

Association of Body Mass Index With Clinical Outcomes in Patients With Atrial Fibrillation: A Report From the FANTASIA Registry

Vicente Bertomeu-Gonzalez, MD, PhD;* José Moreno-Arribas, MD, PhD;* María Asunción Esteve-Pastor, MD, PhD; Inmaculada Roldán-Rabadán, MD, PhD; Javier Muñoz, MD, PhD; Paula Raña-Míguez, PhD; Martín Ruiz-Ortiz, MD, PhD; Ángel Cequier, MD, PhD; Vicente Bertomeu-Martínez, MD, PhD; Lina Badimón, MD, PhD; Manuel Anguita, MD, PhD; Gregory Y. H. Lip, MD; Francisco Marín, MD, PhD; on behalf of FANTASIA Study Investigators[†]

Background—Obesity and atrial fibrillation (AF) frequently coexist and independently increase mortality. We sought to assess the association between obesity and adverse events in patients receiving oral anticoagulants for AF.

Methods and Results—Consecutive AF outpatients receiving anticoagulant agents (both vitamin K antagonists and direct oral anticoagulants) were recruited into the FANTASIA (Atrial fibrillation: influence of the level and type of anticoagulation on the incidence of ischemic and hemorrhagic stroke) registry. This observational, multicenter, and prospective registry of AF patients analyzes the quality of anticoagulation, incidence of events, and differences between oral anticoagulant therapies. We analyzed baseline patient characteristics according to body mass index, normal: $<25 \text{ kg/m}^2$, overweight: $25\text{--}30 \text{ kg/m}^2$, and obese: $\geq 30 \text{ kg/m}^2$, assessing all-cause mortality, stroke, major bleeding and major adverse cardiovascular events (a composite of ischemic stroke, myocardial infarction, and total mortality) at 3 years' follow-up. In this secondary prespecified substudy, the association of weight on prognosis was evaluated. We recruited 1956 patients (56% men, mean age 73.8 ± 9.4 years): 358 (18.3%) had normal body mass index, 871 (44.5%) were overweight, and 727 (37.2%) were obese. Obese patients were younger ($P < 0.01$) and had more comorbidities. Mean time in the therapeutic range was similar across body mass index categories ($P = 0.42$). After a median follow-up of 1070 days, 255 patients died (13%), 45 had a stroke (2.3%), 146 a major bleeding episode (7.5%) and 168 a major adverse cardiovascular event (8.6%). Event rates were similar between groups for total mortality ($P = 0.29$), stroke ($P = 0.90$), major bleeding ($P = 0.31$), and major adverse cardiovascular events ($P = 0.24$). On multivariate Cox analysis, body mass index was not independently associated with all-cause mortality, cardiovascular mortality, stroke, major bleeding, or major adverse cardiovascular events.

Conclusions—In this prospective cohort of patients anticoagulated for AF, obesity was highly prevalent and was associated with more comorbidities, but not with poor prognosis. (*J Am Heart Assoc.* 2020;9:e013789. DOI: 10.1161/JAHA.119.013789.)

Key Words: atrial fibrillation • mortality • obesity • prognosis • risk factors

Obesity and atrial fibrillation (AF) are increasing in epidemic proportions worldwide, and both increase the incidence of cardiovascular events.^{1,2} AF has long been

recognized as a risk factor for stroke, and its association with all-cause mortality is also widely acknowledged.³ While obesity significantly increases the risk of many metabolic

From the Department of Cardiology, Hospital Universitario de San Juan de Alicante, Universidad Miguel Hernández, Alicante, Spain (V.B.-G., J.M.-A., V.B.M.); Department of Cardiology, Hospital Clínico Universitario Virgen de la Arrixaca, Instituto Murciano de Investigación Biosanitaria (IMIB-Arrixaca), Murcia, Spain (M.A.E.-P., F.M.); Department of Cardiology, Hospital La Paz, Madrid, Spain (I.R.-R.); Instituto Universitario de Ciencias de la Salud, Instituto de Investigación Biomédica de A Coruña (INIBIC), Universidade da Coruña, La Coruña, Spain (J.M.); ODDS, SL, A Coruña, Spain (P.R.-M.); Department of Cardiology, Hospital Universitario Reina Sofía, Córdoba, Spain (M.R.-O., M.A.); Department of Cardiology, Hospital de Bellvitge, Barcelona, Spain (A.C.); Cardiovascular Research Center (CSIC-ICCC), Hospital de la Santa Creu i Sant Pau, Barcelona, Spain (L.B.); Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom (G.Y.H.L.); Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark (G.Y.H.L.); Centro de Investigación Biomédica en Red-Enfermedades Cardiovasculares: CIBER-CV, Madrid, Spain (V.B.-G., J.M.-A., M.A.E.-P., I.R.-R., J.M., A.C., V.B.M., L.B., F.M.).

Accompanying Appendix, Tables S1 through S3 are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013789>

*Dr Bertomeu-Gonzalez and Dr Moreno-Arribas contributed equally to this work.

[†]A complete list of the FANTASIA Study Investigators can be found in the Appendix.

Correspondence to: María Asunción Esteve-Pastor, MD, PhD, Department of Cardiology, Hospital Clínico Universitario Virgen de la Arrixaca, IMIB-Arrixaca. Ctra. Madrid-Cartagena s/n 30120, Murcia, Spain. E-mail: masunep@gmail.com

Received June 29, 2019; accepted October 4, 2019.

© 2019 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Clinical Perspective

What Is New?

- Obesity is not associated with prognosis in patients anticoagulated for atrial fibrillation.

What Are the Clinical Implications?

- While obesity is one of the main risk factors we target to prevent and treat cardiovascular disease, in the setting of atrial fibrillation obese patients show similar incidence of mortality and nonfatal adverse clinical outcomes.

and cardiovascular diseases,^{1–3} it is also associated with a lower incidence of events once the cardiovascular disease has been established, as has been proven with conditions such as diabetes mellitus, chronic kidney disease, stroke, dementia, coronary artery disease, and heart failure.^{4–8} This phenomenon is known as the “obesity paradox.”

Obesity has been related to the incidence and progression of AF,^{9,10} but its effect on prognosis in AF patients is controversial.¹¹ Two subanalyses from randomized clinical trials have shown lower rates of adverse events in patients with higher body mass index (BMI), the AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management)¹² and ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trials,¹³ but this observation has not been confirmed in observational registries with real-world data.¹⁴ Some authors have proposed that obese patients may have a more favorable prognosis because of better anticoagulation control or to a more complete pharmacological treatment compared with nonobese patients, but results have not been consistent among different studies.^{12,14}

We sought to assess the role of obesity and BMI on prognosis in real-world patients receiving oral anticoagulants for AF.

Methods

The FANTASIIA (Spanish acronym for “Atrial fibrillation: influence of the level and type of anticoagulation on the incidence of ischemic and hemorrhagic stroke”) registry design is described in detail elsewhere.¹⁵ In brief, this is an observational, prospective, national, and multicenter study of clinical and demographic characteristics of Spanish patients with AF. Its main objective is to assess the incidence of thromboembolic and bleeding events in an unselected population of patients with AF, assessing the type of oral anticoagulant (ie, vitamin K antagonists (VKA) or direct oral anticoagulants) used, and the quality of anticoagulation with

VKA. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

Between June 2013 and March 2014, outpatients with confirmed diagnosis of paroxysmal, persistent, or permanent AF were prospectively enrolled. All patients included had been receiving oral anticoagulation for at least 6 months at the time of recruitment. By design, each investigator included 16 patients taking VKA and 4 patients who were taking direct oral anticoagulants. Eighty investigators, working in 50 outpatient clinics, performed the study. Exclusion criteria were as follows: patients with valvular heart disease (rheumatic valve disease, moderate–severe valve disease, and prosthesis or valve repair surgery), age younger than 18 years, or with recent hospital admission. The study aimed to assess the influence of the anticoagulant treatment in prognosis; thus, patients admitted or with an admission in the prior 3 months were excluded. All patients provided signed informed consent.

