Korean Circ J. 2023 Dec;53(12):843-854
https://doi.org/10.4070/kcj.2023.0159
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Original Research

Check for updates

Association Between Body Mass Index and Clinical Outcomes According to Diabetes in Patients Who Underwent Percutaneous Coronary Intervention

Byung Gyu Kim, MD[1,*], Sung-Jin Hong, MD[2,*], Byeong-Keuk Kim, MD, PhD[2], Yong-Joon Lee, MD[2], Seung-Jun Lee, MD[2], Chul-Min Ahn, MD[2], Dong-Ho Shin, MD[2], Jung-Sun Kim, MD[2], Young-Guk Ko, MD[2], Donghoon Choi, MD[2], Myeong-Ki Hong, MD[2], and Yangsoo Jang, MD[3]

[1]Division of Cardiology, Department of Internal Medicine, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea
[2]Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Korea
[3]Division of Cardiology, Department of Internal Medicine, CHA Bundang Medical Center, CHA University College of Medicine, Seongnam, Korea

OPEN ACCESS

Received: Jun 7, 2023
Revised: Aug 8, 2023
Accepted: Aug 23, 2023
Published online: Sep 20, 2023

Correspondence to
Byeong-Keuk Kim, MD, PhD
Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, 50-1, Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
Email: kimbk@yuhs.ac

*Byung Gyu Kim and Sung-Jin Hong contributed equally to this work.

ORCID iDs
Byung Gyu Kim
https://orcid.org/0000-0001-5780-9642
Sung-Jin Hong
https://orcid.org/0000-0003-4893-039X
Byeong-Keuk Kim
https://orcid.org/0000-0003-2493-066X
Yong-Joon Lee
https://orcid.org/0000-0003-4526-6120
Seung-Jun Lee
https://orcid.org/0000-0002-9201-4818
Chul-Min Ahn
https://orcid.org/0000-0002-7071-4370
Dong-Ho Shin
https://orcid.org/0000-0002-7874-5542

AUTHOR'S SUMMARY

Although obesity paradox phenomenon has been frequently reported in populations with established coronary artery disease as well as those with diabetes, it remains uncertain whether there is a difference in the association between body mass index (BMI) and cardiovascular outcomes after percutaneous coronary intervention according to the diabetes status. In this registries data, better clinical outcome of the overweight to obese group over the normal weight group was found only in diabetic patients but not in non-diabetic patients showing a significant interaction. Our findings suggest that the association between BMI and outcomes may differ according to the diabetic status.

ABSTRACT

Background and Objectives: We evaluated the effect of diabetes on the relationship between body mass index (BMI) and clinical outcomes in patients following percutaneous coronary intervention (PCI) with drug-eluting stent implantation.
Methods: A total of 6,688 patients who underwent PCI were selected from five different registries led by Korean Multicenter Angioplasty Team. They were categorized according to their BMI into the following groups: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight to obese (≥25.0 kg/m^2). Major adverse cardiac and cerebrovascular events (MACCE), defined as a composite of death, nonfatal myocardial infarction, stroke, and target-vessel revascularization, were compared according to the BMI categories (underweight, normal and overweight to obese group) and diabetic status. All subjects completed 1-year follow-up.
Results: Among the 6,688 patients, 2,561 (38%) had diabetes. The underweight group compared to normal weight group had higher 1-year MACCE rate in both non-diabetic (adjusted hazard ratio [HR], 2.24; 95% confidence interval [CI], 1.04–4.84; p=0.039) and

kcj
Korean Circulation Journal

Jung-Sun Kim
https://orcid.org/0000-0003-2263-3274
Young-Guk Ko
https://orcid.org/0000-0001-7748-5788
Donghoon Choi
https://orcid.org/0000-0002-2009-9760
Myeong-Ki Hong
https://orcid.org/0000-0002-2090-2031
Yangsoo Jang
https://orcid.org/0000-0002-2169-3112

Funding
This study was supported by the Cardiovascular Research Center, Seoul, Republic of Korea.

Conflict of Interest
The authors have no financial conflicts of interest.

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

Author Contributions
Conceptualization: Kim BK; Data curation: Hong SJ, Shin DH, Kim JS, Hong MK, Jang Y, Kim BK; Formal analysis: Kim BG, Hong SJ; Funding acquisition: Kim BK; Investigation: Lee YJ, Lee SJ, Ahn CM, Kim JS, Ko YG, Choi D, Hong MK, Jang Y, Kim BK; Methodology: Kim BG, Hong SJ, Kim BK; Resources: Lee YJ, Lee SJ, Ahn CM, Shin DH, Kim JS, Ko YG, Choi D, Hong MK, Jang Y; Supervision: Kim BK; Writing - original draft: Kim BG, Hong SJ; Writing - review & editing: Kim BG, Hong SJ.

diabetic patients (adjusted HR, 2.86; 95% CI, 1.61–5.07; p<0.001). The overweight to obese group had a lower MACCE rate than the normal weight group in diabetic patients (adjusted HR, 0.67 [0.49–0.93]) but not in non-diabetic patients (adjusted HR, 1.06 [0.77–1.46]), with a significant interaction (p-interaction=0.025).
Conclusions: Between the underweight and normal weight groups, the association between the BMI and clinical outcomes was consistent regardless of the presence of diabetes. However, better outcomes in overweight to obese over normal weight were observed only in diabetic patients. These results suggest that the association between BMI and clinical outcomes may differ according to the diabetic status.

Keywords: Body mass index; Obesity paradox; Diabetes mellitus; Percutaneous coronary intervention

INTRODUCTION

Excessive body weight is associated with metabolic syndrome that predisposes individuals to insulin resistance and increases the risk of developing type 2 diabetes and cardiovascular disease (CVD).[1)2)] However, better survival and cardiovascular outcomes in overweight or obese patients than in patients with normal weight, which is called the obesity paradox, have been reported in populations with established CVD.[3)4)] Diabetes mellitus is an established risk factor for CVD, and patients with CVD who have diabetes demonstrate worse clinical outcomes than those without diabetes.[5-7)] However, it is not well established whether there is a difference in the association between body mass index (BMI) and cardiovascular outcomes after percutaneous coronary intervention (PCI) according to the diabetes status. Therefore, we evaluated the association between BMI and clinical outcomes according to diabetes status in patients with CVD who underwent PCI with drug-eluting stents (DES).

