Effect of Body Mass Index on Ischemic and Bleeding Events in Patients Presenting With Acute Coronary Syndromes (from the START-ANTIPLATELET Registry)

Paolo Calabrò, MD, PhD[a,b,*], Elisabetta Moscarella, MD[a,b], Felice Gragnano, MD[a,b], Arturo Cesaro, MD[a,b], Pia Clara Pafundi, PhD[c], Giuseppe Patti, MD[d,e], Ilaria Cavallari, MD[e], Emilia Antonucci, MD[f], Plinio Cirillo, MD[g], Pasquale Pignatelli, MD[h], Gualtiero Palareti, MD[f], Ferdinando Carlo Sasso, MD, PhD[c], Vittorio Pengo, MD[i], Paolo Gresele, MD[j], Rossella Marcucci, MD[k], the START-ANTIPLATELET collaborators, Marzia Conte[l], Fabio Fimiani[l], Luigi Di Serafino, MD[m], Maurizio del Pinto, MD[n], Gentian Denas, MD[o], Daniele Pastori, MD[p], Camilleri Eleonora, MD[q], and Tiziana Fierro, MD[n]

The protective effect of obesity on mortality in acute coronary syndromes (ACS) patients remains debated. We aimed at evaluating the impact of obesity on ischemic and bleeding events as possible explanations to the obesity paradox in ACS patients. For the purpose of this substudy, patients enrolled in the START-ANTIPLATELET registry were stratified according to body mass index (BMI) into 3 groups: normal, BMI <25 kg/m^2; overweight, BMI: 25 to 29.9 kg/m^2; obese, BMI ≥30 kg/m^2. The primary end point was net adverse clinical end points (NACE), defined as a composite of all-cause death, myocardial infarction, stroke, and major bleeding. In n = 1,209 patients, n = 410 (33.9%) were normal, n = 538 (44.5%) were overweight and n = 261 (21.6%) were obese. Compared to the normal weight group, obese and overweight patients had a higher prevalence of cardiovascular risk factors but were younger, with a better left ventricular ejection fraction and lower PRECISE-DAPT score. At 1-year follow-up net adverse clinical endpoints was more frequently observed in normal than in overweight and obese patients (15.1%, 8.6%, and9.6%, respectively; p = 0.004), driven by a significantly higher rate of all-cause death (6.3%, 2.6%, and 3.8%, respectively; p = 0.008), whereas no significant differences were noted in terms of myocardial infarction, stroke, and major bleeding. When correcting for confounding variables, BMI loses its power in independently predicting outcomes, failing to confirm the obesity paradox in a real-world ACS population. In conclusion, our study conflicts the obesity paradox in real-world ACS population, and suggest that the reduced rate of adverse events and mortality in obese patients may be explained by relevant differences in the clinical risk profile and medications rather than BMI per se. **(Am J Cardiol 2019;124:1662−1668)**

In recent decades, obesity has dramatically increased. It is estimated that half of the adults are obese or overweight, as defined by the body mass index (BMI).[1,2] In the general population, obesity is associated with higher cardiovascular morbidity and mortality rate.[3] Nevertheless, it has been shown that obesity can play a protective role in a variety of

[a]Division of Cardiology, A.O.R.N. "Sant'Anna e San Sebastiano", Caserta, Italy; [b]Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy; [c]Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Caserta, Italy; [d]Università degli Studi, L'Aquila, Italy; [e]Dipartimento di Malattie dell'Apparato Cardiovascolare, Policlinico Campus Bio-Medico, Roma, Italy; [f]Arianna Anticoagulazione Foundation, Bologna, Italy; [g]Department of Advanced Biomedical Sciences, School of Medicine, "Federico II" University, Naples, Italy; [h]Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Rome, Italy; [i]Department of Cardiothoracic and Vascular Sciences, University Hospital of Padua, Padua, Italy; [j]Department of Medicine, Division of Internal and Cardiovascular Medicine, University of Perugia, Perugia, Italy; [k]Department of Experimental and Clinical Medicine, Center for Atherothrombotic diseases, University of Florence, Florence, Italy; [l]Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy; [m]Department of Advanced Biomedical Sciences, School of Medicine, "Federico II" University, Naples, Italy; [n]Department of Medicine, Division of Internal and Cardiovascular Medicine, University of Perugia, Perugia, Italy; [o]Department of Cardiothoracic and Vascular Sciences, University Hospital of Padua, Padua, Italy; [p]Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Rome, Italy; and [q]Department of Experimental and Clinical Medicine, Center for Atherothrombotic diseases, University of Florence, Florence, Italy. Manuscript received June 10, 2019; revised manuscript received and accepted August 26, 2019.

See page 1667 for disclosure information.

*Corresponding author: Tel: +39-0823-232395; fax: +39-0823-232395.

E-mail address: paolo.calabro@unicampania.it (P. Calabrò).

0002-9149/
https://doi.org/10.1016/j.amjcard.2019.08.030

disease conditions, such as end-stage chronic renal failure, heart failure (HF) and coronary artery disease (CAD).[4–6] Different studies have also shown this "obesity paradox"[7–10] in obese patients presenting with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI). Several possible explanations have been advanced.[9] However, to date, the association between BMI and other major cardiovascular or bleeding events has not been defined yet. We sought to investigate the impact of BMI on ischemic and bleeding events, and the possible interaction with treatment strategies, in consecutive ACS patients, including unstable angina, non-ST-elevation myocardial infarction and ST-elevation myocardial infarction, enrolled in the START-ANTIPLATELET registry.