The study complied with the ethical principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. It was approved by the Spanish Agency of Medicine and Health Products as a prospective follow-up postauthorization study (approval number SEC-ACO-2012–01) and by the Ethics Committee of the Hospital Universitario San Juan de Alicante.

Study Variables and Data Collection

Clinical and demographic data for all AF patients were collected in a detailed medical history. We defined previous heart disease as the composite of coronary artery disease, heart failure, and other structural cardiomyopathies (such as hypertrophic cardiomyopathy, chronic pericardial disease, or congenital diseases). Coagulation status was determined by the international normalized ratio values at 6 months before study entry and at 1 year of follow-up. The estimated time spent in the therapeutic range was assessed by the Rosendaal method. Stroke risk was calculated using the CHADS₂ and CHA₂DS₂-VASc scores,^{16,17} bleeding risk using the HAS-BLED score,¹⁸ and comorbidity according to the Charlson index. Serum creatinine levels were collected at baseline and the estimated glomerular filtration rate was calculated using the Cockcroft-Gault formula: $[(140 - \text{age}) \times [\text{weight in kg}] \times [0.85 \text{ if female}]] / [72 \times \text{creatinine}]$. Obesity was assessed at baseline by means of BMI and stratified as normal weight ($<25 \text{ kg/m}^2$), overweight ($25 \text{ to } <30 \text{ kg/m}^2$), and obese ($\geq 30 \text{ kg/m}^2$).

At 3 years, we assessed incidence of stroke, major bleeding, all-cause mortality, cardiovascular mortality, and major adverse cardiovascular events (MACE, defined as the

Table 1. Baseline Characteristics Stratified by BMI

	All Patients	Normal Weight (BMI<25 kg/m ²)	Overweight (BMI 25–30 kg/m ²)	Obese (BMI≥30 kg/m ²)	P Value
N	1956	358	871	727	
Demographic data					
Age (y, mean±SD)	73.8±9.4	75.3±9.5	74.5±9.5	72.1±9.2	<0.01
Women, %	44.0	46.7	40.6	46.6	0.03
Comorbidities and cardiovascular risk factors					
Arterial hypertension, %	80.4	69.8	79.7	86.5	<0.01
Dyslipidemia, %	52.2	48.6	51.8	54.5	0.18
Diabetes mellitus, %	29.4	24.3	25.5	36.5	<0.01
Smoking habit, %	5.1	5.6	3.9	6.2	0.10
CODP/OSAS, %	17.5	14.5	13.9	23.4	<0.01
Chronic kidney failure, %	19.3	22.6	19.5	17.3	0.11
Liver dysfunction, %	1.2	1.1	1.2	1.4	0.90
Cancer	8.6	9.8	8.2	8.5	0.65
Aortic or peripheral artery disease	6.0	6.7	6.4	5.2	0.51
History of stroke	17.0	20.7	17.6	14.4	0.03
History of systemic embolism	2.2	1.1	1.5	3.6	<0.01
Thyroid dysfunction	11.1	12.0	11.7	10.0	0.49
Alcohol abuse	3.7	3.9	2.3	5.2	<0.01
Charlson index	1.14±1.16	1.16±1.20	1.04±1.14	1.26±1.15	<0.01
Previous cardiac disease					
AF, %	100	100	100	100	
Cardiac disease, %	48.0	44.1	45.6	52.7	<0.01
Heart failure, %	28.9	28.2	25.8	32.9	<0.01
Coronary artery diseases, %	18.2	16.2	19.4	17.7	0.39
Acute coronary syndrome, %	13.8	12.6	14.6	13.5	0.62
Coronary revascularization, %	11.5	10.9	12.2	10.9	0.67
Coronary stent, %	9.4	6.9	10.5	9.4	0.17
Dilated cardiomyopathy or LVEF <45% (%)	11.7	13.1	10.6	12.2	0.37
Hypertrophic cardiomyopathy, %	2.6	2.8	2.9	2.2	0.68
Congenital heart disease, %	0.6	1.1	0.2	0.8	0.13
Aortic valve disease, %	3.2	6.2	2.4	2.8	<0.01
Left ventricular hypertrophy, %	15.6	10.3	15.6	18.3	<0.01
Atrial flutter, %	4.4	5.6	3.8	4.5	0.37
Sinus node dysfunction, %	2.6	3.1	2.8	2.1	0.54
Pacemaker	6.5	7.8	6.9	5.4	0.25
Bleeding episodes in the last 6 mo					
Major bleeding episodes, %	4.1	5.6	4.1	3.3	0.20
Bleeding requiring transfusion (% within bleedings)	32.5	35.0	38.9	20.8	0.33
Bleeding requiring surgery (% within bleedings)	8.8	10.0	5.6	12.5	0.63

Continued

Table 1. Continued

	All Patients	Normal Weight (BMI<25 kg/m ²)	Overweight (BMI 25–30 kg/m ²)	Obese (BMI≥30 kg/m ²)	P Value
Type of AF					
Paroxysmal, %	29.1	32.7	31.0	25.2	0.14
Persistent, %	16.8	16.8	15.9	17.7	
Longstanding persistent, %	4.7	4.2	4.4	5.2	
Permanent, %	49.4	46.4	48.7	51.9	
Previous electrical cardioversion, %	18.1	14.3	17.3	20.9	0.02
Previous pharmacological cardioversion, %	21.8	21.8	20.8	22.9	0.57
Previous AF ablation, %	4.3	4.5	4.6	3.9	0.76
Control strategy in the baseline visit					0.79
Rhythm control, %	38.2	39.7	37.6	38.2	
Rate control, %	61.8	60.3	62.5	61.8	
CHADS ₂ (mean±SD)	2.25±1.24	2.23±1.34	2.22±1.21	2.31±1.24	0.37
CHA ₂ DS ₂ -VASC (mean±SD)	3.71±1.59	3.73±1.64	3.67±1.53	3.74±1.62	0.79
HAS-BLED (mean±SD)	2.01±1.05	2.03±1.10	1.98±1.02	2.02±1.05	0.72
Physical examination					
Systolic blood pressure (mm Hg, mean±SD)	132.1±18.5	127.1±17.4	132.5±17.7	134.2±19.5	<0.01
Diastolic blood pressure (mm Hg, mean±SD)	75.9±11.5	72.2±11.0	75.8±11.1	77.97±11.7	<0.01
Heart rate (bpm, mean±SD)	72.7±15.1	71.8±16.0	71.8±14.2	74.1±15.5	<0.01
Weight (kg, mean±SD)	78.5±14.4	63.4±8.8	75.0±8.4	90.2±13.1	<0.01
Height (cm, mean±SD)	164.5±8.9	164.7±9.0	165.4±8.5	163.3±9.1	<0.01
BMI (kg/m ² , mean±SD)	28.9±4.9	23.0±2.6	27.4±1.4	33.8±3.7	<0.01
Complementary examinations					
Rhythm at baseline					0.05
Sinus, %	33.0	35.8	35.3	29.0	
AF, %	60.6	57.3	57.9	65.5	
Pacemaker, %	5.7	5.9	6.2	4.9	
Other, %	0.7	1.1	0.6	0.6	
LVEF (%; mean±SD)	58.6±11.4	57.8±12.3	59.1±11.2	58.3±11.1	0.09
Left ventricular hypertrophy, %	40.0	33.0	38.1	45.7	<0.01
Hemoglobin (g/dL, mean±SD)	13.7±1.7	13.4±1.7	13.7±1.7	13.7±1.8	<0.01
Serum creatinine (mg/dL, mean±SD)	1.1±0.5	1.1±0.8	1.0±0.4	1.0±0.4	0.05
Glomerular filtration rate (mL/min per 1.73 m ² , mean±SD)	66.2±22.9	60.9±20.3	64.5±20.7	70.8±25.8	<0.01
Total cholesterol (mg/dL, mean±SD)	177.1±38.6	179.8±40.8	177.2±36.5	175.6±39.9	0.10
Glucose (mg/dL, mean±SD)	108.6±31.6	103.2±27.8	106.3±29.5	114.1±34.8	<0.01
HBA1C (%; mean±SD)	6.2±1.3	5.9±1.2	6.2±1.1	6.3±1.6	<0.01

