Body-Weight Fluctuations and Outcomes in Coronary Disease

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ABSTRACT

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BACKGROUND

Body-weight fluctuation is a risk factor for death and coronary events in patients without cardiovascular disease. It is not known whether variability in body weight affects outcomes in patients with coronary artery disease.

METHODS

We determined intraindividual fluctuations in body weight from baseline weight and follow-up visits and performed a post hoc analysis of the Treating to New Targets trial, which involved assessment of the efficacy and safety of lowering low-density lipoprotein cholesterol levels with atorvastatin. The primary outcome was any coronary event (a composite of death from coronary heart disease, nonfatal myocardial infarction, resuscitated cardiac arrest, revascularization, or angina). Secondary outcomes were any cardiovascular event (a composite of any coronary event, a cerebrovascular event, peripheral vascular disease, or heart failure), death, myocardial infarction, or stroke.

RESULTS

Among 9509 participants, after adjustment for risk factors, baseline lipid levels, mean body weight, and weight change, each increase of 1 SD in body-weight variability (measured according to average successive variability and used as a time-dependent covariate) was associated with an increase in the risk of any coronary event (2091 events; hazard ratio, 1.04; 95% confidence interval [CI], 1.01 to 1.07; P=0.01), any cardiovascular event (2727 events; hazard ratio, 1.04; 95% CI, 1.02 to 1.07; P<0.001), and death (487 events; hazard ratio, 1.09; 95% CI, 1.07 to 1.12; P<0.001). Among patients in the quintile with the highest variation in body weight, the risk of a coronary event was 64% higher, the risk of a cardiovascular event 85% higher, death 124% higher, myocardial infarction 117% higher, and stroke 136% higher than it was among those in the quintile with the lowest variation in body weight in adjusted models.

CONCLUSIONS

Among participants with coronary artery disease, fluctuation in body weight was associated with higher mortality and a higher rate of cardiovascular events independent of traditional cardiovascular risk factors. (Funded by Pfizer; ClinicalTrials.gov number, NCT00327691.)

OBESITY IS AN INDEPENDENT RISK FACtor for cardiovascular death and disease.[1,2] Among participants in the Framingham Heart Study who were between 35 and 75 years of age and were followed for up to 44 years, overweight and obese participants were at a higher risk for the development of cardiovascular disease than participants of normal weight.[3] Weight gain is strongly associated with an increased risk of death and disease among participants without evident cardiovascular disease at baseline.[4,5] Indeed, in obese persons, bariatric surgery followed by weight loss reduces the risk of cardiovascular disease, including hypertension, hypercholesterolemia, and diabetes.[6-8] Although such findings hold in the general population, the relation between body weight and outcomes in patients with established cardiovascular disease is complex.[9-14]

Weight loss is commonly prescribed as a lifestyle intervention in obese patients. However, weight loss is frequently followed by weight gain (or "weight cycling") or by other patterns of weight fluctuation. Whether such fluctuations in body weight are associated with worse prognosis is controversial.[15-18] We used data from the Treating to New Targets (TNT) trial, which involved patients with established coronary artery disease, in a post hoc analysis to explore the relation between intraindividual fluctuations in body weight and the risk of cardiovascular events.

METHODS

STUDY DESIGN

We conducted a post hoc analysis of data from the TNT trial, a randomized trial involving 10,001 patients with clinically evident coronary artery disease and levels of low-density lipoprotein (LDL) cholesterol below 130 mg per deciliter (3.4 mmol per liter) who had been randomly assigned to receive either 10 mg or 80 mg of atorvastatin per day. The design and the principal results have been described previously.[19,20] The major criteria for exclusion are outlined in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. For our analysis, patients with at least two postbaseline measurements of body weight were included.

Patients were followed at 3, 6, and 9 months, at 1 year, and every 6 months thereafter, at which times data on vital signs, including body weight,

were collected. Patients were followed for a median of 4.9 years.[20]

The study was sponsored by Pfizer. The institutional review boards of participating centers approved the trial, and written informed consent was obtained from each patient. The first author designed the study, prepared the first draft of the manuscript, and decided to submit the manuscript for publication. The lead statistician had full access to the data, analyzed the data, and vouches for the completeness, authenticity, integrity, and reliability of the data. None of the academic authors received any compensation for the work on this article.