Methods

The START-ANTIPLATELET is a branch of the investigators-driven, nonsponsored, START registry (Survey on anticoagulated pAtients RegisTer, NCT02219984),[11] promoted by the Arianna Anticoagulazione Foundation, Bologna. The START ANTIPLATELET is a prospective, real-world registry performed on consecutive patients >18 years, admitted for ACS in seven Italian institutions. No explicit exclusion criteria were applied. Each center identified 2 fixed days for enrolment during the week, and all consecutive patients admitted in those 2 days were included in the registry. All patients underwent a clinical assessment during the hospital stay for the index event (baseline visit), and subsequently at 6 months and 1 year. Results from previous subanalyses have been reported elsewhere.[12–16] For the purpose of this substudy, as a part of the prospective data collection, BMI was calculated using the following formula: BMI = body weight (in kg)/square of stature (height, in meters).[17] Patients were stratified into 3 BMI-groups[18]: normal, BMI <25 kg/m^2; overweight, BMI: 25 to 29.9 kg/m^2; obese, BMI ≥30 kg/m^2.

The primary end point was the occurrence of net adverse clinical end points (NACE) defined as a composite of all-cause death, myocardial infarction (MI), stroke, and major bleeding events at follow-up. The secondary end points were major adverse cardiac and cerebral events (MACCE), defined as a composite of all-cause death, MI and stroke, each individual component of NACE and MACCE, cardiovascular death, and any revascularization. MI, cardiovascular death, and all-cause death were defined by the Academic Research Consortium criteria.[19] Coronary revascularization was defined as PCI (with or without stenting) or coronary artery bypass surgery. Stroke was defined as an abrupt onset of a focal neurologic deficit, generally distributed in the territory of a single brain artery (including the retinal artery), lasting more than 24 hours.[20] Major bleeding was classified according to the thrombolysis in myocardial infarction criteria, as intracranial bleeding or clinically overt bleeding associated with a decrease in hemoglobin >5 g/dl.[21] Anemia was defined as hemoglobin <11.5 g/dl for females, and <12.5 g/dl for males. Clinical, angiographic, procedural characteristics, and 1-year outcomes were analyzed stratified by BMI-group (normal vs overweight vs obese).

Data are shown as either mean and SD or median and interquartile range, in the case of continuous variables and number and percentage, for categorical variables. The normal/not normal distribution was preliminarily assessed through a Kolmogorov-Smirnov Goodness-of-Fit K-S test. Categorical data were compared using either the Pearson Chi-square test (with Mantel-Haenszel common odds ratio estimate) or Fisher exact test when indicated, and continuous variables by nonparametric Mann-Whitney *U* test or Kruskal-Wallis test, as appropriate. All the analyses were stratified according to BMI groups. Cumulative event rates were estimated by the Kaplan-Meier method and compared using the log-rank test, hazard ratios and 95% confidence intervals were calculated. A multivariable Cox regression model for NACE was performed, correcting for those clinical variables significantly different between groups. Variables significant in the univariate analysis at a p level of 0.15 were entered in the multivariable model using a backward stepwise selection approach with a threshold then set at 0.1". A 2-sided p value <0.05 was considered as statistically significant. All analyses were performed with the SPSS software (IBM, Armonk, New York), version 24 and R software (CRAN 3.3.4).

Results

A total of 1,209 patients have been enrolled. BMI calculation was available for all patients. According to BMI values, patients were classified as follows: 410 (33.9%) normal, 538 (44.5%) overweight, and 261 (21.6%) obese. Baseline clinical and demographic characteristics are depicted in Table 1. Compared with the normal weight group, obese, and overweight patients had a worse cardiovascular risk profile but were more frequently females, younger, and showed lower bleeding risk profile with better left ventricular ejection fraction (LVEF) and renal function, a lower rate of anemia, thrombocytopenia, and atrial fibrillation. Indeed, PRECISE DAPT score[22] for the bleeding risk was significantly higher in normal-weight patients compared with the other groups.

At median follow-up time of 12.6 months (interquartile range 11.7 to 12.3) NACE rate was more frequently observed in normal-weight than in overweight and obese patients (respectively, 15.1% vs 8.6% vs 9.6, p = 0.004), as well as MACCE rate (13.7% vs 7.1% vs 9.2%, p = 0.003), both mainly driven by a significantly higher rate of all-cause death in normal-weight patients compared with other groups (6.3% vs 2.6% vs 3.8%, p = 0.008) (Table 2). Cardiovascular death rate was significantly higher in normal-weight patients compared with the other groups, and mainly driven by sudden arrhythmic death and end-stage chronic HF, whereas no differences were noted in terms of MI, stroke, major bleeding or repeat revascularization Figure 1 shows the Kaplan-Meier curves at 1-year follow-up for NACE. The unadjusted correlation between BMI and NACE is shown in Figure 2. After adjusting for confounding variables by multivariable Cox regression model, BMI loses its significance in predicting NACE whereas LVEF <40%, PRECISE-DAPT score, and hypertension, remained independent predictors of NACE.

