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## Obesity paradox in patients undergoing coronary intervention: A review

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### Abstract

There is strong relationship between obesity and cardiovascular disease including coronary artery disease (CAD). However, the literature has shown better outcomes in higher obese patients who undergo percutaneous cardiovascular interventions for CAD, a phenomenon known as the obesity paradox (OX). In this review, we performed extensive search for OX in patients undergoing percutaneous coronary intervention. We also discussed possible mechanism OX and disparities in different race and sex.

**Key words:** Obesity paradox; Coronary artery disease; Obesity; Percutaneous coronary intervention; Racial disparities

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**Core tip:** Literatures have shown strong association between obesity and coronary artery disease (CAD). However, a phenomenon known as obesity paradox (OX) exist which means that obese patients who undergo percutaneous coronary intervention for CAD, they have better outcome compared to normal and underweight patients. New studies also suggest racial and sexual disparities in OX. Multiple mechanisms and patho-physiology have been implicated for OX. In this review, we performed literature search of OX undergoing percutaneous intervention, propose mechanism of OX and racial and sexual disparities.

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## INTRODUCTION

Obesity is a condition in which the body mass index (BMI) is above 30.0 kg/m<sup>2</sup><sup>[1]</sup>. According to the Centers for Disease Control and Prevention (CDC), more than one-third of United States adults, which account for 78.6 million people, are obese<sup>[1]</sup>. It is one of the leading health problems in the United States<sup>[2]</sup> and is strongly associated with a higher risk of developing cardiovascular diseases such as hypertension, coronary artery disease (CAD), heart failure (HF), and arrhythmias like atrial fibrillation<sup>[3]</sup>.

Obese individuals generally have increased total blood volume which is associated with hypertension, high stroke volume, and increased cardiac output as the heart has to pump blood against high pressure<sup>[4]</sup>. Increased cardiovascular workloads typically lead to left ventricular hypertrophy and dilation which can further contribute to dyslipidemia and diabetes mellitus - syndromes typically associated with obesity. In addition, obesity is also an independent risk factor for CAD, a condition which arises when blood flow through the arteries becomes constricted following a steady buildup of atherosclerotic plaques along the arterial walls. CAD also increases the cardiovascular workload and leads to the pathologies discussed above. A common strategy of treating CAD is through percutaneous coronary intervention (PCI), a non-surgical approach that involves catheterization of the coronary arteries. Interestingly, research has shown that obese people have better outcomes and fewer complications following a PCI, despite the high health risk of CAD, a phenomenon that has been termed as the obesity paradox<sup>[5]</sup>.

Since most studies suggest a significant relationship between obesity and cardiovascular risks, it is imperative to review the information available in case studies and controlled trials. Thus, the aim of the study is to present a better understanding of how obesity relates to specific medical conditions and their associated outcomes.

## RESEARCH METHODS

We searched PubMed, Ovid, and Google Scholar for English language articles using terms obesity, paradox, PCI, CAD in various combinations. The abstracts were reviewed and articles related to OX and PCI were examined in detail.

## OBESITY AND PCI

Obese individuals are at a higher risk of developing (CVD)<sup>[6]</sup> and obesity is a poor prognostic factor for cardiovascular mortality<sup>[7]</sup>. Nevertheless, a growing body of evidence suggest better outcome and prognosis

in this very population following some forms of intervention<sup>[5,8-13]</sup>. This obesity paradox basically refers to the observation that while the risk of developing coronary heart disease is greater in obese individuals, the clinical outcomes - including cardiovascular mortality, myocardial infarction (MI), and related complications - are less common in these individuals after a PCI (Table 1).

A systemic review by Gurm *et al*<sup>[14]</sup> of four different randomized controlled trials of platelet glycoprotein II b/IIIa inhibition showed that the 30-d and one-year post-PCI complications were worse in patients with low (below 18.4 kg/m<sup>2</sup>), normal (18.5-24.9 kg/m<sup>2</sup>), overweight (25-29.9 kg/m<sup>2</sup>), and excessive (above 40 kg/m<sup>2</sup>) BMI compared to the obese individuals (BMI 30-39.9 kg/m<sup>2</sup>). They analyzed the Prevention of Ischemic Complication (EPIC) trial, the Long-term Outcome with Abciximab GP II b/IIIa blockade (EPILOB) trial, the Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis- II (IMPACT- II) trial and The Evaluation of Platelet II b/IIIa Inhibitor for Stenting (EPISTENT) trial. They analyzed 11300 patients for 30-d morbidity and mortality and 7290 patients for a 12-mo follow-up. They also observed a paradoxical effect in the obese group compared to the low, normal and overweight BMI patients after PCI. The 30-d mortality was statistically significantly lower and similar results were detected in the long-term follow-up.