MEASURES OF BODY-WEIGHT VARIABILITY

Body-weight variability was defined as intraindividual variability in body weight between visits. Various measures of variability were used, including average successive variability, which was defined as the average absolute difference between successive values, standard deviation (SD), the coefficient of variation, and variability independent of the mean, which was calculated as $100 \times SD \div mean^{beta}$, where beta is the regression coefficient based on a natural logarithm of standard deviation on the natural logarithm of the mean. The uncorrected variability independent of the mean was corrected with the use of this formula: (variability independent of the uncorrected mean × mean of coefficient of variation) ÷ mean of variability independent of the uncorrected mean. Average successive variability was used as the primary variability measure.

STUDY OUTCOMES

The primary outcome was the occurrence of any coronary event (a composite of death from coronary heart disease, nonfatal myocardial infarction, resuscitated cardiac arrest, revascularization, or angina).[20] The secondary outcomes were any cardiovascular event (a composite of any coronary event or cerebrovascular event, peripheral vascular disease, or heart failure) and individual end points of death, myocardial infarction, and stroke.[20] In addition, new-onset diabetes was evaluated as an outcome.

STATISTICAL ANALYSIS

The relation between body-weight variability (as measured by average successive variability) and the risk of outcomes was evaluated with the use

of body-weight variability as both a continuous and a categorical variable. Any outcome reported before the visit at 3 months (the minimal time point at which to calculate body-weight variability) was censored. The primary analyses evaluated body-weight variability as a time-dependent covariate. Secondary analyses used non–time-dependent covariate models. To account for body-weight variability as a continuous variable, a Cox proportional-hazards regression model was constructed, in which the variability measure was entered to calculate the hazard ratio for outcomes per increase in variability of 1 SD. Four models were used, with model 1 being unadjusted; model 2 adjusting model 1 for treatment effect (80 mg of atorvastatin vs. 10 mg of atorvastatin); model 3 adjusting model 2 for mean body weight and change in weight, taking directionality into account (continuous variable); and model 4 adjusting model 3 for age, sex, race, diabetes, hypertension, and smoking status; chronic kidney disease and congestive heart failure; baseline levels of LDL cholesterol, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides; and time between initial and final weight measurement (for non–time-dependent variable models).

For the treatment of body-weight variability as a categorical variable, patients were divided into quintiles of measures of body-weight variability. The rate of outcomes was evaluated for each of the quintiles. Cox proportional-hazards regression analysis (fitting the above four models) was performed to evaluate the risk of outcomes in the group in the highest quintile of body-weight variability versus the lowest quintile (reference hazard ratio, 1.0). Further analyses were performed to explore the relation between body-weight variability and outcomes on the basis of baseline body-mass index (BMI; the weight in kilograms divided by the square of the height in meters). These analyses were performed to address the question of whether fluctuation in body weight is more harmful in an overweight or obese person than in a person of normal weight. Patients were assigned to one of three categories: normal weight (BMI, <25), overweight (BMI, 25 to <30), or obese (BMI, ≥30). For each of these three groups, patients were further divided into two groups on the basis of high variability (greater than or equal to the median) or low variability (below the median). Unadjusted and adjusted models were constructed to evaluate the association of high variability in

weight and the risk of the primary and secondary outcomes in each of the three BMI categories.

Sensitivity analyses were conducted as follows: first, by excluding patients with only two body-weight measurements; second, by excluding patients with a history of heart failure; third, by calculating body-weight variability after excluding measurements in months 3 and 9 (in order to use evenly spaced measurements of body weight); fourth, by using other measures of variability (±SD, coefficient of variation, and variability independent of the mean) to evaluate the consistency of the results; and fifth, by calculating body-weight variability over different cutoff points (18 months, 24 months, and 30 months) and evaluating the risk of the primary and secondary outcomes beyond those cutoff points.

