, thromboembolism (TE), and all-cause death.[12] Another consideration is the risk of adverse outcomes while on anticoagulation in patients with AF with low body weight, being associated with a greater bleeding risk[13,14]; this leads some guidelines recommending a lower therapeutic target to mitigate bleeding risks.[15,16] The aims of this study were (1) to describe the prevalence of overweight and obesity in an anticoagulated clinical trial cohort of patients with nonvalvular AF (NVAF); (2) define risks related to each weight category for the occurrence of stroke, all-cause death, and their composite outcome; and (3) to determine the relation between quality of anticoagulation control (as reflected by time in therapeutic range, [TTR]) and being overweight or obese.

Methods

For the purposes of the present study, we analyzed pooled data sets from the Stroke Prevention using an Oral Thrombin Inhibitor in patients with atrial Fibrillation (SPORTIF) III and V trials. Details on the trial protocol have been reported elsewhere.[17] In brief, the SPORTIF trials were 2 large multicenter phase III clinical trials comparing the efficacy and safety of the direct thrombin inhibitor, ximelagatran, compared against warfarin in NVAF. SPORTIF III was an open-label trial, whereas SPORTIF V was a double-blind study.[17] From the pooled data sets, we included all patients assigned to warfarin treatment where

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See page 6 for disclosure information.

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http://dx.doi.org/10.1016/j.amjcard.2016.04.013

data on height and weight were recorded, to obtain body mass index (BMI) measurements for this post hoc analysis.

BMI values were used to define weight categories. According to the standard World Health Organization definition (*http://www.who.int/mediacentre/factsheets/fs311/en/index.html*), patients were categorized as (1) BMI from 18.5 to 24.9 kg/m^2 ("normal weight"); (2) BMI 25.0 to 29.9 kg/m^2 ("overweight")l and (3) BMI $\geq$30 kg/m^2 ("obese"). Patients with a BMI $<$18.5 kg/m^2 were excluded from these analyses because of the small numbers.

TE risk was categorized according to CHA_2DS_2-VASc score.[18] "Low-risk" patients were defined as men with a CHA_2DS_2-VASc = 0 or women with CHA_2DS_2-VASc = 1; "moderate risk" was defined as male patients with CHA_2DS_2-VASc = 1; and "high risk" with CHA_2DS_2-VASc $\geq$2. Anticoagulation control, as reflected by TTR, was calculated according to the standardized Rosendaal interpolation method. Based on the European Society of Cardiology recommendations, optimal anticoagulation was defined as a TTR $>$70%.[19]

Stroke was clinically defined as the acute onset of a focal neurologic deficit in any of the carotid, vertebral, or cerebral artery distribution territories lasting $>$24 hours, irrespective of the pathophysiological mechanism. This was the trial protocol−defined primary outcome, which was formally adjudicated. Myocardial infarction (MI) diagnosis required 2 of 3 of the following criteria: (1) typical chest pain lasting at least 20 minutes; (2) electrocardiographic changes clearly indicating an acute MI; (3) significant, that is, $>$2$\times$ upper limit, elevation of cardiac biomarkers (creatine-kinase-MB, troponin). Major bleeding, according to International Society of Thrombosis and Hemostasis criteria, was defined by one of the following criteria: clinically overt bleeding with a concomitant decrease in hemoglobin levels $\geq$2 g/dl or requiring blood transfusion of at least 2 U of whole blood or erythrocytes; bleeding episode involving a critical site (i.e., intracranial, retroperitoneal, intraocular, intraspinal, atraumatic intraarticular, or pericardial). Mortality was related to the reported occurrence of death by any investigator. A composite outcome of stroke and all-cause death was also considered. All outcomes were assessed by a central adjudication committee.

All continuous variables were tested for normality. Variables normally distributed were expressed as mean and SD and tested for differences using one-way analysis of variance. Nonparametric variables were expressed as median and interquartile range (IQR) and differences tested using the Kruskal−Wallis test. Categorical variables, expressed as counts and percentages, were analyzed by the chi-square test. Crude and age-adjusted study outcomes rates were estimated. Logistic regression analysis, crude and adjusted for age, gender, and TE risk, was computed to analyze the association between weight categories and outcomes. Linear regression analysis, adjusted for age, gender, and TE risk, was used to examine the relation between BMI and TTR.

