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Obesity and cardiovascular events in patients with established coronary disease

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KEYWORDS
Coronary artery disease;
Obesity;
Sex

Aims To explore the association between obesity and major adverse coronary events (MACE) in patients with established coronary artery disease (CAD).
Methods and results The Prevention of Events with Angiotensin Converting Enzyme-Inhibition (PEACE) Trial randomized 8290 patients with stable CAD and left ventricular (LV) ejection fraction (EF) (LVEF) $\geq$0.40 to trandolapril or placebo and followed them for a median of 4.8 years. In PEACE patients who were non-diabetic at baseline (5693 men and 1171 women), we used proportional hazards models to conduct a *post hoc* analysis to examine whether obesity, defined as a body mass index (BMI) $\geq$30 kg/m^2, is an independent risk factor for the composite endpoint of MACE, defined as cardiovascular death, non-fatal myocardial infarction, coronary revascularization, or stroke. The analysis was conducted separately for men and women. The baseline prevalence of obesity was 28.5% in men and 28.9% in women. After adjusting for significant confounders, obesity was associated with MACE in men [hazard ratio (HR) = 1.28, 95% CI 1.13–1.46, $P < 0.01$], but not in women (HR = 0.96, 95% CI 0.70–1.31, $P = 0.77$). Further categorization of BMI showed a J-shaped association between BMI and MACE in the men, and no association in the women.
Conclusion In the presence of established CAD, obesity is associated with risk for MACE in men, but there is no support of an association in women. This finding requires further evaluation.

Introduction

Obesity has reached epidemic proportions in USA and Western Europe, with 65% of the population overweight and almost one-third obese, and the incidence and prevalence of obesity continue to increase.[1,2] Obesity is strongly associated with reduced longevity as well as with stroke, diabetes, thrombosis, and the development of coronary artery disease (CAD).[3–5] The degree to which obesity contributes to acute, thrombosis-based coronary events, or to the progression of atherosclerosis leading to coronary revascularization is less clear. Few studies have examined the relation between obesity and cardiovascular events in patients with existing CAD independent of traditional coronary risk factors.[6–11] The results have been variable and a gender difference in the independent association of body mass index (BMI) and adverse cardiovascular events has been suggested.

In view of the varying results in the literature, we chose to explore whether the association between obesity and adverse cardiovascular events is independent of traditional coronary risk factors, in a large cohort of stable coronary patients randomized in the Prevention of Events with Angiotensin Converting Enzyme-Inhibition (PEACE) Trial.[12,13] Because of the strong association between obesity and diabetes and the effects of anti-diabetic drugs on obesity, we excluded patients reporting diabetes at baseline from this analysis.

Methods

The design of the PEACE Trial has been reported elsewhere.[12,13] Briefly, patients at least 50-years-old, with stable CAD and normal or mildly reduced left ventricular (LV) function (LVEF >0.40), were randomly assigned to treatment with the angiotensin converting enzyme-inhibitor trandolapril or to placebo and followed-up to 7 years, with a median of 4.8 years. Patients were excluded from PEACE if at the time of screening they had been hospitalized for unstable angina in the preceding 2 months, had coronary revascularization within the prior 3 months, or had planned elective coronary revascularization. This study complied with the Declaration of Helsinki, and the locally appointed Ethics Committees of each clinical site and the coordinating centre approved the research protocol. A total of 8290 patients provided informed consent and were

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randomized. Of these, 6904 patients reported at baseline that they were not diabetic and not taking anti-diabetic medications and hence were eligible for this analysis. Forty patients had missing data on height and/or weight and were therefore excluded, leaving 5693 men and 1171 women that were the subjects of this report.

Baseline measures

During the baseline visit with clinic research staff, patients self-reported their smoking status, medication use, and history of hypertension, diabetes, angina, intermittent claudication, transient ischaemic attack, stroke, myocardial infarction, and coronary revascularization. The study documented myocardial infarctions, coronary revascularizations, and ventricular function. To aid in categorizing baseline medications, the clinic research staff used a list of generic and brand names for calcium channel blockers, beta-blockers, potassium-sparing diuretics, other diuretics, digitalis, anticoagulants, aspirin and other antiplatelet therapy, hormone replacement therapy, and lipid-lowering therapy. Laboratory measures of serum creatinine, potassium, and total cholesterol were abstracted from recent medical records or obtained for the study from a local laboratory, and were measured on an average of 104 (SD 124) days before the baseline visit. The clinic research staff measured height, weight, and blood pressure using standard clinic procedures. Height and weight were measured without shoes or outdoor garments, with patients standing on the centre of a level scale with the head erect and eyes looking forward. Height was measured when the patient inhaled deeply, just before the patient exhaled. A patient whose BMI (weight in kilograms divided by height in meters squared) was 30 kg/m^2 or greater was considered obese.[14]