Discussion

The main findings of our study can be summarized as follows: (1) in consecutive ACS patients a significantly

Table 1
Baseline, treatment and procedural characteristics

Variable	Total (n = 1,209)	Body mass index (Kg/m^2) <25 (n = 410)	≥25 <30 (n = 538)	≥30 (n = 261)	p Value
Body mass index (Kg/m^2; median [IQR])	26.4 [24.2 − 29.4]	23.4 [22 − 24.2]	27.1 [26 − 28.4]	32.7[31 − 34.4]	<0.001
Age (years, median [IQR])	66 [57.5 − 75]	68.5 [60 − 77]	66 [58 − 75]	64 [54 − 72.5]	<0.001
Male	878 (72.6%)	279 (68.0%)	421 (78.3%)	178 (68.2%)	<0.001
Arterial hypertension	880 (72.8%)	284 (69.3%)	390 (72.5%)	206 (78.9%)	0.023
Smoker	605 (50.0%)	206 (50.2%)	265 (49.3%)	134 (51.3%)	0.854
Diabetes mellitus	326 (27.0%)	88 (21.5%)	144 (26.8%)	94 (36.0%)	<0.001
Insulin treatment	31 (2.6%)	7 (1.7%)	14 (2.6%)	10 (3.8%)	0.263
Hyperlipidaemia*	653 (54.0%)	196 (47.8%)	307 (57.1%)	150 (57.5%)	0.008
Chronic kidney disease (estimated Glomerular filtration rate <50 ml/min)	199 (16.5%)	107 (26.1%)	72 (13.4%)	20 (7.7%)	<0.001
Family history of coronary artery disease	366 (30.3%)	118 (28.8%)	162 (30.1%)	86 (33.0%)	0.515
Previous myocardial infarction	229 (18.9%)	77 (18.8%)	95 (17.7%)	57 (21.8%)	0.366
Previous percutaneous coronary intervention (PCI)	236 (10.5%)	73 (17.8%)	105 (19.5%)	58 (22.2%)	0.371
Previous major bleeding	22 (1.8%)	12 (2.9%)	6 (1.1%)	4 (1.5%)	0.109
Previous minor bleeding	7 (0.6%)	1 (0.2%)	3 (0.6%)	3 (1.1%)	0.320
Previous transient ischemic attack	34 (2.8%)	15 (3.7%)	11 (2.0%)	8 (3.1%)	0.317
Previous ischemic stroke	42 (3.5%)	22 (5.4%)	12 (2.2%)	8 (3.1%)	0.030
Peripheral artery disease	90 (7.4%)	25 (6.1%)	35 (6.5%)	30 (11.5%)	0.042
Carotid stenosis	271 (22.4%)	82 (20.0%)	123 (22.9%)	66 (25.3%)	0.415
Multivessel coronary artery disease	145 (12.0%)	49 (12.0%)	62 (11.5%)	34 (13.0%)	0.165
Left ventricular ejection fraction	49 [42 − 55]	48 [40 − 54.8]	50 [44 − 55%]	48 [43 − 54]	0.062
Left ventricular ejection fraction <40%	181 (15.0%)	81 (19.8%)	67 (12.5%)	33 (12.6%)	0.004
Chronic heart failure	25 (2.1%)	10 (2.4%)	9 (1.7%)	6 (2.3%)	0.107
Conditions requiring oral anticoagulation therapy					
Atrial fibrillation	113 (9.3%)	51 (12.4%)	43 (8.0%)	19 (7.3%)	0.029
Nonvalvular atrial fibrillation	100 (8.3%)	46 (11.2%)	38 (7.1%)	16 (6.1%)	0.026
Valve prosthesis	8 (0.7%)	4 (1.0%)	4 (0.7%)	0 (0%)	0.300
Pulmonary hypertension	3 (0.2%)	1 (0.2%)	2 (0.4%)	0 (0%)	0.615
Ventricular thrombosis	9 (0.7%)	4 (1.0%)	3 (0.6%)	2 (0.8%)	0.759
Venous thromboembolism	11 (0.9%)	5 (1.2%)	5 (0.9%)	1 (0.4%)	0.538
Anemia†	222 (18.4%)	94 (22.9%)	88 (16.4%)	40 (15.3%)	0.013
hematocrit	41.4 [37.8 − 44.6]	40.5 [36.8 − 43.5]	41.5 [38.2 − 44.6]	42.6 [39.2 − 45.4]	<0.001
Platelets <100.000 (mm^3)	19 (1.6%)	8 (2.0%)	11 (2.0%)	0 (0%)	0.05
Creatinine	0.9 [0.8 − 1.1]	0.9 [0.78 − 1.1]	0.9 [0.8 − 1.1]	0.9 [0.79 − 1.1]	0.571
Creatinine clearance	80 [59 − 107]	65.5 [48 − 90]	83.5 [64 − 104.3]	104 [77 − 137]	<0.001
Clinical presentation					
• Unstable angina patients	147 (12.2%)	45 (11.0%)	75 (13.9%)	27 (10.3%)	0.254
• NSTEMI patients	423 (35.0%)	147 (35.9%)	174 (32.3%)	102 (39.1%)	
• STEMI patients	639 (52.9%)	218 (53.2%)	289 (53.7%)	132 (50.6%)	
PRECISE DAPT Score	16 [6 − 28]	22 [12 − 34]	16 [7 − 27]	10 [3 − 20.5]	<0.001
PRECISE DAPT score ≥25	381 (31.5%)	179 (43.7%)	152 (28.3%)	50 (19.2%)	<0.001
Therapy for the index event					
Medical therapy	168 (13.9%)	64 (15.6%)	74 (13.8%)	30 (11.5%)	0.321
Coronary bypass	25 (2.1%)	10 (2.4%)	13 (2.4%)	2 (0.8%)	0.248
PCI	1031 (85.3%)	347 (84.6%)	460 (85.5%)	224 (85.8%)	0.896
Stent use	978 (94.9%)	326 (93.9%)	444 (96.5%)	208 (92.9%)	0.080
Drug-eluting Stent	938 (91.0%)	310 (89.3%)	429 (93.3%)	199 (88.8%)	0.185
Multivessel PCI	111 (10.8%)	33 (9.5%)	44 (9.6%)	34 (15.2%)	0.136
Therapy at discharge					
Proton-pump inhibitors	1173 (97%)	398 (97.1%)	527 (98.0%)	248 (95.0%)	0.072
Acetylsalicylic acid	1185 (98.0%)	398 (97.1%)	533 (99.1%)	254 (97.3%)	0.061
Clopidogrel	369 (30.5%)	134 (32.7%)	162 (30.1%)	73 (28.0%)	0.417
Ticagrelor	623 (51.5%)	207 (50.5%)	276 (51.3%)	140 (53.6%)	0.721
Prasugrel	153 (12.7%)	41 (10.0%)	75 (13.9%)	37 (14.2%)	0.138
Oral anticoagulation	114 (9.4%)	49 (12.0%)	46 (8.6%)	19 (7.3%)	0.084
• New oral anticoagulants (OAT)	25 (2.1%)	11 (2.7%)	6 (1.1%)	8 (3.1%)	0.108
Dual antiplatelet therapy (DAPT)	1128 (93.3%)	375 (91.5%)	509 (94.6%)	244 (93.5%)	0.157
Triple therapy (DAPT+ OAT)	89 (7.4%)	34 (8.3%)	40 (7.4%)	15 (5.7%)	0.467