METHODS

Ethical statement

The Institutional Review Board of Severance Hospital of Yonsei University Health System (IRB No. 4-2015-1094) approved this study and waived the requirement for informed consent for this retrospective analysis.

Study design and population

The patient selection and reasons for exclusion are shown in **Figure 1**. Our data were derived from five Korean multicenter DES studies. Four registries (REVOLUTE, registry to evaluate clinical outcomes following new-generation DES; Nobori; CONSTANT, clinical, optical coherence tomography, and angiographic outcomes following Resolute zotarolimus-eluting stent implantation for patients with or without diabetes mellitus; and PCI-CABG, clinical outcomes of PCI versus coronary artery bypass graft for multivessel disease from the Korean multicenter angioplasty team registry) have been summarized previously.[8)] CPR-IMT (ClinicalTrial.gov NCT01872845) was a randomized trial comparing the effects of pravastatin and rosuvastatin on atherosclerosis progression measured by carotid intima media thickness in patients with coronary artery disease after biolimus-eluting stent implantation. A brief explanation of the REVOULTE, Nobori, CONSTANT, and PCI-CABG registries is provided in Supplementary Methods (**Supplementary Data 1**). These studies were designed to

https://doi.org/10.4070/kcj.2023.0159

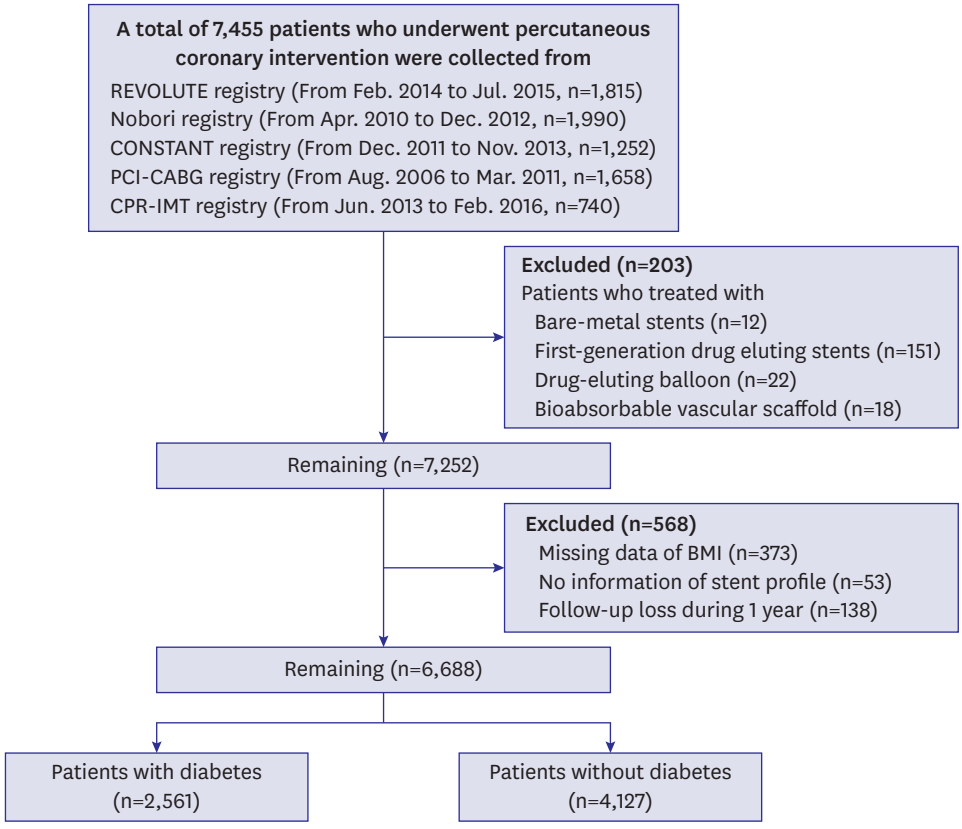


Figure 1. Patients' selection. Study flow.
BMI = body mass index; CONSTANT = clinical, optical coherence tomography, and angiographic outcomesfollowing Resolute zotarolimus-eluting stent implantation for patients with or without diabetes mellitus; CPR-IMT = randomized trial comparing the effect of pravastatin and rosuvastatin on atherosclerosis progression measured by carotid intima-media thickness in patients with coronary artery disease after Biolimus-eluting stent implantation; PCI-CABG registry = clinical outcomes of percutaneous coronary intervention versus coronary artery bypass graft for multivessel disease; REVOLUTE = registry to evaluate clinical outcomes following new-generation drug-eluting stents.

include patients who underwent DES implantation without specific inclusion or exclusion criteria, reflecting real-world clinical practice. Data were merged and rigorously reviewed for completeness and consistency.

Among a total of 7,455 patients, 6,688 consecutive patients who underwent PCI with new-generation DES and completed 1-year follow-up with BMI information were finally enrolled in this study (**Figure 1**). To minimize the impact of the types of stent, patients who implanted bare metal stent, first-generation DES, and bioresorbable vascular scaffold, or those with lesions treated with drug eluting balloon were excluded, and only patients with new generation DES were enrolled. The enrolled patients were categorized according to their BMI, according to the World Health Organization guidelines as follows: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight to obese (≥25.0 kg/m^2).[8] The main comparisons were performed 1) between the underweight and the normal weight groups and 2) between the normal and overweight to obese groups according to the diabetic status. Diabetes was defined as either known diabetes for which patients receiving glucose-lowering agents or insulin, or newly diagnosed diabetes defined as a HbA1C level ≥6.5%, and/or fasting glucose ≥126 mg/dL.

https://doi.org/10.4070/kcj.2023.0159

Study endpoints and follow-up

The primary endpoint was the occurrence of major adverse cardiac and cerebrovascular events (MACCE), defined as a composite of all-cause death, nonfatal myocardial infarction (MI), stroke, and target-vessel revascularization (TVR) at 12 months after PCI. The secondary endpoint was 12-month all-cause mortality. Cardiovascular-specific outcome was evaluated as a composite of cardiac death, non-fatal MI, stroke and target vessel revascularization. The individual components of the primary endpoint were also evaluated. Clinical events were defined according to the Academic Research Consortium definition.[9] All-cause mortality was defined as death after PCI. MI was defined as cardiac biomarker elevation with at least one value above the 99th percentile of the upper reference limit, with concomitant ischemic symptoms or electrocardiographic findings indicative of ischemia unrelated to the interventional procedure. Stroke was defined as the occurrence of a new neurological deficit confirmed by abnormal findings on brain imaging studies and a neurologist after PCI. TVR was defined as any repeat PCI or bypass surgery of the target vessel performed for restenosis with either 1) ischemia symptoms or a positive stress test and angiographic diameter stenosis of >50% or 2) angiographic diameter stenosis of >70% without ischemia symptoms or a positive stress test.

