Relation of Obesity to Outcomes of Hospitalizations for Atrial Fibrillation

Manyoo A. Agarwal, MD[a,*], Lohit Garg, MD[b], Mahek Shah, MD[b], Brijesh Patel, DO[b], Nidhi Jain, MD[a], Sameer Jain, MD[c], Rajesh Kabra, MD[d], Csaba Kovesdy, MD[e], Guy L. Reed, MD[f], and Carl J. Lavie, MD[g]

Obesity has been linked with increased incidence of atrial fibrillation (AF), but impact of presence of obesity on outcomes of hospitalizations for AF has not been investigated. We used the National Inpatient Sample database 2010 to 2014 to identify all adult hospitalizations aged ≥18 years with a primary diagnosis of AF. Obese patients were identified using the co-morbidity variable for obesity, as defined in National Inpatient Sample databases. Multivariable logistic regression was used to compare in-hospital outcomes (mortality, acute stroke events) between obese and non-obese patients with AF. Of 431, 734 hospitalizations for AF, 66,138 (15.3%) were obese. Obese patients were younger and more likely to be African-Americans compared with non-obese patients. Despite being younger, obese patients had significantly higher prevalence of cardiovascular co-morbidities such as hypertension, diabetes mellitus, dyslipidemia, smoking, heart failure, and chronic renal failure (p <0.001 for all). After multivariate risk-adjustment, obese patients had a lower observed in-hospital mortality (0.5% vs 1.0%; unadjusted odds ratio = 0.52, 95% confidence interval [CI] 0.46 to 0.58, p <0.001; adjusted odds ratio = 0.83, 95% CI 0.73 to 0.94, p <0.001) and acute stroke events (0.4% vs 0.7%, unadjusted odds ratio = 0. 65, 95% CI 0.57 to 0.73, p < 0.001; adjusted odds ratio = 0.82, 95% CI 0.72 to 0.94) compared with non-obese patients. In conclusion, in this large retrospective analysis of an unselected nationwide cohort of patients hospitalized for AF, obese patients demonstrated lower risk-adjusted odds of in-hospital mortality and stroke events, consistent with an "obesity paradox." **(Am J Cardiol 2019;123:1448−1452)**

Although obesity is an independent risk factor for the incidence and progression of cardiovascular diseases (CVD), data suggests a better prognosis in obese patients with CVD than non-obese cohorts.[1−4] This counterintuitive observation has been termed as "obesity paradox." Atrial fibrillation (AF) is a commonly encountered arrhythmia with growing prevalence and increasing healthcare burden.[3] Obesity adversely impacts cardiovascular hemodynamics and cardiac structure and function, and is an independent risk factor for AF.[3,5] However, data describing the association between obesity and outcomes of AF are conflicting and limited only to long-term follow-up.[6−12] Hence, we analyzed the association of obesity with hospital outcomes of AF patients using a large, unselected cohort of 431, 734 patients in the National (Nationwide) Inpatient Sample (NIS) 2010 to 2014 databases.

Methods

Our study population was derived from the NIS of the Healthcare Cost and Utilization Project sponsored by Agency for Healthcare Research and Quality.[13] The first diagnosis in the database is referred to as the "principal diagnosis" and is considered the primary reason for admission to the hospital. The NIS also provides ≤29 secondary diagnoses during that hospitalization and each entry also carries information on patient demographics, insurance status, comorbidities, and hospitalization outcome.[13]

All hospitalizations with a primary diagnosis of AF in patients with age ≥18 years were identified using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes 427.31, which has been externally validated and used previously.[14−16] Obese patients were identified using the predetermined Agency for Healthcare Research and Quality-defined Elixhauser comorbidity measure "CM_obese," which was used as a surrogate marker (as done previously) due to lack of anthropometric measurements and BMI values in the dataset.[17] This includes the following ICD-9-CM codes: 278.0, 278.00 to 278.03, 649.10 to 649.14, 793.91, V85.30 to V85.39, V85.41 to V85.45, and V85.54 and excludes the following diagnosis related group: 288, 296 to 298, 619 to 621, and

[a]Department of Internal Medicine, University of Tennessee Health Science Center, Memphis, Tennessee; [b]Division of Cardiovascular Medicine, Lehigh Valley Health Network, Allentown, Pennsylvania; [c]Department of Interventional Pain, Thomas Jefferson University, Philadelphia, Pennsylvania; [d]Division of Cardiovascular Medicine, Department of Internal Medicine, University of Tennessee Health Science Center, Memphis, Tennessee; [e]Division of Nephrology, Department of Internal Medicine, University of Tennessee Health Science Center, Memphis, Tennessee; [f]Department of Internal Medicine, University of Arizona Medical Center, Phoenix, Arizona; and [g]Department of Cardiovascular Medicine, John Ochsner Heart and Vascular Institute, Ochsner Clinical School−The University of Queensland School of Medicine, New Orleans, Los Angeles. Manuscript received November 7, 2018; revised manuscript received and accepted January 25, 2019.