Survival analysis, assessed by an intention-to-treat approach, was performed according to the different weight categories, and differences in survival were analyzed using the log-rank test. Evaluation of clinical characteristics significantly associated with outcomes was explored using a Cox proportional hazards analysis. All variables analyzed at baseline underwent univariate analysis (see Supplementary Tables 1 to 3). All variables with a p value $<$0.10 for the association in the univariate analysis were included in the forward stepwise multivariate model. A linear regression analysis, adjusted for age, gender, and TE risk, between outcomes risk and BMI was also conducted. A 2-sided p value $<$0.05 was considered statistically significant. All analyses were performed using SPSS v. 22.0 (IBM, New York).

Results

From the original SPORTIF pooled cohorts of 7,329 patients, patients assigned to the warfarin treatment arm were selected. Of the 3,665 patients treated with warfarin, data on BMI were available for 3,651 (99.6%). After the exclusion of patients with BMI $<$18.50 kg/m^2 (n = 21 [0.6%]), a total of 3,630 patients (median [IQR] age 72 [66 to 77]; 30.3% women) were included in this analysis. Overweight was recorded for 1,446 (39.8%) patients, whereas 1,310 (36.1%) patients were categorized as obese.

High TE risk was recorded in 86.7% (n = 3,149) and median TTR for the overall population was 65.6% (IQR 55.2% to 79.3%). Median age progressively decreased from normal weight to obese patients (p $<$0.001). Patients in the normal-weight category were more commonly women compared to obese and overweight patients (p $<$0.001). Median creatinine clearance levels progressively increased, from normal-weight to obese categories (p $<$0.001).

Baseline characteristics, according to BMI categories, are reported in Table 1. Prevalence of hypertension and diabetes mellitus progressively increased from normal-weight to obese patients (p $<$0.001). Patients with normal weight were more frequently smokers (p = 0.006) and more likely to have had a previous stroke/transient ischemic attack (TIA; p $<$0.001) compared to overweight and obese subjects. High TE risk was more prevalent in normal-weight patients, compared to overweight and obese patients (p $<$0.001).

Mean (SD) and median (IQR) follow-up time was 566.52 $\pm$ 142.84 days and 567 (492 to 652) days, respectively. During the entire follow-up observation, 90 (2.5%) strokes, 164 (4.5%) major bleeding, 52 (1.4%) MIs, and 195 (5.4%) all-cause death events were observed. Hemorrhagic stroke was recorded only in 11 patients (0.3%), so these were not considered separately from ischemic stroke. For the composite outcome of stroke/all-cause death, a total of 266 (7.3%) events were recorded. Crude study outcomes rates progressively decreased from the normal-weight to obese category for stroke (p = 0.016), all-cause death (p = 0.001), and the composite outcome of stroke/all-cause death (p $<$0.001, Table 2). Taking into account age-adjusted rates, patients with normal weight reported consistently higher rates for stroke, all-cause death, and composite outcome (Table 2).

Stroke incidence was significantly higher in patients with normal weight (2.5% patient-years) than in overweight and obese patients (1.4% and 1.2% patient-years, respectively). All-cause death and composite outcome incidence progressively decreased from normal weight to overweight to obese patients (5.2% vs 3.3% vs 2.6% patient-years, 7.2% vs 4.3% vs 3.6% patient-years, respectively). No difference was seen in major bleeding or MI incidence rates in the 3 BMI categories. Logistic regression analysis showed that both

Table 1
Demographic and clinical characteristics according to body mass index category

