Obesity paradox in coronary artery bypass grafting: Myth or reality?

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Objective: A high body mass index has been suggested to be protective in patients with coronary artery disease and in those undergoing coronary artery bypass grafting (CABG). However, these conflicting results might be related to the different risk profiles among the various body mass index categories. We sought to clarify the effect of varying degrees of excessive body weight on hard clinical outcomes in patients undergoing CABG.

Methods: A retrospective analysis of prospectively collected data was conducted to investigate the effect of a high body mass index on early and late mortality after first-time isolated CABG. Propensity score matching was used to adjust for confounding factors.

Results: The study sample consisted of 3269 normal weight, 6662 overweight, 3821 obese, and 211 morbidly obese patients. After matching, early mortality was not affected by overweight (mean difference, 0.7%; 95% confidence interval [CI], −0.2% to 1.5%), obesity (mean difference, 0.5%; 95% CI, −0.7% to 1.7%), and morbid obesity (mean difference, 1.6%; 95% CI, −1.0% to 1.0%), regardless of the patients' risk profile according to the European system for cardiac operative risk evaluation. Overweight status was not protective for late death (hazard ratio, 1.05; 95% CI, 0.9-1.08; $P = .4$). Compared with normal weight patients, both obese and morbidly obese patients had a higher risk of late death (hazard ratio, 1.22; 95% CI, 1.07-2.66; $P = .006$ for obese patients; hazard ratio, 1.36; 95% CI, 0.74-2.49; $P = .3$ for morbidly obese patients).

Conclusions: Obesity did not increase operative mortality, but it was associated with reduced late survival in patients undergoing primary isolated CABG. Our results raise concerns in supporting any protective effect of obesity in cardiovascular disease, specifically in patients undergoing surgical myocardial revascularization. (J Thorac Cardiovasc Surg 2014;147:1517-23)

According to the World Health Organization, the prevalence of obesity nearly doubled from 1980 to 2008, with more than 1.4 billion adults being overweight and more than half a billion obese. At least 2.8 million people die annually as a result of being overweight or obese. Obesity is a well known cardiometabolic risk factor, and the prevalence of almost every cardiovascular disease, including hypertension, heart failure, peripheral arterial disease, atrial fibrillation, and coronary artery disease, is markedly increased in the presence of obesity.[1] However, despite these adverse effects of obesity, numerous studies have suggested the existence of an ''obesity paradox,'' according to which normal weight patients with established coronary artery disease have a worse clinical prognosis than their more overweight or obese counterparts.[2]

The number of obese patients referred for coronary artery bypass grafting (CABG) has been increasing.[3] Obese patients have traditionally been considered at higher risk of perioperative morbidity and mortality, and, occasionally, they have not even been considered suitable for surgery solely because of their obese status. However, conflicting results have recently been reported,[4-8] with some investigations showing that a high body mass index (BMI) might even have a beneficial effect on early and late mortality, supporting the existence of an ''obesity paradox'' in patients undergoing CABG.[4-7] The biological basis for this seemingly contradictory clinical observation remains unclear. One possible explanation can be found in the different characteristics of patients in the obese and normal weight groups. For example, overweight and obese patients were reported to be significantly younger than the normal weight patients at the time of CABG.[4-7] Therefore, the different risk profile, rather than obesity per se, might have accounted for the apparently better prognosis of this patient population. To date, only a few studies have reported on the effect of a high BMI on survival after CABG, with several limitations, including a small sample size and significant differences in baseline characteristics in patients across the different BMI categories. Because obesity is a potentially treatable condition,[9] additional studies are warranted to confirm or refute this ''obesity paradox'' and to improve the treatment of such challenging patients.

Using a large database with 17 years of follow-up, we investigated the effect of a high BMI on the early and late mortality of patients undergoing first-time isolated CABG.

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Abbreviations and Acronyms

BMI = body mass index
CABG = coronary artery bypass grafting
CI = confidence interval
EuroSCORE = European system for cardiac operative risk evaluation
HR = hazard ratio
OR = odds ratio

ACD

METHODS

Study Population

The present study was performed with permission from the local medical ethics committee. We retrospectively analyzed prospectively collected data from the surgical database of Papworth Hospital (Cambridge, UK). This database is maintained by a team of full-time clinical information analysts, who are responsible for continuous prospective data collection as a part of a continuous audit process that is linked to a national database. Data collection is validated regularly. Information about death from any cause is obtained from the General Register Office approximately 1 week after the event. Patients undergoing first-time isolated CABG from March 1996 to May 2012 were included in the present analysis. Patients with missing data on important baseline clinical covariates were excluded from the study sample.

The patients were divided into 5 groups according to their BMI: underweight (BMI < 18.5 kg/m^2), normal weight (BMI, 18.5-24.9 kg/m^2), overweight (BMI, 25-29.9 kg/m^2), obese (BMI, 30-34.9 kg/m^2), and morbidly obese (BMI $\geq$ 35 kg/m^2). Because of the small sample size (n = 67), underweight patients were not included in the present analysis.

