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CLINICAL RESEARCH STUDY

Obesity Paradox in Patients with Hypertension and Coronary Artery Disease

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ABSTRACT

PURPOSE: An obesity paradox, a “paradoxical” decrease in morbidity and mortality with increasing body mass index (BMI), has been shown in patients with heart failure and those undergoing percutaneous coronary intervention. However, whether this phenomenon exists in patients with hypertension and coronary artery disease is not known.

METHODS: A total of 22,576 hypertensive patients with coronary artery disease (follow-up 61,835 patient years, mean age 66 ± 9.8 years) were randomized to a verapamil-SR or atenolol strategy. Dose titration and additional drugs (trandolapril and/or hydrochlorothiazide) were added to achieve target blood pressure control according to the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure targets. Patients were classified into 5 groups according to baseline BMI: less than 20 kg/m^2 (thin), 20 to 25 kg/m^2 (normal weight), 25 to 30 kg/m^2 (overweight), 30 to 35 kg/m^2 (class I obesity), and 35 kg/m^2 or more (class II-III obesity). The primary outcome was first occurrence of death, nonfatal myocardial infarction, or nonfatal stroke.

RESULTS: With patients of normal weight (BMI 20 to $<25 \text{ kg/m}^2$) as the reference group, the risk of primary outcome was lower in the overweight patients (adjusted hazard ratio [HR] 0.77 , 95% confidence interval [CI], 0.70 - 0.86 , $P < .001$), class I obese patients (adjusted HR 0.68 , 95% CI, 0.59 - 0.78 , $P < .001$), and class II to III obese patients (adjusted HR 0.76 , 95% CI, 0.65 - 0.88 , $P < .001$). Class I obese patients had the lowest rate of primary outcome and death despite having smaller blood pressure reduction compared with patients of normal weight at 24 months ($-17.5 \pm 21.9 \text{ mm Hg}$ / $-9.8 \pm 12.4 \text{ mm Hg}$ vs $-20.7 \pm 23.1 \text{ mm Hg}$ / $-10.6 \pm 12.5 \text{ mm Hg}$, $P < .001$).

CONCLUSION: In a population with hypertension and coronary artery disease, overweight and obese patients had a decreased risk of primary outcome compared with patients of normal weight, which was driven primarily by a decreased risk of all-cause mortality. Our results further suggest a protective effect of obesity in patients with known cardiovascular disease in concordance with data in patients with heart failure and those undergoing percutaneous coronary intervention. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Beta-blockers; Calcium antagonists; Coronary artery disease; Hypertension; INVEST; Obesity paradox

Obesity has been an established risk factor for increased cardiovascular mortality in men and women.¹⁻¹⁰ The in-

creased risk of obesity for cardiovascular disease is thought to be mediated in part by the clustering of risk factors such as hypertension, hypercholesterolemia, and diabetes mellitus (metabolic syndrome).¹¹ In an epidemiologic study of 527,265 men and women, there was an increased risk of death associated with excess body weight during midlife.⁷ Similarly, in a Korean cohort of 1,213,829 men and women, obese people had higher rates of death than people of normal weight.⁸

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Although obesity increases the likelihood of metabolic syndrome and its consequences, obesity has not been associated with a worse outcome in all patient populations. In patients with known cardiovascular disease (eg, those with heart failure), those undergoing percutaneous coronary interventions, and those with known coronary artery disease referred for single-photon emission computed tomography, an “obesity paradox,” a paradoxical decrease in morbidity and mortality with increasing body mass index (BMI), has been described.¹²⁻¹⁸ In patients undergoing percutaneous coronary intervention, obese patients had a 5.7% absolute decrease in incidence of death at 1 year compared with normal-weight patients.¹⁴ In patients with congestive heart failure there was a 19% relative reduction in the risk of death in obese patients compared with normal-weight patients.¹² These findings, in contrast with earlier literature, suggest a protective effect associated with obesity in patients with known cardiovascular disease.

However, in patients with hypertension and coronary artery disease, the role of BMI in the risk of cardiovascular events is not defined. The objective of the present study was to investigate the effect of obesity on cardiovascular outcomes in treated hypertensive patients with known coronary artery disease. To study this relationship, the INternational Verapamil SR-trandolopril STudy (INVEST) cohort provided an ideal population.¹⁹

METHODS

Study Design

INVEST was a prospective, randomized, international study of 22,576 patients with hypertension and coronary artery disease. The inclusion and exclusion criteria, study design, and results have been published elsewhere.¹⁹ In brief, eligible patients were randomized to a verapamil-SR-based or an atenolol-based treatment strategy to achieve the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure targets (<140/90 mm Hg or <130/85 mm Hg in those with diabetes or renal dysfunction).²⁰ Patients were eligible if they were 50 years or older and had essential hypertension and documented coronary artery disease. Coronary artery disease was defined as a myocardial infarction 3 months or more before enrollment, coronary angiogram with more than 50% stenosis in at least 1 major coronary artery, angina pectoris, or evidence of ischemia on at least 2 different modalities of stress tests (electrocardiogram, echocardiogram, radionuclide scan) that were consistent. Exclusion

criteria included patients receiving beta-blockers within 2 weeks of randomization.

This analysis was designed to study the effects of obesity in patients with hypertension and coronary artery disease. At each study visit, an extensive cardiovascular examination was performed, and body weight and height were recorded into the electronic web-based data capture system. BMI was calculated by the system as weight in kilograms/height in meters squared, stored in the database, and recorded in the patient’s visit summary, which was printed for the patient’s medical record.

Statistical Analysis

Patients were classified into 5 groups according to their baseline BMI: less than 20 kg/m² (thin), 20 to 25 kg/m² (normal weight), 25 to 30 kg/m² (overweight), 30 to 35 kg/m² (class I obesity), and 35 kg/m² or more (class II-III obesity). Four patients with presumed erroneous data, defined as BMI

greater than 100 kg/m², were excluded. All analyses were conducted on the remaining 22,572 patients in the intention-to-treat population. Primary outcome was the first occurrence of all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes were all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke with cardiovascular-related death as an additional outcome. Patient groups were compared using analysis of variance for continuous variables and the chi-square test for categorical variables. For each outcome, a single unadjusted Cox proportional hazards model was used to compare risk among the 5 BMI categories (BMI 20-25 kg/m² as reference). A stepwise Cox proportional hazard regression model was used to evaluate the role of BMI on the risk of primary outcome. Prespecified covariates forced into the model included treatment, age, race (white as reference), gender, history of myocardial infarction, and heart failure. Other baseline covariates were selected for the model on the basis of a *P* value of .10 or less. All analyses were performed using standard software (SAS 9.1.3, SAS Institute Inc, Cary, NC).

RESULTS

Baseline Characteristics

The mean age was 66 ± 9.8 years, and the mean follow-up was 2.7 years (range, 1 day to 5.4 years) with 61,835 patient years accumulated. Of the 22,572 patients included in this analysis, 2.2% were thin, 20.0% were normal weight, 39.9%

CLINICAL SIGNIFICANCE

- In a hypertensive population with coronary artery disease, overweight or obese patients were less likely to die or experience nonfatal myocardial infarction or stroke.
- This “obesity paradox” occurred in men and women across all age groups, even though blood pressure was better controlled in patients of normal weight (BMI 20-25 kg/m²).
- The reasons for the apparent protective effect of increased BMI are unclear.

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