Variable	Normal Weight (n= 874)	Overweight (n= 1,446)	Obese (n= 1,310)	p
Age *(years)*				
Median [IQR]	76 [70-80]	73 [67-77]	68 [62-74]	<0.001
Female	328 (37.5%)	369 (25.5%)	403 (30.8%)	<0.001
Creatinine Clearance *(ml/min)*				
Median [IQR]	58.82 [47.89-72.59]	76.93 [60.67-92.85]	100.52 [78.39-130.11]	<0.001
Type of Atrial Fibrillation*				0.418
Paroxysmal	104 (11.9%)	159 (11.0%)	125 (9.5%)	
Chronic	770 (88.1%)	1,826 (88.9%)	1,184 (90.4%)	
Hypertension	580 (66.4%)	1,077 (74.5%)	1,134 (86.6%)	<0.001
Diabetes Mellitus	138 (15.8%)	306 (21.2%)	412 (31.5%)	<0.001
Current Smoker	101 (11.6%)	110 (7.6%)	119 (9.1%)	0.006
Coronary Heart Disease	392 (44.9%)	635 (43.9%)	578 (44.2%)	0.906
Previous Stroke/TIA	234 (26.8%)	310 (21.4%)	203 (15.5%)	<0.001
Chronic Heart Failure	320 (36.6%)	524 (36.2%)	515 (39.3%)	0.211
Previous Bleeding	50 (5.7%)	93 (6.4%)	65 (5.0%)	0.253
Aspirin Treatment	190 (21.7%)	292 (20.2%)	239 (18.2%)	0.123
TTR† *(%)*				
Median [IQR]	66.5 [52.1-78.7]	69.7 [56.7-80.5]	68.6 [55.9-78.8]	0.002
TTR>70%†	382 (44.2%)	702 (49.1%)	605 (46.7%)	0.070
CHA_2DS_2-VASc				<0.001
Median [IQR]	3 [2-4]	3 [2-4]	3 [2-4]	
CHA_2DS_2-VASc Risk Categories				<0.001
Low	1 (0.1%)	2 (0.1%)	3 (0.2%)	
Intermediate	58 (6.6%)	177 (12.2%)	240 (18.3%)	
High	815 (93.2%)	1,267 (87.6%)	1,067 (81.5%)	

IQR = interquartile range; SD = standard deviation; TIA = transient ischemic attack; TTR = time in therapeutic range.
* 3,628 patients.
† 3,589 patients.

Table 2
Rate of study outcomes according to body mass index categories

	Normal Weight (n= 874)	Overweight (n= 1,446)	Obese (n= 1,310)	p
Stroke/All-Cause Death	94 / 266 (10.8%)	97 / 266 (6.7%)	75 / 266 (5.7%)	<0.001
Age-adjusted rate	10.1%	6.6%	5.9%	
OR (95%CI) *crude*	Ref	0.60 (0.44-0.80)	0.50 (0.37-0.69)	<0.001*
Adjusted†	Ref	0.64 (0.48-0.87)	0.61 (0.44-0.85)	<0.001*
Stroke	33 / 90 (3.8%)	32 / 90 (2.2%)	25 / 90 (1.9%)	0.016
Age-adjusted rate	3.4%	2.2%	1.9%	
OR (95%CI) *crude*	Ref	0.58 (0.35-0.95)	0.50 (0.29-0.84)	0.022*
Adjusted†	Ref	0.58 (0.35-0.95)	0.50 (0.29-0.84)	0.022*
Major Bleeding	47 / 164 (5.4%)	61 / 164 (4.2%)	56 / 164 (4.3%)	0.372
Age-adjusted rate	5.6%	4.1%	4.5%	
OR (95%CI) *crude*	Ref	0.91 (0.58-1.43)	0.93 (0.59-1.46)	0.919*
Adjusted†	Ref	-	-	-
Myocardial Infarction	14 / 52 (1.6%)	19 / 52 (1.3%)	19 / 52 (1.5%)	0.850
Age-adjusted rate	1.2%	1.3%	1.4%	
OR (95%CI) *crude*	Ref	0.82 (0.41-1.64)	0.90 (0.45-1.81)	0.851*
Adjusted†	Ref	-	-	-
All-Cause Death	68 / 195 (7.8%)	73 / 195 (5.0%)	54 / 195 (4.1%)	0.001
Age-adjusted rate	7.4%	5.0%	4.3%	
OR (95%CI) *crude*	Ref	0.63 (0.45-0.89)	0.51 (0.35-0.74)	0.001*
Adjusted†	Ref	0.66 (0.46-0.93)	0.62 (0.42-0.91)	<0.001*

BMI = body mass index; CI = confidence interval; OR = odds ratio.
* Chi-square for entire model.
† adjusted for age, sex and thromboembolic risk.