In a cohort study, Angerås *et al*<sup>[15]</sup> analyzed 64436 patients from the Swedish Coronary Angiography and Angioplasty Registry. They divided the patients into two groups based on the significance of CAD and the treatment options (PCI, coronary artery bypass, or medical treatment). These patients were followed for up to 3 years for overall mortality. Their analysis showed a U-shaped mortality curve, with the least mortality in obese and overweight patients compared with normal, underweight, and morbidly obese patients. Hence, this study provides additional evidence of an obesity paradox.

In the Using the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry, Younge *et al*<sup>[16]</sup> analyzed 1019 patients who underwent PCI and followed them for 7 years for all-cause mortality to determine the association between health status, BMI, and mortality. They found that the overall mortality was decreased in overweight compared with obese and normal weight patients.

Lazzeri *et al*<sup>[17]</sup> conducted a retrospective analysis to study the relationship between age and obesity in the outcome of ST-elevation MI (STEMI) in patients treated with primary PCI therapy. The study included 1268 patients who were divided based on their BMI and age. The study had 2.9% patients with a lean BMI, 31.8% with normal, 51.7% with overweight, and 13.6% with an obese BMI, out of which 68.1% were less than 75 years of age and 31.9% were above 75 years of age. All-cause mortality was measured during in-hospital stay and at 1-year follow-up. They

**Table 1** Summary of association between percutaneous coronary intervention and obesity

Ref.	Study population	Study design	Outcome measures	Relationship with obesity
Akin <i>et al</i> <sup>[2]</sup>	1436 normal weight, 2839 overweight, and 1531 obese patients	Retrospective Cohort Study	Primary endpoints were the rate of major adverse cardiac and cerebrovascular events and target vessel revascularization	Baseline clinical parameters were more severe in overweight and obese patients
Angerås <i>et al</i> <sup>[15]</sup>	64436 patients going under angiography. Patients were divided into 9 groups based upon BMI	Cohort Study	To investigate the relationship between BMI and mortality in patients with ACSs	Obese and overweight patients have least mortality compared with normal, underweight, and morbidly obese patients
Gurm <i>et al</i> <sup>[14]</sup>	4 randomized, controlled trials	Systematic Review	To study the impact of BMI on outcome patients undergoing PCI	Increased BMI is associated with reduced risk of complications after PCI
Kaneko <i>et al</i> <sup>[11]</sup>	1205 patients: 92 lean, 640 normal-weight; 417 overweight, and 56 obese	Retrospective Cohort Study	Impact of obesity on Japanese patients who undergo primary PCI	Over-weight and obese patients were independently associated with favorable long-term clinical outcomes after PCI
Lazzeri <i>et al</i> <sup>[17]</sup>	1268 patients: 37 lean, 403 normal, 656 overweight, 172 obese patients	Case Series	Impact of age on the prognostic value of BMI	In patients < 75 yr, overweight patients showed increased in-hospital mortality rate and a poorer long-term survival rate
Kosuge <i>et al</i> <sup>[20]</sup>	3076 patients undergoing PCI	Case Control Study	In-hospital mortality	BMI itself had no impact on in-hospital mortality in patients undergoing primary PCI
Sharma <i>et al</i> <sup>[19]</sup>	36 studies (12 CABG; 26 PCI)	Meta-Analysis	Total mortality, CV mortality, and myocardial infarction	The risk of total mortality, CV mortality, and MI was highest among underweight patients as defined by low BMI and CV mortality was lowest among overweight patients
Stähli <i>et al</i> <sup>[9]</sup>	1993 patients: 461 (23.1%) were of normal weight, 985 (49.4%) overweight, 396 (19.9%) obese, and 144 (7.2%) very obese	Retrospective Cohort Study	All-cause mortality	Overweight and obese patients had lower all-cause mortality
Lancefield <i>et al</i> <sup>[10]</sup>	4762 patients undergoing PCI	Meta-Analysis	In-hospital and 12-mo MACE and mortality rates after PCI	Overweight and obese patients had lower in-hospital and 12-mo MACE and mortality rates after PCI
Uretsky <i>et al</i> <sup>[5]</sup>	22576 hypertensive patients with coronary artery disease	Randomized Control Trial	Primary outcomes include first occurrence of death, nonfatal myocardial infarction, or nonfatal stroke	Obese patients had a decreased risk of primary outcomes
Kang <i>et al</i> <sup>[12]</sup>	3824 STEMI patients: 129 underweight, 1253 normal weight, 1959 overweight, 483 obese	Retrospective Cohort Study	In-hospital mortality, revascularization in 1 yr, mortality in 1 yr, and overall mortality	Obese patients had significantly lower in-hospital and overall mortalities
Numasawa <i>et al</i> <sup>[13]</sup>	10142 patients: 462 underweight, 5945 normal, 3100 overweight and 635 obese	Retrospective Cohort Study	In-hospital outcomes	Obese patients are at a lower risk for in-hospital complications during and after PCI
Younge <i>et al</i> <sup>[16]</sup>	1019 patients: 354 normal, 468 overweight, and 197 obese	Prospective Cohort Study	All-cause mortality	Overweight, but not obesity, was associated with a lower risk for 7-yr mortality in PCI patients
Wang <i>et al</i> <sup>[21]</sup>	6083 patients (normal: 1592; overweight: 3026; obese: 1465)	Retrospective Cohort Study	Clinical-driven repeat revascularization, including TLR and non-TLR	Obesity was not associated with TLR, but was associated with a higher risk of non-TLR