Endpoints

This analysis used a composite major adverse coronary event (MACE) endpoint, consisting of cardiovascular death, non-fatal myocardial infarction, coronary revascularization, or stroke. All patient-reported outcomes were new/incident outcomes and classified following a critical review of the patients' medical records by an events adjudication committee.

Statistical analysis

We used Cox proportional hazards models to conduct a *post hoc* analysis to examine the association between BMI and the composite endpoint MACE. Patients were censored at their last visit. Based on the obesity literature, we decided *a priori* to conduct the analysis separately for men and women,[15–17] however, we also tested the interaction between sex and BMI in a Cox model. Because of interaction terms, in general, being underpowered and because we had a relatively small number of women (1171), an α of 0.15 was used to define statistical significance for the interaction term between sex and BMI. Cox models were also used to adjust for treatment group and for variables known to be important predictors of MACE: age (continuous); history of myocardial infarction; history of angina; history of revascularization; history of hypertension; history of stroke; current smoking; measured systolic blood pressure (continuous); measured diastolic blood pressure (continuous); total cholesterol (continuous); LVEF percent (continuous); use of a calcium channel blocker; use of a beta-blocker; use of aspirin or an antiplatelet; use of a lipid-lowering drug; use of a diuretic; and, in women, hormone replacement therapy. A treatment–BMI interaction term was also tested. Residual analysis was used to assess model fit. The collinearity index was used to check for intercorrelations among covariates.[18] Models using the following categories of BMI were also examined to determine if there was a gradient effect: underweight ($<$18.5 kg/m^2); normal (18.5–24.9 kg/m^2, reference group), overweight (25.0–29.9 kg/m^2); obese (30–39.9 kg/m^2); and morbidly obese ($>$39.9 kg/m^2). The SAS analysis system version 8.2 was used for all analyses (SAS Institute Inc., Cary, NC, USA).

Results

The baseline prevalence of obesity (BMI $\geq$30 kg/m^2) was 28.5% in men and 28.9% in women. Further breakdown of BMI groups showed the percentage of men and women that were underweight to be 0.4% and 1.3%, respectively; normal, 22.0 and 29.4%; overweight, 49.1 and 40.4%; obese, 27.1 and 25.9%; and morbidly obese, 1.4 and 3.1%. *Table 1* shows baseline characteristics by sex and BMI (BMI $\geq$30 kg/m^2 vs. BMI $<$30 kg/m^2). At baseline, compared with non-obese men, obese men were more likely younger, enrolled in the United States, hypertensive, taking medications to control hypertension, to have had a previous coronary revascularization, past smokers, and taking lipid-lowering therapy. Compared with non-obese women, obese women were more likely younger, enrolled in the United States, hypertensive, taking medications to control hypertension, and less likely taking aspirin or antiplatelet medication.

During the median 4.8 years of follow-up (interquartile range = 1.6 years), the incidence rates per 100 years in men and women were; 0.7 and 0.6 for cardiovascular death; 1.1 and 0.8 for myocardial infarction; 4.0 and 3.5 for revascularization, and 0.4 and 0.4 for stroke. Several patients experienced more than one event, and the patients experienced a total of 1491 first MACE events (5.3 and 4.6 incidence per/100 person-years in men and women, respectively). The study drug trandolapril was not associated with MACE in either men or women. This is consistent with the overall study results reported earlier.[7] The interaction between trandolapril and BMI was not significant. The interaction between sex and BMI was considered significant (*P*-value for interaction term = 0.09), which the sex-stratified results clearly support, therefore, the results are reported separately for men and women.

In men, obesity was an independent risk factor for MACE (adjusted HR, 1.28; 95% CI, 1.13–1.46; $P < 0.01$ for BMI $\geq$30 kg/m^2 vs. BMI, $<$ 30 kg/m^2) (*Table 2A*). Other baseline factors independently associated with an increased risk of MACE in men were increasing age, a history of angina, current smoking, increasing total cholesterol, and use of a calcium channel blocker, beta-blocker, or diuretic. Further adjustment for the additional variables listed in *Table 1* did not alter the results of the association between obesity and MACE in men.

