Catheterization and Cardiovascular Interventions 85:952–958 (2015)

Impact of Body Mass Index on Long-Term Clinical Outcomes After Second-Generation Drug Eluting Stent Implantation: Insights From the International Global RESOLUTE Program

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Background: An increased body mass index (BMI) is associated with a high risk of cardiovascular disease and reduction in life expectancy. However, several studies reported improved clinical outcomes in obese patients treated for cardiovascular diseases. The aim of the present study is to investigate the impact of BMI on long-term clinical outcomes after implantation of zotarolimus eluting stents. Methods: Individual patient data were pooled from the RESOLUTE Clinical Program comprising five trials worldwide. The study population was sorted according to BMI tertiles and clinical outcomes were evaluated at 2-year follow-up. Results: Data from a total of 5,127 patients receiving the R-ZES were included in the present study. BMI tertiles were as follow: I tertile ($\leq$ 25.95 kg/m^2—Low or normal weight) 1,727 patients; II tertile (>25.95 $\leq$ 29.74 kg/m^2—overweight) 1,695 patients, and III tertile (>29.74 kg/m^2—obese) 1,705 patients. At 2-years follow-up no difference was found for patients with high BMI (III tertile) compared with patients with normal or low BMI (I tertile) in terms of target lesion failure (I–III tertile, HR [95% CI] = 0.89 [0.69, 1.14], *P* = 0.341; major adverse cardiac events (I–III tertile, HR [95% CI] = 0.90 [0.72, 1.14], *P* = 0.389; cardiac death (I–III tertile, HR [95% CI] = 1.20 [0.73, 1.99], *P* = 0.476); myocardial infarction (I–III tertile, HR [95% CI] = 0.86 [0.55, 1.35], *P* = 0.509; clinically-driven target lesion revascularization (I–III tertile, HR [95% CI] = 0.75 [0.53, 1.08], *P* = 0.123; definite or probable stent thrombosis (I–III tertile, HR [95% CI] = 0.98 [0.49, 1.99], *P* = 0.964. Conclusions: In the present study, the patients' body mass index was found to have no impact on long-term clinical outcomes after coronary artery interventions.

Key words: obesity paradox; coronary artery disease; zotarolimus eluting stents

Additional Supporting Information may be found in the online version of this article.

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Contract grant sponsor: Medtronic.

Conflict of interest: M.L. and F.v.L., are employed by Medtronic.

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Received 7 June 2014; Revision accepted 3 January 2015

DOI: 10.1002/ccd.25828
Published online 17 February 2015 in Wiley Online Library (wileyonlinelibrary.com)

INTRODUCTION

An increased body mass index (BMI) has been shown to be associated with a higher rate of cardiovascular risk factors [1], an increased risk of developing cardiovascular diseases, a higher mortality rate [2–4], and reduction in life expectancy [5].

However, several studies reported improved clinical outcomes in overweight and obese patients treated for cardiovascular diseases compared to normal weight patients, suggesting a paradoxical survival benefit [6,7]. This phenomenon termed as obesity paradox has been reported in patients with coronary artery disease (CAD) [7], heart failure [8], and post-percutaneous coronary intervention patients [9]. The mechanisms leading to this paradox are currently unclear.

On the other hand, weight loss has been demonstrated to be associated with improvement in pre-existing cardiovascular risk factors [10–12], clinical events, and prognosis [13,14].

Several hypotheses for the obesity paradox have been previously proposed. BMI has been criticized as an inaccurate method to investigate the real body fatness [15]; however, observations based on more direct measurements of body fat mass such as percent body fat assessments, consistently showed improved outcomes in obese patients [16]. Obese patients may be exposed to a higher rate of optimal medical treatment [17]; however, obesity status was demonstrated to be associated with an increased rate of suboptimal platelet response to standard treatment with clopidogrel and aspirin [18,19] due to a functional under-dosage of antiplatelet therapy if adjusted to BMI, possibly with a higher risk of stent thrombosis [20,21].

Adipose tissue is a well recognized endocrine organ, producing soluble tissue necrosis factor receptors associated with a overall reduction of tumor necrosis factor-α that has been shown to play an important role in the pathophysiology of heart failure [22]; however, the favorable endocrine function of fat tissue appears in contradiction with the reported improved clinical outcomes in obese patients after weight loss.

Conversely, underweight patients may be associated with advanced heart failure, neoplastic disease, and overt cachexia burdened by a higher mortality [9].