Baseline data including age, sex, BMI, blood chemistry, smoking status, medication use, comorbidities, and echocardiographic, angiographic, and procedural findings were collected. Chronic kidney disease was defined as a baseline estimated glomerular filtration rate <60 mL/min/1.73 m^2. Subjects who smoked more than 100 cigarettes in their lifetime were considered ever-smokers. Bifurcation lesion was defined as coronary artery narrowing occurring adjacent to and/or involving a side branch ≥2 mm. Severe calcification was defined as calcification noted without cardiac motion before contrast injection, and generally involving both sides of the arterial wall. Clinical follow-up was performed in-hospital and after 1, 3, 6, and 12 months, either through a clinic visit or a telephone interview.

Statistical analysis

Data are reported as the mean ± standard deviation for continuous variables and as numbers and percentages for categorical variables. Baseline and procedural characteristics were compared among the groups using one-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. Time-to-event data according to BMI groups were presented using Kaplan-Meier curves, and the differences between groups were examined using the log-rank test. Event rates between the groups were analyzed by multivariate analyses using a Cox regression model. Hazard ratios (HR) and 95% confidence intervals (CIs) for the primary endpoint and for all endpoints were calculated using the BMI category 18.5–24.9 kg/m^2 as reference in Cox regression models adjusted (a) for age as a continuous variable and sex (minimum adjustment) and (b) for age as a continuous variable, sex, and relevant covariates known to be associated with overweight and obesity or categorical variables with a p value of <0.1 in both diabetes and non-diabetes, such as hypertension, dyslipidemia, chronic kidney disease, smoking status, previous cerebrovascular accident, severe calcification, acute coronary syndrome, reduced ejection fraction (EF) (EF <40%), and multivessel disease (full adjustment). Analyses of baseline medical conditions and angiographic findings were reported using the available data with no imputation for missing data, given the low rate of missing data (<3%). There were no missing data regarding the clinical events. All tests were two-sided, and a p value of <0.05 was considered statistically significant. Statistical comparisons were performed using R Statistical Software (version 3.5.3; R Foundation for Statistical Computing, Vienna, Austria).

https://doi.org/10.4070/kcj.2023.0159

kcj
Korean Circulation Journal

RESULTS

Baseline characteristics

Among the 6,688 patients fulfilling the study criteria, 2,561 (38.3%) were diabetic. The mean BMI of this cohort was 24.5±3.3 kg/m^2. Density plotting showed that there was no significant difference in the distribution of BMI according to the diabetes status (**Supplementary Figure 1**). Patients with diabetes were older, more likely to be female, non-smokers, had a higher BMI, and had more frequent diagnoses of hypertension, dyslipidemia, chronic kidney disease, previous cerebrovascular accident, and previous PCI compared with those without diabetes (**Supplementary Table 1**). Patients with diabetes were less likely to present with acute coronary syndrome; however, they had more frequent left ventricular dysfunction (EF <40%), multivessel disease, and severe calcific lesions. The baseline characteristics according to the diabetes status and BMI categorization are summarized in **Table 1**. Regardless of diabetes status, as the BMI categories increased, the patients tended to be younger and had more frequent diagnoses of hypertension and dyslipidemia and worse lipid profiles. In contrast, the lower the BMI category, the higher the proportion of reduced EF. HbA1C levels were not significantly different among the BMI categories of patients with diabetes. In the angiographic findings, the proportion of severe calcific lesions was higher in the lower BMI groups, regardless of diabetes (**Table 2**).

Clinical outcomes by diabetes status and body mass index

Compared with non-diabetic patients, those with diabetes had a higher risk of MACCE (HR, 1.66; 95% CI, 1.35–2.04; p<0.001) and all-cause death (HR, 2.26; 95% CI, 1.67–3.07; p<0.001)

Table 1. Baseline characteristics according to BMI in diabetic and non-diabetic patients