All analyses were performed with the use of SAS Software, version 9.0 (SAS Institute). A P value of less than 0.05 (two-sided) was considered to indicate statistical significance. Given the exploratory nature of the analyses, no adjustment was made for multiple testing.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Among the 10,001 patients enrolled in the trial, 9509 fulfilled the inclusion criteria for the present post hoc analysis. The mean baseline weight of the patients was 85±15 kg. The median time between the first and last measurements of weight was 4.7 years. The median number of weight measurements was 12 (range, 2 to 14) (Fig. S1A in the Supplementary Appendix). The median body-weight variability (as measured by average successive variability) was 1.76 kg (Fig. S1B in the Supplementary Appendix). The characteristics of patients with low body-weight variability (below the median) versus high body-weight variability (greater than or equal to the median) are outlined in Table 1.

BODY-WEIGHT VARIABILITY AS A CONTINUOUS VARIABLE AND OUTCOMES

When body-wight variability was used as a time-dependent covariate in the fully adjusted model (model 4), each increase in body-weight variability of 1 SD (1.5 to 1.9 kg) increased the risk of any coronary event (2091 events; hazard ratio, 1.04; 95% confidence interval [CI], 1.01 to 1.07; P=0.01), any cardiovascular event (2727 events;

Table 1. Characteristics of the Patients.*

Characteristics	Low Body-Weight Variability (N = 4754)	High Body-Weight Variability (N = 4755)	Total (N = 9509)	P Value
Age				
Median — yr	63.4	60.4	61.8	<0.001
≥65 yr — no. (%)	2061 (43.4)	1550 (32.6)	3611 (38.0)	<0.001
Male sex — no. (%)	3752 (78.9)	3955 (83.2)	7707 (81.0)	<0.001
Race — no. (%)†				
White	4462 (93.9)	4497 (94.6)	8959 (94.2)	0.001
Black	123 (2.6)	144 (3.0)	267 (2.8)	
Asian	65 (1.4)	32 (0.7)	97 (1.0)	
Other	104 (2.2)	82 (1.7)	186 (2.0)	
Current smoker — no. (%)	523 (11.0)	722 (15.2)	1245 (13.1)	<0.001
Weight — kg				<0.001
Median	79.0	88.43	83.3	
Range	38.5–166.5	44.1–170.1	38.5–170.1	
Mean	79.4±12.6	90.1±16.1	84.7±15.4	
Hypertension — no. (%)	2409 (50.7)	2714 (57.1)	5123 (53.9)	<0.001
Diabetes mellitus — no. (%)	654 (13.8)	744 (15.6)	1398 (14.7)	0.01
Known cerebrovascular disease — no. (%)	204 (4.3)	267 (5.6)	471 (5.0)	0.003
Previous coronary-artery bypass grafting — no. (%)	2242 (47.2)	2190 (46.1)	4432 (46.6)	0.28
Previous percutaneous coronary intervention — no. (%)	2495 (52.5)	2620 (55.1)	5115 (53.8)	0.01
Known chronic heart failure — no. (%)	312 (6.6)	416 (8.7)	728 (7.7)	<0.001
Chronic kidney disease — no. (%)	1588 (33.4)	1468 (30.9)	3056 (32.1)	0.01
Cholesterol at baseline — mg/dl				
LDL	97.2±17.5	97.7±17.5	97.4±17.5	0.23
HDL	48.8±11.4	45.9±10.3	457.3±10.9	<0.001
Total	174.5±23.7	174.8±23.8	174.7±23.8	0.66
Triglycerides at baseline — mg/dl	143.5±67.8	157.3±72.5	150.4±70.5	<0.001
Systolic blood pressure <140 mm Hg — no. (%)	3134 (65.9)	3284 (69.1)	6418 (67.5)	0.001
Randomization according to treatment with atorvastatin — no. (%)				0.66
10 mg	2364 (49.7)	2386 (50.2)	4750 (50.0)	
80 mg	2390 (50.3)	2369 (49.8)	4759 (50.0)	
Outcomes — no. (%)				
Any coronary event	884 (18.6)	1207 (25.4)	2091 (22.0)	<0.001
Any cardiovascular event	1149 (24.2)	1578 (33.2)	2727 (28.7)	<0.001
Death	185 (3.9)	302 (6.4)	487 (5.1)	<0.001
Myocardial infarction — no. (%)	198 (4.2)	293 (6.2)	491 (5.2)	<0.001
Stroke — no. (%)	101 (2.1)	145 (3.0)	246 (2.6)	0.004
New-onset diabetes — no./total no. (%)	222/3772 (5.9)	418/3633 (11.5)	640/7405 (8.6)	<0.001

* Plus–minus values are means ±SD. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. to convert the values for triglycerides to millimoles per liter, multiply by 0.01129. Low body-weight variability is variability below the median and high body-weight variability is variability above the median. Median average successive variability equals 1.76 kg. The total includes all participants studied. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.
† Race was reported by participants.