The aim of the present study is to provide further insights into the impact of body mass index on clinical outcomes after implantation of second-generation drug eluting stents. Data were obtained from the large-scale RESOLUTE Clinical Program comprising five stent trials worldwide evaluating the performance of the zotarolimus eluting stent for treatment of CAD.

METHODS

The RESOLUTE Clinical Program comprises five trials (RESOLUTE FIM, RESOLUTE All Comers, RESOLUTE International, RESOLUTE US, and RESOLUTE Japan trials) worldwide evaluating the Resolute zotarolimus-eluting stent (R-ZES), which were prospectively designed with similar methods and homogeneous data collection forms, adverse event definitions and adjudication procedures, statistical programming algorithms, and data sets to allow database pooling. Independent Clinical Events Committees (CEC) adjudicated all serious adverse events.

Clinical events definitions have been already reported [23,24]. Briefly, target lesion failure (TLF) was defined as a composite of cardiac death, target vessel myocardial infarction (MI), and ischemia-driven target lesion revascularization (TLR). Major adverse cardiac events (MACE) were defined as the composite of all-cause death, any MI, emergent coronary artery bypass, and ischemia-driven revascularization. Deaths were considered cardiac unless a non-cardiac cause was confirmed. All MIs not clearly attributable to a non-target vessel were considered as target vessel MI. Stent thrombosis was adjudicated according to the Academic Research Consortium (ARC) criteria.

All patients signed written informed consent.

Patients were followed-up for 2 years; clinical outcomes were prospectively collected and compared according to different BMI strata. BMI was defined as the weight (kg) divided by the height in squared meters (m^2).

Given the fact that previously studies investigating the impact of BMI on clinical outcomes using the classical BMI classes showed remarkable unbalances among groups in term of number of patients [9,25,26], in the present investigation the study population was sorted according to BMI tertiles.

However, in order to provide additional insights on the distribution of the BMI and to confirm our hypothesis, this population was further stratified according to the following previously reported BMI classes [25,27]: underweight ($BMI < 18.5$ kg/m^2), normal weight ($BMI \geq 18.5 < 25$ kg/m^2), overweight ($BMI \geq 25 < 30$ kg/m^2), obese ($BMI \geq 30$ kg/m^2) and data reported in the Supporting Information.

Statistical Analysis

Categorical variables were reported as percentages, and differences among subgroups were assessed using logistic regression. Continuous variables were reported as mean $\pm$ SD and were compared using analysis of variance. Clinical outcomes were compared among subgroups using Cox proportional hazard regression model, with first tertile as reference (normal weight as reference