Characteristic	Diabetes (n=2,561)			p value	Non-diabetes (n=4,127)			p value	p value§
	BMI (kg/m^2)				BMI (kg/m^2)				
	<18.5* (n=41)	18.5–24.9† (n=1,406)	≥25.0‡ (n=1,114)		<18.5* (n=117)	18.5–24.9† (n=2,381)	≥25.0‡ (n=1,629)		
Age (years)	69.4±11.2	67.6±10.0	64.8±10.5	<0.001	73.3±10.2	66.1±11.1	61.9±11.5	<0.001	<0.001
Male	24 (58.5)	978 (69.6)	754 (67.7)	0.228	73 (62.4)	1,715 (72.0)	1,237 (75.9)	0.001	<0.001
Comorbidities									
Hypertension	32 (80.0)	1,032 (73.6)	911 (81.9)	<0.001	56 (47.9)	1,338 (56.4)	1,023 (62.9)	<0.001	<0.001
Dyslipidemia	24 (58.5)	1,015 (72.3)	864 (77.8)	<0.001	68 (58.6)	1,613 (67.9)	1,128 (72.6)	<0.001	<0.001
Ever-smoker	12 (30.0)	628 (45.3)	486 (44.3)	0.150	52 (45.6)	1,060 (45.4)	805 (50.0)	0.016	0.045
CKD	11 (26.8)	201 (14.4)	129 (11.7)	0.006	8 (6.9)	107 (4.5)	46 (2.8)	0.007	<0.001
Previous CVA	8 (20.5)	191 (13.7)	131 (11.8)	0.149	18 (15.5)	235 (9.9)	115 (7.1)	<0.001	<0.001
Previous PCI	8 (19.5)	377 (26.8)	288 (25.9)	0.529	19 (16.2)	489 (20.5)	355 (21.8)	0.286	<0.001
Clinical ACS	21 (52.5)	677 (48.2)	512 (46.2)	0.487	63 (53.8)	1,256 (53.0)	809 (50.0)	0.163	<0.001
Laboratory data									
Hemoglobin (g/L)	11.1±2.0	12.7±2.1	13.2±2.1	<0.001	12.1±2.2	13.5±1.9	14.1±1.8	<0.001	<0.001
WBC count (k/mm^3)	8.3±3.5	8.0±3.2	8.0±2.7	0.419	7.7±3.3	7.8±3.2	7.9±2.9	0.568	0.014
LDL-C (mg/dL)	88.8±38.5	88.1±36.3	89.5±33.0	0.407	95.2±37.0	99.4±37.0	101.7±40.3	0.039	<0.001
HDL-C (mg/dL)	44.9±14.3	40.5±11.4	39.5±10.1	0.011	46.5±14.1	43.7±11.3	41.7±10.5	<0.001	<0.001
Serum Cr (mg/dL)	2.1±1.9	1.6±2.0	1.5±2.0	0.087	1.1±0.8	1.2±1.3	1.1±1.3	0.812	<0.001
HbA1C (%)	7.6±1.7	7.5±1.5	7.4±1.3	0.129	-	-	-	-	
EF (%)	44.5±16.1	54.9±15.1	58.5±12.9	<0.001	52.4±14.5	58.0±13.4	60.1±11.7	<0.001	<0.001
EF <40%	13 (40.6)	214 (17.5)	89 (9.6)	<0.001	24 (22.6)	212 (10.3)	90 (6.4)	<0.001	<0.001
Medication at discharge									
Statin	31 (75.6)	1,256 (89.7)	1,006 (90.5)	0.008	100 (86.2)	2,151 (90.8)	1,478 (91.0)	0.233	0.247
Beta-blocker	23 (56.1)	946 (67.5)	753 (67.8)	0.292	62 (53.4)	1,552 (65.5)	1,093 (67.3)	0.009	0.191
ACEi or ARB	25 (61.0)	649 (67.3)	803 (72.1)	0.018	67 (57.3)	1,403 (58.9)	1,014 (62.2)	0.090	<0.001

Values are presented as mean ± standard deviation or number (%).
ACEi = angiotensin-converting-enzyme inhibitor; ACS = acute coronary syndrome; ARB = angiotensin receptor blocker; BMI = body mass index; CKD = chronic kidney disease; Cr = creatinine; CVA = cerebrovascular accident; EF = ejection fraction; HDL-C = High-density lipoprotein cholesterol; LDL-C = Low-density lipoprotein cholesterol; PCI = percutaneous coronary intervention; WBC = white blood cell.
*Underweight, †Normal, ‡Overweight to obese. §p for the comparison between diabetes and non-diabetes.

https://doi.org/10.4070/kcj.2023.0159

Table 2. Angiographic and procedure characteristics according to BMI in diabetic and non-diabetic patients

Characteristic	Diabetes (n=2,561)			p value	Non-diabetes (n=4,127)			p value
	BMI (kg/m²)				BMI (kg/m²)			
	<18.5* (n=41)	18.5–24.9† (n=1,406)	≥25.0‡ (n=1,114)		<18.5* (n=117)	18.5–24.9† (n=2,381)	≥25.0‡ (n=1,629)	
Angiographic characteristics								
Multivessel disease	35 (87.5)	1,054 (75.1)	829 (74.8)	0.189	74 (65.5)	1,523 (64.3)	1,078 (66.8)	0.269
Left main lesion	4 (9.8)	154 (11.0)	116 (10.4)	0.892	8 (6.8)	253 (10.6)	138 (8.5)	0.044
Severe calcification	15 (37.5)	153 (11.1)	91 (8.3)	<0.001	17 (14.8)	219 (9.4)	95 (6.0)	<0.001
Severe tortuosity	2 (5.1)	38 (2.8)	22 (2.1)	0.299	4 (3.6)	65 (2.9)	41 (2.7)	0.830
Bifurcation	14 (35.9)	351 (25.9)	259 (24.1)	0.183	22 (21.0)	588 (25.5)	390 (24.9)	0.564
Thrombus	0	65 (6.3)	67 (7.9)	0.141	6 (7.1)	188 (10.5)	137 (11.1)	0.494
Target vessel								
Left main	2 (4.9)	92 (6.5)	59 (5.3)	0.405	4 (3.4)	161 (6.8)	83 (5.1)	0.045
Left anterior descending	26 (63.4)	658 (46.8)	525 (47.1)	0.110	58 (49.6)	1,126 (47.3)	758 (46.5)	0.767
Left circumflex	3 (7.3)	267 (19.0)	215 (19.3)	0.157	17 (14.5)	461 (19.4)	327 (20.1)	0.331
Right coronary	11 (26.8)	416 (29.6)	346 (31.1)	0.650	37 (31.6)	683 (28.7)	499 (30.6)	0.365
Bypass graft	0	9 (0.6)	13 (1.2)	0.303	0	6 (0.3)	12 (0.7)	0.056
Procedure characteristics								
Number of vessels treated, 2 or 3	11 (26.8)	361 (25.7)	319 (28.6)	0.251	25 (21.4)	514 (21.6)	414 (25.4)	0.120
Total number of stents implanted	1.6±0.6	1.5±0.6	1.5±0.7	0.220	1.3±0.5	1.4±0.6	1.4±0.6	0.022
Multiple stenting	22 (53.7)	571 (40.6)	465 (41.7)	0.229	38 (32.5)	808 (33.9)	602 (37.0)	0.120
Stent length (mm)	33.9±14.4	34.5±19.3	35.2±20.3	0.384	31.3±16.4	31.9±17.9	32.9±18.6	0.073
Stent diameter (mm)	2.9±0.3	3.1±0.8	3.1±0.5	0.688	3.1±0.5	3.1±0.4	3.1±0.6	0.124

Values are presented as mean ± standard deviation or number (%).
BMI = body mass index.
*Underweight, †Normal, ‡Overweight to obese.