(*continued*)

Table 1 (***Continued***)

Variable	Total (n = 1,209)	Body mass index (Kg/m^2) <25 (n = 410)	≥25 <30 (n = 538)	≥30 (n = 261)	p Value
Angiotensin converting enzyme inhibitor/Sartans	795 (65.8%)	232 (56.6%)	370 (68.8%)	193 (73.9%)	<0.001
Beta-blockers	829 (68.6%)	268 (65.4%)	375 (69.7%)	186 (71.3%)	0.207
Statins	1163 (96.2%)	392 (95.6%)	521 (96.8%)	250 (95.8%)	0.573
Proprotein convertase subtilisin/kexin type 9 inhibitors	9 (0.7%)	1 (0.2%)	4 (0.7%)	4 (1.5%)	0.112

NSTEMI = non ST-elevation miocardial infarction; STEMI = ST-elevation myocardial infarction.
* Defined as total Cholesterol >240 mg/dl.
† Defined as hemoglobin <12.5 g/dl if men and <11.5 g/dl if women.

Table 2
One-year clinical outcomes

Variable	Total (n = 1,209)	Body mass index (Kg/m^2) <25 (n = 410)	≥25 <30 (n = 538)	≥30 (n = 261)	p Value
NACE	133 (11.0%)	62 (15.1%)	46 (8.6%)	25 (9.6%)	0.004
MACCE	118 (9.8%)	56 (13.7%)	38 (7.1%)	24 (9.2%)	0.003
• All cause death	84 (6.9%)	41 (10.0%)	26 (4.8%)	17 (6.5%)	0.008
• Cardiovascular death	50 (4.1%)	26 (6.3%)	14 (2.6%)	10 (3.8%)	0.016
• Myocardial Infarction	43 (3.6%)	19 (4.6%)	14 (2.6%)	10 (3.8%)	0.238
• Revascularization	22 (1.8%)	4 (1.0%)	13 (2.4%)	5 (1.9%)	0.257
• Stroke	9 (0.7%)	5 (1.2%)	2 (0.4%)	2 (0.8%)	0.322
• Major bleeding	24 (2.0%)	9 (2.2%)	11 (2.0%)	4 (1.5%)	0.828
Dual antiplatelet therapy at follow-up					
Acetylsalicylic Acid at follow-up	1114 (92.1%)	376 (91.5%)	504 (93.7%)	235 (90%)	0.245
Clopidogrel at follow-up	270 (22.3%)	98 (23.9%)	116 (21.6%)	56 (21.5%)	0.579
Prasugrel at follow-up	74 (6.1%)	15 (3.7%)	36 (6.7%)	23 (8.8%)	0.044
Ticagrelor at follow-up	355 (29.4%)	117 (28.5%)	161 (29.9%)	77 (29. %5)	0.709
DAPT Duration					0.215
• Never done	74 (6.1%)	31 (7.6%)	28 (5.2%)	15 (5.8%)	
• <30 days	19 (1.6%)	9 (2.2%)	7 (1.3%)	3 (1.2%)	
• ≥30-days <6 months	58 (4.8%)	29 (7.1%)	18 (3.3%)	11 (4.2%)	
• ≥6 months <1-year	261 (21.7%)	85 (20.9%)	115 (21.4%)	61 (24.5%)	
• 1 year	731 (60.7%)	232 (57.0%)	342 (63.6%)	157 (60.4%)	
• >1 year	62 (5.1%)	21 (5.2%)	28 (5.2%)	13 (5.0%)	
DAPT ≥1 year	793 (65.8%)	253 (62.2%)	370 (68.8%)	170 (65.4%)	0.075