TABLE I. Baseline Clinical Characteristics According to BMI Tertiles

Baseline characteristics	I Tertile <=25.95 kg/m^2 ($N = 1,727$)	II Tertile >25.95 ≤ 29.74 kg/m^2 ($N = 1,695$)	III Tertile >29.74 kg/m^2 ($N = 1,705$)	*P* value
Men	74.6% (1,289/1,727)	80.8% (1,369/1,695)	69.4% (1,183/1,705)	<0.001
Age (years)	64.8 ± 11.5 (1,727)	64.4 ± 10.8 (1,695)	62.3 ± 10.5 (1,705)	<0.001
Hyperlipidemia	62.8% (1,085/1,727)	72.0% (1,220/1,695)	80.0% (1,364/1,705)	<0.001
History of hypertension	61.6% (1,064/1,727)	74.2% (1,257/1,695)	84.5% (1,440/1,705)	<0.001
Diabetes mellitus	21.4% (369/1,727)	25.5% (432/1,695)	43.0% (734/1,705)	<0.001
Current smoker	27.0% (467/1,727)	23.2% (394/1,695)	20.6% (352/1,705)	<0.001
Renal insufficiency	4.3% (65/1,529)	3.5% (54/1,543)	4.2% (65/1,563)	0.499
LVEF<30%	2.3% (26/1,142)	2.0% (22/1,126)	1.7% (21/1,240)	0.184
Prior MI	26.3% (452/1,720)	27.8% (468/1,682)	25.3% (425/1,683)	0.235
Prior PCI	31.1% (537/1,727)	30.2% (512/1,695)	31.4% (536/1,705)	0.725
Prior CABG	7.5% (1,29/1,727)	9.8% (166/1,695)	8.4% (144/1,705)	0.052
Stable angina	36.7% (634/1,727)	39.1% (663/1,695)	39.8% (679/1,705)	0.145
Unstable angina	24.8% (429/1727)	26.2% (444/1,695)	26.7% (456/1,705)	0.423
Acute myocardial infarction within 72 hr	19.3% (333/1,727)	14.8% (251/1,695)	12.4% (212/1,705)	<0.001
Bifurcation	21.0% (279/1,330)	21.0% (270/1,283)	20.7% (207/998)	0.986
Multivessel treatment	14.4% (248/1,727)	16.5% (280/1,695)	14.2% (242/1,705)	0.109
Left main artery	2.2% (38/1,727)	2.1% (35/1,695)	1.3% (22/1,705)	0.093
LAD	50.0% (863/1,727)	49.6% (840/1,695)	48.8% (832/1,705)	0.786
LCX	27.6% (477/1,727)	31.0% (526/1,695)	31.2% (532/1,705)	0.034
RCA right coronary artery	34.7% (600/1,727)	33.4% (566/1,695)	32.3% (551/1,705)	0.321
Bypass graft, no. (%)	1.2% (21/1727)	1.5% (25/1,695)	1.1% (18/1,705)	0.557
At least one small vessel (RVD <=2.75 mm)	56.1% (933/1,663)	55.5% (905/1,631)	56.9% (942/1,656)	0.721
At least one total occlusion	7.1% (122/1,724)	8.7% (147/1,689)	6.0% (102/1,701)	0.010
Aspirin at 1 year	96.9% (1,621/1,673)	97.0% (1,602/1,652)	96.2% (1,587/1,650)	0.386
Clopidogrel at 1 year	89.7% (1,501/1,673)	91.0% (1,504/1,652)	92.5% (1,527/1,650)	0.016
DAPT at 1 year	89.1% (1,491/1,673)	89.3% (1,476/1,652)	89.6% (1,477/1,649)	0.918
Continental analysis				
Africa	0.6% (11/1,727)	0.9% (15/1,695)	0.8% (14/1,705)	0.691
Asia	10.4% (180/1,727)	4.0% (68/1,695)	1.5% (26/1,705)	<0.001
Europe	68.0% (1,174/1,727)	68.6% (1,163/1,695)	53.8% (918/1,705)	<0.001
Oceania	2.5% (43/1,727)	2.9% (50/1,695)	2.7% (46/1,705)	0.706
North America	18.2% (315/1,727)	22.9% (388/1,695)	41.0% (699/1,705)	<0.001
South America	0.2% (4/1,727)	0.6% (11/1,695)	0.1% (2/1,705)	0.020

MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; RVD = reference vessel diameter; DAPT = dual antiplatelet therapy. Data are reported as percentage and count or mean ± standard deviation.

for per classes analysis—Supporting Information). Both univariate and multivariate analyses were performed to account for the differences in baseline characteristics among subgroups. Findings after multivariate analysis were confirmed with propensity match analysis. The Kaplan–Meier curves were presented to demonstrate the differences in clinical endpoints among subgroups.

RESULTS

A total of 5,127 patients were followed-up for 2 years and clinical outcomes stratified according to BMI at baseline. The per-tertiles analysis showed the following BMI tertiles: I tertile ($\leq$ 25.95 kg/m^2) 1,727 patients; II tertile ($>25.95 \leq 29.74$ kg/m^2) 1,695 patients, and III tertile (>29.74 kg/m^2) 1,705 patients (Table I). Given the BMI distribution among tertiles, the first tertile could be considered representative of normal weight patients, second tertile representative of over-weighted patients, and third tertile as representative of obese patients.

In the per BMI classes analysis, a total of 1,634 patients had a BMI ≥ 30 kg/m^2 (obese group), 2,256 patients had a BMI ≥ 25 and <30 kg/m^2 (overweight group), 1,220 patients had a BMI ≥ 18.5 and <25 kg/m^2 (normal weight group), and only 17 patients had a BMI value <18.5 kg/m^2 (underweight group).

Due to the high numerical mismatch among BMI classes—especially considering the underweight group—the analysis was undertaken taking into consideration the per-tertile division. (As additional information the analysis using the BMI classes is reported in the Supporting Information).