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*Corresponding author: Tel: (901) 448-7550; fax: (901) 448-7836.
E-mail address: magarwa3@uthsc.edu (M.A. Agarwal).

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Table 1
Baseline characteristics according to the absence or presence of obesity in atrial fibrillation patients

Variable	Overall (n = 431, 734)	Non-obese (n = 365,596)	Obese (n = 66,138)	p value (non-obese vs obese)
Age, mean (SD) (years)	70.4 (13.8)	71.8 (13.6)	63.2 (12.3)	<0.001
Age groups (years)				<0.001
18-40	11,975 (2.8%)	9,234 (2.5%)	2,741(4.1%)	
41-65	132,593 (30.7%)	98,759 (27.0%)	33,834 (51.2%)	
66-80	169,689 (39.3%)	145,156 (39.7%)	24,533 (37.1%)	
81 and above	117,477 (27.2%)	112,447 (30.8%)	5,030 (7.6%)	
Women	225,022 (52.1%)	191,797 (52.5%)	33,225 (50.2%)	<0.001
White	332,142 (83.2%)	282,555 (83.6%)	49,587 (80.9%)	<0.001
Black	30,636 (7.7%)	24,251(7.2%)	6,385 (10.4%)	<0.001
Primary expected payer status				<0.001
Medicare	28,988 (67.1%)	254,518(69.7%)	34,470 (52.2%)	
Medicaid	19,447 (4.5%)	14,592 (4.0%)	4,855 (7.4%)	
Private insurance	99,658 (23.1%)	77,923 (21.3%)	21,735 (32.9%)	
*Hospital bed size				<0.001
Small	65,057 (15.1%)	55,735 (15.3%)	9.322 (14.1%)	
Medium	111,320 (25.9%)	93,685 (25.7%)	17,635 (26.7%)	
Large	253,774 (59.2%)	214,796 (59.0%)	38,978 (59.1%)	
Urban−Teaching Facility	198,996 (46.3%)	167,571 (46.0%)	31,425 (47.7%)	<0.001
US Region				0.038
Northeast	92,187 (21.4%)	79,588 (21.8%)	12,599 (19.0%)	
Midwest	105,794 (24.5%)	87,597 (24.0%)	18,197 (27.5%)	
South	168,672 (39.1%)	142,728 (39.0%)	25,944 (39.2%)	
West	65,081 (15.1%)	55,683(15.2%)	9,398 (14.2%)	
Elective admission	59,150 (13.7%)	49,536(13.6%)	9,614 (14.6%)	<0.001
Weekend admission	86,924 (20.1%)	74,294(20.3%)	12,630 (19.1%)	<0.001
†Clinical Comorbidities				
Smoking	109,470 (25.4%)	90,055 (24.6%)	19,415 (29.4%)	<0.001
Dyslipidemia	199,336 (46.2%)	164,560 (45.0%)	34,776 (52.6%)	<0.001
Diabetes mellitus (uncomplicated)	97,057 (22.5%)	72,451(19.8%)	24,606(37.2%)	<0.001
Diabetes mellitus (complicated)	13,684 (3.2%)	9,639 (2.6%)	4,045(6.1%)	<0.001
Hypertension	299,541 (69.4%)	249,366 (68.2%)	50,175(75.9%)	<0.001
Congestive heart failure	1,522 (0.4%)	1,241 (0.3%)	281 (0.4%)	0.001
Prior MI	31,434 (7.3%)	26,827 (7.3%)	4,607 (7.0%)	0.001
Prior PCI	34,849 (8.1%)	29,590 (8.1%)	5,259 (8.0%)	0.22
Prior CABG	31,925 (7.4%)	28,260(7.7%)	3,665 (5.5%)	<0.001
Prior CVA	32,125 (7.4%)	28,381 (7.8%)	3,744 (5.7%)	<0.001
Peripheral vascular disease	30,135 (7.2%)	26,315 (7.2%)	3,820 (5.8%)	<0.001
Valvular disease	740 (0.2%)	630 (0.2%)	110 (0.2%)	0.73
Chronic pulmonary disease	97,113 (22. 5%)	78,978 (21.6%)	18,135 (27.4%)	<0.001
Liver disease	7,562 (1.8%)	6,024 (1.6%)	1,538 (2.3%)	<0.001
Fluid and electrolyte disorder	90,279 (20.9%)	77,436 (21.2%)	12,843 (19.4%)	<0.001
Chronic renal failure	64,055 (14.2%)	50,886 (13.9%)	9,569 (14.5%)	<0.001
Length of stay, mean (SE), (days)	3.4 (0.01)	3.4 (0.01)	3.7 (0.01)	<0.001

SD = standard deviation; SE = standard error; MI = myocardial infarction; CABG = coronary artery bypass grafting; CVA = cerebrovascular accident.
* Bed size categories are specific for hospital location and teaching status.
† Co-morbidities were extracted from the database using *International Classification of Diseases, Ninth Edition, Clinical Modification* Diagnosis or Clinical Classification Software codes.

