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Association between body mass index and clinical outcomes after new-generation drug-eluting stent implantation: Korean multi-center registry data

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HIGHLIGHTS

- Lower BMI was linked to worse outcomes after new-generation DES implantation.
- This result was driven by not only mortality but also ischemic adverse events.
- A BMI below 24 kg/m^2 was an independent predictor of MACCEs.
- Patients with low BMI might have more atherosclerotic burden than those with high BMI.
- Physicians should identify other risk factors and comorbidities in patients with low BMI.

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ABSTRACT

Background and aims: It is unclear whether the obesity paradox is still apparent in the new-generation drug-eluting stent (DES) era. Therefore, we assessed the impact of body mass index (BMI) on clinical outcome after percutaneous coronary intervention (PCI) with new-generation DESs.

Methods: A total of 5264 consecutive patients from 4 new-generation DES registries were divided into 4 categories according to BMI: 1) underweight (BMI < 18.5 kg/m^2, n = 130), 2) normal weight (18.5 ≤ BMI < 25 kg/m^2, n = 2943), 3) overweight (25 ≤ BMI < 30 kg/m^2, n = 1932), and 4) obese (BMI ≥ 30 kg/m^2, n = 259). The primary endpoint was the occurrence of major adverse cardiac and cerebrovascular event (MACCE) at 12 months, including all-cause mortality, nonfatal myocardial infarction, stroke, and target-vessel revascularization.

Results: The 12-month MACCE rates decreased according to increasing BMI categories. (underweight, 13.1%; normal, 6.0%; overweight, 4.8%; obese, 4.2%; $p < 0.001$). After adjustment for other confounders, the underweight group had significantly higher MACCE rates than the normal-weight (hazard ratio [HR], 0.57; 95% confidence interval [CI], 0.33–0.99; $p = 0.049$), overweight (HR, 0.49; 95% CI, 0.27–0.88; $p = 0.017$), and obese (HR, 0.41; 95% CI, 0.18–0.98; $p = 0.044$) groups. These differences were mainly driven by all-cause mortality and target-vessel revascularization. When BMI was treated as a continuous variable, BMI per 1 kg/m^2 was also an independent predictor for MACCE (HR, 0.95; 95% CI, 0.91–0.99; $p = 0.008$) and a MACE increase began below a BMI of 24 kg/m^2.

Conclusions: Lower BMI was significantly associated with higher rates of MACCE and all-cause mortality after PCI. The obesity paradox is manifested in Korean patients in the new-generation DES era.

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1. Introduction

In the general population, it is well known that obesity is an independent risk factor of cardiovascular diseases [1] and is related to adverse clinical outcomes [2]. In the population with established coronary artery disease (CAD), however, several studies have reported that obese patients have better outcomes than non-obese patients after percutaneous coronary intervention (PCI) [3–6]. This peculiar phenomenon, known as the obesity paradox, has been replicated in Western populations [3,5] as well as in Eastern populations [4,6], although there is still an ongoing debate regarding its uncertain mechanism and the possibility of misconception owing to some bias. Recently, new-generation drug-eluting stents (DES), characterized by thinner stent struts, biocompatible durable or biodegradable polymers, and limus-based antiproliferative agents, have been widely used and have demonstrated superior clinical outcomes in various high-risk patients and lesions over the first-generation DES [7]. However, there is a paucity of data on whether body mass index (BMI) still has a prognostic impact on clinical outcomes in patients treated with new-generation DES. Therefore, this study, using data from Korean multicenter registries, aimed to evaluate the association between BMI and the clinical outcomes of CAD patients who underwent PCI with a new-generation DES.

2. Materials and methods

2.1. Study population

The study flow and reasons for exclusion are provided in Supplementary Fig. 1. The data in the present study were derived from 3 different prospective and 1 retrospective Korean multicenter DES registries (5712 patients): 1) REVOLUTE (registry to evaluate clinical outcomes following new-generation drug-eluting stents), a prospective, multicenter registry for patients who underwent PCI, evaluating clinical efficacy of new-generation DES, including sirolimus-eluting silicon carbide coating stent, novolimus-eluting stent, and biolimus-eluting abluminal biodegradable polymer stent; 2) NOBORI (*ClinicalTrial.gov* NCT01348360), a prospective, multicenter registry, investigating efficacy and safety of biolimus A9-eluting stent for coronary lesions in high-risk patients; 3) CONSTANT (clinical, optical coherence tomography, and angiographic outcomes following Resolute zotarolimus-eluting stent implantation for patients with or without diabetes mellitus; *ClinicalTrial.gov* NCT01869842), a prospective, multicenter registry, evaluating the impact of optical coherence tomography-guided percutaneous coronary intervention on the neointimal coverage and malapposition following zotarolimus-eluting stent implantation; and 4) PCI-CABG (clinical outcomes of PCI versus coronary artery bypass graft for multivessel disease from the Korean multicenter angioplasty team registry), a retrospective, multicenter observational registry, evaluating efficacy and safety of various DESs for complex coronary lesions and long-term clinical outcomes compared with coronary artery bypass graft surgery [8]. These registries included all eligible patients without specific inclusion or exclusion criteria, reflecting real-world practice. A detailed list of the participating institutes is given in Supplementary Data.