TABLE II. Baseline Lesions Characteristics According to BMI Tertiles

	I Tertile	II Tertile	III Tertile	
Lesions characteristics	<=25.95 kg/m^2 (2,218)	>25.95 ≤ 29.74 kg/m^2 (2,221)	>29.74 kg/m^2 (2,153)	*P* value
Mean lesion length (mm)	16.0 ± 9.1 (2,118)	16.0 ± 10.1 (2,113)	15.2 ± 9.1 (2,062)	0.009
Reference vessel diameter (mm)	2.8 ± 0.5 (2,128)	2.8 ± 0.5 (2,121)	2.8 ± 0.5 (2,069)	0.073
Minimum lumen diameter (mm)	0.7 ± 0.5 (2,211)	0.7 ± 0.5 (2,211)	0.7 ± 0.5 (2,144)	0.132
Percent stenosis (%)	75.7 ± 16.7 (2,211)	75.7 ± 16.9 (2,211)	75.2 ± 15.6 (2,144)	0.449
Moderate/Severe Calcification	32.3% (713/2,206)	32.9% (725/2,205)	30.8% (661/2,145)	0.322
Thrombus	8.4% (184/2,185)	7.6% (164/2,171)	5.4% (114/2,119)	<.001
TIMI score of 0 or 1	14.8% (329/2,218)	13.3% (295/2,221)	10.9% (234/2,153)	<.001

TIMI = thrombolysis in myocardial infarction. Data are reported as percentage and count or mean ± standard deviation.

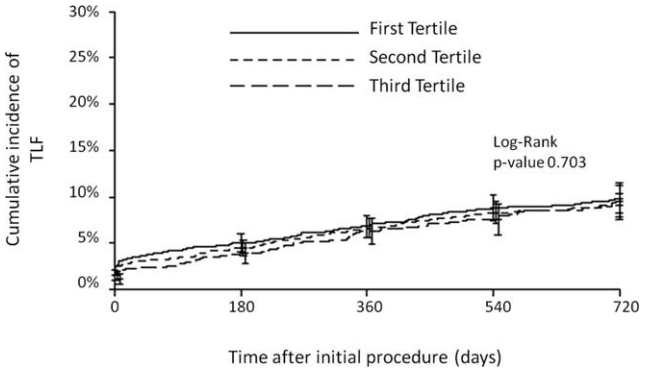

Fig. 1. Cumulative incidence of TLF. No differences in terms of the device-oriented endpoint TLF were observed among BMI groups at 2-year follow-up—per-tertiles analysis.

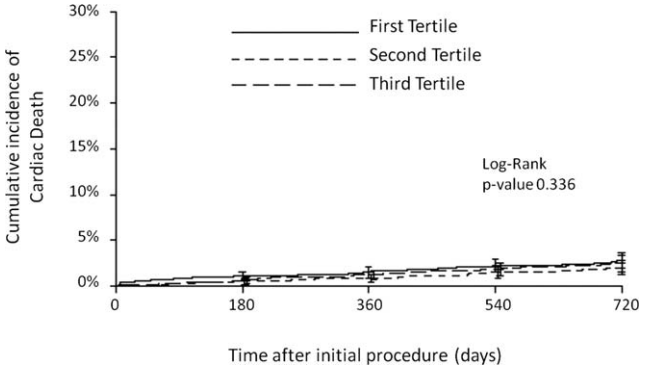

Fig. 2. Cumulative incidence of cardiac death. No survival benefit was observed for obese patients at 2-year follow-up—per-tertiles analysis.

At baseline, the III tertile (> 29.74 kg/m^2—high BMI) cohort was characterized by a higher rate of female gender, younger age, hyperlipidemia, hypertension, and diabetes mellitus. The I tertile (≤ 25.95 kg/m^2—normal BMI) was characterized by patients more frequently current smokers, with an acute presentation (acute myocardial infarction) (Table I), more frequently with thrombotic lesions, and TIMI flow 0 or 1 (Table II).

At 2-year follow-up, no difference was observed between the III tertile and the I tertile in terms of TLF

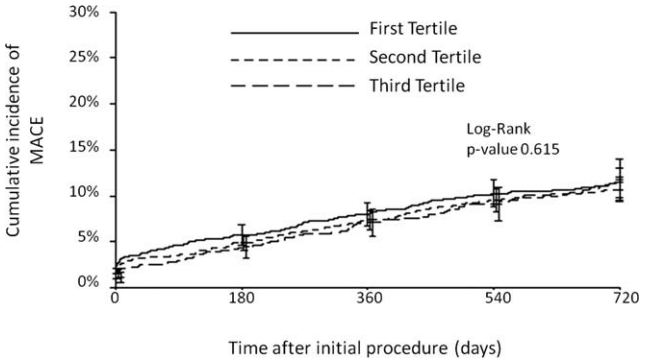

Fig. 3. Cumulative incidence of major adverse cardiovascular events. No significant differences in term of MACE were observed among BMI groups at 2-year follow-up—per-tertiles analysis.