AF indicates atrial fibrillation; BMI, body mass index; bpm, beats per minute; COPD, chronic obstructive pulmonary disorder; HBA1C, hemoglobin A1c; LVEF, left ventricular ejection fraction; OSAS, obstructive sleep apnea syndrome.

composite of ischemic stroke, myocardial infarction, and cardiovascular and all-cause mortality). Thromboembolic events were defined as stroke or transient ischemic attack and peripheral artery embolism. All strokes were evaluated by

computed tomography or magnetic resonance imaging according to the neurologist's criteria. Bleeding events were assessed according to the 2005 International Society of Thrombosis and Haemostasis criteria.¹⁹ All-cause and

Table 2. Pharmacological Treatment at Baseline Stratified by BMI

	Normal Weight (BMI<25 kg/m ²)	Overweight (BMI 25–30 kg/m ²)	Obese (BMI≥30 kg/m ²)	P Value
N	358	871	727	
Diuretics, %	48.9	54.9	64.5	<0.01
Aldosterone antagonists, %	16.2	11.3	16.1	<0.01
ACE inhibitors, %	26.8	31.7	31.8	0.19
Angiotensin receptor blockers, %	32.4	39.5	46.2	<0.01
Statins, %	46.1	55.6	58.7	<0.01
Antiplatelets, %	9.5	11.6	9.9	0.42
β-Blockers, %	55.9	58.1	65.2	<0.01
Digoxin, %	20.9	16.9	18.3	0.24
Antiarrhythmic drugs, %	25.4	25.7	22.9	0.42

ACE indicates angiotensin-converting enzyme; BMI, body mass index.

cardiovascular mortality were also recorded. Death was classified as cardiovascular when caused by acute coronary syndrome, heart failure, lethal arrhythmia or sudden death, artery aneurysm rupture, or stroke. An external event assignment committee evaluated all adverse events.

Statistical Analyses

The Kolmogorov-Smirnov method was used to test the normality of continuous variables, which were reported as mean±SD or median (interquartile range), as appropriate. Categorical variables were expressed as relative frequencies (%). We used the ANOVA test to compare continuous variables across BMI categories and the post hoc Tukey test to assess intergroup differences. Qualitative variables were compared using the χ^2 test. Cox regression analyses were used to test the associations between BMI and mortality, bleeding, and cardiovascular events. The independent effect

of clinical variables on adverse clinical outcomes was calculated using a Cox proportional hazards regression; the multivariate model included variables yielding a $P<0.15$ on univariable analysis. The models included BMI, age, sex, hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, heart failure, aortic or peripheral artery disease, chronic kidney disease, Charlson index, history of stroke, and CHA₂DS₂-VAsC and HAS-BLED scores. Differences in event-free survival were examined with the log-rank test, and Kaplan-Meier curves were drafted accordingly. To test nonlinear association between the continuous variable BMI and the events, analyses of restricted cubic splines were performed by generating restricted cubic splines for 4 knots and adjusting the Cox multivariate model for each event, including splines as covariates. $P<0.05$ were considered statistically significant. All statistical analyses were performed with Stata version 12 (Stata Corporation, College Station, TX).

Table 3. Events During Follow-Up, Stratified by BMI

	Normal Weight (BMI<25 kg/m ²) N=358		Overweight (BMI 25–30 kg/m ²) N=871		Obese (BMI≥30 kg/m ²) N=727		P Value
	n	Annual Rate (%/year)	n	Annual Rate (%/year)	n	Annual Rate (%/year)	
All-cause mortality	52	(4.84)	119	(4.55)	84	(3.85)	0.29
Cardiovascular mortality	16	(1.51)	56	(2.18)	35	(1.63)	0.26
Stroke	9	(0.85)	19	(0.74)	17	(0.79)	0.90
Systemic embolism	9	(0.85)	22	(0.84)	17	(0.79)	0.96
Major bleeding	23	(2.18)	75	(2.91)	48	(2.24)	0.22
MACE	24	(2.27)	84	(3.27)	60	(2.79)	0.24

BMI indicates body mass index; MACE, major adverse cardiovascular event (composite of ischemic stroke, myocardial infarction, and cardiovascular and total mortality).

Results

The final study sample comprised 1956 patients (56% men, mean age 73.8 ± 9.4 years). Table 1 shows the baseline characteristics of the study population. BMI was in the normal range in 358 (18.3%) patients, while 871 (44.5%) patients were overweight and 727 (37.2%) were obese. Obese patients were significantly younger and showed a higher prevalence of comorbidities such as hypertension, diabetes mellitus, previous heart failure, and pulmonary disease compared with normal weight and overweight patients.

Pharmacological Treatment

There were significant differences in most cardiovascular medications (Table 2), but not in the quality of anticoagulation control with VKA according to BMI. Mean time in the therapeutic range was similar across BMI categories (normal weight: 61.1% versus overweight: 62.5% versus obese: 63.1%; $P=0.42$). No significant differences were found in the percentage of VKA patients achieving $<65\%$ or 70% of their time in the therapeutic range (Table S1).

Events During Follow-Up

After a median of 1070 (interquartile range 750–1110) days of follow-up, 255 (13.04%) patients had died, including 107

(5.47%) from cardiovascular causes. Forty-five (2.30%) patients had suffered a stroke, 48 (2.45%) a systemic embolism, 146 (7.46%) a major bleeding episode, and 168 (8.59%) a MACE. Annual event rates were similar across BMI groups for total mortality (normal weight: 4.84% versus overweight: 4.55% versus obese: 3.85%; $P=0.29$), cardiovascular mortality (normal weight: 1.51% versus overweight: 2.18% versus obese: 1.63%; $P=0.26$), stroke (normal weight: 0.85% versus overweight: 0.74% versus obese: 0.79% $P=0.90$), systemic embolism (normal weight: 0.85% versus overweight: 0.84% versus obese: 0.79%; $P=0.96$), major bleeding (normal weight: 2.18% versus overweight: 2.91% versus obese: 2.24%; $P=0.31$), and MACE (normal weight: 2.27% versus overweight: 3.27% versus obese: 2.79%; $P=0.24$) (Table 3 and Figure 1).

On univariable analysis, obesity was not statistically related to all-cause mortality (odds ratio [OR] 1.24, 95% CI 0.94–1.64; $P=0.14$, cardiovascular mortality OR 1.23, 95% CI 0.81–1.86; $P=0.33$), stroke (OR 0.97, 95% CI 0.53–1.79; $P=0.93$), systemic embolism (OR 1.08, 95% CI 0.59–1.97; $P=0.80$), major bleeding (OR 1.23, 95% CI 0.86–1.75; $P=0.27$), or MACE (OR 1.07, 95% CI 0.77–1.49; $P=0.68$) (Table S2).