Among a total of 5712 patients, 186 patients without a new-generation DES, 151 patients with no data regarding stent type or BMI, and 111 patients without follow-up were excluded. Thus, a total of 5264 consecutive patients, who underwent PCI with new-generation DES in 26 centers of South Korea and fulfilled the study criteria, were finally included in these analyses. The enrolled patients were classified into 4 categories according to BMI status, according to the World Health Organization: 1) underweight (BMI $< 18.5\,kg/m^2$), 2) normal weight ($18.5 \leq$ BMI $< 25.0\,kg/m^2$), 3) overweight ($25.0 \leq$ BMI $< 30.0\,kg/m^2$), and 4) obese (BMI $\geq 30.0\,kg/m^2$) [9].

New-generation DESs included zotarolimus-eluting (Endeavor Resolute; Medtronic, Minneapolis, MN, USA), everolimus-eluting (Xience; Abbot Vascular, Santa Clara, CA, USA; and Promus; Boston Scientific, Marlborough, MA, USA), biolimus-eluting (BioMatrix; Biosensors International, Singapore; and Nobori; Terumo, Tokyo, Japan), novolimus-eluting (DESyne; Elixir Medical Corporation, Sunnyvale, CA, USA), and sirolimus-eluting (Orsiro; Biotronik, Bülach, Switzerland) stents. The study protocol was approved by the institutional review board at each participating site, and all participants provided written informed consent.

2.2. Endpoints and definitions

The primary endpoint was the occurrence of major adverse cardiac and cerebrovascular events (MACCE) at 12 months, including all-cause mortality, nonfatal myocardial infarction (MI), stroke, and target-vessel revascularization (TVR). The secondary endpoint was all-cause mortality at 12 months. The individual components of the primary endpoint were also evaluated.

Clinical events were defined according to the Academic Research Consortium [10]. All-cause mortality included any death after PCI. MI was defined as a creatine kinase muscle/brain fraction elevation above the upper limit of normal or troponin T/I > 99th percentile of the upper limit of normal, with concomitant ischemic symptoms or electrocardiographic findings indicative of ischemia unrelated to an interventional procedure [10]. Stroke was defined as any occurrence of a focal neurological deficit confirmed by abnormal findings of brain imaging studies and a neurologist after PCI. Stent thrombosis was defined as definite or probable stent thrombosis [10]. Clinical follow-up was performed in-hospital, and after 1, 3, 6, and 12 months, either by a clinic visit or a telephone interview.

2.3. Procedures and clinical data

Stent implantation was performed according to current standard techniques and medical guidelines. Intravenous heparin was given at the start of the procedure (8000 to 10,000 IU bolus) to maintain an activated clotting time of 220–300 s. All patients were administered 300 mg of aspirin and clopidogrel 300–600 mg before procedure and maintained 100 mg of aspirin and 75 mg of clopidogrel after PCI. Details of the intervention, such as lesion predilation, post-stent dilation, and the application of mechanical support or concomitant medication, were left to the discretion of the operator.

Baseline data including age, sex, BMI, blood chemistries, smoking status, medication use, comorbidities, and echocardiographic, angiographic, and procedural findings were collected. Chronic renal failure was defined as a baseline estimated glomerular filtration rate < 60 ml/min/1.73 m^2. Severe calcification was defined as calcification noted without cardiac motion before contrast injection and generally involving both sides of the arterial wall [11].

2.4. Statistical analysis

Continuous variables are reported as mean ± standard deviation, and categorical variables as actual number and percentage. Baseline and procedural characteristics among groups were compared using 1-way analysis of variance or Mann-Whitney *U* test for continuous variables and Pearson's χ^2 test or Fisher's exact test for categorical variables. Hazard ratios (HR) for the primary endpoint and for all endpoints were calculated with multivariable analyses using a Cox proportional hazards model and shown with the 95% confidence interval (CI). To determine the predictors for the occurrence of MACCE, multivariate regression analysis was performed; all variables with a p value of < 0.10, age, and sex were entered into the model. Kaplan-Meier survival analysis using the log-rank test was used to compare cumulative incidence of all-cause mortality and MACCE among groups.

To examine the relationship between BMI as the continuous variables and MACCE, restricted cubic splines were plotted to explore