640 to 641. Patient-level characteristics included demographics, clinical comorbidities, length of stay (in days), admission, and hospitalization characteristics (Table 1). As shown in Table 2, the outcomes of interest were in-hospital mortality, labeled as "died" in the NIS, and acute ischemic stroke events. For the acute ischemic stroke events, only those were included who had a stroke (identified using ICD-9-CM codes) and survived the hospitalization. A list of all ICD-9 codes used in the study is available in supplementary Table 1.

Categorical variables are expressed as percentages and continuous variables as mean ± standard deviation. We initially compared the baseline patient demographics, admission and hospital characteristics, and clinical comorbidities between non-obese and obese patients. The Pearson chi-squared test was used for categorical variables and the Student's t test was used for continuous variables. Multivariate logistic regression was then used to compare outcomes of interest between obese and those without obesity. The regression models were adjusted based on previous considerations: demographics, admission and hospital characteristics, calendar year, length of stay, and clinical comorbidities. When selecting the number of predictor parameters in regression analysis, we followed the ''*one in*

Table 2
In-hospital mortality and acute stroke events of atrial fibrillation patients

	Overall (n = 431,734)	Non-Obese (n = 365,596)	Obese (n = 66,138)	p value (obese vs non-obese)
In-hospital mortality	3,955 (0.9%)	3,615 (1.0%)	340 (0.5%)	<0.001
Unadjusted odds ratio, (95% CI)	—	Reference	0.52, (0.46 to 0.58)	<0.001
*Adjusted odds ratio, (95% CI)	—	Reference	0.83, (0.73 to 0.94)	<0.001
Acute stroke	2,658 (0.6%)	2,397 (0.7%)	279 (0.4%)	<0.001
Unadjusted odds ratio, (95% CI)	—	Reference	0.65, (0.57 to 0.73)	<0.001
*Adjusted odds ratio, (95% CI)	—	Reference	0.82, (0.72 to 0.94)	0.005

* Adjusted for patient demographics, clinical comorbidities, calendar year, length of stay, admission, and hospitalization characteristics. Of the variables included in the regression model, data points were missing for race (7.5%), insurance status (0.2%), hospital bed size (0.4%), teaching status (0.4%), and elective admission status (0.3%).

ten'' rule to reduce the risk of overfitting the model.[18] Adjusted odds ratios (AOR) and 95% confidence intervals (CI) were used to report the results of logistic regression (Table 2). Statistical analysis was performed using IBM SPSS Statistics 23.0 (IBM Corp., Armonk, New York).

Results

Among 431,734 patients hospitalized with a primary diagnosis of AF, 66,138 (15.3%) were obese. Table 1 summarizes the clinical characteristics of the cohort. Obesity in patients admitted for AF was associated with better survival outcomes compared with non-obese patients. Specifically, in-hospital mortality was lower (0.5% vs 1.0 %; unadjusted OR 0.52, 95% CI 0.46 to 0.58, p <0.001) as was the occurrence of acute stroke events (0.4% vs 0.7%, unadjusted OR 0.65, 95%CI 0.57 to 0.73, p <0.001). After adjustment for patient demographics, calendar year, clinical comorbidities, length of stay, hospital and admission characteristics, in-hospital mortality (AOR = 0.83, 95% CI 0.73 to 0.94) and acute stroke events (AOR = 0.82, 95% CI 0.72 to 0.94) occurred at a significantly lower rate in obese patients compared with those without obesity (Table 2).

Discussion

In our study from a large unselected "real world" cohort at a national level, obesity was paradoxically associated with lower all-cause mortality and stroke events in patients hospitalized for AF, even after extensive adjustment for patient demographics, hospitalization characteristics, and clinical co-morbidities.