NACE = net adverse clinical end points, defined as a composite of all-cause death, myocardial infarction, stroke, and major bleeding events.
MACCE = major adverse cardiac and cerebral events, defined as a composite of all-cause death, myocardial infarction, and stroke.

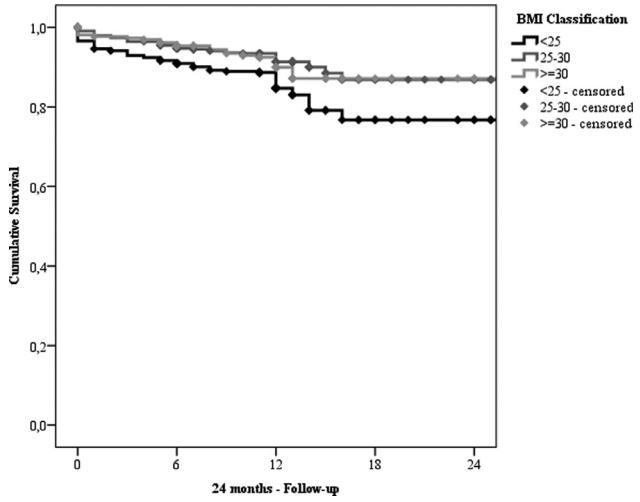

Figure 1. Kaplan-Meier curves at 2-years follow-up showing the incidence of the net adverse clinical endpoints (NACE) between body mass index (BMI) groups.

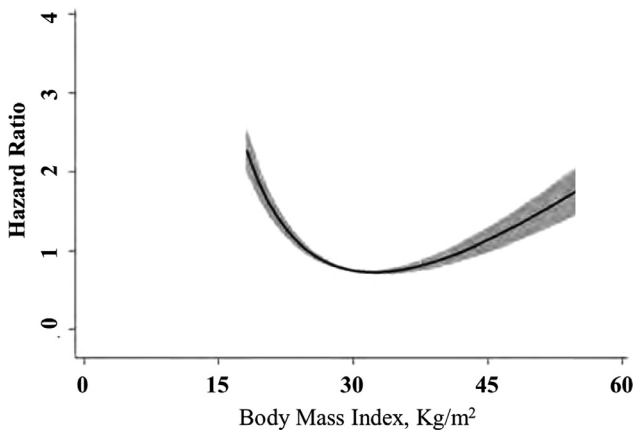

Figure 2. Cox proportional hazards regression (95% CI, *shaded area*) with continuous risk relationship between body mass index (BMI) and net adverse clinical endpoints (NACE)

higher rate of NACE and MACE was observed in normal-weight compared with overweight and obese patients, mainly driven by a higher rate of all-cause and cardiovascular death; (2) when correcting for confounding variables, BMI loses its power in independently predicting outcomes, failing to confirm the obesity paradox in a real-world ACS population.

In the general population, obesity is associated with a higher frequency of cardiovascular risk factors and increased mortality.[3] Nevertheless, once CAD has been established a protective role of obesity on mortality has been described, but the potential mechanisms underlying this phenomenon remain controversial. A large registry[7] including ACS patients, provided data in favor of the obesity paradox concept. However, authors were not able to provide an evident explanation for this paradox. A large individual metanalysis[9] confirmed the obesity paradox in ACS patients and also showed that obese categories were associated with a significantly lower risk of bleeding and refractory ischemia. In partial agreement with previous studies, our analysis shows a lower rate of fatality in overweight and obese patients. However, our results do not support the obesity paradox, questioning the role of BMI as an independent predictor of outcomes in real-world ACS patients. For the first time, our study prospectively investigates the impact of BMI on both ischemic and bleeding events in ACS patients offering further insights into this controversial phenomenon. We can speculate that the obesity paradox may be a consequence of several confounders present in the obese population. Indeed, when correcting for potential confounding factors, BMI loses its significance as predictor of NACE. As previously reported, we found in overweight and obese patients a higher prevalence of cardiovascular risk factors that together with their younger age suggest for an earlier acute presentation of atherosclerotic disease, potentially due to a more aggressive disease phenotype. This high ischemic risk was accompanied by a low bleeding risk as expressed by their younger age and a lower rate of anemia, chronic renal failure, thrombocytopenia, and conditions requiring oral anticoagulation therapy. Accordingly, the PRECISE DAPT score was significantly lower in overweight and obese patients in our population. This was followed by a significantly higher use of new more potent P2Y12 inhibitors in the obese group, and a numerically (albeit not statistically significant) higher rate of prolonged DAPT over 1 year in overweight and obese patients, potentially resulting in a more pronounced platelet inhibition in these patients that are deemed to have enhanced platelet reactivity and altered response to antiplatelet agents.[23] Of note, this was also complemented by more aggressive use of antihypertensive and antiremodeling medications, with a significantly higher prescription of ACE inhibitors or sartans. These factors potentially translated in a more efficient ischemic protection, without any increase of major bleeding occurrence. This is in line with a recent study[24] showing that patients without high bleeding risk features are those who benefit most of a prolonged DAPT, and that the ischemic protection offered by long-term DAPT tends to be greater in high ischemic risk patients such as those presenting with ACS.