Table 2. Continuous Body-Weight Variability and Risk of Outcomes.*

Outcome	Model 1†		Model 2‡		Model 3§		Model 4¶	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Any coronary event	1.06 (1.03–1.08)	<0.001	1.05 (1.03–1.08)	<0.001	1.04 (1.01–1.07)	0.003	1.04 (1.01–1.07)	0.01
Any cardiovascular event	1.05 (1.03–1.08)	<0.001	1.05 (1.03–1.07)	<0.001	1.04 (1.02–1.07)	<0.001	1.04 (1.02–1.07)	<0.001
Death	1.08 (1.06–1.11)	<0.001	1.09 (1.06–1.11)	<0.001	1.08 (1.06–1.11)	<0.001	1.09 (1.07–1.12)	<0.001
Myocardial infarction	1.06 (1.01–1.10)	0.008	1.05 (1.01–1.10)	0.01	1.04 (0.99–1.09)	0.09	1.04 (0.98–1.09)	0.17
Stroke	1.05 (0.98–1.12)	0.17	1.04 (0.99–1.12)	0.19	1.04 (0.96–1.12)	0.31	1.05 (0.97–1.13)	0.20
New-onset diabetes	1.16 (1.11–1.21)	<0.001	1.16 (1.11–1.21)	<0.001	1.07 (1.00–1.15)	0.05	1.07 (0.99–1.14)	0.08

* Results were calculated with the use of the measure of body-weight variability as a time-dependent covariate. Continuous body-weight variability is per 1-SD change in body-weight variability.
† Model 1 was unadjusted.
‡ Model 2 was adjusted for treatment (80 mg of atorvastatin vs. 10 mg).
§ Model 3 was adjusted for treatment (80 mg of atorvastatin vs. 10 mg), mean body weight, and weight change, taking the direction of weight change into account.
¶ Model 4 was adjusted for the same variables as model 3 and for age, sex, race, diabetes, hypertension, smoking history, baseline levels of LDL cholesterol, HDL cholesterol, total cholesterol, and triglycerides and for chronic kidney disease and chronic heart failure.

hazard ratio, 1.04; 95% CI, 1.02 to 1.07; P<0.001), and death (487 events; hazard ratio, 1.09; 95% CI, 1.07 to 1.12; P<0.001), with a numerical increase in myocardial infarction (hazard ratio, 1.04; 95% CI, 0.98 to 1.09; P=0.17) and stroke (hazard ratio, 1.05; 95% CI, 0.97 to 1.13; P=0.20) (Table 2, and Table S2A through S2F in the Supplementary Appendix). Furthermore, in the non–time-dependent covariate model, each increase in body-weight variability of 1 SD (1.62 kg) increased the risk of any coronary event (hazard ratio, 1.04; 95% CI, 1.02 to 1.06; P<0.001), any cardiovascular event (hazard ratio, 1.04; 95% CI, 1.03 to 1.06; P<0.001), death (hazard ratio, 1.03; 95% CI, 1.01 to 1.06; P=0.01), myocardial infarction (hazard ratio, 1.04; 95% CI, 1.00 to 1.07; P=0.04), and stroke (hazard ratio, 1.05; 95% CI, 1.00 to 1.09; P=0.03) independent of traditional risk factors (Table S3 in the Supplementary Appendix). In addition, an increase in body-weight variability was associated with an increase in new-onset diabetes (hazard ratio, 1.08; 95% CI, 1.02 to 1.14; P=0.009) (Table S3 in the Supplementary Appendix).