In women, obesity was not associated with MACE (adjusted HR, 0.96; 95% CI, 0.70–1.31; $P = 0.77$ for BMI $\geq$30 kg/m^2 vs. BMI $<$30 kg/m^2) (*Table 2B*). Baseline factors independently associated with an increased risk of MACE in women were a history of angina (borderline significance), increasing total cholesterol, and use of a calcium channel blocker. Hormone replacement therapy was independently associated with a decreased risk of MACE (borderline significance). Further adjustment for the additional variables listed in *Table 1* did not alter the results of the association between obesity and MACE in women.

A comparison of categories of BMI in men showed a J-shaped association with MACE, with a non-significant increased risk in the underweight group, and a graded increased risk in the obese and morbidly obese groups

Table 1 Baseline characteristics by sex and BMI

Baseline characteristic (percents unless otherwise indicated)	Men ($N = 5693$)			Women ($N = 1171$)		
	BMI < 30 kg/m^2 ($N = 4072$)	BMI ≥ 30 kg/m^2 ($N = 1621$)	*P*-value[a]	BMI < 30 kg/m^2 ($N = 832$)	BMI ≥ 30 kg/m^2 ($N = 339$)	*P*-value[a]
Assigned to trandolapril	48.7	50.0	0.39	52.0	54.6	0.41
Age (years) (mean $\pm$ SD)	64.1 $\pm$ 8.3	61.8 $\pm$ 7.8	<0.01	66.4 $\pm$ 8.2	64.1 $\pm$ 8.1	<0.01
Race Caucasian	94.9	94.7	0.76	91.2	87.6	0.06
Region						
USA	52.6	62.9	<0.01	56.6	66.1	0.02
Canada	32.0	28.9		30.9	24.8	
Puerto Rico	0.9	1.0		2.5	2.4	
Italy	14.5	7.1		10.0	6.8	
Medical history						
Documented myocardial infarction	56.7	56.3	0.75	51.2	56.0	0.13
Angina pectoris	68.2	69.8	0.24	70.3	74.6	0.14
PCI or coronary-artery bypass grafting	71.0	73.8	0.03	69.0	68.4	0.86
Hypertension	39.2	49.0	<0.01	48.4	62.2	<0.01
Stroke	3.9	3.8	0.87	3.7	2.7	0.36
Transient ischaemic attack	3.1	3.3	0.64	3.6	2.4	0.28
Cigarette use						
Current	15.0	12.7	<0.01	14.3	15.0	0.74
Past	62.8	70.7		46.8	44.2	
Never	22.2	16.6		38.9	40.7	
Blood pressure						
Systolic (mmHg) (mean $\pm$ SD)	132 $\pm$ 16	134 $\pm$ 16	<0.01	135 $\pm$ 18	136 $\pm$ 17	0.16
Diastolic (mmHg) (mean $\pm$ SD)	77 $\pm$ 9	80 $\pm$ 10	<0.01	76 $\pm$ 10	78 $\pm$ 9	<0.01
Laboratory determinations						
Serum total cholesterol (mg/dL) (mean $\pm$ SD)	190 $\pm$ 36	191 $\pm$ 37	0.30	205 $\pm$ 43	207 $\pm$ 43	0.31
LVEF > 0.40 and < 0.50	16.4	15.1	0.22	8.9	8.6	0.85
Medications						
Calcium channel blocker	32.8	36.1	0.02	38.1	42.8	0.14
Beta-blocker	57.2	65.4	<0.01	61.0	66.1	0.10
Aspirin or antiplatelet medication	91.6	91.4	0.85	91.5	87.0	0.02
Lipid-lowering therapy	69.4	73.7	<0.01	72.3	73.7	0.62
Potassium-sparing diuretic	2.0	3.0	0.04	5.3	8.0	0.08
Other diuretic	6.1	11.3	<0.01	14.0	23.0	<0.01
Digitalis	3.4	3.0	0.39	4.0	1.2	0.01
Hormone replacement therapy				34.9	31.7	0.30

[a]Based on *t*-tests for continuous variables and χ^2 for categorical variables, comparing obese and non-obese individuals within each sex.