Another explanation for the reduced mortality is in the lower rate of LV dysfunction in obese categories. In ACS patients, severe LVEF reduction at admission is a strong independent predictor mortality and MACE.[25–27] Indeed, patients with poor LV function are less able to tolerate hemodynamic instability and are more likely to experience progressive HF, arrhythmic deaths, and major bleeding after PCI.[25] It had been supposed that obesity might protect against malignant arrhythmias. However, according to our results, the obesity protection against sudden arrhythmic death is more likely to be related with the better LV function rather than having its own protective effect.

Unfortunately, underweight patients (BMI <18.5 Kg/m^2) had a low prevalence in our study (7 patients, 0.6%) and were analyzed together with normal-weight patients. Thus, no conclusions can be drawn for this subgroup. Underweight patients are at increased risk of both spontaneous and periprocedural bleeding during PCI.[28,29] Underweight is associated with malnutrition, cachexia, depression, and advanced age.[30] The higher frailty of these patients might be a consequence of less aggressive pharmacological treatment with lower ischemic protection and subsequent increased cardiovascular mortality. Moreover, the potential effect of malnutrition and cachexia on all-cause mortality should also be considered. This is in line with a recent study[31] showing that in consecutive ACS patients, cardiac mortality was similar across BMI subgroups while noncardiac mortality was significantly higher in low BMI patients (<20 Kg/m^2) compared with other groups after adjustment for confounders.

This is a substudy of the START ANTIPLATELET registry. The observational design of the study limits our conclusions. BMI was calculated during the index event but was not reassessed during the follow-up. Our registry enrolled consecutive ACS patients presenting in 2 fixed days per week. This selection criterion might be the cause of a higher rate of ST-elevation myocardial infarction compared with NSTE-ACS and a low rate of multivessel disease, and then of the relatively lower events rate than expected in a real-world ACS population. The extension of CAD was assessed based on the presence of single-vessel versus multivessel disease at coronary angiography. Although a more detailed evaluation of coronary lesions complexity (as by using the SYNTAX score) would have been of value for a more accurate definition of patients' ischemic risk, these data were not available in our dataset. Our analysis does not take into account the difference between peripheral versus abdominal obesity or waist circumference. Although the use of radial rather the femoral access is associated with a significant reduction in major bleeding complications,[32,33] our database did not provide information on the access site used, which would have added important data to our analysis. Bleeding risk was only assessed by the PRECISE-DAPT score, while additional bleeding risk scores (such as CRUSADE, ACUITY or HAS-BLED) were not calculated for the absence of required data in the study dataset.

In conclusion, our study conflicts the obesity paradox in real-world ACS population, not confirming an independent association between BMI and adverse outcomes after confounders adjustment. Our results suggest that the better

outcomes in obese patients may be related to a more favorable clinical profile (rather than the BMI per se) that may confer protection against adverse events, and prompt the treating physicians toward a more aggressive secondary prevention treatment, including a more intense and prolonged antiplatelet therapy.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.08.030.

