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ORIGINAL ARTICLE

Obesity paradox in the era of percutaneous coronary intervention with 2nd-generation drug-eluting stents: an analysis of a multicenter PCI registry

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Abstract

Being overweight has been identified as independent risk factors for coronary artery disease. However, overweight patients have been reported frequently to have better mortality outcomes, and there is little data showing they are at a disadvantage regarding secondary prevention of cardiovascular events. We analyzed the influence of being overweight (defined as body mass index > 25 kg/m^2) on adverse events in patients who underwent everolimus-eluting stent (EES) implantation using a multicenter registry with a maximum follow-up of 3 years. Propensity score matching was done for adjusting baseline characteristics. We defined primary end points as major adverse cardiac and cerebrovascular events (MACCE: a composite of mortality from all causes, nonfatal myocardial infarction, and nonfatal stroke) and "MACCE excluding non-cardiac mortality". Other adverse events were analyzed as key secondary end points. Out of 1918 patients, 450 pairs were obtained through propensity score matching. Overweight patients were superior to non-overweight patients regarding MACCE (event rates: 8.2 vs. 13.8% in overweight vs. non-overweight, respectively; log-rank $p = 0.009$) and "MACCE excluding non-cardiac mortality" (5.9 vs. 10.1%, $p = 0.03$). On secondary end points, not only did overweight patients have significantly fewer major bleeding events (2.2 vs. 4.8%, $p = 0.02$), but they also had smaller adverse event rates for almost all such events; the differences were not statistically significant. Overweight patients had better outcomes for MACCE, even on excluding non-cardiac mortalities. No result was supportive of an evident advantage to non-overweight EES-implanted patients in terms of secondary prevention of cardiovascular events.

Keywords Percutaneous coronary intervention · Overweight · Obesity · Drug-eluting stent · Mortality · Major adverse cardiac or cerebrovascular events

Introduction

Being obese has been recognized as an independent risk factor of coronary artery disease [1, 2], and the influence on adverse cardiovascular events has been reported to be more critical in Asian populations than in Western populations [3]. However, the concerns associated with being obese are not well established in patients who have undergone coronary revascularization as secondary prevention. Moreover, several studies have reported that being obese or overweight was associated with lower mortality in patients with cardiovascular diseases, including coronary artery disease (CAD); this phenomenon has been known as "the obesity paradox" [4–8]. To oversee previous studies, being obese is advantageous in terms of mortality and major adverse cardiac and cerebrovascular events (MACCE) or major bleeding;

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however, the effects of obesity on secondary prevention of CAD are yet controversial [4–12]. Moreover, we expected that being obese or overweight would have a slight disadvantageous influence on the recurrence of cardiac and cerebrovascular events, with current improved risk management and advanced medical equipment represented by prevalent stents. This study included only Japanese patients, and being overweight has much influence in the Asian population; considering these, we thought comparing outcomes between overweight and non-overweight patients would be generally acceptable. Thus, the aim of the present study was to evaluate whether and in what subjects being overweight has a relation with the recurrence of cardiac and cerebrovascular events among patients that underwent current coronary intervention.

Methods

This study was performed as a sub-study of the Tokyo-MD PCI registry, a physician-initiated, multicenter, observational registry in Japan. The registry was explained previously [13–15]. The registry included consecutive patients who underwent everolimus-eluting stent (EES) (Xience V, Abbott, Abbott Park, IL, USA; Promus, Boston Scientific, Natick, MA, USA) implantation in 22 centers in Japan from January 2010 to December 2011. All data were anonymized at each center and collated at the data center in the Department of Cardiovascular Medicine, Tokyo Medical and Dental University, Tokyo, Japan, and were put under the management of the last author. The institutional ethical review board at the Tokyo Medical and Dental University approved this registry. According to the Ethical Guidelines for Epidemiological Research, we published all relevant details of this registry instead of obtaining informed consent. We excluded patients with cardiogenic shock or cancer at hospitalization, those who were lost to follow-up within 30 days since the procedure, or those for whom BMI data was lacking from this study. A total of 1684 patients (out of 1918 patients who underwent EES implantation) were included in this study (Fig. 1).