Subgroup Analyses

The event rates were analyzed in prespecified subgroups. We did not find significant differences between sexes or age groups. Event rates for death or MACE are shown in Table S2. Only 7

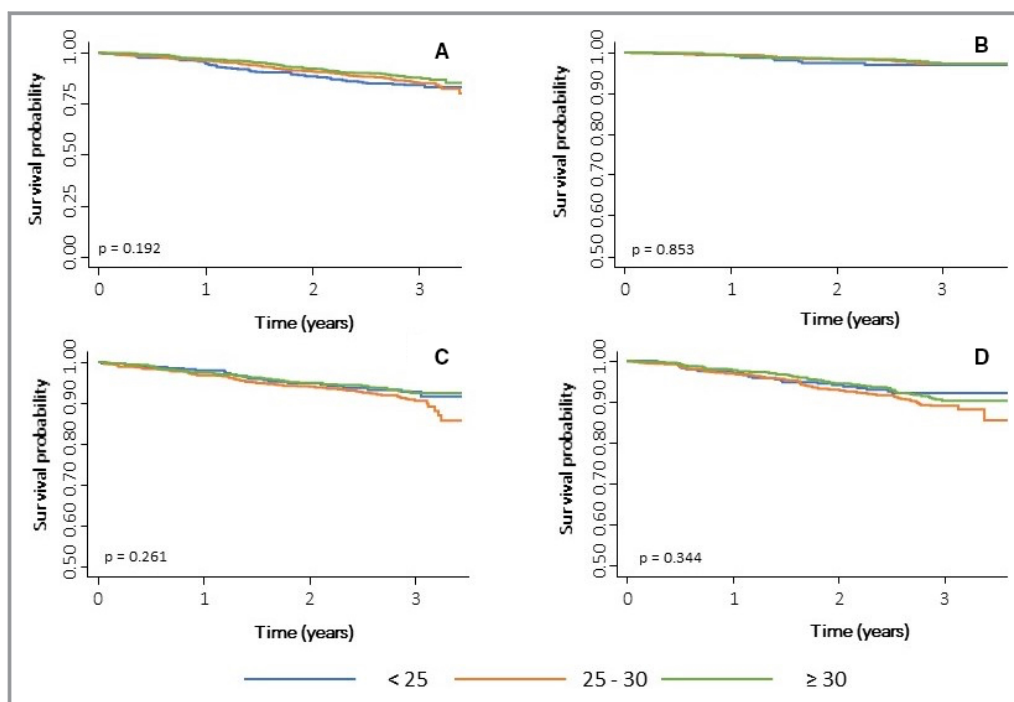


Figure 1. Kaplan–Meier survival estimates. **A**, Mortality, **B** stroke, **C** major bleeding, and **D** MACE (composite of ischemic stroke, myocardial infarction, and cardiovascular and total mortality). MACE indicates major adverse cardiovascular events.

Table 4. Multivariate Cox regression

	HR	95% CI		P Value
Total mortality				
BMI (reference <30 kg/m ²)	0.94	0.71	1.25	0.69
Age, per y	1.09	1.07	1.11	<0.01
Heart failure	1.72	1.26	2.36	<0.01
Charlson index	1.33	1.15	1.54	<0.01
CHA2DS2-VASc	0.81	0.69	0.95	0.01
HAS-BLED	1.34	1.16	1.55	<0.01
Stroke				
BMI (reference <30 kg/m ²)	1.17	0.62	2.22	0.63
Cerebrovascular disease	2.54	1.10	5.88	0.03
Major bleeding				
BMI (reference <30 kg/m ²)	0.88	0.61	1.28	0.51
Dyslipidemia	0.57	0.41	0.81	0.01
Chronic kidney failure	1.50	1.01	2.23	0.04
HAS-BLED	1.29	1.08	1.55	<0.01
MACE				
BMI (reference <30 kg/m ²)	1.00	0.72	1.41	0.98
Age, per y	1.06	1.03	1.09	<0.01
Coronary artery disease	1.99	1.26	3.13	<0.01
Heart failure	2.01	1.27	3.16	<0.01
HAS-BLED	1.21	1.01	1.44	0.04

Model adjustment: The models included BMI, age, sex, hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, heart failure, aortic or peripheral artery disease, chronic kidney disease, Charlson index, history of stroke, CHA2DS2-VASc and HAS-BLED scores. BMI indicates body mass index; HR, hazard ratio; MACE, major adverse cardiovascular event (composite of ischemic stroke, myocardial infarction, and cardiovascular and total mortality).

patients in our population were underweight (BMI<18.5 kg/m²), precluding further analyses in this category (Table S3).

Multivariate Analysis

In the multivariate Cox analysis performed to adjust for confounding variables, BMI was not independently associated with all-cause mortality, cardiovascular mortality, stroke, major bleeding, or MACE (Table 4). The restricted cubic splines analyses showed nonlinear relationship between BMI and events (Figure 2).

An additional model including only BMI and age was performed in order to further study the effect of age in the relationship between BMI and events (Figure 3).

Discussion

In a real-world cohort of patients receiving oral anticoagulant therapy for AF, half of the patients were overweight and a

third were obese. Despite the higher prevalence of cardiovascular risk factors in overweight and obese patients, there were no significant differences in adverse events between normal and obese patients. Moreover, higher BMI was not independently associated with a higher risk of mortality or adverse outcomes in multivariate analysis.

Whether obesity is a protective factor or has no effect is a matter of debate. In 2 substudies of the ARISTOTLE trial, overweight and obesity were associated with lower risk of all-cause mortality, cardiovascular mortality, and stroke even after adjusting for biomarkers of cardiac and renal dysfunction and inflammatory activity.^{13,20} A large meta-analysis and systematic review evaluated the relationship between BMI and clinical outcomes in AF patients, finding that the risk of stroke, death, and cardiovascular death were lower in overweight and obese patients compared with patients with a normal BMI,²¹ but other studies, such as the EORP-AF (EURObservational Research Programme-Atrial Fibrillation),²² did not find significant differences.

Studies including clinical trial data show reduced events among obese patients (the so-called “obesity paradox”), while most observational registries report similar event rates between obese and normal weight patients, suggesting that comorbidities have an important role in determining outcomes.²² Proietti et al²³ performed a systematic review studying the relationship between overweight or obesity and cardiovascular prognosis and observed an obesity paradox for adverse events only in clinical trials cohorts, whereas observational studies fail to show this relationship, in accordance with our results in the FANTASIA registry. Indeed, in our study, the Charlson index was significantly higher among obese patients, and in the multivariate analyses it was an independent predictor of mortality, while obesity did not show significant association. While clinical trials are considered to provide the highest grade of evidence, observational registries are better suited for studying broader populations without strict inclusion criteria, obtaining information more representative of real-life daily clinical practice.