1. Ortega FB, Lavie CJ, Blair SN. Obesity and cardiovascular disease. *Circ Res* 2016;118:1752–1770. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27230640. Accessed February 1, 2019.
2. Rosenbaum M, Leibel RL, Hirsch J. Obesity. *N Engl J Med* 1997;337:396–407. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9241130. Accessed February 1, 2019.
3. Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB. Years of life lost due to obesity. *JAMA* 2003;289:187–193. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12517229. Accessed February 13, 2019.
4. Degoulet P, Legrain M, Réach I, Aimé F, Devriès C, Rojas P, Jacobs C. Mortality risk factors in patients treated by chronic hemodialysis. *Nephron* 1982;31:103–110. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7121651. Accessed February 6, 2019.
5. Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. *Am Heart J* 2008;156:13–22. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18585492. Accessed February 6, 2019.
6. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, Mookadam F, Lopez-Jimenez F. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet* 2006;368:666–678. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16920472. Accessed February 6, 2019.
7. Angerås O, Albertsson P, Karason K, Råmunddal T, Matejka G, James S, Lagerqvist B, Rosengren A, Omerovic E. Evidence for obesity paradox in patients with acute coronary syndromes: a report from the Swedish Coronary Angiography and Angioplasty Registry. *Eur Heart J* 2013;34:345–353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22947610. Accessed February 6, 2019.
8. Ellis SG, Elliott J, Horrigan M, Raymond RE, Howell G. Low-normal or excessive body mass index: newly identified and powerful risk factors for death and other complications with percutaneous coronary intervention. *Am J Cardiol* 1996;78:642–646. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8831397. Accessed February 6, 2019.
9. Lamelas P, Schwalm J-D, Quazi I, Mehta S, Devereaux PJ, Jolly S, Yusuf S. Effect of body mass index on clinical events after acute coronary syndromes. *Am J Cardiol* 2017;120:1453–1459. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28916239. Accessed February 4, 2019.
10. Moscarella E, Spitaleri G, Brugaletta S, Sentí Farrarons S, Pernigotti A, Ortega-Paz L, Cequier A, Iñiguez A, Serra A, Jiménez-Quevedo P, Mainar V, Campo G, Tespili M, Heijer P den, Bethencourt A, Vazquez N, Valgimigli M, Serruys PW, Sabaté M. Impact of body mass index on 5-year clinical outcomes in patients with ST−segment elevation myocardial infarction after everolimus-eluting or bare-metal stent implantation. *Am J Cardiol* 2017;120:1460–1466.
11. Antonucci E, Poli D, Tosetto A, Pengo V, Tripodi A, Magrini N, Marongiu F, Palareti G, START-Register. The Italian START-Register on Anticoagulation with Focus on Atrial Fibrillation. *PLoS One* 2015;10:e0124719. Available at: http://dx.plos.org/10.1371/journal.pone.0124719. Accessed February 8, 2019.
12. Patti G, Ricottini E, Nenna A, Cavallari I, Antonucci E, Calabrò P, Cirillo P, Gresele P, Palareti G, Pengo V, Pignatelli P, Bisignani A, Marcucci R. Impact of chronic renal failure on ischemic and bleeding events at 1 year in patients with acute coronary syndrome (from the Multicenter START ANTIPLATELET Registry). *Am J Cardiol* 2018;122:936–943. Available at: http://www.ncbi.nlm.nih.gov/pubmed/30057232. Accessed March 8, 2019.
13. Cirillo P, Serafino L Di, Patti G, Antonucci E, Calabrò P, Gresele P, Palareti G, Pengo V, Pignatelli P, Marcucci R. Gender-related differences in antiplatelet therapy and impact on 1-year clinical outcome in patients presenting with ACS: the START ANTIPLATELET Registry. *Angiology* 2019;70:257–263. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29969919. Accessed March 11, 2019.
14. Patti G, Cavallari I, Antonucci E, Calabrò P, Cirillo P, Gresele P, Palareti G, Pengo V, Pignatelli P, Ricottini E, Marcucci R. Prevalence and predictors of dual antiplatelet therapy prolongation beyond one year in patients with acute coronary syndrome. *PLoS One* 2017;12:e0186961. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29059255. Accessed March 11, 2019.
15. Calabrò P, Gragnano F, Maio M Di, Patti G, Antonucci E, Cirillo P, Gresele P, Palareti G, Pengo V, Pignatelli P, Pennacchi M, Granatelli A, Servi S De, Luca L De, Marcucci R, for EYESHOT Study and Start Antiplatelet Register. Epidemiology and management of patients with acute coronary syndromes in contemporary real-world practice: evolving trends from the EYESHOT Study to the START-ANTIPLATELET Registry. *Angiology* 2018;69:795–802. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29544348. Accessed March 8, 2019.
16. Marcucci R, Patti G, Calabrò P, Gori AM, Grossi G, Cirillo P, Pengo V, Gresele P, Pignatelli P, Antonucci E, Mario C di, Valente S, Palareti G. Antiplatelet treatment in acute coronary syndrome patients: real-world data from the START-Antiplatelet Italian Registry. *PLoS One* 2019;14:e0219676. Available at: http://www.ncbi.nlm.nih.gov/pubmed/31306454. Accessed August 19, 2019.
17. Eckel RH, Krauss RM. American Heart Association call to action: obesity as a major risk factor for coronary heart disease. AHA Nutrition Committee. *Circulation* 1998;97:2099–2100. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9626167. Accessed February 8, 2019.
18. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, Hu FB, Hubbard VS, Jakicic JM, Kushner RF, Loria CM, Millen BE, Nonas CA, Pi-Sunyer FX, Stevens J, Stevens VJ, Wadden TA, Wolfe BM, Yanovski SZ, American College of Cardiology/American Heart Association Task Force on Practice Guidelines, Obesity Society. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults. *J Am Coll Cardiol* 2014;63:2985–3023. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24239920. Accessed February 8, 2019.
19. Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, Onuma Y, Morel M, Es G-A van, Zuckerman B, Fearon WF, Taggart D, Kappetein A-P, Krucoff MW, Vranckx P, Windecker S, Cutlip D, Serruys PW, Academic Research Consortium. Standardized end point definitions for coronary intervention trials: the academic research consortium-2 consensus document. *Circulation* 2018;137:2635–2650. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29891620. Accessed August 30, 2018.
20. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ (Buddy), Culebras A, Elkind MSV, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee J-M, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV, American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, Council on Nutrition, Physical Activity and Metabolism. An updated definition of stroke for the 21st century. *Stroke* 2013;44:2064–2089. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23652265. Accessed February 13, 2019.
21. Jolly SS, Cairns JA, Yusuf S, Meeks B, Pogue J, Rokoss MJ, Kedev S, Thabane L, Stankovic G, Moreno R, Gershlick A, Chowdhary S, Lavi S, Niemelä K, Steg PG, Bernat I, Xu Y, Cantor WJ, Overgaard CB, Naber CK, Cheema AN, Welsh RC, Bertrand OF, Avezum A, Bhindi R, Pancholy S, Rao SV, Natarajan MK, Berg JM ten, Shestakovska O, Gao P, Widimsky P, Džavík V, TOTAL Investigators. Randomized trial of primary PCI with or without routine manual thrombectomy. *N Engl J Med* 2015;372:1389–1398. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25853743. Accessed January 31, 2018.