We defined overweight as body mass index (BMI) >25 kg/m^2 referring to the BMI range pertaining to the overweight status in Asian populations [3]. Primary end points were MACCE: a composite of all-cause mortality, nonfatal myocardial infarction (MI), or nonfatal stroke, and "MACCE excluding non-cardiac mortality" wherein the events of non-cardiac mortality were excluded from MACCE to include only cardio-cerebral vascular events. Key secondary end points were all-cause mortality, cardiac mortality, non-cardiac mortality, nonfatal MI, stent thrombosis, nonfatal stroke, hospitalization due to heart failure (HF), and major bleeding. The details of each criterion have been described previously [13–15].

Normally distributed variables were presented as the mean ± standard deviation and were compared using Student's *t* test. Non-normally distributed variables were presented as the median with 25th and 75th percentile and compared using Mann–Whitney *U* test. Categorical variables were summarized as percentages, and the Chi square test was used to compare categorical variables. Propensity score matching was performed to adjust the baseline characteristics [16]. Possible confounders were chosen for their association with the outcome of interest based on clinical knowledge. The propensity score of being overweight was calculated by fitting a logistic regression model with confounding factors with p values <0.5 in the baseline characteristic analyses. Based on the score, we performed rigorous

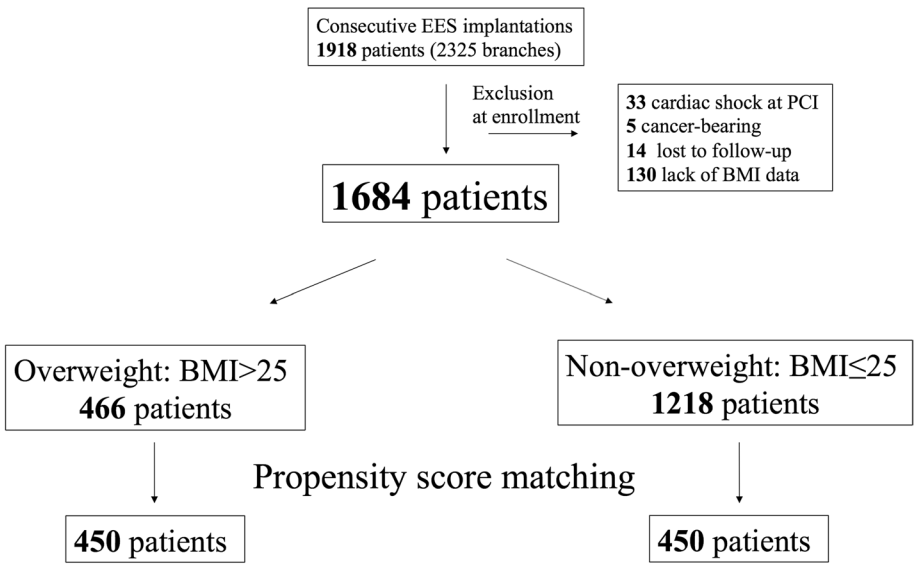


Fig. 1 Study design. *EES* everolimus-eluting stent, *PCI* percutaneous coronary intervention, *BMI* body mass index

adjustment for significant differences in the baseline characteristics of patients using propensity score matching through the following algorithm: 1:1 optimal match with a ±0.03 caliper and no replacement, and covariate balance was assessed via standardized differences. Kaplan–Meier estimates were presented of the cumulative incidence of each end point with log-rank analysis at the follow-up periods of 30 days, 1 year, 2 years, and 3 years. Multivariate Cox regression was performed in baseline-adjusted patients to ensure the independence of overweight on primary outcomes. All the variables with a univariate $p < 0.05$ were subsequently entered into the model. In this study, 130 patients were excluded from analysis because of lacking BMI data. We performed sensitivity analysis to check the robustness of the outcomes. The sensitivity analysis comprised two hypotheses: "sensitivity analysis 1" considered all the patients for whom BMI data were not available as overweight, while "sensitivity analysis 2" considered them as non-overweight.

All p values were two sided. A $p < 0.1$ for correlation analyses and $p < 0.05$ for all other analyses were considered statistically significant. Computations were performed with software 'R' (version 3.4.2) packages "Tableone," "Matching," and "RcmdrPlugin. EZR" [17].