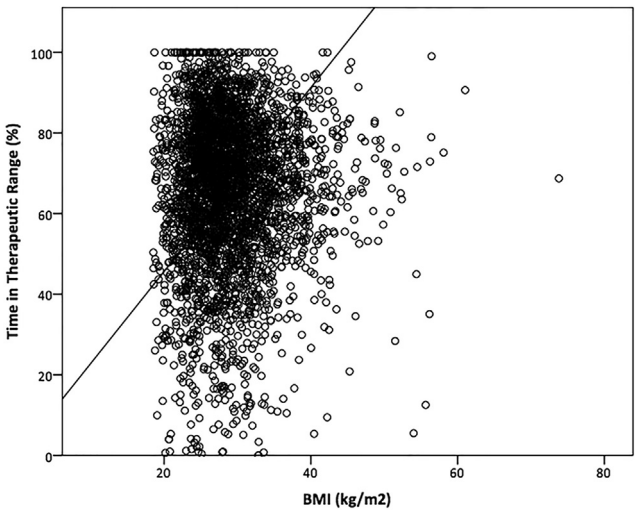

Figure 1. Scatterplot and regression line between BMI and TTR. Standardized β: 0.038, 95% confidence interval: 0.009 to 0.243; p = 0.035.

overweight and obese categories were inversely associated with the composite outcome, stroke, and all-cause death, after adjustment for age, gender, and TE risk categories (Table 2).

Considering TTR as a continuous variable, lower median (IQR) values were found in normal-weight patients (p = 0.002). The proportion of patients with good anticoagulation control (TTR >70%) was lower in patients with normal weight, with a nonsignificant trend to being greater in overweight and obese patients (p = 0.070).

Linear regression analysis, adjusted for age, gender, and TE risk, showed a significant linear association between BMI and TTR (Figure 1). Similar relationships were found for regressions according to age classes, gender, and TE risk categories using CHA_2DS_2-VASc (see Supplementary Figures 1 to 3). No significant association was found between weight categories and TTR >70%.

Kaplan–Meier curves show that both overweight and obese patients had a lower risk for the occurrence of the composite outcome, stroke, and all-cause death (Figure 2).

On univariate analysis (see Supplementary Tables 1 to 3), a Cox multivariate analysis model (Table 3) adjusted for the interactions between weight categories and TTR shows that the composite outcome was inversely associated to both overweight and obese categories, as well as good anticoagulation control. Stroke was inversely associated with being overweight and obese. Conversely, the association of all-cause death and weight categories was attenuated by good-quality anticoagulation control (TTR >70%) and creatinine clearance.

With Cox models using TTR as a continuous variable, a significant inverse association was found between the obese category and stroke. The composite end point was also inversely associated with both overweight and obese categories. The inverse association between weight categories and all-cause death was nonsignificant (Table 3).

A linear regression analysis, adjusted for age, gender, and TE risk, between outcomes and BMI was performed. Regression models both for the composite outcome and stroke ($F = 253.13$, p <0.001 and $F = 565.55$, p <0.001, respectively) show an inverse linear relation between BMI and these outcomes (standardized β: −0.165, p <0.001 and standardized β: −0.397, p <0.001, respectively). For the outcome of all-cause death, the regression model ($F = 128.76$, p <0.001) shows a significant inverse association with BMI (standardized β: −0.163, p <0.001).

In sensitivity analyses, we considered CV disease-free patients, elderly patients (age ≥75 years), patients with high TE risk, and patients with TTR >70% (see Supplementary Tables 4 and 5). The subgroup for CV disease-free patients was defined as all the patients without any previous stroke/TIA, coronary heart disease (CHD), and congestive heart failure. Similar results to the overall cohort were found for the patients at high TE risk, in relation to the weight categories. In CV disease-free patients, those with normal weight had a lower risk for both stroke and the composite outcome (see Supplementary Figure 4), but not for all-cause death. In patients with TTR >70%, the normal-weight category had a lower risk for all-cause death and the composite outcome (see Supplementary Figure 5), but not for stroke. In elderly patients, no significant differences in outcomes was found between the 3 weight categories (see Supplementary Table 4).

