Obesity paradox in a cohort of 4880 consecutive patients undergoing percutaneous coronary intervention

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Received 7 January 2009; revised 22 May 2009; accepted 21 July 2009; online publish-ahead-of-print 17 August 2009

See page 146 for the editorial comment on this article (doi:10.1093/eurheartj/ehp339)

Aims
We sought to investigate the impact of body mass index (BMI) on long-term all-cause mortality in patients following first-time elective percutaneous coronary intervention (PCI).

Methods and results
We used the Scottish Coronary Revascularisation Register to undertake a cohort study of all patients undergoing elective PCI in Scotland between April 1997 and March 2006 inclusive. We excluded patients who had previously undergone revascularization. There were 219 deaths within 5 years of 4880 procedures. Compared with normal weight individuals, those with a BMI /C21 /C27.5 and /C30 were at reduced risk of dying (HR 0.59, 95% CI 0.39–0.90, 95% CI, P = 0.014). There was no attenuation of the association after adjustment for potential confounders, including age, hypertension, diabetes, and left ventricular function (adjusted HR 0.59, 95% CI 0.39–0.90, P = 0.015), and there were no statistically significant interactions. The results were unaltered by restricting the analysis to events beyond 30 days of follow-up.

Conclusion
Among patients undergoing percutaneous intervention for coronary artery disease, increased BMI was associated with improved 5 year survival. Among those with established coronary disease, the adverse effects of excess adipose tissue may be offset by beneficial vasoactive properties.

Keywords
Angioplasty ● Body mass index ● Hypertension ● Mortality ● Obesity

Introduction
In the general population, obesity is associated with an increased risk of cardiovascular disease incidence and mortality.1–5 Among those with established coronary artery disease, the evidence is somewhat contradictory. However, a number of studies have suggested an ‘obesity paradox’ whereby obesity appears to be protective against an adverse prognosis.6,7

Romero-Corral et al.8 undertook a systematic review of patients with coronary artery disease. Compared with normal weight patients, overweight patients had significantly lower cardiovascular and all-cause mortality, obese patients had comparable mortality, and severely obese [body mass index (BMI) /C35] patients had higher mortality. Conversely, in a meta-analysis of 10 cohorts of patients undergoing percutaneous coronary intervention (PCI), Oreopoulos et al.9 demonstrated a lower risk of dying among both overweight and obese patients. Most of the PCI studies included in the meta-analysis failed to exclude patients undergoing non-elective procedures and those with a past history of revascularization, and none adjusted for socioeconomic deprivation which is associated with both obesity and cardiovascular risk. The component studies used different methodologies. Some small studies

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had to use composite endpoints to achieve sufficient power, and some studies reported simple event rates or used logistic regression whereas others used survival analysis.

In this study, we examine the association between BMI and all-cause death up to 5 years following first-time elective PCI and explore whether this is explained by peri-procedural events or potential confounding factors.

**Methods**

**Data sources**

The Scottish Coronary Revascularisation Register has recorded information prospectively on all PCIs undertaken in Scottish National Health Service hospitals since April 1997. Data are collected on demographics, severity of cardiac disease, drug therapy, medical and surgical history, co-morbid conditions, and intervention details. The Register is linked annually to the General Registrar’s Office for Scotland database which collates data obtained from all death certificates, including the cause of death classified using the International Classification of Diseases Code (ICD 10).

**Inclusion and exclusion criteria**

We obtained, from the Register, data on all elective PCI procedures undertaken over 9 years: from April 1997 to March 2006 inclusive. Patients who underwent primary or rescue procedures for acute coronary syndrome were excluded. We also excluded patients who had previously undergone PCI or coronary artery bypass grafting and those whose BMI was recorded as <18 or >50. The remaining patients comprised the study cohort.

**Definitions**

Weight was categorized as underweight (BMI <20), normal weight (BMI ≥20 and <25), overweight I (BMI ≥25 and <27.5), overweight II (BMI ≥27.5 and <30), and obese (BMI ≥30). Patients were categorized using general population quintiles of socioeconomic status derived from the Carstairs deprivation index.**10**. The Carstairs index is an aggregated measure of material deprivation. It is derived from Census data on unemployment, social class, car ownership, and overcrowding and is determined for postcode sectors of residence (mean population of 5700). The extent of coronary disease was classified according to the number of coronary arteries with severe (>75%) stenoses; one, two, or three vessel disease or left main stem stenosis (>50%). High risk coronary anatomy was defined as either three vessel disease or left main stem stenosis. Hypertension was defined as either blood pressure ≥140/90 mmHg or anti-hypertensive therapy. Current smoking, diabetes mellitus, previous myocardial infarction, and left ventricular impairment were treated as binary (yes/no) variables. Our primary outcome, of all-cause death, was censored at 5 year follow-up.