Table 1 Baseline characteristics of the included patients

Factor	Whole patients			Adjusted patients (with PSM)		
	Overweight	Non-overweight	*p*	Overweight	Non-overweight	*p*
Total number	466	1218		450	450	
Age, y.o ± SD	66.8 ± 9.9	71.2 ± 9.5	<0.001	67.2 ± 9.8	67.5 ± 9.5	0.63
Gender male, *n* (%)	360 (77.3)	874 (71.8)	0.02	345 (76.7)	346 (76.9)	1.00
Smoking, *n* (%)	237 (50.9)	533 (43.8)	0.01	227 (50.4)	224 (49.8)	0.89
Comorbidity						
Hypertension, *n* (%)	372 (79.8)	863 (70.9)	<0.001	356 (79.1)	354 (78.7)	0.94
Hyperlipidemia, *n* (%)	405 (86.9)	987 (81.0)	<0.01	389 (86.4)	396 (88.0)	0.55
Diabetes mellitus, *n* (%)	233 (50.0)	471 (38.7)	<0.001	217 (48.2)	221 (49.1)	0.84
Chronic kidney disease, *n* (%)	94 (20.2)	323 (26.5)	0.01	91 (20.2)	82 (18.2)	0.50
Cerebrovascular accident, *n* (%)	49 (10.5)	131 (10.8)	0.93	46 (10.2)	49 (10.9)	0.83
Peripheral arterial disease, *n* (%)	37 (7.9)	141 (11.6)	0.03	35 (7.8)	37 (8.2)	0.90
Chronic heart failure, *n* (%)	32 (6.9)	111 (9.1)	0.14	31 (6.9)	30 (6.7)	1.00
EF ≤ 50%, *n* (%)	83 (17.8)	281 (23.1)	0.02	82 (18.3)	83 (18.5)	0.93
Previous MI, *n* (%)	145 (31.1)	364 (29.9)	0.64	139 (30.9)	141 (31.3)	0.94
Previous PCI, *n* (%)	176 (37.8)	430 (35.3)	0.36	164 (36.4)	163 (36.2)	1.00
Previous CABG, *n* (%)	23 (4.9)	83 (6.8)	0.18	23 (5.1)	27 (6.0)	0.66
Medication at discharge						
Thienopyridine, *n.* (%)	456 (97.9)	1203 (98.8)	0.18	444 (98.7)	441 (98.0)	0.60
Anticoagulant, *n* (%)	55 (11.8)	132 (10.8)	0.60	53 (11.8)	40 (8.9)	0.19
DAPT, *n* (%)	456 (97.9)	1199 (98.4)	0.54	444 (98.7)	441 (98.0)	0.60
Duration of DAPT, months ± SD	30.1 ± 15.0	27.1 ± 15.7	<0.001	30.2 ± 15.0	28.2 ± 15.7	0.05
DAPT termination due to major bleeding, *n* (%)	4 (0.9)	27 (2.2)	0.10	4 (0.9)	11 (2.4)	0.12
Statin, *n* (%)	388 (83.3)	961 (78.9)	0.05	375 (83.3)	379 (84.2)	0.79
ARB or ACE-I, *n* (%)	300 (64.4)	702 (57.6)	0.01	286 (63.6)	293 (65.1)	0.68
Beta-blocker, *n* (%)	234 (50.2)	584 (47.9)	0.41	227 (50.4)	208 (46.2)	0.23
Procedural characteristics						
PCI for ACS, *n* (%)	139 (29.8)	386 (31.7)	0.48	313 (69.6)	311 (69.1)	0.94
Multivessel disease, *n* (%)	208 (44.6)	552 (45.3)	0.80	200 (44.4)	195 (43.4)	0.74
Restenotic site, *n* (%)	65 (13.9)	125 (10.3)	0.04	59 (13.1)	60 (13.3)	1.00
Mean stent size, mm (IQR)	3.00 (2.75, 3.50)	3.00 (2.75, 3.25)	0.06	3.00 (2.75, 3.50)	3.00 (2.75, 3.25)	0.69
Total stent length, mm (IQR)	23.0 (18.0, 34.5)	23.0 (18.0, 41.0)	0.14	23.0 (18.0, 35.0)	23.0 (18.0, 40.0)	0.76