Multivariate Cox regression analyses for patients' subgroups, adjusted for the interactions between weight categories and TTR, are summarized in the Supplementary Table 5. In the CV disease-free subgroup, when considering TTR as a categorical variable, still remained a significant positive association between weight categories and TTR. With TTR as a continuous variable, weight categories were still inversely associated with the composite outcome, but the effect of TTR was still present, attenuating the inverse association with outcomes.

In the high TE risk subgroup, the stroke outcome was inversely associated only with the obese category (see Supplementary Table 5). Conversely, the composite outcome in CV disease-free patients was inversely associated with both the overweight and obese categories. For all-cause death, a similar finding as the overall populations was found, with TTR as categorical and continuous variables, attenuating the effect of weight categories. In patients with TTR >70%, no significant association was found both for the composite outcome and all-cause death (see Supplementary Table 5).

Discussion

In this study, we found a high prevalence of both overweight and obesity in patients with NVAF. Second, the presence of both overweight and obesity in patients with NVAF was associated with a lower risk for the composite outcome of stroke/all-cause death, as well as stroke and all-cause death. Finally, the main novel finding of our article was that by achieving good anticoagulation control, this lower risk of both overweight and obesity was no longer evident, emphasizing the concept that effective anticoagulation treatment is essential for reducing major adverse events in AF.

Few studies have evaluated the prevalence of overweight and obesity in the AF population[11,12,20] and both commonly present. For example, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial reported that 74.4% of patients did not have a normal-weight

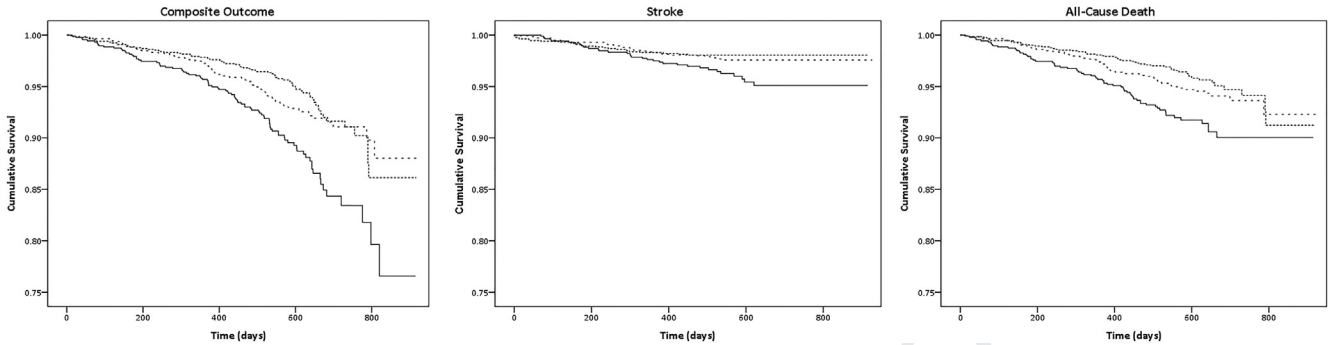

Figure 2. Kaplan–Meier curves for stroke and all-cause death. *Solid line* = normal weight; *dotted line* = overweight; *dashed line* = obese; composite outcome = log-rank: 24.860, p <0.001; stroke = log-rank: 9.204, p = 0.010; all-cause death = log-rank: 16.801, p <0.001.