(I–III tertile, HR [95% CI] = 0.89 [0.69, 1.14], $P = 0.341$; MACE (I–III tertile, HR [95% CI] = 0.90 [0.72, 1.14], $P = 0.389$; cardiac death (I–III tertile, HR [95% CI] = 1.20 [0.73, 1.99], $P = 0.476$); myocardial infarction (I–III tertile, HR [95% CI] = 0.86 [0.55, 1.35], $P = 0.509$; clinically driven TLR (I–III tertile, HR [95% CI] = 0.75 [0.53, 1.08], $P = 0.123$; definite or probable stent thrombosis (I–III tertile, HR [95% CI] = 0.98 [0.49, 1.99], $P = 0.964$.(Table III, Figs. 1–3).

The II tertile (> 25.95 ≤ 29.74 kg/m^2—overweight status) showed a reduction in the incidence of the composite end-point of definite or probable stent thrombosis compared to the other BMI tertiles (Table III).

DISCUSSION

The main finding of the present investigation is that after second-generation drug-eluting stent implantation, BMI had no impact on mortality, MACE, myocardial infarction, and repeated revascularization at 2-year follow-up. These results are in contrast with previous reports showing a survival benefit associated with obesity, but are consistent with recent observations in post-PCI populations [28].

TABLE III. Clinical Outcomes at 2-Years Follow-Up According to BMI Tertiles (I Tertile as reference)

	Univariate HR[a] (95% CI)	*P* value	Multivariate adjusted HR[b] (95% CI)	*P* value	*P* value[c]
TLF					
Second tertile	0.96 [0.76, 1.20]	0.697	0.92 [0.73, 1.16]	0.495	0.579
Third tertile	0.91 [0.72, 1.14]	0.402	0.89 [0.69, 1.14]	0.341	0.391
MACE					
Second tertile	0.97 [0.78, 1.19]	0.744	0.94 [0.76, 1.16]	0.543	0.649
Third tertile	0.90 [0.72, 1.11]	0.331	0.90 [0.72, 1.14]	0.389	0.427
All cause of death					
Second tertile	0.86 [0.59, 1.24]	0.413	0.94 [0.64, 1.37]	0.742	0.422
Third tertile	0.87 [0.60, 1.28]	0.487	1.18 [0.78, 1.77]	0.429	0.854
Cardiac death					
Second tertile	0.70 [0.43, 1.13]	0.143	0.78 [0.47, 1.28]	0.320	0.126
Third tertile	0.89 [0.56, 1.41]	0.612	1.20 [0.73, 1.99]	0.476	0.907
All myocardial infarction (MI)					
Second tertile	0.89 [0.63, 1.26]	0.516	0.80 [0.53, 1.21]	0.289	0.997
Third tertile	0.85 [0.59, 1.22]	0.385	0.86 [0.55, 1.35]	0.509	0.454
Target-vessel myocardial infarction (MI)					
Second tertile	1.07 [0.75, 1.54]	0.702	1.07 [0.74, 1.55]	0.726	0.770
Third tertile	0.89 [0.61, 1.31]	0.557	0.97 [0.64, 1.46]	0.870	0.445
Clinically driven target lesion revascularization (TLR)					
Second tertile	1.08 [0.79, 1.48]	0.645	0.98 [0.71, 1.35]	0.889	0.731
Third tertile	0.92 [0.66, 1.29]	0.629	0.75 [0.53, 1.08]	0.123	0.367
Stent thrombosis (definite or probable)					
Second tertile	0.44 [0.20, 0.95]	0.038	0.44 [0.20, 0.99]	0.047	0.026
Third tertile	0.80 [0.42, 1.54]	0.504	0.98 [0.49, 1.99]	0.964	0.391

HR = hazard ratio; CI = confidence interval.

[a]Comparison of other BMI tertile to tertile 1.

[b]Comparison of other BMI tertile to tertile 1, adjusted using variables listed in table 2 and table 4.