Overweight was defined as BMI > 25, *PSM* propensity score matching, *y.o* years old, *SD* standard deviation, *n.* number, *EF* ejection fraction, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft, *ARB* angiotensin II receptor blocker, *ACE-I* angiotensin converting enzyme inhibitor, *ACS* acute coronary syndrome, *IQR* interquartile range

Results

Out of 1918 patients who underwent EES implantation, 1684 patients were included and divided into two groups according to BMI; 466 patients belonged to the overweight group, while 1218 belonged to the non-overweight group. Follow-up rates were 98.5% at 30 days, 87.8% at 1 year, 74.2% at 2 years, and 53.4% at 3 years. Among the patients in the overweight group, 450 (96.6%) were matched to the patients from the non-overweight group. The covariate balance in the matched cohort was considerably improved (Table 1, and details in Supplemental Table 1).

The Kaplan–Meier estimate of primary end points in baseline-adjusted patients presented the superiority of the

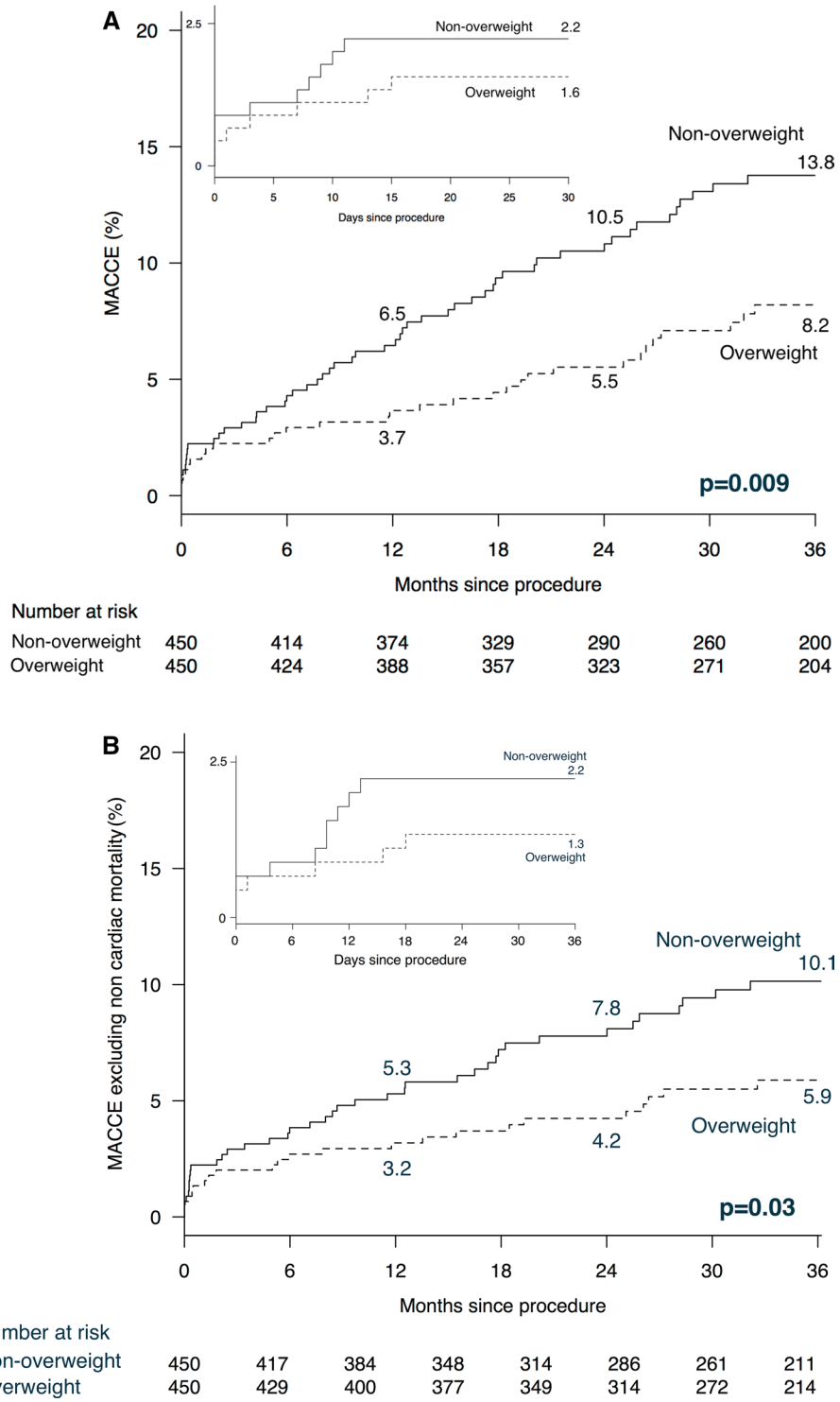


Fig. 2 Kaplan–Meier analysis with log-rank analysis on primary end points in baseline-adjusted patients (with propensity score matching). **a** Major adverse cardiac and cerebrovascular events (MACCE), **b** MACCE excluding non-cardiac mortality. The inset shows the same data focusing on 30 days since procedure

overweight group to non-overweight group (Fig. 2), and the results were similar in the analysis among overall patients (Supplemental Fig. 1). Multivariate Cox regression showed that being overweight was an independent predictor for the better outcomes on both primary end points (Supplemental Table 2A, 2B).

The outcomes for each adverse event of interest at 30 days, 1 year, and 3 years in baseline-adjusted patients are shown in Table 2. Higher event rates were observed in the non-overweight group for MACCE, MACCE excluding non-cardiac mortality, all-cause mortality, and major bleeding at 1 and 3 years, although the occurrence of MACCE at 1 year was not significant. The event rates were higher in the non-overweight group on almost all outcomes, although some end points were absent of significance. The results were similar in the analysis of overall patients (Supplemental Table 3).

On subgroup analysis in baseline-adjusted patients, ejection fraction (EF) showed correlation with being overweight for both primary end points (Fig. 3a), while sex showed significant correlation with that only for a primary end point of "MACCE excluding non-cardiac mortality" (Fig. 3b). The tendency of corroboration was roughly similar with the results in whole patients.

The baseline characteristics and outcomes of sensitivity analysis are shown in Supplemental Tables 3 and 4. The outcomes with sensitivity analysis were similar to the outcomes without sensitivity analysis.