Table 3
Q5 Cox proportional hazards multivariate models for the outcomes of stroke, death and the composite outcome

	HR (95% CI)		HR (95% CI)
Stroke/All-Cause Death		Stroke/All-Cause Death	
Normal Weight *(ref.)*	–	Normal Weight *(ref.)*	–
Overweight	0.69 (0.52-0.92)	Overweight	0.71 (0.53-0.96)
Obese	0.59 (0.42-0.82)	Obese	0.60 (0.43-0.83)
TTR>70%	0.66 (0.51-0.84)	TTR (%)	0.98 (0.98-0.99)
Age *(per year)*	1.03 (1.01-1.04)	Age *(per year)*	1.03 (1.01-1.04)
Chronic Heart Failure	1.53 (1.20-1.96)	Previous Stroke/TIA	1.60 (1.23-2.09)
Previous Stroke/TIA	1.58 (1.21-2.07)	Chronic Heart Failure	1.54 (1.21-1.98)
Coronary Heart Disease	1.63 (1.26-2.10)	Coronary Heart Disease	1.64 (1.27-2.11)
Current Smoker	1.73 (1.19-2.50)	Current Smoker	1.74 (1.20-2.52)
Stroke		Stroke	
Normal Weight *(ref.)*	–	Normal Weight *(ref.)*	–
Overweight	0.61 (0.37-0.99)	Overweight	0.64 (0.39-1.04)
Obese	0.47 (0.27-0.81)	Obese	0.49 (0.28-0.84)
TTR>70%	0.62 (0.40-0.96)	TTR (%)	0.98 (0.97-0.99)
Previous Stroke/TIA	2.26 (1.46-3.50)	Coronary Heart Disease	1.53(1.01-2.35)
		Previous Stroke/TIA	2.28 (1.48-3.53)
All-Cause Death		All-Cause Death	
Creatinine Clearance *(per ml)*	0.99 (0.98-0.99)	Creatinine Clearance *(per ml)*	0.99 (0.98-0.99)
TTR>70%	0.64 (0.47-0.85)	TTR (%)	0.98 (0.98-0.99)
Current Smoker	1.66 (1.08-2.56)	Current Smoker	1.64 (1.07-2.52)
Previous Stroke/TIA	2.02 (1.51-2.72)	Previous Stroke/TIA	2.04 (1.52-2.74)

CI = confidence interval; HR = hazard ratio; TIA = transient ischemic attack; TTR = time in therapeutic range.

BMI category, with 35.7% being obese.[11] A post hoc analysis from the Danish Diet, Cancer and Health (DCH) study found a lower percentage of obese patients with AF.[12] In the present study, 2/3 of patients did not have a "normal-weight" BMI category, and approximately 35% were obese.

The importance of obesity in determining greater risks for CV disease, CV death, stroke, and all-cause death, has been addressed by previous studies.[1,4] Despite this relation between obesity and CV outcomes, an "obesity paradox" seems evident in some patient populations.[21] Indeed, an "obesity paradox" regarding both CV and all-cause death has been described for hypertension, CHD, congestive heart failure, and peripheral arterial disease.[2,22,23] Our data show that overweight and obese patients with AF have a lower risk for stroke, but no significant impact of obesity on major bleeding or MI was seen. For the outcome of all-cause death, our data suggest that the influence of BMI categories on was attenuated by good anticoagulation control and creatinine clearance, the latter being significantly associated with mortality in patients with AF.[24] The role of good anticoagulation control in attenuating, and even reversing, the impact of BMI categories appears evident from our subgroup analyses, representing the most relevant novel findings of this study, compared to previous studies. The linear association between BMI and risk of adverse outcomes remained evident, even after statistical adjustments.

Similar data were reported from the AFFIRM trial, where overweight and obese patients had a significant reduction in both CV and all-cause death,[11] whereas no significant difference was seen for stroke occurrence.[25] Data from another randomized clinical trial showed that obesity was associated with a lower stroke and mortality rate in elderly patients with AF.[20] From observational AF studies, the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation

(ORBIT-AF) registry reported that the apparent lower risk for adverse events (in particular stroke/TIA and all-cause death) was no longer evident after multivariate analysis, adjusting for CV risk factors.[26] Conversely, data from the DCH cohort found that overweight and obese patients had a greater risk for death and the composite outcome of ischemic stroke/TE/death; however, the relation with the occurrence of ischemic stroke/TE only was nonsignificant.[12]