Table 3. Incidence of adverse outcomes according to diabetes status and BMI categories

Cardiovascular outcome	Diabetes (n=2,561)			p value	Non-diabetes (n=4,127)			p value
	BMI (kg/m²)				BMI (kg/m²)			
	<18.5* (n=41)	18.5–24.9† (n=1,406)	≥25.0‡ (n=1,114)		<18.5* (n=117)	18.5–24.9† (n=2,381)	≥25.0‡ (n=1,629)	
MACCE	8 (19.5)	117 (8.3)	56 (5.0)	<0.001	14 (12.1)	99 (4.2)	66 (4.1)	<0.001
All-cause death	8 (19.5)	67 (4.8)	23 (2.1)	<0.001	7 (6.0)	42 (1.8)	23 (1.4)	0.011
Cardiovascular-specific outcome	3 (7.5)	83 (5.9)	49 (4.4)	0.200	10 (8.5)	80 (3.4)	54 (3.3)	0.010
Cardiovascular death	3 (7.5)	29 (2.1)	12 (1.1)	0.003	3 (2.6)	18 (0.8)	11 (0.7)	0.078
Non-fatal MI	0	17 (1.3)	12 (1.1)	0.757	0	13 (0.6)	12 (0.8)	0.523
TVR	0	36 (2.7)	25 (2.3)	0.534	6 (5.2)	44 (1.9)	35 (2.2)	0.054
Stroke	0	16 (1.2)	5 (0.5)	0.137	1 (0.9)	14 (0.6)	6 (0.4)	0.543

Values are presented as number (%).
BMI = body mass index; MACCE = major adverse cardiac and cerebrovascular event; MI = myocardial infarction; TVR = target vessel revascularization.
*Underweight, †Normal, ‡Overweight to obese.

(**Supplementary Figure 2**). The incidence rates of clinical outcomes according to diabetes status and BMI categories are summarized in **Table 3**. Kaplan-Meier curves showed that compared to the normal group, the underweight group had a higher incidence of MACCE and mortality in both diabetic and non-diabetic patients (**Figure 2A and B**). After adjustment, the underweight group compared to the normal weight group still had higher MACCE rate in both non-diabetic (adjusted HR, 2.06; 95% confidence interval [CI], 1.01–4.36; p=0.046) and diabetic patients (adjusted HR, 2.63; 95% CI, 1.45–4.75; p=0.001) (**Figure 3** and **Supplementary Table 2**). There was no significant interaction according to diabetes status for MACCE (p=0.761) and all-cause death (p=0.508).

When the normal weight, overweight and obese groups were compared, the incidence of MACCE or mortality was lower in the overweight or obese group than in the normal BMI group in diabetic patients, but it was not significantly different in non-diabetic patients (**Figure 2A and B**). These findings were consistent after adjustment. Among patients with

https://doi.org/10.4070/kcj.2023.0159

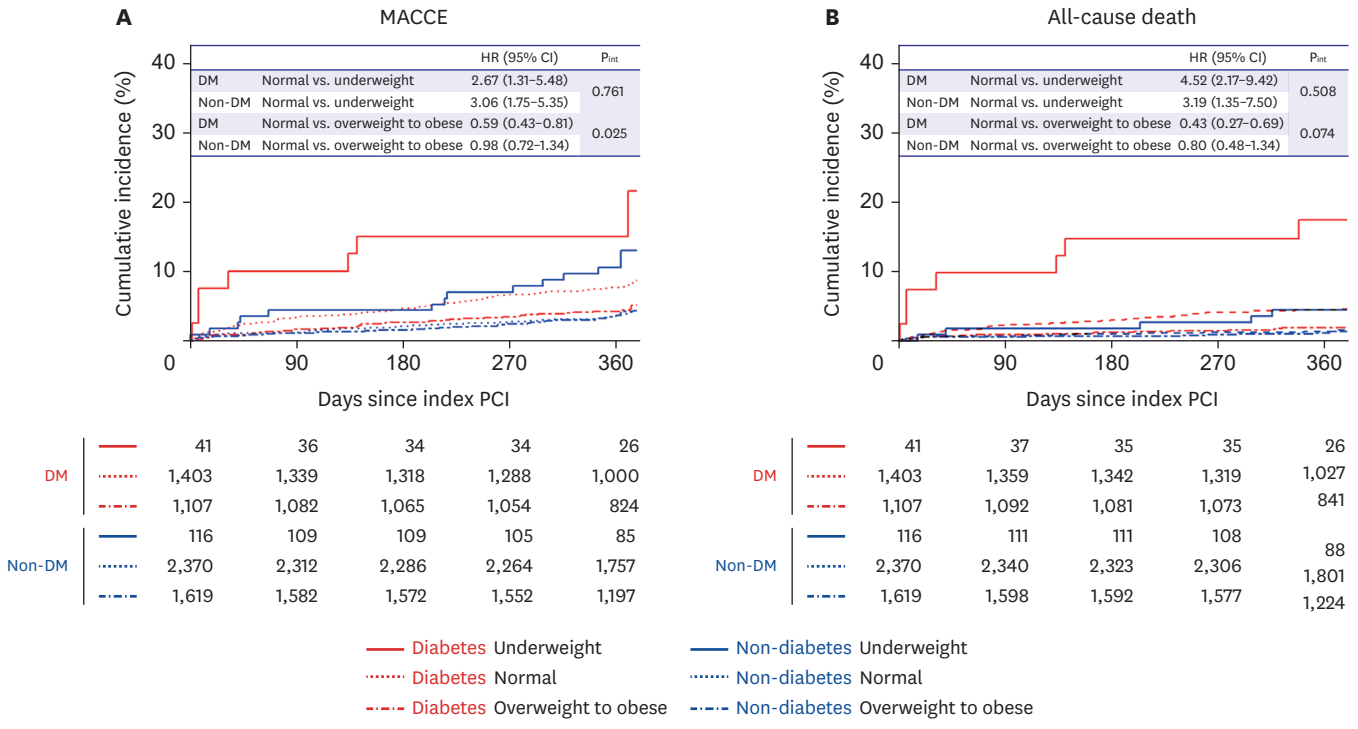
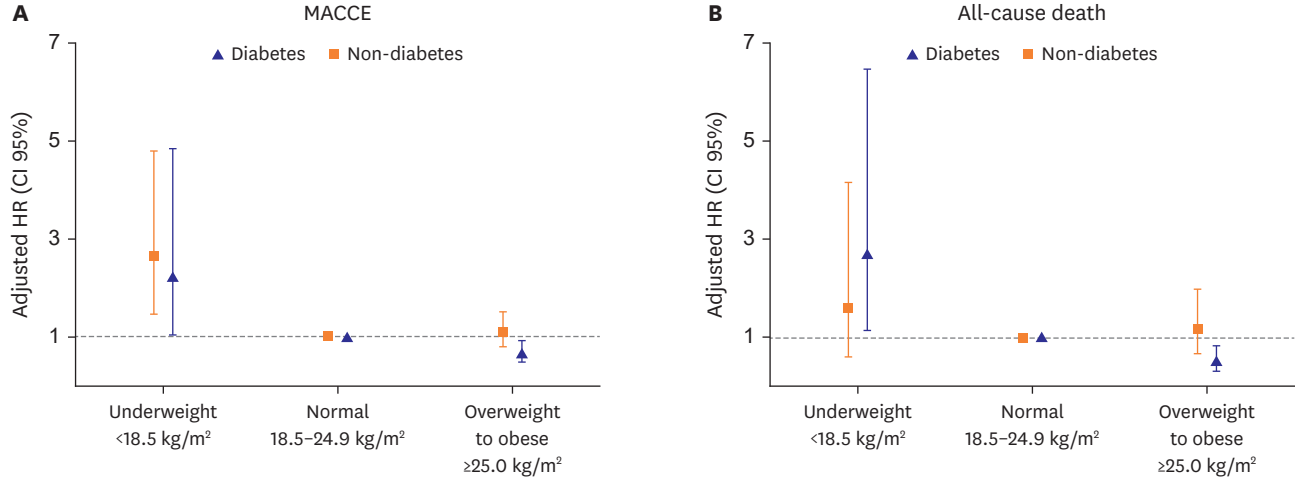