Discussions

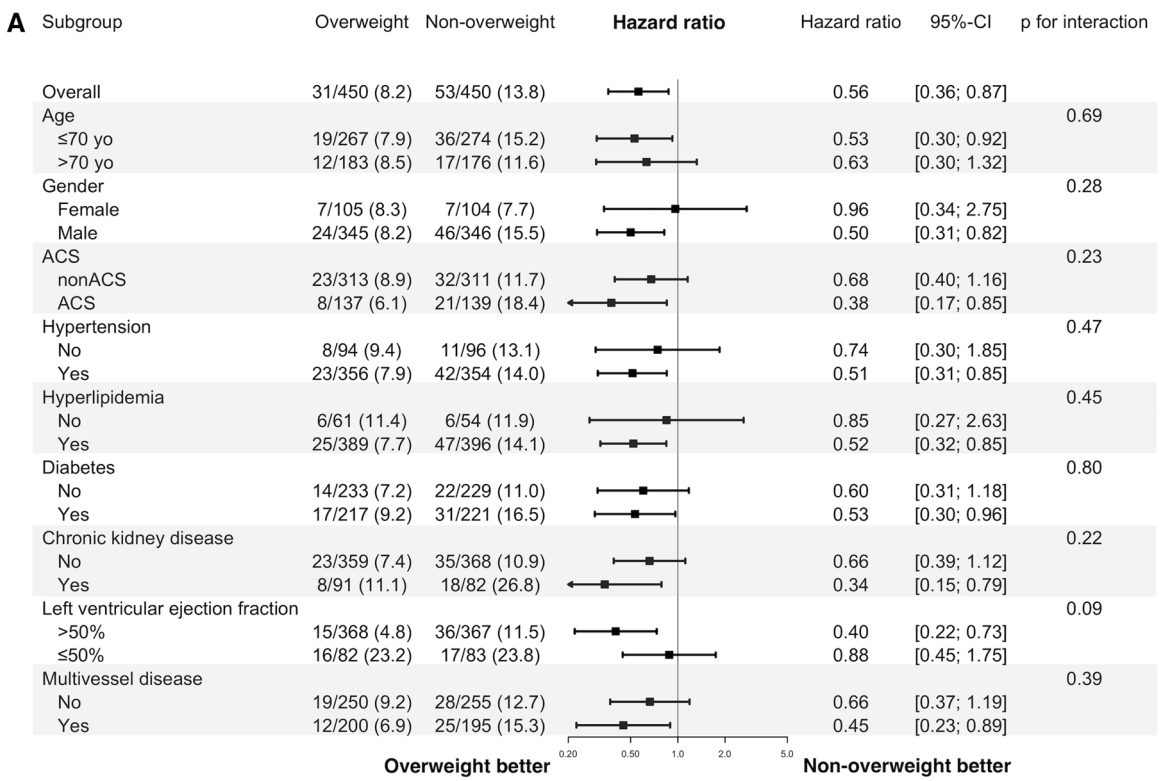
Our study focused on the influence of being overweight on the secondary prevention of CVD. The main findings of our study were as follows: (1) non-overweight patients were more vulnerable to MACCE, both including and excluding non-cardiac mortality; (2) overweight patients had generally lower adverse event rates, although the differences were not significant for some end points; (3) major bleeding was significantly less frequent in the overweight group; and (4) preprocedural EF showed a correlation with being overweight on both MACCE and MACCE excluding non-cardiac mortality, whereas sex showed correlation only with the latter.

Overweight patients had no disadvantage on any outcome of interest and had evident survival advantage in the present study. Given the lower adverse event rates for almost all end points, being overweight seems advantageous rather than disadvantageous. In fact, there is limited evidence on the positive effect of weight loss in overweight individuals for secondary prevention of CAD, although the recommendation has been adopted in the guidelines of secondary prevention [18–20]. Compared with the subjects of primary prevention, those of secondary prevention have a more severe risk profile and undertake more intensive treatments, such as coronary intervention, medical therapy (e.g., antiplatelet therapy), and lifestyle modifications. The interplay of being overweight, risk profile, and treatments could lead to a different benefit of weight loss between primary and secondary prevention. Although the present study suggested that there was less benefit to non-overweight subjects with

Table 2 Clinical outcomes in baseline-adjusted patients (with propensity score matching)

Outcomes	30 days			1 year			3 years		
	Overweight	Non-overweight	*p*	Overweight	Non-overweight	*p*	Overweight	Non-overweight	*p*
	n. of patients (%)			*n*. of patients (%)			*n*. of patients (%)		
MACCE	7 (1.6)	10 (2.2)	0.46	16 (3.7)	28 (6.5)	0.06	31 (8.2)	53 (13.8)	**0.009**
MACCE excluding non-cardiac mortality	6 (1.3)	10 (2.2)	0.32	14 (3.2)	23 (5.3)	0.13	23 (5.9)	39 (10.1)	**0.03**
All-cause mortality	0 (0)	3 (0.7)	0.08	3 (0.7)	11 (2.6)	**0.03**	11 (3.2)	27 (7.2)	**0.01**
Cardiac mortality	0 (0)	2 (0.4)	0.16	2 (0.5)	4 (0.9)	0.41	5 (1.4)	12 (3.3)	0.07
Non-cardiac mortality	0 (0)	1 (0.2)	0.32	1 (0.2)	7 (1.6)	**0.03**	6 (1.8)	15 (4.0)	**0.04**
Nonfatal MI	3 (0.7)	5 (1.1)	0.48	9 (2.1)	9 (2.1)	0.98	12 (3.0)	13 (3.2)	0.79
Stent thrombosis	2 (0.4)	4 (0.9)	0.42	3 (0.7)	5 (1.1)	0.48	3 (0.7)	6 (1.4)	0.31
Nonfatal stroke	2 (0.4)	1 (0.2)	0.57	2 (0.4)	8 (1.9)	0.05	5 (1.3)	11 (2.9)	0.12
Heart failure	1 (0.2)	3 (0.7)	0.31	5 (1.2)	8 (1.9)	0.38	16 (4.6)	16 (4.3)	0.88
Major bleeding	0 (0)	1 (1.0)	0.32	2 (0.5)	10 (2.4)	**0.02**	8 (2.2)	18 (4.8)	**0.04**