Other evidence on an inverse association between weight/BMI categories and adverse outcomes comes from phase III trials for non−vitamin K antagonist oral anticoagulants. Data from the "Randomized Evaluation of Long-Term Anticoagulant Therapy" (RE-LY) trial showed that a greater weight (≥82 kg) was inversely associated with overall mortality (hazard ratio [HR] 0.73, 95% confidence interval [CI] 0.62 to 0.85).[27] In the "Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation" (ROCKET AF) trial. An increase of 5 kg/m^2 was found inversely associated with stroke/systemic embolism (HR 0.891, 95% CI 0.811 to 0.980).[28] Finally, an ancillary analysis from the "Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation" (ARISTOTLE) showed that both overweight (HR 0.72, 95% CI 0.64 to 0.81) and obese (HR 0.67, 95% CI 0.58 to 0.76) categories were inversely associated with all-cause death.[29]

Our results are in agreement with previous observations that an obesity paradox may exist, whereby obesity is associated with a lower incidence of CV events, even in several clinical subgroups. Even if partially mitigated by good anticoagulation control (TTR >70%), in our patients with AF without any previous CV disease, BMI categories were still inversely associated with adverse events (particularly, stroke), thus reinforcing the "obesity paradox" in the AF setting. In contrast with previous reports showing an influence of weight, in particular low weight or BMI in increasing bleeding risk in warfarin-treated patients,[13] we did not find any significant differences in major bleeding between BMI categories.

Among potential reasons to explain the obesity paradox, the presence of several confounders has been proposed.[2] Perhaps the most important factor in determining a greater risk for CV disease would be body fat (BF) composition.[2] Recent data in patients with stable CHD suggest that low lean mass index (LMI) predicts all-cause death, and although the greatest risk is seen for patients with low LMI and low BF, patients with high LMI and high BF had the lowest risk of mortality.[30] Another possible explanation to explain the obesity paradox previously considered in patients with AF was the higher prevalence of co-morbidities which could result in more aggressive pharmacological treatments leading to better management of CV risk.[11] This hypothesis is supported by our data, with the highest prevalence of both hypertension and diabetes mellitus in overweight and obese patients, that in the context of a randomized controlled trial would be routinely checked and treated to optimize CV risk factors. Moreover, the influence of BMI categories is more evident in patients with poorer anticoagulation control, and good anticoagulation control appears to mitigate the association between BMI categories and adverse events. Indeed, the linear association between BMI and TTR could be an expression of more intensive treatment and monitoring, reinforcing the concept that is the TTR the main driver for the risk reduction seen in the overweight and obese categories. As far as we are aware, no previous studies have reported on the relation between BMI (and weight) categories and TTR.

Our results do not advocate or encourage a greater weight or BMI in patients with AF. These data should be interpreted as highlighting the need for intensive and comprehensive management of comorbidities in obese patients with AF and in the general population.[5]

This study was an ancillary post hoc analysis of a controlled clinical trial cohort, and therefore, this population may not necessarily represent the "real-world" prevalence of overweight and obese subjects among patients with AF. Furthermore, we cannot elucidate the impact of low BMI, given the low numbers. Because the study was not powered to detect differences in survival according to BMI categories, our results should be considered as hypothesis generating and not causal. Also, the various subgroups analyses should be cautiously interpreted because of the lower numbers of patients and event rates. Our study is also hypothesis generating and does not establish any causal relation between higher BMI and lower risk of major adverse events.

Acknowledgment: Drs. Proietti and Lip conceived the study, analyzed the data, interpreted the results, and drafted the manuscript. Dr. Lane performed a critical comprehensive review of the manuscript. Drs. Proietti and Lip had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

Dr. Lane received investigator-initiated educational grants from Bayer Healthcare, Boehringer Ingelheim, and Bristol Myers Squibb; is a speaker at educational symposia for Boehringer Ingelheim, Bayer, Bristol Myers Squibb/Pfizer; and is a Steering Committee member for a phase IV trial sponsored by Bristol Myers Squibb. Dr. Lip is a steering committee member for various phase II and III studies, Health Economics and Outcomes Research, and so forth; is an investigator in various clinical trials in cardiovascular disease, including those on antithrombotic therapies in atrial fibrillation, acute coronary syndrome, lipids, and so forth; is a consultant for Bayer/Janssen, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo; is a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo. Dr. Proietti has no disclosures.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2016.04.013.

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