(*Figure 1A*). No BMI category was associated with an increased risk of MACE in women (*Figure 1B*). An examination of BMI as a continuous variable resulted in significance for men, but not for women (unadjusted HR, 1.02; 95% CI, 1.01–1.04; $P < 0.01$ in men and unadjusted HR 1.00; 95% CI 0.97–1.02; $P = 0.76$ in women for each incremental increase in kg/m^2).

Based on the regression diagnostics performed, there was no evidence of a lack-of-fit of the Cox regression models and there was not a high degree of multicollearity between the covariates.

Discussion

This study suggests a sex-specific difference in the impact of obesity on adverse cardiovascular events in patients with established CAD. Specifically, in patients with chronic stable coronary disease, we report a significant association between obesity and MACE, independent of traditional coronary risk factors, in men, but not in women.

Our findings, regarding an association between obesity and cardiovascular events in men with coronary disease, are supported by Wolk *et al.*[19] They studied 382 patients with coronary stenosis >10% culled from a consecutive series of 504 patients coming to catheterization for various clinical indications. They reported a strong, independent cross-sectional association between BMI and the presence of an acute coronary syndrome, defined as a diagnosis of unstable angina or acute myocardial infarction [odds ratio (OR) = 1.49 for every 1 SD increase in BMI]. Based on the dose-response observed, the authors concluded that the risk of acute coronary events might be elevated even in the range considered to be normal or mildly elevated BMI. This contrasts with our results in which an increased risk of MACE was not observed in the overweight group in men. In men, we observed a J-shaped risk between BMI group and MACE, with a non-significant increased risk in the underweight group and a graded increased risk in the obese and morbidly obese groups. In women, our results show no association. These investigators did not report a difference

Table 2 Treatment adjusted and final multivariable adjusted Cox regression models predicting time to MACE[a]