All percentages are Kaplan–Meier estimates at the specific time point. *p* values are calculated by log-rank analysis. Statistically significant ($p < 0.05$) values are shown in bold. *MACCE* major adverse cardiac and cerebrovascular event defined as a composite end point of a composite of all-cause mortality, nonfatal myocardial infarction (MI), or nonfatal stroke; *MI* myocardial infarction



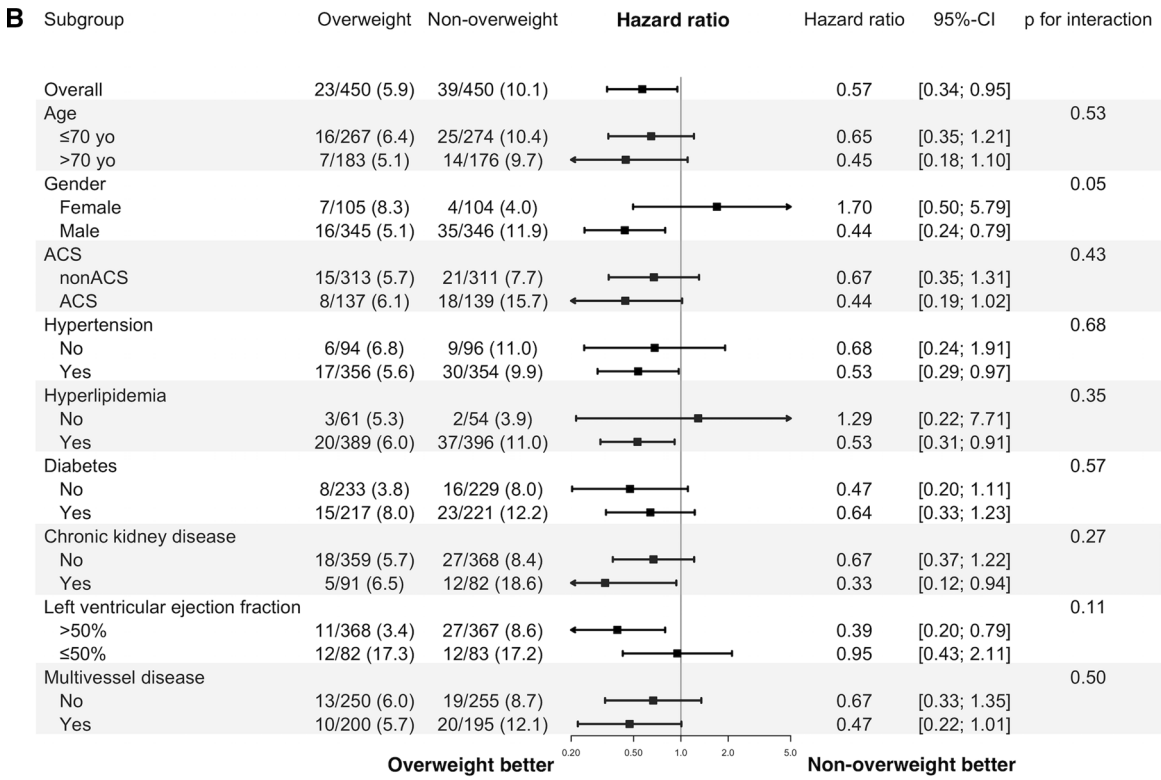


Fig. 3 Subgroup analysis of primary end points in baseline-adjusted patients (with propensity score matching) for the maximum follow-up period. **a** Major adverse cardiac and cerebrovascular events (MACCE), **b** MACCE excluding non-cardiac mortality. All percentages are Kaplan–Meier estimates and thus do not equal the number of patients divided by the total number in the study group. All figures are calculated at the maximum follow-up period of each patient. *n.* number, *CI* confidence interval, *ACS* acute coronary syndrome

established CAD, this does not dismiss the notion that the recommendation of weight loss in obese patients may be of benefit for secondary prevention of CAD. To verify if this recommendation is favorable, a randomized controlled trial focusing on targeted weight reduction in obese patients with established CAD is required.