Obesity has been shown to be an independent risk factor for thromboembolic events in the general population with no AF,^{14,24} but the relationship between stroke and BMI in patients with AF is debated. Indeed, scores to predict stroke do not include BMI, and the 2 variables (stroke and obesity) are not associated in observational studies.^{17,25} Our results corroborate these observations. Although most studies in patients with AF show neutral or protective effects for higher BMI, overweight and obesity were associated with a worse prognosis in the Danish Diet, Cancer, and Health study of incident AF, a prospective nationwide study.²⁶ The protection conferred by obesity seems more evident in patients with established cardiovascular disease, and the selection of

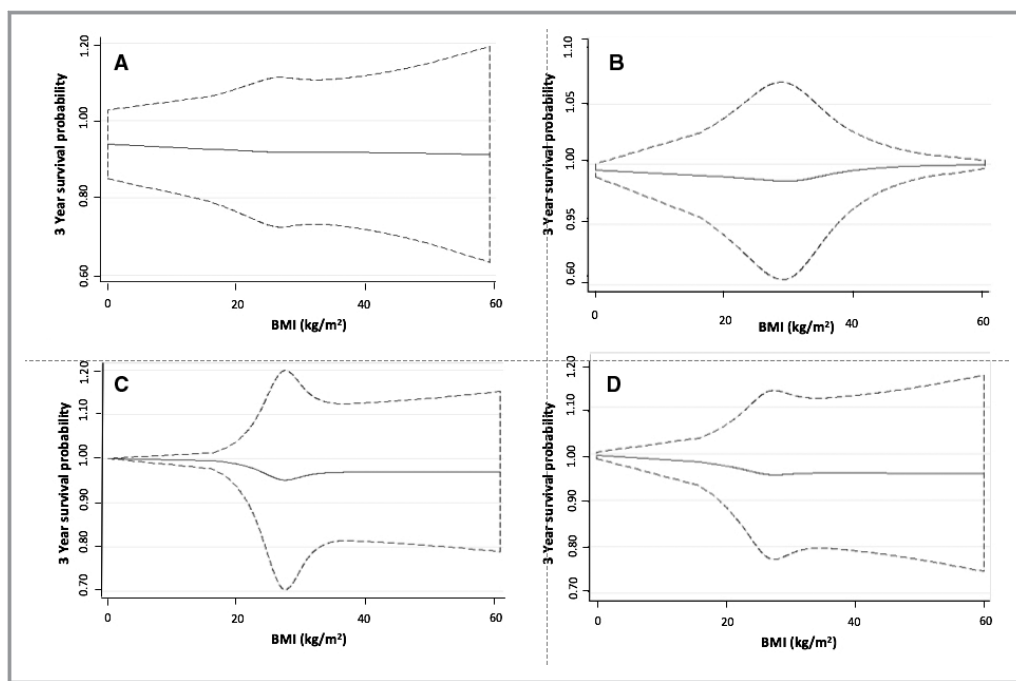


Figure 2. Association between BMI and the estimated 3-year survival probability including BMI as a continuous variable using restricted cubic splines with 3 degrees of freedom. The dotted lines represent the 95% CI. (A) Mortality, (B) stroke, (C) major bleeding, and (D) MACE (composite of ischemic stroke, myocardial infarction, and cardiovascular and total mortality). The models were adjusted by age, sex, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, heart failure, aortic artery disease, chronic kidney disease, Charlson index, previous stroke, CHA₂DS₂-VASc, and HAS-BLED. BMI indicates body mass index; MACE, major adverse cardiovascular events.

patients with incident AF could result in a lower-risk population. In fact, in heart failure—the paradigm of advanced cardiac disease—the obesity paradox is more pronounced.²⁷

The risk of bleeding has scarcely been studied. Our results suggest that obesity does not modify bleeding risk in patients anticoagulated for AF, and other studies have shown only that underweight could be associated with increased bleeding risk,^{25,28} but not overweight or obesity. Again, obesity is not included in any bleeding risk score: neither HAS-BLED nor ATRIA, HAEMORR2HAGES, or ORBIT include weight among the variables that predict bleeding episodes.²⁹

Age is one of the strongest predictors of mortality. In our study, mean age decreased as BMI increased, and this finding is consistent with other studies.^{13,20,30} In the subanalysis including only age and BMI, BMI still did not show a significant relationship with events in the follow-up.

The higher risk of developing a cardiovascular disease caused by obesity is probably not as strong as the effect of cachexia worsening prognosis in any chronic disease. We speculate that obesity increases the probability of developing cardiovascular diseases, but it also helps patients survive their complications. Underweight patients have an increased mortality risk^{21,31} and are more prone to have diseases as a result of poor nutritional status, whereas obesity confers

metabolic reserves that may help to cope with heart disease. Our results support this hypothesis. Figure 2 shows that rather than a decrease of risk for obesity, there is an increase of risk for BMI values <25.

Finally, obese patients may have better tolerance for cardiovascular drugs with proven prognostic benefits. In our study, obese patients received a significantly higher proportion of renin-angiotensin system blockers, diuretics, statins, and β -blockers. This finding is consistent with previous reports and could explain, at least in part, the good prognosis associated with obesity. In agreement with other groups, we found similar international normalized ratio control among BMI categories,²⁵ but the effect of overweight and obesity on prognosis did not change after adjustment for these potential confounders. A nonlinear relationship between BMI and events was also tested (Figure 2) and we did not find significant changes in the event rates through all the spectrum of BMI of our population, reinforcing the lack of association between weight and prognosis in this scenario.

Limitations

This study has some limitations. BMI was collected only at baseline, so we could not assess the associations between

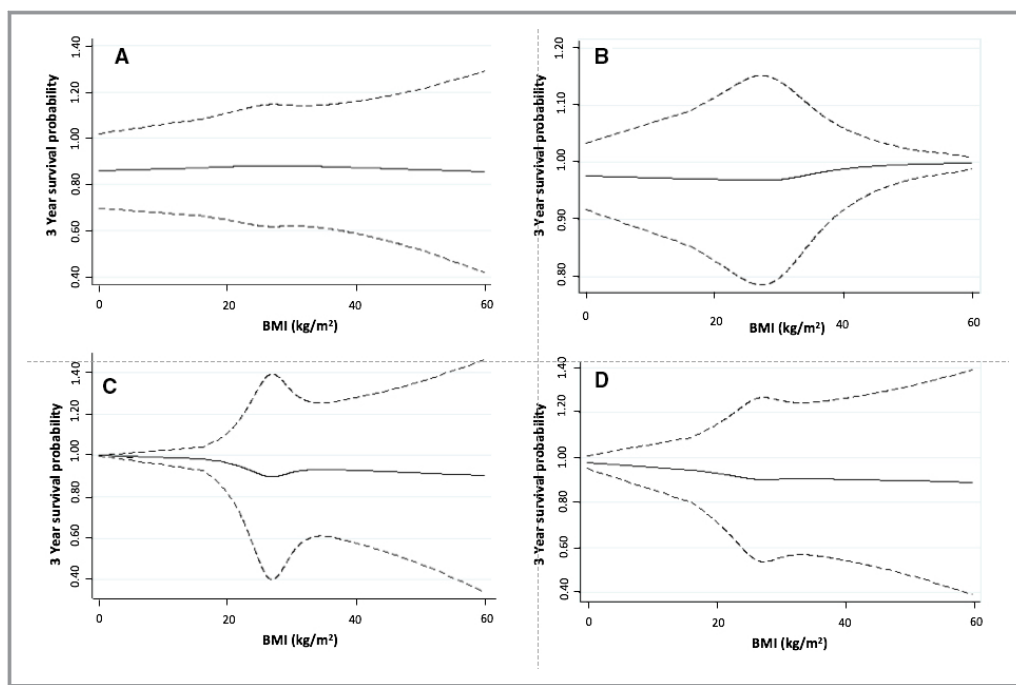


Figure 3. Association between BMI and the estimated 3-year survival probability including BMI as a continuous variable using restricted cubic splines with 3 degrees of freedom. The dotted lines represent the 95% CI. **A**, Mortality, **(B)** stroke, **(C)** major bleeding, and **(D)** MACE (composite of ischemic stroke, myocardial infarction, and cardiovascular and total mortality). The models were adjusted by age. BMI indicates body mass index; MACE, major adverse cardiovascular events.

long-term changes in BMI over time on outcomes. The measurement of obesity by means of BMI is a limited approach, because it does not assess the distribution of fat, the amount of lean body weight, body fat, fat-free mass, or fat composition.³² While most studies assess obesity with BMI, results are similar in studies evaluating it by waist circumference.^{13,20} The lack of more detailed information about the type of bleeding or the cause of cardiovascular death prevented further analyses. The Cockcroft-Gault formula tends to overestimate creatinine clearance in obese patients. Although multivariate adjustment was performed, the effects of residual confounding cannot be fully excluded. A propensity-score matched analysis would have reinforced the strength of the findings, but the limited sample size of our study prevented us from performing this analysis. On the other hand, the observational nature of our study provides real-world data.