Figure 2. Kaplan-Meier curves according to BMI categories and diabetes status.
Rate of MACCE (A) and all-cause death (B) according to BMI categories and diabetes status.
BMI = body mass index; CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio; MACCE = major adverse cardiac and cerebrovascular event; PCI = percutaneous coronary intervention.



HR			
Diabetes	2.06*	1.0	0.67*
Non-diabetes	2.63**	1.0	1.09

HR			
Diabetes	2.71*	1.0	0.51**
Non-diabetes	1.62	1.0	1.18

Figure 3. Association of BMI categories with clinical outcomes in diabetes and non-diabetes patients.
Multivariate adjusted hazard ratio and its confidence interval for (A) MACCE and (B) all-cause mortality according to BMI categories in patients with and without diabetes. The normal weight (BMI 18.5–24.9 kg/m²) group was considered as the reference group. Adjusted for age, sex, hypertension, dyslipidemia, chronic kidney disease, smoking status, previous cerebrovascular accident, acute coronary syndrome, reduced ejection fraction, and multivessel disease.
BMI = body mass index; CI = confidence interval; HR = hazard ratio; MACCE = major adverse cardiac and cerebrovascular event.
*p<0.05, as compared to the reference group; **p<0.01, as compared to the reference group.

https://doi.org/10.4070/kcj.2023.0159

diabetes, the overweight to obese group had a lower risk of MACCE (HR, 0.67; 95% CI, 0.49–0.93; p=0.018) and mortality (HR, 0.51; 95% CI, 0.31–0.83; p=0.007) (**Figure 3** and **Supplementary Table 2**). In contrast, in non-diabetic patients, there were no differences in clinical outcomes between the normal group and the overweight to obese group (**Figure 3** and **Supplementary Table 2**). There was a significant interaction between MACCE rate and diabetes status (p for interaction=0.025). HRs of other adjustment variables other than BMI groups are shown in **Supplementary Table 3**.

DISCUSSION

The main findings of this study are as follows: i) the underweight group had a higher incidence of MACCE regardless of diabetic or non-diabetic patients; ii) better clinical outcome of the overweight to obese group over the normal weight group was found only in patients with diabetes but not in non-diabetic patients showing a significant interaction, suggesting that the association between BMI and outcomes may differ according to the diabetic status.

Obesity and overweight are considered systemic diseases that cause abnormal metabolism, such as inflammation and insulin resistance, which increase the risk of CVD, similar to the mechanism of diabetes.[10][11] Up to 30% of Europeans and 40% of Americans are obese, with the prevalence rising steeply worldwide,[12] and they are at a higher risk of incidental coronary artery disease[13] and death.[14][15] The prevalence of obesity as measured by BMI, is considerably lower among the Asian population than that reported for the Western population.[16] For example, the proportion of obese individuals with BMI ≥30 kg/m^2 reported in Korea in 2019 was 5.4%.[17] However, Asians are more likely to develop obesity-related diseases, including coronary artery disease, for a given BMI than the Western people.[16] In this pooled analysis of Korean multicenter PCI registries, the proportion of overweight patients was 36.2%, which was similar to that of the Western population, but only 4.8% were obese, which was much lower than the Western data.[3][18] In particular, severely obese patients with BMI ≥35 kg/m^2 are known to have worse clinical outcomes.[18][19] In this study, only 0.5% of the patients were severely obese, therefore it was difficult to assess their clinical outcomes in this study. The proportion of patients with diabetes accounted for 38.3% of the total population, similar to other PCI data.[20] Compared to non-diabetic patients, patients with diabetes demonstrated worse clinical outcomes, which is consistent with previous data.[5][7]

Obesity and diabetes are closely associated. More than half of the diabetic patients are overweight or obese,[21] and the risk of type 2 diabetes increases by 20% for every 1 kg/m^2 increase in BMI.[22] Given that patients with diabetes have a greater risk of developing coronary artery disease, in individuals with excessive body weight and concomitant diabetes, the risk of CVD may further increase. However, a peculiar phenomenon showing better survival and cardiovascular outcomes in overweight or obese patients compared with normal-weight patients, which is called the obesity paradox, has been frequently reported regardless of race in populations with established coronary artery disease.[3][4] Similar findings with nadir mortality in overweight to obese class I were also observed in the diabetic population.[23-25] However, there is a lack of evidence regarding the influence of diabetic status on the relationship between BMI and PCI outcomes. In this study, we found that the association between BMI and outcomes may differ according to diabetic status. The obesity paradox phenomenon was observed in patients with diabetes after PCI. In contrast, there was no

https://doi.org/10.4070/kcj.2023.0159

difference in the incidence of MACCE or death between the normal weight, overweight and obese patients without diabetes.