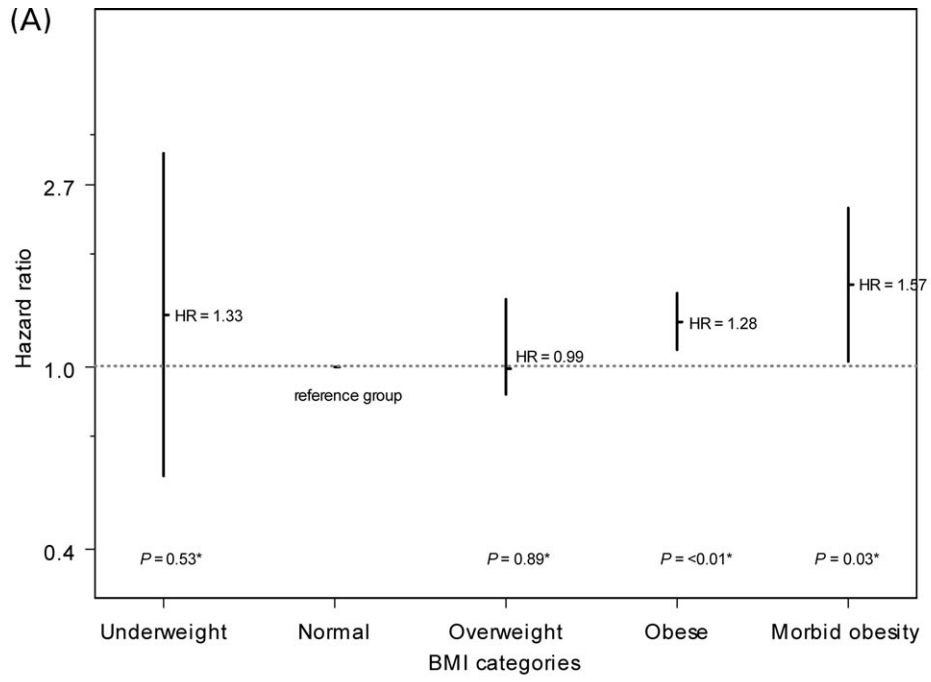
Baseline characteristics	HR	95% CI	*P*-value
A. Men			
Treatment adjusted model			
BMI $\geq$ 30 kg/m^2 (vs. $<$30 kg/m^2)	1.30	(1.16–1.46)	$<$0.01
Trandolapril (vs. placebo)	0.93	(0.84–1.04)	0.23
Final multivariable adjusted model			
BMI $\geq$ 30 kg/m^2 (vs. $<$30 kg/m^2)	1.28	(1.13–1.46)	$<$0.01
Trandolapril (vs. placebo)	0.91	(0.81–1.02)	0.12
Age at randomization (per year increase)	1.01	(1.01–1.02)	$<$0.01
History of MI (vs. no)	1.02	(0.91–1.16)	0.70
History of angina (vs. no)	1.34	(1.17–1.54)	$<$0.01
History of revascularization (vs. no)	0.93	(0.82–1.06)	0.27
History of hypertension (vs. no)	1.05	(0.92–1.19)	0.47
History of stroke (vs. no)	0.95	(0.71–1.28)	0.75
Current smoking (vs. never/past)	1.29	(1.10–1.51)	$<$0.01
Systolic BP (per mmHg increase)	1.00	(1.00–1.01)	0.20
Diastolic BP (per mmHg increase)	1.00	(0.99–1.01)	0.74
Serum total cholesterol (per mg/dL increase)	1.00	(1.00–1.00)	0.01
LVEF (per percent increase)	1.00	(0.99–1.00)	0.20
Calcium channel blocker use (vs. no)	1.47	(1.30–1.66)	$<$0.01
Beta-blocker use (vs. no)	1.36	(1.20–1.54)	$<$0.01
Aspirin or antiplatelet use (vs. no)	0.97	(0.80–1.19)	0.80
Lipid-lowering drug use (vs. no)	0.90	(0.79–1.02)	0.11
Diuretic use (vs. no)	1.34	(1.12–1.59)	$<$0.01
B. Women			
Treatment adjusted model			
BMI $\geq$ 30 kg/m^2 (vs. $<$30 kg/m^2)	1.01	(0.76–1.34)	0.95
Trandolapril (vs. placebo)	0.96	(0.74–1.24)	0.75
Final multivariable adjusted model			
BMI $\geq$ 30 kg/m^2 (vs. $<$30 kg/m^2)	0.96	(0.70–1.31)	0.77
Trandolapril (vs. placebo)	0.94	(0.71–1.25)	0.68
Age at randomization (per year increase)	1.01	(1.00–1.04)	0.14
History of MI (vs. no)	0.96	(0.71–1.29)	0.78
History of angina (vs. no)	1.43	(1.00–2.03)	0.05
History of revascularization (vs. no)	1.21	(0.89–1.65)	0.23
History of hypertension (vs. no)	1.20	(0.88–1.65)	0.25
History of stroke (vs. no)	0.81	(0.36–1.83)	0.61
Current smoking (vs. never/past)	1.36	(0.94–1.99)	0.11
Systolic BP (per mmHg increase)	1.00	(0.99–1.01)	0.89
Diastolic BP (per mmHg increase)	1.00	(0.99–1.02)	0.57
Serum total cholesterol (per mg/dL increase)	1.00	(1.00–1.01)	$<$0.01
LVEF (per percent increase)	1.00	(0.98–1.01)	0.58
Calcium channel blocker use (vs. no)	1.39	(1.03–1.88)	0.03
Beta-blocker use (vs. no)	1.22	(0.89–1.66)	0.22
Aspirin or antiplatelet use (vs. no)	1.09	(0.67–1.79)	0.73
Lipid-lowering drug use (vs. no)	0.87	(0.64–1.19)	0.38
Diuretic use (vs. no)	1.05	(0.75–1.48)	0.77
Hormone replacement therapy (vs. no)	0.74	(0.55–1.00)	0.05

[a]Major adverse coronary events: cardiovascular death; non-fatal myocardial infarction; coronary revascularization; or stroke.

between men and women in the association between BMI and acute coronary syndrome, nor did they report if such a possibility was examined, but the number of patients in their study was small (266 men and 116 women).

Other studies do report differences between men and women with regard to obesity and cardiovascular events. Kragelund *et al.*[10] reported 6676 patients with a prior myocardial infarction screened for entry into the Trandolapril Cardiac Evaluation (TRACE) study. There was no association between BMI and mortality in men or women, however, the waist to hip ratio (WHR) was a risk factor for mortality in men in this study, but not in women.