The primary endpoints were all-cause early (within 30 days or hospital discharge, whichever was earlier) and late (>30 days or after hospital discharge) death. We focused on all-cause death, which represents the most robust and unbiased index event, because no adjudication was required, thus avoiding inaccurate or biased documentation and clinical assessments.

Statistical Analysis

Baseline risk factors were selected among the variables included in the European system for cardiac operative risk evaluation (EuroSCORE).[10] The year of the operation was included in the analysis to correct for variable standards of perioperative care over time. Operative risk was derived by calculating the logistic EuroSCORE. The additive EuroSCORE was used to classify the patient risk profile into 3 groups: low risk (0-2), with an expected mortality of <2%; medium risk (3-5), with an expected mortality of <5%; and high risk ($\geq$6), with an expected mortality of >6%.[10]

The results are presented as the mean $\pm$ standard deviation for continuous variables and as proportions for categorical variables, according to the stated BMI categories.

Before matching, an analysis of the unmatched patient population was conducted to assess the effect of a high BMI on early and late mortality using logistic and Cox regression analysis, respectively, after adjusting for all covariates significantly associated with the chosen endpoints on univariate analysis ($P < .5$). The BMI was forced into the models as a categorized and continuous variable, using normal weight as the control.

Propensity score matching was used to minimize the bias related to the baseline differences among the BMI groups.[11] To estimate the propensity score, 3 logistic regression models were used, in which the BMI categories were regressed on the baseline characteristics listed in Table 1. Pairs of normal weight versus overweight, obese, and morbidly obese patients were derived using 1:1 matching. To optimize the matching process, we used "optimal" matching implemented by the MatchIt package (R project, R Foundation for Statistical Analysis, Vienna, Austria),[11] which finds the matched samples with the smallest average absolute distance across all the matched pairs. The commonly used nearest-neighbor matching method is greedy matching, in which the closest control match for each treated unit is chosen 1 at a time, without trying to minimize a global distance measure. The standardized mean difference was used to quantify the differences in the mean or prevalence between overweight and obese versus normal weight patients in the overall sample size and in the matched samples; a value >0.10 represented a meaningful imbalance in a given covariate.[12]

The difference in the probability of 30-day mortality among the BMI groups was assessed by directly estimating the difference in proportions among the BMI categories in the matched samples.[11] To investigate the effect of patient risk profile on early mortality in the BMI categories, we conducted a separate analysis according to 3 EuroSCORE risk groups (low, medium, and high risk, as previously specified).

The effect of the BMI categories on the interval to late death (>30 days) was assessed using Kaplan-Meier survival curves in the matched samples and the stratified log-rank method.[12]

All statistical analyses were performed using R, version 2.15.2 (R Foundation for Statistical Analysis).

RESULTS

Baseline

The study sample consisted of 3269 normal weight, 6662 overweight, 3821 obese, and 211 morbidly obese patients. The baseline characteristics of the patients according to BMI status are listed in Table 1. Several variables had standardized differences that exceeded 0.10, indicating significant differences in the baseline characteristics among the overweight, obese, and morbidly obese patients versus the normal weight patients. Normal weight patients tended to be older, more likely to have extracardiac arteriopathy, and to have an increased serum creatinine. They were more likely to undergo nonelective CABG. Subjects with a normal BMI presented with an increased overall risk profile, as assessed by the logistic EuroSCORE (5.9% $\pm$ 8.5%) compared with overweight (4.7% $\pm$ 6.8%; analysis of variance, $P < .05$ vs normal weight), obese (4.3% $\pm$ 6.9%, $P < .05$ vs normal weight), and morbidly obese (3.6% $\pm$ 5.3%; $P < .05$ vs normal weight) patients.

Unmatched Sample Analysis

In the unmatched sample, crude mortality within 30 days for normal weight, overweight, obese, and morbidly obese patients was 3.81%, 1.99%, 2.23%, and 1.43%, respectively. After adjusting for other risk factors, overweight status showed a protective effect on early mortality compared with normal weight (odds ratio [OR], 0.62; 95% CI, 0.48-0.81; $P = .0005$). However, this protective effect was no longer significant in the obese (OR, 0.79; 95% CI, 0.58-1.08; $P = .14$) and morbidly obese (OR, 0.74; 95% CI, 0.22-2.41; $P = .6$) patients. When the analysis was conducted according to the patient risk profile, being overweight was protective for high-risk ($P = .004$) and medium-risk ($P = .02$) but not for low-risk ($P = .7$) profile patients. As a continuous variable, BMI showed a U-shaped effect on the adjusted risk of early mortality with a significant risk reduction for BMI values of 26 to 32 kg/m^2 (Figure 1, *top*).