**Statistical analyses**

Binary and ordinal data were summarized using percentages and compared using χ² tests and χ² tests for trend, respectively. Continuous data were summarized using medians and compared using the Kruskal–Wallis (KW) test. The overall association between BMI and risk of all-cause death was examined using univariate and multivariate Cox proportional hazard models. In the multivariate model, we adjusted for the potential confounders of age, sex, smoking status, diabetes, left ventricular impairment, previous myocardial infarction, deprivation quintile, number of arteries stenosed, and hypertension.

The proportional hazards assumption for Cox regression analysis was tested in StataMP 10 with both the ‘linktest’ based on re-estimation, and the ‘stphtest’ based on Schoenfeld residuals.

We formally tested for statistical interactions with all covariates, including hypertension. In the primary analyses, the Cox models were based on survival from the time of the index procedure. We then repeated the Cox models using survival from 30 days after the index procedure. Finally, all models were repeated including year as a covariate to adjust for potential bias due to changes in technique and obesity over time.

**Results**

Over the 9 years, there were 14 270 elective PCIs. We excluded 2347 patients who had a past history of PCI, 1115 who had previously undergone coronary artery bypass grafting, and 1230 for whom this information was missing. None of the remaining 9578 patients had their BMI recorded as <18 or >50. Of the 9578 patients, 4880 (51%) had complete data for all covariates and were included in the analyses. Of the study cohort, 2495 (51%) were hypertensive and 2385 (49%) were normotensive.

In total, 1059 (22%) patients were normal weight, 1184 (24%) were in the overweight I category, 1007 (21%) were in the overweight II category, and 1576 (32%) were obese. Across the range from normal weight to obese, there was a decrease in age (KW test, P < 0.001), and an increasing prevalence of smoking, diabetes, and hypertension (χ² for trend, all P < 0.001) (Table 1). There were no significant differences in the proportions of patients with left ventricular impairment, a history of myocardial infarction, or high-risk coronary anatomy. Fifty-four (1.1%) patients were classified as underweight. Compared with normal weight patients, they had a significantly higher prevalence of hypertension (Mann–Whitney U test, P = 0.045) and a non-significantly higher prevalence of diabetes (Mann–Whitney U test, P = 0.357).

Over 5 year follow-up, there were 219 deaths. On univariate analysis, the overweight II group had a significantly lower risk of all-cause mortality (HR 0.59, 95% CI 0.39–0.90, P = 0.014) compared with patients of normal weight (Table 2; Figure 1). This association persisted after adjustment for potential confounders. In particular, there was no attenuation of the association after full adjustment, including hypertension (overweight II adjusted HR 0.59, 95% CI 0.39–0.90, P = 0.015) (Table 2; Figure 2). There were no statistically significant interactions with any of the covariates, including hypertension. The ‘linktest’ based on re-estimation, and the ‘stphtest’ based on Schoenfeld residuals were not violated in any of the models.

Fifteen (7%) deaths occurred within 30 days of the index procedure. Exclusion of these had no effect on the results. Compared with normal weight patients, overweight II patients had a reduced risk of dying after 30 days (adjusted HR 0.58, 95% CI 0.38–0.90, P = 0.016) (Table 2). Inclusion of year of procedure as a covariate in the multivariate model did not alter the results. Compared with normal weight patients, overweight II patients had a reduced risk of dying from procedure date (adjusted HR 0.59, 95% CI 0.39–0.90, P = 0.015) and from 30 day post-procedure (adjusted HR 0.58, 95% CI 0.38–0.90, P = 0.016).
Discussion

Our results are supportive of an ‘obesity paradox’ among patients undergoing elective PCI for established coronary artery disease, whereby overweight patients have a significantly lower risk of dying than normal weight patients. Our association was U-shaped with a non-significant trend towards poorer survival among underweight patients than normal weight patients. This may be due to reverse causation since patients are likely to be underweight because of malnutrition or cachexia. Underweight patients have a higher prevalence of comorbid conditions, such as occult malignancy and heart failure, and older patients are more likely to be underweight. Underweight patients may receive anti-coagulation doses that are too high for their body size, making them more prone to peri-procedural bleeding complications. In light of the above, we treated underweight patients separately in our analyses.