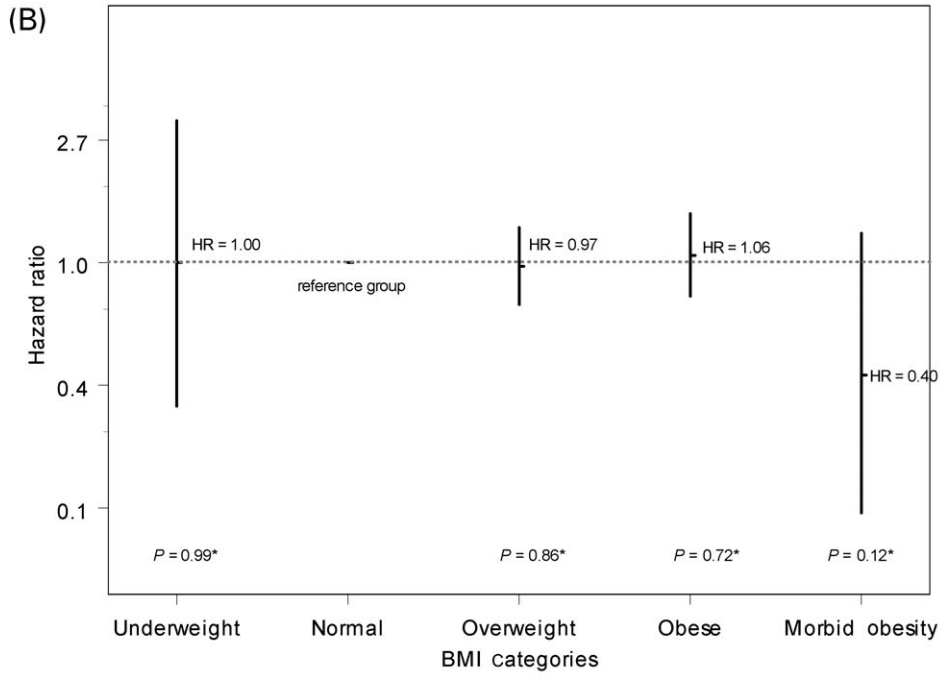
Dagenais *et al.*[6] studied 6620 men and 2182 women entered into the Heart Outcomes Prevention Evaluation (HOPE) study. Increasing BMI was independently associated with an increased risk of myocardial infarction in men but not in women, a finding comparable to our study. Increasing BMI, however, was not associated with cardiovascular death or stroke in men or women. Increasing waist circumference was associated with an increased risk of myocardial infarction in men but not women; however, increasing waist circumference was not associated with cardiovascular death or stroke in men or in women. On the other hand, increasing WHR was associated with an



* MACE: cardiovascular death; non-fatal myocardial infarction; coronary revascularization; or stroke.

† Adjusted for assigned treatment group.

* Compared with the reference group.



* MACE: cardiovascular death; non-fatal myocardial infarction; coronary revascularization; or stroke.

† Adjusted for assigned treatment group.

* Compared with the reference group.

Figure 1 (*A*) HR and 95% CI for categories of BMI predicting time to MACE* in men.† (*B*) HR and 95% CI for categories of BMI predicting time to MACE* in women†.

increased risk of myocardial infarction, cardiovascular death, and stroke in women but not in men.

Widlansky *et al.*[11] examined 5010 men excluded from the Physician's Health Study because of a history of myocardial infarction or stroke. They found no independent association of total or cardiovascular mortality and BMI.

Potential mechanism of obesity-associated adverse cardiovascular events

Obesity contributes to the development of atherosclerosis and transition to the acute coronary syndromes.[3–5] Obesity leads to insulin resistance that, in turn, leads to a cluster of traditional risk factors, known as the metabolic syndrome, which facilitates atherogenesis.[20] In insulin-resistant individuals, the adipose tissues have a diminished capacity to take up free fatty acids. These free fatty acids are available to the liver that, as a result, secretes an increased amount of very low-density lipoprotein.[21] Very low-density lipoprotein delivers cholesterol to the vessel wall facilitating atherogenesis. Also, in insulin-resistant individuals, the high-density lipoprotein cholesterol concentration is reduced and dense low-density lipoprotein cholesterol particles are generated.