Our data suggest that diabetes may act as a modifier that contributes to the intensifying effect of the obesity paradox. The exact pathophysiological mechanisms that explain the worse clinical outcomes in diabetic patients with normal or subnormal BMI are uncertain. In fact, among the diabetic patients, subjects who were not overweight or obese and developed CVD may have inherited a specific sensitivity to CVD compared to those who developed CVD due to obesity. In our cohort, for example, patients in the normal or subnormal BMI groups had fewer traditional risk factors, such as hypertension and dyslipidemia, than overweight or obese patients, but they were more likely to have severe calcification in coronary artery lesions. Our findings are in agreement with prior reports demonstrating an inverse relationship between body weight and coronary calcification in intravascular ultrasound findings[26] or more severe carotid plaque in patients with low BMI who underwent PCI.[27] In addition, patients with normal or subnormal BMI are more often elderly and more likely to have poor renal function, which may be associated with more advanced coronary atherosclerosis and calcification. And low body weight can be the result of not only aging process with sarcopenia but also some fragile conditions including malnutrition or non-cardiac comorbidities such as malignancy, autoimmune disease, inflammatory disease, which can be one of the possible reasons of obesity paradox.[8] In addition, overweight or obese patients may have been detected and treated in the early stages of coronary artery disease due to more serious symptoms and functional impairment caused by excess body weight.[28] Moreover, physicians may have used more aggressive medical treatment and strengthened their recommendations for lifestyle modification in the obese patients.[29]

The present study provides additional evidence that the obesity paradox among patients with CVD is obvious in the Korean population and is more pronounced in patients with diabetes. In particular, diabetic patients with low body weight had the worst outcomes after PCI. Our findings suggest that, compared with overweight or obese patients, leaner diabetic patients may have some factors other than obesity-related factors that render them susceptible to CVD. Thus, efforts to identify the individual factors sensitive to CVD and more comprehensive management to prevent recurrent cardiovascular events are needed after PCI, especially in normal or underweight diabetic patients.

This study had several limitations. First, although this study analyzed the five Korean multicenter DES registries containing a large population of over 6,000 subjects, it was a retrospective and observational study. Second, since our findings were based on a single BMI value before PCI, fluctuations or changes in BMI during the follow-up period, which could have affected clinical outcomes, were not evaluated. Third, the BMI value does not indicate the body fat distribution because its calculation is not based on the distinction between muscle mass and adipose tissue. Other indices of central obesity, including waist circumference and waist-to-hip ratio, which are more related to clinical outcomes, were not evaluated in the present study. Fourth, most patients belonged to the normal or overweight groups, and there were only a small number of obese patients with a BMI of ≥30 kg/m^2. Thus, the clinical outcomes for the severely obese group with BMI ≥35 kg/m^2 could not be evaluated. Likewise, although underweight (BMI <18.5) was found to be have clinical impact in both diabetes and non-diabetes, the number of underweight group was also small, with only 41 (1.6%) among diabetic patients and 117 (2.8%) among non-diabetic patients. Fifth, some components of clinical outcomes were difficult to compare because of the small number of events. Sixth, our

https://doi.org/10.4070/kcj.2023.0159

main results was largely attributed by non-cardiac conditions, which raises questions about the effectiveness of more intensive medical therapy for normal and subnormal BMI patients. Furthermore, detailed information about coexisting noncardiac diseases or the causes of non-cardiac death was lacking. However, although there was no statistical difference in cardiovascular specific outcomes except for non-cardiac death, a similar trend was observed. A longer period of observation in a larger cohort may be needed to confirm the long-term cardiovascular impact of BMI on diabetes after PCI. Lastly, information regarding the duration, complications, type, and treatment of diabetes was not evaluated. Thus, there is a possibility that residual confounding factors or collider stratification bias remained.

In this cohort study, between the underweight and normal weight groups, worse clinical outcomes in the underweight group were observed in both diabetic and non-diabetic patients. However, compared to the normal weight group, better outcomes in overweight to obese group were observed only in diabetic patients, suggesting that the association between BMI and clinical outcomes may be different according to the diabetic status.

SUPPLEMENTARY MATERIALS

Supplementary Data 1
Supplementary Method

Click here to view

Supplementary Table 1
Baseline characteristics by diabetes status

Click here to view

Supplementary Table 2
HR of clinical outcomes according to diabetes status and body mass index categories

Click here to view

Supplementary Table 3
Multivariate analysis for MACCE according to diabetes status

Click here to view

Supplementary Figure 1
Density plot representing the distribution of body mass index of total cohort according to diabetes status.

Click here to view

Supplementary Figure 2
Kaplan-Meier analysis of clinical outcomes according to diabetes status.