ACS: Acute coronary syndrome; BMI: Body mass index; CV: Cardiovascular; CABG: Coronary artery bypass grafting; MACE: Major adverse cardiac event; PCI: Percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; TLR: Target lesion revascularization.

concluded that patients with a lean BMI had the highest mortality across all age subgroups at short and long-term follow-ups, and younger obese patients (age < 75 years) showed the lowest mortality only at short-term follow-up. Their findings indicate that obese populations develop cardiovascular heart disease at a younger age compared with the lean population and therefore, have less all-cause mortality at short-term. They also concluded that the obesity paradox is age-related because most of the obese individuals included in the study were in the younger age groups and their current medical condition was based on their consistent weight in the obese range. Therefore, with intervention

and appropriate weight loss regimen, a majority of the health problems could potentially dissipate with the decrease in the patients' weights. The lowest mortality at short-term observed in the younger obese patients is an expected result because the medical intervention helped them to recover from their medical conditions. Therefore, based on the above findings, it can be inferred that the obesity paradox is related to age in some instances.

A study by Akin *et al*<sup>[2]</sup> analyzed the relationship between BMIs after PCI with drug-eluting stent (DES). The investigators followed patients who underwent PCI with DES to determine if they had major cardiac,

cerebrovascular events (MACCE), such as death, MI, or cerebrovascular accident, and target vessel revascularization (TVR) during their in-hospital stay and at 1-year follow-up. A total of 5806 patients were enrolled in this study, out of which 24.7% had normal BMI, 48.9% were overweight, and 26.4% obese. No difference was observed in overall in-hospital MACCE rate in relation to BMI. However, in-hospital death was noted to be significantly higher in patients with normal BMI compared with overweight and obese patients. At one-year follow-up, there was no significant difference in MACCE-free and TVR-free survival in relation to BMI. It can be concluded that no "obesity paradox" was observed in patients after PCI with DES.

Sharma *et al.*<sup>[19]</sup> conducted a meta-analysis of 36 studies [12 coronary artery bypass graft (CABG) and 26 PCI] to investigate the relationship of BMI with total mortality, cardiovascular mortality, and MI post-PCI and CABG. They reported that the relative risk of total mortality, cardiovascular mortality, and MI was the highest among patients with low BMI and lowest among overweight patients<sup>[19]</sup>.

In another analysis limited to post-PCI patients, Sharma *et al.*<sup>[19]</sup> noted that the total mortality, CV mortality, and MI were the highest among patients with low BMI at the end of a mean follow-up period of 1.6 years. The CV mortality was the lowest among overweight patients. The investigators explained that better outcomes in overweight and obese patients could have been influenced by age, as the severely obese patients in the study were younger than the normal-weight patients on average by 7 years for PCI and 4 years for CABG. Because their study was not a randomized trial, patients could have had unmeasured CVD risk factors that affected outcomes. They also reported that in the CABG subgroup, CV mortality was highest among severely obese patients; therefore, they stated that prospective studies were needed to determine associations between weight and outcomes and to explore any underlying mechanisms.

Stähli *et al.*<sup>[9]</sup> assessed long-term mortality of 1993 patients undergoing chronic total occlusion (CTO) PCI at a tertiary care center. They studied patients according to different BMI categories: 23.1% were of normal weight, 49.4% were overweight, 19.9% were obese, and 7.2% were very obese. They found that compared with normal weight BMI patients (16.3%), overweight patients had a lower all-cause mortality (10.2%, log-rank  $P = 0.001$ ), while obese (11.1%, log-rank  $P = 0.08$ ) and severely obese (13.2%, log-rank  $P = 0.39$ ) patients had similar mortality rates. Being overweight was significantly associated with lower all-cause mortality. They concluded that overweight is associated with an improved survival in patients undergoing PCI for CTO, particularly in men.

Kosuge *et al.*<sup>[20]</sup> studied 3076 patients to determine the impact of BMI on outcomes after PCI for acute myocardial infarction (AMI). They reported that obese patients had a higher frequency of diabetes mellitus,

hyperlipidemia, hypertension and smoking.