The development of acute coronary syndromes is usually due to plaque rupture and may be mediated by inflammatory cytokines secreted by adipose tissue. Adipose tissue is now recognized as a highly active endocrine organ secreting a variety of cytokines that mediate inflammatory and atherosclerotic processes as well as the activity of the coagulation system. These include tumour necrosis factor-alpha, interleukin-6, interleukin-1β, adiponectin, plasminogen activator inhibitor-1, and tissue factor, as well as others.[1,2,22] In the aggregate, the various substances secreted by adipose tissue appear to be a likely mechanism for the development of plaque rupture and coagulation that are the basis for the transition from chronic progression of atherosclerosis to the acute coronary syndromes. The presence of multiple active plaques in many acute coronary syndrome patients supports the notion of this sort of system stimulus.[22,23]

Synthesis, strengths, and limitations

Although there is a compelling outline of a possible mechanism for the association of adipose tissue with the development of acute coronary syndromes, both the differences in the association of obesity measures and adverse cardiovascular events and the gender difference that we and the HOPE investigators observed remain to be explained. It is possible that our findings of a gender difference in the association of BMI and adverse events in men, but not women, results from the simple play of chance. The similar finding in the HOPE study patients[6] makes this less likely.

Another possibility is that the obesity measures used are not optimal for the task of diagnosing and quantifying obesity. Underwater weighing is the best approach to determine total body fat but is unsuitable for routine use, either in epidemiological studies or in clinical practice.[24] Computed tomography is considered the 'gold standard'[24] for assessing abdominal fat but is costly and involves radiation making it cumbersome and difficult to use for repeated follow-up. In our analysis, obesity was defined by BMI using the current definition for obesity, a widely used surrogate for adiposity. However, BMI is altered by parameters other than body fat, such as muscle mass and fluid status. Abdominal obesity, measured by waist circumference or WHR, has been suggested as a better predictor of cardiovascular events in women,[25] and supported by recent data.[6] It is therefore possible that the lack of association between obesity and cardiovascular events in women in this study could be due in part to limitations of BMI in quantifying obesity. In addition, risk factor profile differences in men compared with women may have been responsible for the absence of an adverse association in women. For example, the women in this study, compared with the men, were older, less likely Caucasian, less likely to have a history of revascularization, more likely to have hypertension, and more likely taking calcium channel blockers, beta-blockers, and diuretics (data not shown). It is possible that more competing risks in the women reduced the obesity impact, although most of these factors were adjusted for in the final multivariable analysis and the others were tested for possible confounding.

Another limitation of this study was our inability to adjust for factors related to diet and physical activity. Patients with a higher BMI are more likely to consume a less heart healthy diet and less likely to engage in physical activity and their lifestyle, rather than BMI *per se*, may have increased their risk of cardiovascular events. However, obesity may serve as an intermediate outcome in this pathway. Incomplete ascertainment of baseline diabetes status, may have influenced our results. It is possible that some patients at baseline were undiagnosed and therefore misclassified as non-diabetic and included in the analysis. Sample size should also be considered when interpreting the observed gender differences. The sample size for women in this study ($n = 1171$) was much smaller than the sample size for men ($n = 5693$) and the observed sex-based differences should be considered more as hypothesis generating.

The strength of this study includes prospectively collected data. Height and weight were measured by clinic research staff, rather than relying on self-report. In addition, the outcomes observed in this study were classified according to an adjudication process that included the review of medical records by multiple cardiologists. Another strength of this study is that we did consider numerous confounding factors, including age, race, cardiovascular medical history, smoking status, health status (blood pressure, LVEF, serum creatinine, potassium, and total cholesterol) and medication use, and excluded patients with diabetes at baseline. This provides us with a more conservative estimate of the association between BMI and cardiovascular outcomes, as those with diabetes may be more likely obese and at risk of a cardiovascular outcome.

Future direction

An examination of other large databases for a possible role of sex-based differences in the impact of obesity in modulating atherosclerosis progression and the risk of transition to an acute coronary syndrome is needed to further examine the independent role of obesity. Further elucidation of the mechanisms by which substances secreted by adipose tissue are atherogenic, how they act to cause transition to an acute coronary syndrome, and whether sex-related differences are needed. A better understanding of

how to best use simple, practical measures of adiposity, despite their limitations, would also be of great value.

Conclusion

In the presence of established CAD, obesity was independently associated with risk for MACE in men, but a similar association was not detected in women. The reason is not clear. Further study is needed to determine whether this finding is based on true biological differences between men and women, on methodological limitations associated with simple measures of obesity, or to the play of chance.

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Conflict of interest: Dr. Braunwald reports having received research grant support and lecture fees from Bristol-Myers Squibb and Merck. Brigham and Women's Hospital has been awarded patents regarding the use of inhibition of the renin–angiotensin system in selected survivors of myocardial infarction; Dr. Braunwald is among the coinventors. The licensing agreement with Abbott and Novartis is not linked to sales.

Appendix A.

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