There are a number of possible explanations for the reduced risk of dying observed among overweight patients. As with any observational study, there may be confounding. While obesity is not an independent predictor of the severity of coronary artery disease per se,15 there appears to be a lead time bias whereby obese patients are investigated and treated at an earlier stage in the disease process. In a study of 130 139 patients hospitalized for coronary artery disease, higher BMI was associated with increased use of standard medical therapies such as aspirin, beta-blockers, renin–angiotensin inhibitors, and lipid lowering therapy, increased use of anti-coagulation doses that are too high for their body size, making them more prone to peri-procedural bleeding complications. In the above, we treated underweight patients separately in our analyses.

As in previous studies,18–20 we demonstrated that increased weight is associated with an increased prevalence of other cardiovascular risk factors, such as diabetes and hypertension. It has been suggested that the increased risk associated with obesity in the general population may be mediated through these factors. However, in our cohort of patients with established coronary disease, we found no evidence of an interaction with these risk factors. The reduced risk among overweight patients was independent of their effect and the association with increased BMI was not attenuated by their inclusion in the model.

Previous studies have tended to analyse risk of death from the time of PCI. However, it has been shown that peri-procedural complications, such as hypotension, pulmonary oedema, renal impairment, major bleeding, access site haematoma, vascular complications, and mortality occur more frequently in lean patients than overweight or obese patients. Therefore, the improved survival among overweight patients may simply represent a perpetuation of peri-procedural risk. We used landmark analysis to demonstrate that our results were unaltered when peri-procedural events were excluded.

In our study, the only measure of obesity was BMI. Subcutaneous body fat is relatively inert with respect to metabolic and inflammatory effects. Compared with peripheral obesity, individuals with central obesity have higher total body fat, greater insulin resistance, and a higher prevalence of comorbidity. Body mass index is poor at distinguishing between lean body mass and body fat, and between central and peripheral adiposity. The ratio of central to peripheral obesity may increase with increasing BMI. Therefore, waist–hip ratio would have been a preferable measure of obesity, had it been available to us.

A causal link between obesity and improved prognosis is biologically plausible. Adipose tissue is now recognized as a major endocrine organ.21–23 Obesity is associated with high serum levels of low density lipoproteins that scavenge unbound circulating lipoproteins and consequently have an anti-inflammatory effect. Among patients with heart failure, obese individuals have lower levels of tumour necrosis factor and other inflammatory cytokines. Adipose tissue produces soluble tissue necrosis factor receptor which is believed to neutralize the deleterious effects
of tumour necrosis factor-alpha on the myocardium. We postulate that, in moderately overweight individuals, these beneficial effects may be sufficient to offset the adverse effects of obesity.

Funding
This work was supported by the Chief Scientist Office and British Heart Foundation.

Conflict of interest
None declared.

Reference

Table 2
Crude and adjusted Cox proportional hazard models of all-cause death following elective percutaneous coronary intervention

<table>
<thead>
<tr>
<th>BMI Group</th>
<th>Follow-up from procedure date</th>
<th>Follow-up from 30 day post-procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>Univariate HR (95% CI)</td>
<td>Multivariate a HR (95% CI)</td>
</tr>
<tr>
<td>Normal weight</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Overweight I</td>
<td>0.71 (0.49–1.04)</td>
<td>0.080</td>
</tr>
<tr>
<td>Overweight II</td>
<td>0.59 (0.39–0.90)</td>
<td>0.014</td>
</tr>
<tr>
<td>Obese</td>
<td>0.84 (0.60–1.19)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval.

aAdjusted for age, sex, smoking status, diabetes, left ventricular impairment, previous myocardial infarction, Carstairs socioeconomic deprivation quintile, and number of arteries stenosed (1, 2, 3 vessel disease, left main stem stenosis).

bAdjusted for above plus hypertension.

Figure 1
Crude hazard over 5 years following elective percutaneous coronary intervention by body mass index category.

Figure 2
Adjusted cumulative risk of all-cause death 5 years following elective percutaneous coronary intervention by body mass index category referent to normal weight individuals. CI, confidence interval; HR, hazard ratio.