Click here to view

https://doi.org/10.4070/kcj.2023.0159

REFERENCES

1. Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Arch Intern Med* 2002;162:1867-72.
PUBMED | CROSSREF
2. Vazquez G, Duval S, Jacobs DR Jr, Silventoinen K. Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis. *Epidemiol Rev* 2007;29:115-28.
PUBMED | CROSSREF
3. Holroyd EW, Sirker A, Kwok CS, et al. The relationship of body mass index to percutaneous coronary intervention outcomes: does the obesity paradox exist in contemporary percutaneous coronary intervention cohorts? Insights from the British Cardiovascular Intervention Society Registry. *JACC Cardiovasc Interv* 2017;10:1283-92.
PUBMED | CROSSREF
4. Kaneko H, Yajima J, Oikawa Y, et al. Obesity paradox in Japanese patients after percutaneous coronary intervention: an observation cohort study. *J Cardiol* 2013;62:18-24.
PUBMED | CROSSREF
5. Preis SR, Hwang SJ, Coady S, et al. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1950 to 2005. *Circulation* 2009;119:1728-35.
PUBMED | CROSSREF
6. Kim YH, Her AY, Jeong MH, et al. Outcomes between prediabetes and type 2 diabetes mellitus in older adults with acute myocardial infarction in the era of newer-generation drug-eluting stents: a retrospective observational study. *BMC Geriatr* 2021;21:653.
PUBMED | CROSSREF
7. Lee YJ, Cho JY, You SC, et al. Moderate-intensity statin with ezetimibe vs. high-intensity statin in patients with diabetes and atherosclerotic cardiovascular disease in the RACING trial. *Eur Heart J* 2023;44:972-83.
PUBMED | CROSSREF
8. Kim BG, Hong SJ, Kim BK, et al. Association between body mass index and clinical outcomes after new-generation drug-eluting stent implantation: Korean multi-center registry data. *Atherosclerosis* 2018;277:155-62.
PUBMED | CROSSREF
9. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;115:2344-51.
PUBMED | CROSSREF
10. Kim SH, Després JP, Koh KK. Obesity and cardiovascular disease: friend or foe? *Eur Heart J* 2016;37:3560-8.
PUBMED | CROSSREF
11. Powell-Wiley TM, Poirier P, Burke LE, et al. Obesity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 2021;143:e984-1010.
PUBMED | CROSSREF
12. Finucane MM, Stevens GA, Cowan MJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9·1 million participants. *Lancet* 2011;377:557-67.
PUBMED | CROSSREF
13. Folsom AR, Stevens J, Schreiner PJ, McGovern PG; Atherosclerosis Risk in Communities Study Investigators. Body mass index, waist/hip ratio, and coronary heart disease incidence in African Americans and whites. *Am J Epidemiol* 1998;148:1187-94.
PUBMED | CROSSREF
14. Abdelaal M, le Roux CW, Docherty NG. Morbidity and mortality associated with obesity. *Ann Transl Med* 2017;5:161.
PUBMED | CROSSREF
15. Adams KF, Schatzkin A, Harris TB, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *N Engl J Med* 2006;355:763-78.
PUBMED | CROSSREF
16. Yoon KH, Lee JH, Kim JW, et al. Epidemic obesity and type 2 diabetes in Asia. *Lancet* 2006;368:1681-8.
PUBMED | CROSSREF
17. Yang YS, Han BD, Han K, et al. Obesity fact sheet in Korea, 2021: trends in obesity prevalence and obesity-related comorbidity incidence stratified by age from 2009 to 2019. *J Obes Metab Syndr* 2022;31:169-77.
PUBMED | CROSSREF

18. Neeland IJ, Das SR, Simon DN, et al. The obesity paradox, extreme obesity, and long-term outcomes in older adults with ST-segment elevation myocardial infarction: results from the NCDR. *Eur Heart J Qual Care Clin Outcomes* 2017;3:183-91.
PUBMED | CROSSREF

19. Das SR, Alexander KP, Chen AY, et al. Impact of body weight and extreme obesity on the presentation, treatment, and in-hospital outcomes of 50,149 patients with ST-Segment elevation myocardial infarction results from the NCDR (National Cardiovascular Data Registry). *J Am Coll Cardiol* 2011;58:2642-50.
PUBMED | CROSSREF

20. Ali ZA, Maehara A, Généreux P, et al. Optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation (ILUMIEN III: OPTIMIZE PCI): a randomised controlled trial. *Lancet* 2016;388:2618-28.
PUBMED | CROSSREF

21. Hossain P, Kawar B, El Nahas M. Obesity and diabetes in the developing world--a growing challenge. *N Engl J Med* 2007;356:213-5.
PUBMED | CROSSREF

22. Hartemink N, Boshuizen HC, Nagelkerke NJ, Jacobs MA, van Houwelingen HC. Combining risk estimates from observational studies with different exposure cutpoints: a meta-analysis on body mass index and diabetes type 2. *Am J Epidemiol* 2006;163:1042-52.
PUBMED | CROSSREF

23. Pagidipati NJ, Zheng Y, Green JB, et al. Association of obesity with cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease: Insights from TECOS. *Am Heart J* 2020;219:47-57.
PUBMED | CROSSREF

24. Kwon Y, Kim HJ, Park S, Park YG, Cho KH. Body mass index-related mortality in patients with type 2 diabetes and heterogeneity in obesity paradox studies: a dose-response meta-analysis. *PLoS One* 2017;12:e0168247.
PUBMED | CROSSREF

25. Salehidoost R, Mansouri A, Amini M, Yamini SA, Aminorroaya A. Body mass index and the all-cause mortality rate in patients with type 2 diabetes mellitus. *Acta Diabetol* 2018;55:569-77.
PUBMED | CROSSREF

26. Dangas GD, Maehara A, Evrard SM, et al. Coronary artery calcification is inversely related to body morphology in patients with significant coronary artery disease: a three-dimensional intravascular ultrasound study. *Eur Heart J Cardiovasc Imaging* 2014;15:201-9.
PUBMED | CROSSREF

27. Giustino G, Dangas GD. Surgical revascularization versus percutaneous coronary intervention and optimal medical therapy in diabetic patients with multi-vessel coronary artery disease. *Prog Cardiovasc Dis* 2015;58:306-15.
PUBMED | CROSSREF

28. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH. The relationship between obesity and mortality in patients with heart failure. *J Am Coll Cardiol* 2001;38:789-95.
PUBMED | CROSSREF

29. Steinberg BA, Cannon CP, Hernandez AF, Pan W, Peterson ED, Fonarow GC. Medical therapies and invasive treatments for coronary artery disease by body mass: the "obesity paradox" in the Get With The Guidelines database. *Am J Cardiol* 2007;100:1331-5.
PUBMED | CROSSREF