Our findings could attract some traditional criticisms owing to lacking evidence supporting the obesity paradox. Smoking has been reported as a strong confounding factor in several reports [21, 22]. As smoking increases the mortality rate and smokers typically have a lean physique, inadequate adjustment for smoking would lead to underestimations of the risk associated with being overweight. Another factor clouding the association between CVD risk and BMI is reverse causation due to illness-induced weight loss [23, 24]. Our findings suggest an advantage of being overweight after adjustment for the risk profiles of patients, including smoking habit, which were considered even if non-cardiac mortality was excluded.

Lower bleeding rate has frequently been reported in overweight individuals [25, 26], as overweight individuals reportedly have higher levels of multiple coagulation factors [27]. Moreover, overweight patients were found more commonly to have a suboptimal response to clopidogrel [28, 29]. Lower bleeding rate in overweight group was also observed in the present study. In addition, the shorter duration of dual antiplatelet therapy and the relatively higher rate of DAPT termination due to major bleeding in the non-overweight group were supportive to the suboptimal response.

In the subgroup analysis, the benefit of being overweight disappeared in reduced EF patients. HF is a well-known disease with obesity paradox. Particularly, a strong inverse relationship between BMI and mortality was reported in reduced EF subjects [30, 31]. In contrast, some studies reported obesity paradox to be absent in patients with ischemic HF, but present in those with non-ischemic HF [32, 33]; our results based on patients with established CVD support the latter. Breaking down each end point of our study, the association of reduced EF with being overweight was relatively strong on nonfatal MI (in adjusted patients, the event rates of Kaplan–Meier estimates for overweight vs. non-overweight were 1.7 vs. 3.1% with preserved EF and 9.1 vs. 3.7% with reduced EF; $p = 0.17$). More frequent occurrence of MI in overweight patients may cancel out the advantage of being overweight in ischemic HF. Conversely, a breakdown of correlation analysis between sex and being overweight did not present a specific end point with a tendency of interaction. As a recent study suggested that BMI tended to underestimate body fat in postmenopausal women [34], the classification based on BMI in the present study would be different for the sexes; this difference could lead to a significant association between the female sex and being overweight.

Our study has several limitations. This is a retrospective analysis, and the design was not published beforehand. Further, as the registry was not designed for this analysis, the database of the registry lacks a lot of information essential for investigating the influence of being overweight on CVD. In particular, the lack of weight, height, and BMI data of each patient was a crucial limitation. Each center involved in the study calculated the BMI of their patients and separated them into two groups: overweight and non-overweight. Since the data were anonymized before aggregation, we could not assess the patients' level of BMI despite the retrospective design of our study. Moreover, the absence of patient BMI level data hampered their allocation into more categorized groups. Several studies reported worse outcomes of lean (generally defined as BMI < 18.5) or obese (BMI > 30) CVD patients compared to CVD patients of normal ($18.5 <$ BMI ≤ 25) and overweight ($25 <$ BMI ≤ 30). Considering that the present study divided patients into only two groups, the possibility that lean or obese patients affected the results cannot be avoided. Some patients were dropped in allocation of study groups; those missing data could have an effect on results, even though the sensitivity analyses supported the robustness of our results. Finally, our study included only patients who underwent EES implantation; it is important to expand the results to users of other stent types. However, EES is one of the most widely used stents, and the clinical features of outcomes are comparable among all modern stents; therefore, in our opinion, the results have a general applicability in patients undergoing PCI.

In conclusion, overweight patients who underwent EES implantation had fewer adverse events. Non-overweight patients did not show any benefit in terms of reduced adverse events associated with the secondary prevention of CAD. Those results raise a question concerning whether the targeted weight loss is of benefit to the secondary prevention of CAD. Future interventional studies are warranted for a deeper insight into this notion.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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