[c]*P* value is adjusted to propensity score. The propensity scores were calculated with the variables listed in Table II and Supporting Information Table 4 (age, lesion length, Pre-RVD, Pre-MLD, pre-diameter stenosis, number of stents per patient, total stent length per patient, diameter stenosis (%), sex, current smoker, prior PCI, hyperlipidemia, LVEF<30%, diabetes mellitus, history of hypertension, renal insufficiency, prior MI, prior CABG, stable angina, unstable angina, acute myocardial infarction within 72 hr, multivessel treatment, LAD, at least one small vessel (reference vessel diameter, <=2.75 mm), total occlusion, moderate/severe calcification, thrombus, TIMI score of 0 or 1, continents).

Normal weight (>=18.5<25) and I tertile as reference.

In II tertile ($> 25.95 \leq 29.74$ kg/m^2—overweighed patients), we reported an overall reduction in stent thrombosis that was mainly due to a reduction in this clinical endpoint in the first 180 days post-index procedure. This data could be explained considering two important factors increasing the risk of stent thrombosis in the other two BMI categories (I tertile, ≤ 25.95 kg/m^2—normal weight and III tertile, > 29.74 kg/m^2—obese). (1) Patients with normal weight in the present study presented more frequently with acute coronary syndrome (ACS). (2) Obese patients were previously reported to be associated with a possible functional under-dosage of antiplatelet therapy [21]. Considering this background, the advantage of the overweight patients in terms of stent thrombosis is not surprising. Due to the small number of events these differences in stent thrombosis did not translate into significant differences in mortality or MACE.

Several authors suggested that a possible explanation for the BMI paradox is the fact that obese patients are usually presenting at a younger age taking advantage of a beneficial early treatment [26]. Sarno et al. reported this phenomenon describing colinearity between BMI and age of patients' presentation [29].

A younger age could be associated with a lower CAD burden with a lower prevalence of high-risk coronary anatomy compared with the non-obese older counterpart [30]. Consistently, with this hypothesis, obese patients (III tertile) in our study trended to have less multivessel/left main treatment and a significant lower rate of chronic total occlusion, suggesting an earlier stage of the atherosclerotic disease.

An earlier invasive treatment also translates into access to secondary preventive medications at a younger age [17,31]. If we consider that optimal medical therapy improves morbidity and mortality in CAD [32], an advantage in terms of medical treatment in obese patients could be considered an important factor in the understanding of the BMI paradox.

In the present report, the patient classification based on absolute BMI classes showed a remarkable difference in terms of number of patients in the different classes; in particular out of 5,127 only 17 patients

were classified as underweight. Such discrepancy in patients distribution, suggests a possible limitation in analyzing data according to this classification. Notably a similar small number of underweight patients were observed in several previous studies with percentages usually ranging between 1% and 3% of the total population [9,25,26]. Given this background, in the present investigation, the study population was stratified into BMI tertiles in the attempt to have more reliable information on BMI distribution. This classification showed groups substantially reflecting the normal, overweight, and obese classical classes, confirming a limited impact of the underweight group (in post-PCI populations) in the overall BMI distribution. These considerations appear to reduce the relevance of the increased rate of events in underweight patients reported in previous studies. In addition, as already observed this may be due to the so called reverse causation [33] with underweight patients often characterized by malnutrition [34], cachexia, malignancy, severe heart failure, COPD, and peri-procedural bleeding [35]. Therefore, the previously reported U shaped association (27) between BMI and clinical outcomes could be due to an increased events rate in the in a very limited PCI subset (underweight patients) often affected by a higher prevalence of comorbidities.

Finally, evaluation of obesity in elderly patients and the subsequent analysis of clinical implication is a complex matter of debate [36]. In particular, the reliability of the BMI index in those patients may be affected by age-related body changes with age-related height reduction [37] and changes in body composition [38]. These observations suggest that BMI calculation in elderly could be affected in both numerator and denominator in opposite direction possibly resulting in adiposity underestimation [36]. In addition, this particular population is a mixture of subjects with different weight history [39]. Therefore, an evaluation of the patients considering their entire clinical history should be pursued, not only observing the time frame from the starting of the treatment. Such approach could allow reconsidering obese patients as patients who start to be treated earlier and despite a longer absolute treatment-time (pseudo improved clinical outcomes), show an overall reduced life expectancy.

Limitations

The RESOLUTE clinical program was not originally designed for a specific evaluation of the impact of BMI on clinical outcomes and the present study is a *post hoc* analysis. Waist circumference an alternative anthropometric index of obesity more specific for abdominal adiposity was not evaluated in the present report.

CONCLUSION

In the present study, no survival benefit was observed at the long-term follow-up in obese patients compared with normal weight patients, after second-generation zotarolimus eluting stent implantation.

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