Obesity may predispose to AF due to an adverse impact on hemodynamics and cardiac structure and function.[3] Interestingly, we found a paradoxical inverse association between short-term outcomes and obesity in AF hospitalizations. Although studies have reported the impact of obesity on development of AF, literature reporting in-hospital outcomes is lacking, and previous studies have shown conflicting long-term follow-up outcomes in this cohort.[3,6−12,19,20] Proietti et al in a recent meta-analysis of 13 studies found an obesity paradox for long-term all-cause mortality from studies based on subgroup analyses of oral anticoagulation-AF randomized trials, but unlike our study, they found no obesity paradox in observational studies.[6] Potential reasons for the dissimilarities in the overall outcomes from previous observational studies can be attributed to differences in the study sample size, patient characteristics, and temporal discordance (in-hospital vs long-term follow-up). To the best of our knowledge, our study is the first to report the paradoxical protective effect of obesity on in-hospital outcomes in AF hospitalizations at a large, nationwide level.

Multiple studies have described an inverse relation between obesity and outcomes in CV and non-CV conditions.[1,3,17,21−23] The mechanisms underlying the obesity paradox are not clear, although there are several possible explanations. Obesity and AF commonly share co-morbidities (i.e. hypertension, diabetes, dyslipidemia) and hence obese are more likely to be on medications, such as angiotensin converting enzyme inhibitors, β blockers, and lipid-lowering therapies, which may be beneficial.[9,12,24] Obese patients are younger than non-obese counterparts at the time of presentation plausibly due to factors such as poorer functional status and lower atrial natriuretic peptides, which in turn can lead to medical care at a younger age, and ability to receive and better tolerate therapies such as β blockers.[3,12] The presence of excess adipose tissue and lipoproteins in obese patients, can potentially act as better metabolic reserve against higher circulating endotoxins and inflammatory state, providing metabolic tolerance to disease state.[3] For example, obese have higher soluble tumor necrosis factor-alpha type I and II receptors that can act as additional reservoir for atrial arrythmogenic substrates such as TNF-alpha.[25] Additionally, renin-angiotensin system been related to development of atrial remodeling and fibrosis, where obese patients might have an advantage due to attenuated stress response to renin-angiotensin system.[26,27] Interestingly, predictors of mortality in AF patients, such natriuretic peptide levels, are also lower in obesity, which may add a protective mechanism.[28,29]

It is vital to emphasize that our paradoxical observation of favorable survival outcomes in obese-AF patients does not assume causation and must not be seen as encouragement for weight gain. Obesity is an established risk factor for the epidemiology, morbidity, and mortality of CVD. However, the obesity paradox demands further research to better understand and utilize this noteworthy observation for improving patient care and prognosis.

Our study has several limitations, such as inherent biases of retrospective, observational analyses involving large administrative databases. The administrative databases lack precise qualitative details usually available in clinical trials and registries such as the information on clinical variables, type of AF (i.e. paroxysmal or persistent), body mass index, and laboratory values. In particular, the pharmacotherapeutic profile of patients was not available in the NIS database, and, thus, we were unable to analyze the impact of medications on outcomes such as between β-blocker prescription and mortality in the study population. As NIS is a de-identified administrative database, it is not possible to validate individual ICD-9 codes and it includes encounters, not individual patients. There was a lack of anthropometric measurements and BMI values that did not permit stratified analysis comparing the outcomes of obese with overweight and normal-weight. The prevalence of obesity in our study was lower (15.3%) in comparison to those reported by earlier studies (30% to 40%) such Behavioral Risk Factor Surveillance System direct survey, who surveyed a different sample of subjects using different methodologies.[9,10,12,30] The reasons for the lower prevalence of obesity in the NIS versus these surveys are unknown; it may be that obesity was coded only when it was a principal finding or when it was believed to have therapeutic consequences. If undercoding of obesity occurred, it is unlikely to have influenced our findings, as there is no medical or financial reason to code obesity differently in patients with or without AF. Although it cannot be confirmed, patients who were obese might have been misclassified as being non-obese. Assuming misclassification occurred equally regardless of the outcomes, the measures of association in our study would have biased toward the null, making our significant results more conservative. Data in NIS is limited to all cause in-patient mortality, no information on longitudinal follow-up is available, and the possibility of residual measured or unmeasured confounding should be noted. Nonetheless, the NIS database provided a large unselected sample of the "real-world" data without reporting bias (such as from single-center studies) and high statistical power to support accumulating data on the association of obesity with outcomes in AF. Finally, data on physical activity, exercise, or cardio respiratory fitness, which impacts many patients with CVD, including those with AF, was not available.[3] In conclusion, in our large, national, unselected cohort of inpatients with AF, we found that obesity was paradoxically associated with lower risk adjusted in-hospital mortality and lower stroke events. Similar to other CV diseases, an obesity paradox appears to exist for AF patients.

Disclosure

MA, LG, MS, BP, NJ, SJ, RK, GR—none. CJL is the author of the book—"The Obesity Paradox."

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2019.01.051.

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