22. Costa F, Klaveren D van, James S, Heg D, Räber L, Feres F, Pilgrim T, Hong M-K, Kim H-S, Colombo A, Steg PG, Zanchin T, Palmerini T, Wallentin L, Bhatt DL, Stone GW, Windecker S, Steyerberg EW, Valgimigli M, PRECISE-DAPT Study Investigators. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet* 2017;389:1025–1034. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28290994. Accessed February 8, 2019.
23. Beavers CJ, Heron P, Smyth SS, Bain JA, Macaulay TE. Obesity and antiplatelets-does one size fit all? *Thromb Res* 2015;136:712–716. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26205154. Accessed August 13, 2019.
24. Costa F, Klaveren D Van, Feres F, James S, Räber L, Pilgrim T, Hong M-K, Kim H-S, Colombo A, Steg PG, Bhatt DL, Stone GW, Windecker S, Steyerberg EW, Valgimigli M. Dual antiplatelet therapy duration based on ischemic and bleeding risks after coronary stenting. *J Am Coll Cardiol* 2019;73:741–754. Available at: https://www.sciencedirect.com/science/article/pii/S0735109718395421?via%3Dihub. Accessed March 8, 2019.
25. Mamas MA, Anderson SG, O'Kane PD, Keavney B, Nolan J, Oldroyd KG, Perera D, Redwood S, Zaman A, Ludman PF, Belder MA de. Impact of left ventricular function in relation to procedural outcomes following percutaneous coronary intervention: insights from the British Cardiovascular Intervention Society. *Eur Heart J* 2014;35:3004–3012. Available at: https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/ehu303. Accessed February 13, 2019.
26. Perelshtein Brezinov O, Klempfner R, Zekry S Ben, Goldenberg I, Kuperstein R. Prognostic value of ejection fraction in patients admitted with acute coronary syndrome: a real world study. *Medicine (Baltimore)* 2017;96:e6226. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28248882. Accessed February 13, 2019.
27. Lansky AJ, Goto K, Cristea E, Fahy M, Parise H, Feit F, Ohman EM, White HD, Alexander KP, Bertrand ME, Desmet W, Hamon M, Mehran R, Moses J, Leon M, Stone GW. Clinical and angiographic predictors of short- and long-term ischemic events in acute coronary syndromes. *Circ Cardiovasc Interv* 2010;3:308–316. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20647564. Accessed February 13, 2019.
28. Rocca B, Fox KAA, Ajjan RA, Andreotti F, Baigent C, Collet J-P, Grove EL, Halvorsen S, Huber K, Morais J, Patrono C, Rubboli A, Seljeflot I, Sibbing D, Siegbahn A, Berg J Ten, Vilahur G, Verheugt FWA, Wallentin L, Weiss TW, Wojta J, Storey RF. Antithrombotic therapy and body mass: an expert position paper of the ESC Working Group on Thrombosis. *Eur Heart J* 2018;39:1672–1686f. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29509886. Accessed February 3, 2019.
29. Gragnano F, Manavifar N, Valgimigli M. A call for action in bleeding prevention. *Aging (Albany NY)* 2019;11:287–288. Available at: http://www.ncbi.nlm.nih.gov/pubmed/30636170. Accessed March 8, 2019.
30. Knudtson MD, Klein BEK, Klein R, Shankar A. Associations with weight loss and subsequent mortality risk. *Ann Epidemiol* 2005;15:483–491. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16029840. Accessed February 13, 2019.
31. Ariza-Solé A, Salazar-Mendiguchía J, Lorente V, Sánchez-Salado JC, Ferreiro JL, Romaguera R, Ñato M, Gomez-Hospital JA, Cequier Á. Body mass index and acute coronary syndromes: paradox or confusion? *Eur Hear J Acute Cardiovasc Care* 2015;4:158–164. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24923461. Accessed August 6, 2019.
32. Valgimigli M, Frigoli E, Leonardi S, Vranckx P, Rothenbühler M, Tebaldi M, Varbella F, Calabrò P, Garducci S, Rubartelli P, Briguori C, Andó G, Ferrario M, Limbruno U, Garbo R, Sganzerla P, Russo F, Nazzaro M, Lupi A, Cortese B, Ausiello A, Ierna S, Esposito G, Ferrante G, Santarelli A, Sardella G, Cesare N de, Tosi P, 't Hof A van, Omerovic E, Brugaletta S, Windecker S, Heg D, Jüni P, MATRIX investigators. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. *Lancet* 2018;392:835–848. Available at: http://www.ncbi.nlm.nih.gov/pubmed/30153988. Accessed March 11, 2019.
33. Bianchi R, D'Acierno L, Crisci M, Tartaglione D, Cappelli Bigazzi M, Canonico M, Albanese M, Gragnano F, Fimiani F, Russo M, Cirillo P, Calabrò P. From femoral to radial approach in coronary intervention. *Angiology* 2017;68:281–287. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27401210. Accessed March 11, 2019.