In conclusion, in this prospective cohort of real-world patients anticoagulated for AF, obesity was highly prevalent but was not associated with poor prognosis. In contrast to clinical trial cohorts, the obesity paradox does not appear to be evident in real-world studies.

Sources of Funding

The FANTASIIA registry was funded by an unconditional grant from Pfizer/Bristol-Myers-Squibb and by grants from the

Instituto de Salud Carlos III (Madrid)-FEDER (RD16/11/00420, RD12/0042/0068, RD12/0042/0010, RD12/0042/0069, and RD12/0042/0063). The authors are supported by RD12/0042/0049 (RETICS) from ISCIII and PI13/00513/FEDER from ISCIII. Fundación Séneca (19245/PI/14), Instituto Murciano de Investigación Biosanitaria (IMIB16/AP/01/06).

Disclosures

None.

References

1. Börschel CS, Schnabel RB. The imminent epidemic of atrial fibrillation and its concomitant diseases—Myocardial infarction and heart failure—a cause for concern. *Int J Cardiol*. 2019;287:162–173.
2. Ricci G, Tomassoni D, Pirillo I, Sirignano A, Sciotti M, Zaami S, Grappasonni I. Obesity in the European region: social aspects, epidemiology and preventive strategies. *Eur Rev Med Pharmacol Sci*. 2018;22:6930–6939.
3. Ruddox V, Sandven I, Munkhaugen J, Skattebu J, Edvardsen T, Erik Otterstad J. Atrial fibrillation and the risk for myocardial infarction, all-cause mortality and heart failure: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2017;24:1555–1566.
4. Han SJ, Boyko EJ. The evidence for an obesity paradox in type 2 diabetes mellitus. *Diabetes Metab J*. 2018;42:179–187.
5. Mohebi R, Simforoosh A, Tohidi M, Azizi F, Hadaegh F. Obesity paradox and risk of mortality events in chronic kidney disease patients: a decade of follow-up in Tehran lipid and glucose study. *J Ren Nutr*. 2015;25:345–350.
6. Andersen KK, Olsen TS. The obesity paradox in stroke: lower mortality and lower risk of readmission for recurrent stroke in obese stroke patients. *Int J Stroke*. 2015;10:99–104.
7. Wang ZJ, Zhou YJ, Galper BZ, Gao F, Yeh RW, Mauri L. Association of body mass index with mortality and cardiovascular events for patients with coronary

- artery disease: a systematic review and meta-analysis. *Heart*. 2015;101:1631–1638.
8. Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O'Meara ES, Longstreth WT, Luchsinger JA. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. *Arch Neurol*. 2009;66:336–342.
 9. Wang TJ, Parise H, Levy D, D'Agostino RB, Wolf PA, Vasan RS, Benjamin EJ. Obesity and the risk of new-onset atrial fibrillation. *JAMA*. 2004;292:2471.
 10. Tsang TSM, Barnes ME, Miyasaka Y, Cha SS, Bailey KR, Verzosa GC, Seward JB, Gersh BJ. Obesity as a risk factor for the progression of paroxysmal to permanent atrial fibrillation: a longitudinal cohort study of 21 years. *Eur Heart J*. 2008;29:2227–2233.
 11. Elagizi A, Kachur S, Lavie CJ, Carbone S, Pandey A, Ortega FB, Milani RV. An overview and update on obesity and the obesity paradox in cardiovascular diseases. *Prog Cardiovasc Dis*. 2018;61:142–150.
 12. 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;123:646–651.
 13. Sandhu RK, Ezekowitz J, Andersson U, Alexander JH, Granger CB, Halvorsen S, Hanna M, Hijazi Z, Jansky P, Lopes RD, Wallentin L. The 'obesity paradox' in atrial fibrillation: observations from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial. *Eur Heart J*. 2016;37:2869–2878.
 14. Mitchell AB, Cole JW, McArdle PF, Cheng Y-C, Ryan KA, Sparks MJ, Mitchell BD, Kittner SJ. Obesity increases risk of ischemic stroke in young adults. *Stroke*. 2015;46:1690–1692.
 15. Bertomeu-González V, Anguita M, Moreno-Arribas J, Cequier Á, Muñoz J, Castillo-Castillo J, Sanchis J, Roldán I, Marín F, Bertomeu-Martínez V; FANTASIA Study Investigators. Quality of anticoagulation with vitamin K antagonists. *Clin Cardiol*. 2015;38:357–364.
 16. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864–2870.
 17. Lip GYH, Nieuwlaet R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137:263–272.
 18. Pisters R, Lane DA, Nieuwlaet R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138:1093–1100.
 19. Schulman S, Anger SU, Bergqvist D, Eriksson B, Lassen MR, Fisher W. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *J Thromb Haemost*. 2010;8:202–204.
 20. Roopinder D, Sandhu K, Sandhu RK, Ezekowitz JA, Hijazi Z, Westerbergh J, Aulin J, Alexander JH, Granger CB, Halvorsen S, Hanna MS, Lopes RD, Siegbahn A, Wallentin L. Obesity paradox on outcome in atrial fibrillation maintained even considering the prognostic influence of biomarkers: insights from the ARISTOTLE trial. *Open Heart*. 2018;5:e000908.
 21. Zhu W, Wan R, Liu F, Hu J, Huang L, Li J, Hong K. Relation of body mass index with adverse outcomes among patients with atrial fibrillation: a meta-analysis and systematic review. *J Am Heart Assoc*. 2016;5:004006. DOI: 10.1161/JAHA.116.004006.
 22. Boriani G, Laroche C, Diemberger I, Fantecchi E, Meeder J, Kurpesa M, Baluta MM, Proietti M, Tavazzi L, Maggioni AP; Lip GYH, EORP-AF General Pilot Registry Investigators. Overweight and obesity in patients with atrial fibrillation: Sex differences in 1-year outcomes in the EORP-AF General Pilot Registry. *J Cardiovasc Electrophysiol*. 2018;29:566–572.
 23. Proietti M, Guiducci E, Cheli P, Lip GYH. Is there an obesity paradox for outcomes in atrial fibrillation? *Stroke*. 2017;48:857–866.
 24. Guo Y, Yue X, Li H, Song Z, Yan H, Zhang P, Gui Y, Chang L, Li T. Overweight and obesity in young adulthood and the risk of stroke: a meta-analysis. *J Stroke Cerebrovasc Dis*. 2016;25:2995–3004.
 25. Inoue H, Kodani E, Atarashi H, Okumura K, Yamashita T, Origasa H; J-RHYTHM Registry Investigators. Impact of body mass index on the prognosis of Japanese patients with non-valvular atrial fibrillation. *Am J Cardiol*. 2016;118:215–221.
 26. Overvad TF, Rasmussen LH, Skjøth F, Overvad K, Lip GYH, Larsen TB. Body mass index and adverse events in patients with incident atrial fibrillation. *Am J Med*. 2013;126:640.e9–640.e17.
 27. Horwich TB, Fonarow GC, Clark AL. Obesity and the obesity paradox in heart failure. *Prog Cardiovasc Dis*. 2018;61:151–156.
 28. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, Yang S, Alings M, Kaatz S, Hohnloser SH, Diener H-C, Franzosi MG, Huber K, Reilly P, Varrone J, Yusuf S. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation. *Circulation*. 2011;123:2363–2372.
 29. Rivera-Caravaca JM, Roldán V, Esteve-Pastor MA, Valdés M, Vicente V, Lip GYH, Marín F. Importance of time in therapeutic range on bleeding risk prediction using clinical risk scores in patients with atrial fibrillation. *Sci Rep*. 2017;7:12066.
 30. Wang J, Yang YM, Zhu J, Zhang H, Shao XH, Tian L, Huang B, Yu LT, Gao X, Wang M. Overweight is associated with improved survival and outcomes in patients with atrial fibrillation. *Clin Res Cardiol*. 2014;103:533–542.
 31. Simoons ML, Bonneux L. Obesity, cardiology, and beyond. *J Am Coll Cardiol*. 2008;52:986–987.
 32. Alagiakrishnan K, Banach M, Ahmed A, Aronow WS. Complex relationship of obesity and obesity paradox in heart failure—higher risk of developing heart failure and better outcomes in established heart failure. *Ann Med*. 2016;48:603–613.