Wang *et al.*<sup>[21]</sup> examined 6083 patients who were divided into three groups according to BMI: Normal ( $n = 1592$ ), overweight ( $n = 3026$ ), and obese ( $n = 1465$ ). The follow-up focused on clinical-driven repeat revascularization, including target lesion revascularization (TLR) and non-TLR. There was no significant difference in the incidence of TLR among normal, overweight, and obese patients (6.3% vs 6.1% vs 7.1%,  $P = 0.423$ ). In contrast, the incidence of non-TLR was significantly higher in obese patients compared with normal and overweight (8.4% vs 6.0% vs 5.8%,  $P = 0.003$ ). They concluded that, among patients undergoing PCI with DES, obesity was not associated with TLR but was associated with a higher risk of non-TLR.

## MECHANISM OF OBESITY PARADOX

Various possible mechanisms have been proposed for the observed obesity paradox in coronary heart disease. As BMI increases the size of coronary artery proportionally increase as well and small coronary artery are associated with worse outcome after PCI and CABG<sup>[22]</sup>. Another possible explanation could be that the obese patients are protected again malnutrition and wastage of energy, therefore cardiac remodeling after MI would be greater in obese compared to underweight patients. Obese patients have a high calorie reserve which is beneficial in case CAD induces cachexia, a known adverse prognostic factor in HF. The resulting weight loss also improves disease prognosis; in non-obese individuals however, any non-purposeful weight loss due to cachexia will have a detrimental effect on the patients' overall health<sup>[23]</sup>. In addition, the obese patients with heart disease are likely to make lifestyle changes that include better diet, caloric restrictions, daily exercise which can positively shift the disease prognosis. Obese patients also have an altered cytokine and hormonal profile which can be cardio-protective and to neutralize the harmful effects of other biological factors that are upregulated in acute and chronic heart disease. The high levels of the inflammatory  $\text{TNF-}\alpha$  can be quenched by the high density of  $\text{TNF-}\alpha$  receptors on the adipose tissues<sup>[24]</sup>. In addition, obese individuals have been shown to have significantly lower levels of circulating natriuretic peptides, which are associated with HF pathophysiology<sup>[25]</sup>. The higher levels of free lipoproteins in the obese also help block LPS and other inflammatory cytokines<sup>[26]</sup>.

## GENDER AND RACIAL DISPARITY IN OBESITY PARADOX

A recent cohort study by Vest *et al.*<sup>[27]</sup> showed that overweight females with HF had a survival advantage compared to overweight males. They reviewed 3811 HF patients and determined the impact of BMI on mortality. When the data was adjusted for potential confounders,



the overweight and obese males did not show any significant survival advantage; in the females however, the mortality associated with HF was higher in normal weight group compared to the obese even after the confounding factors were adjusted.

An association between race and obesity paradox has also been explored. A retrospective study by Kokkinos *et al.*<sup>[28]</sup> correlated BMI with mortality in 2013 African-American and 2000 Caucasian males with a mean age 60 years. A correlation was observed between BMI and mortality in the entire cohort, the healthy weight participants had a significantly higher risk, a hazard ratio (HR) of 1.7, compared to the obese subjects. This association was stronger in the African-American group (HR 1.95) compared to the Caucasian group (HR 1.53). However, the study was not focused on the obesity paradox specifically among CVD patients as presence of a cardiovascular disease was not considered as an inclusion or an exclusion factor for the participants.

## LIMITATIONS

The hypothesis of obesity paradox is controversial as the respective studies are limited by various biases and limitations. Most studies on the obesity paradox are retrospective in nature and therefore do not present any evidence of a direct link between obesity and better CAD treatment prognosis. Obese patients with CAD usually present earlier to the clinicians compare to their leaner counterparts. Therefore, the prolonged survival seen in the obese may simply be an earlier detection. There is evidence that the higher blood pressures seen in obese individuals makes them tolerate and respond better to CAD medications<sup>[29]</sup>. This may be easily confused with an inherent cardio-protective mechanism in the obese. Smoking is a common risk factor for CAD onset and poor prognosis and is most correlated with individuals with leaner BMIs: This could be another reason for a perceived better prognosis in the obese<sup>[30]</sup>. CAD prognosis is often confounded by the presence of other patho-physiological conditions like cancer<sup>[30]</sup>. The obesity paradox has been negated in one study that used X-ray absorptiometry to directly assess body fat levels instead of using the BMI index<sup>[31]</sup>.

## CONCLUSION

There is an obesity epidemic and obese patients have higher prevalence of co-morbid conditions such as arrhythmia, hypertension, hyperlipidemia, diabetes mellitus, which then increase the risk for CAD. Studies have shown favorable outcome after coronary intervention in obese patients proving phenomenon OX. There is an also strong disparity between different sex and race for OX and further studies are needed to investigate these disparities.

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