SUPPLEMENTAL MATERIAL

Appendix

FANTASIA Registry Investigators

Carmen Rus Mansila¹, Juan Luis Bonilla Palomas¹, Antonio Luis Gámez López¹, Daniel Salas Bravo¹, Miriam Martín Toro¹, Antonio Luis Gámez López¹, Juan Luis Bonilla Palomas¹, Manuel Anguita Sánchez², Mónica Delgado Ortega², Juan Carlos Castillo Domínguez², Martín Ruiz Ortiz², Elías Romo Peña², Mónica Delgado Ortega², Dr. Fátima Esteban³, Dr. Miguel Ángel Casanova³, Dr. Francisco Torres Calvo⁴, Dr. Rafael Bravo Marqués⁴, Dr. Pedro Chinchurreta Capote⁴, Dr. Alejandro Pérez Cabeza⁴, Dr. Raúl Quirós López⁴, Dr. Rodrigo Mayo Cabeza⁴, Dr. Juan José Gómez Doblas⁵, Dr. José Carlos Pérez Sánchez⁵, Dr. Manuel Almendro Delia⁶, Dr. Cristina Jiménez Hidalgo⁶, Dr. Gonzalo Barón⁷, Dr. Silvia Gómez Moreno⁷, Dr. Antonio Fernández⁷, Dr. Lorena García Riesco⁷, Dr. María Laura García Pérez⁸, Dr. José Rozado Castaño⁸, Dr. Jorge Álvarez⁹, Dr. Tomas Ripoll Vera⁹, Dr. Joan Torres Marqués⁹, Dr. Juana Núñez Morcillo⁹, Dr. Marcos Rodríguez Esteban¹⁰, Dr. José Alejandro Medina García¹⁰, Dr. César Sosa¹⁰, Dr. Javier Mesa Fumero¹⁰, Dr. Daniel García Fuertes¹¹, Dr. Manuel Crespín Crespín¹¹, Dr. Inmaculada Coca Prieto¹¹, Dr. José Gonzalo Delgado Díaz-Benito¹¹, Dr. Elena Villanueva Fernández¹¹, Dr. Teresa Cano Mozo¹², Dr. José Luis Moriñigo Muñoz¹², Dr. Ana Martín García¹², Dr. Jesús Manuel Hernández Hernández¹², Dr. Imanol Otaegui¹³, Dr. Jordi Pérez Rodón¹³, Dr. Jaume Francisco Pascual¹³, Dr. Neus Bellera Gotarda¹³, Dr. Eulalia Roig Minguell¹⁴, Dra. Sonia Mirabet Pérez¹⁴, Dr. Vicens Brossa¹⁴, Dr. Laura López¹⁴, Dr. Nicolás Manito Lorite¹⁵, Dr. Ignasi Anguera Camos¹⁵, Dr. David Chivite Guillén¹⁵, Dr. Jorge Antonio Morales Álvarez¹⁶, Dr. Andrés, Fernández Gasalia¹⁶, Dr. Neus Piulats Egea¹⁶, Dr. Josep Casas Rodríguez¹⁶, Dr. Óscar Alcaide¹⁷, Dr. Roger Villuendas¹⁷, Dr. Áxel Sarrias¹⁷, Dr. Mar Domingo¹⁷, Dr. Ramón de Castro¹⁸, Dr. Nuria

Farré¹⁸, Dr. Isabel Serrano Rodríguez¹⁸, Dr. Ingrid Colomer¹⁸, Dr. José Moreno Arribas¹⁹, Dr. Vicente Bertomeu González¹⁹, Dr. Bertomeu Martínez¹⁹, Dr. Francisco Ridocci Soriano²⁰, Dr. Rafael Payá Serrano²⁰, Dr. Jose Antonio Madrigal Vilata²⁰, Dr. José Perez Silvestre²⁰, Dr. Juan Cosín Sales²¹, Dr. Francisco Buendía²¹, Dr. Esther Esteban²¹, Dr. Antonio Lillo²¹, Dr. Dolores Marco Macian²¹, Dr. Yolanda Porrás Ramos²², Dr. M^a Victoria Mongollón Jiménez²², Dr. Pilar Marón Ramos²³, Dr. Alfonso Varela Román²³, Dr. Antonio Pose Reino²³, Dr. Manuel Suárez Tembra²³, Dr. Manuel Lado López²³, Dr. Carlos González Juanatey²⁴, Dr. Inmaculada Roldán²⁵, Dr. Carlos Escobar Cervantes²⁵, Dr. Marta Mateos García²⁵, Dr. M^a Angustias Quesada Simón²⁵, Dr. José Camacho Siles²⁵, Dr. Paloma Eviro García²⁵, Dr. Manuel Martínez Sellés²⁶, Dr. Tomás Datino²⁶, Dr. M^a Teresa Vidán²⁶, Dr. Luis Cornide²⁶, Dr. Pablo García Pavía²⁷, Dr. Marta M^a Cobo Marcos²⁷, Dr. David Vivas²⁸, Dr. Javier Higuera Nafria²⁸, Dr. José Manuel Rubio Campal²⁹, Dr. Pepa Sánchez Borque²⁹, Dr. Francisco Marín Ortuño³⁰, Dr. Miguel García Navarro³⁰, Dr. Raquel Pérez Luján³⁰, Dr. Mariano Leal Hernández³⁰, Dr. Sergio Manzano Fernández³⁰, Dr. Diego Giménez Cervantes³¹, Dr. Francisco José García Amargo³¹, Dr. Manuel González Ortega³¹, Dr. Milagros Gil Ortega³¹, Dr. Nekane Murga Eizagahevarría³², Dr. Esther Recalde³².

Centers: ¹Ciudad de Jaén Hospital, Jaén, Spain. ²Reina Sofía Hospital, Córdoba, Spain. ³Infanta Margarita Hospital, Cabra, Córdoba, Spain. ⁴Costa del Sol Hospital, Marbella, Spain. ⁵Virgen de la Victoria Hospital, Málaga, Spain. ⁶Virgen Macarena Hospital, Sevilla, Spain. ⁷Virgen del Rocío Hospital, Sevilla, Spain. ⁸Central de Asturias Hospital, Asturias, Spain. ⁹Son Llàzer Hospital, Baleares, Spain. ¹⁰Candelaria Hospital, Canarias, Spain. ¹¹Santa Bárbara Hospital, Ciudad Real, Spain. ¹²Clínico de Salamanca Hospital,

Salamanca, Spain. ¹³Vall d'Hebrón Hospital, Barcelona, Spain. ¹⁴Sant Pau Hospital, Barcelona, Spain. ¹⁵Universitari de Bellvitge Hospital, Barcelona, Spain. ¹⁶Del Mar Hospital, Barcelona, Spain. ¹⁷Germans Trias, Barcelona, Spain. ¹⁸Juan XXIII, Tarragona, Spain. ¹⁹San Juan de Alicante Hospital, San Juan, Spain. ²⁰General Hospital, Valencia, Spain. ²¹Arnau de Vilanova Hospital, Valencia, Spain. ²² Cáceres Hospital, Cáceres, Spain. ²³Clínico de Santiago de Compostela, Galicia, Spain. ²⁴Universitario Lucus Augusti Hospital, Galicia, Spain. ²⁵La Paz Hospital, Madrid, Spain. ²⁶Gregorio Marañón Hospital, Madrid, Spain. ²⁷Puerta de Hierro Hospital, Madrid, Spain. ²⁸Clínico San Carlos, Madrid, Spain. ²⁹Fundación Jiménez Díaz Hospital, Madrid, Spain. ³⁰Virgen de la Arrixaca Hospital, Murcia, Spain. ³¹Morales Meseguer Hospital, Murcia, Spain. ³²Basurto Hospital, Vizcaya, Spain

Table S1. Quality of antivitamin k control stratified by BMI.

	Normal weight (BMI < 25 kg/m ²)	Overweight (BMI 25-30 kg/m ²)	Obese (BMI ≥ 30 kg/m ²)	p value
N	266	643	574	
TTR Rosendaal (mean ± SD), %	61.1 ± 19.4	62.5 ± 20.7	63.1 ± 19.2	0.42
TTR < 65% (%)	55.7	52.4	51.1	0.52
TTR < 70% (%)	64.1	62	62.2	0.87

BMI: body mass index; SD: standard deviation; TTR: time in the therapeutic range.

Table S2. Univariate Cox regression.

Total mortality	HR	95% CI		p value
BMI (reference <30 kg/m ²)	0.81	0.62	1.05	0.10
Female sex	0.79	0.61	1.02	0.12
Age, per year	1.09	1.07	1.11	<0.01
Arterial hypertension	1.80	1.25	2.60	<0.01
Diabetes mellitus	1.60	1.24	2.07	<0.01
Dyslipidemia	1.02	0.79	1.30	0.90
Coronary artery disease	1.80	1.37	2.37	<0.01
Heart failure	2.37	1.85	3.03	<0.01
Aortic valve disease	1.49	0.96	2.31	0.07
Chronic kidney failure	2.77	2.13	3.61	<0.01
Charlson index	1.48	1.36	1.62	<0.01
Cerebrovascular disease	1.25	0.92	1.70	0.16
CHA2DS2-VASc	1.39	1.29	1.50	<0.01
HAS-BLED	1.69	1.52	1.50	<0.01
Stroke	HR	95% CI		p value
BMI (reference <30 kg/m ²)	0.99	0.54	1.80	0.97
Female sex	0.76	0.42	1.39	0.37
Age, per year	1.02	0.56	1.89	0.27
Arterial hypertension	1.42	0.63	3.18	0.40
Diabetes mellitus	1.03	0.54	1.97	0.93
Dyslipidemia	1.21	0.67	2.18	0.53

Coronary artery disease	1.97	1.03	3.75	0.04
Heart failure	2.21	1.22	3.99	<0.01
Aortic valve disease	0.76	0.18	3.12	0.69
Chronic kidney failure	2.26	1.23	4.17	<0.01
Charlson index	1.36	1.09	1.70	<0.01
Cerebrovascular disease	2.57	1.38	4.79	<0.01
CHA2DS2-VASc	1.33	1.11	1.60	<0.01
HAS-BLED	1.52	1.17	1.96	<0.01
Major bleeding	HR	95% CI		p value
BMI (reference <30 kg/m ²)	0.80	0.57	1.14	0.22
Female sex	0.96	0.69	1.33	0.81
Age, per year	1.03	1.01	1.05	<0.01
Arterial hypertension	1.11	0.73	1.68	0.62
Diabetes mellitus	1.52	1.08	2.13	0.02
Dyslipidemia	0.67	0.48	0.93	0.02
Coronary artery disease	1.33	0.90	1.97	0.15
Heart failure	1.57	1.12	2.20	<0.01
Aortic valve disease	1.14	0.60	2.17	0.69
Chronic kidney failure	1.98	1.42	2.78	<0.01
Charlson index	1.32	1.17	1.49	<0.01
Cerebrovascular disease	1.47	1.00	2.17	0.05
CHA2DS2-VASc	1.24	1.12	1.38	<0.01
HAS-BLED	1.47	1.27	1.70	<0.01

MACE	HR	95% CI		p value
BMI (reference <30 kg/m ²)	0.91	0.66	1.24	0.54
Female sex	0.90	0.66	1.22	0.49
Age, per year	1.06	1.04	1.08	<0.01
Arterial hypertension	1.52	0.99	2.33	0.06
Diabetes mellitus	2.06	1.51	2.80	<0.01
Dyslipidemia	1.49	1.09	2.04	0.01
Coronary artery disease	2.80	2.05	3.84	<0.01
Heart failure	2.73	2.01	3.69	<0.01
Aortic valve disease	2.20	1.38	3.52	<0.01
Chronic kidney failure	2.46	1.79	3.38	<0.01
Charlson index	1.52	1.36	1.69	<0.01
Cerebrovascular disease	1.39	0.96	2.01	0.08
CHA2DS2-VASc	1.45	1.32	1.59	<0.01
HAS-BLED	1.60	1.40	1.82	<0.01

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

Table S3. Event rates for subgroups, stratified by BMI.

	Normal weight		Overweight		Obese		
	(BMI < 25 kg/m ²)		(BMI 25-30 kg/m ²)		(BMI ≥ 30 kg/m ²)		
	N = 358		N = 871		N = 727		
	Annual		Annual		Annual		
	rate		rate		rate		p
	n	(%/year)	n	(%/year)	n	(%/year)	value
All-cause mortality							
Age							
< 65 years	4	(2.83)	5	(1.32)	4	(0.91)	0.23
65-75 years	9	(2.75)	31	(3.47)	25	(8.33)	0.80
> 75 years	39	(6.44)	83	(6.19)	55	(6.03)	0.93
Sex							
Women	19	(3.79)	44	(2.54)	35	(3.44)	0.68
Men	33	(5.76)	75	(4.84)	49	(4.21)	0.32
MACE							
Age							
< 65 years	4	(2.83)	6	(1.59)	6	(1.37)	0.53

65-75	5	(1.53)	21	(2.35)	23	(2.77)	0.47
years							
> 75	15	(2.48)	57	(4.25)	31	(3.40)	0.12
years							
<i>Sex</i>							
Women	12	(2.39)	27	(2.54)	31	(3.05)	0.70
Men	12	(2.09)	57	(3.67)	29	(2.49)	0.07

BMI: body mass index; MACE: major adverse cardiovascular events (composite of ischemic stroke, myocardial infarction and cardiovascular and total mortality).