QUINTILES OF BODY-WEIGHT VARIABILITY AND OUTCOMES

The rate of any coronary event, any cardiovascular event, death, myocardial infarction, stroke, and new-onset diabetes increased with each higher quintile of body-weight variability (Fig. 1, and Fig. S2A through S2D in the Supplementary Appendix). In the fully adjusted model (model 4), when compared with the lowest quintile, patients with the highest quintile of variability had an increase in the risk of any coronary event of 64%, an increase in the risk of any cardiovascular event of 85%, an increase in the risk of death of 124%, an increase in the risk of myocardial infarction of 117%, an increase in the risk of stroke of 136%, and an increase in the risk of new-onset diabetes of 78% (Table 3), independent of traditional risk factors.

BASELINE BMI, BODY-WEIGHT VARIABILITY, AND OUTCOMES

In patients with normal body weight at baseline, high body-weight variability (greater than or equal to the median) was associated with a numerical increase in any coronary event as compared with low body-weight variability (less than the median), but this difference was not significant. However, among patients who were overweight or obese,

high variability in body weight was associated with a significantly higher risk of any coronary or cardiovascular event than among patients with low variability in body weight (Fig. 2A and 2B).
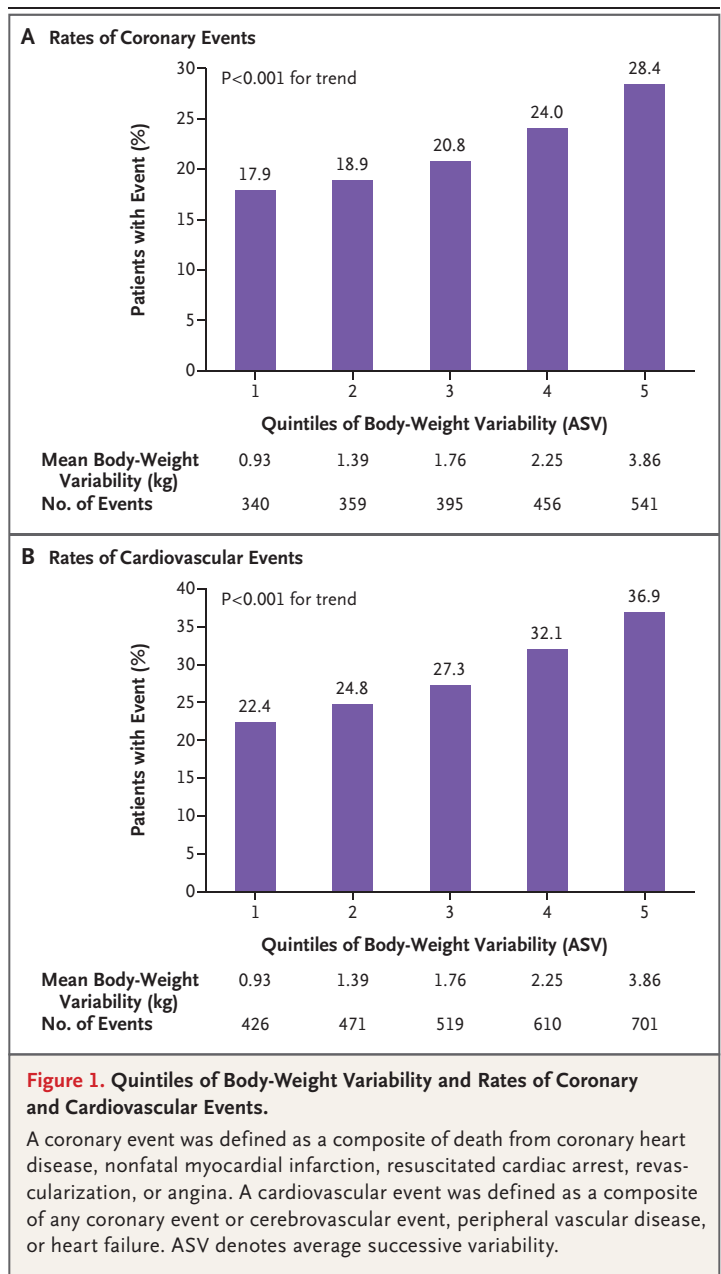
SENSITIVITY ANALYSIS

Sensitivity analyses that excluded patients with only two body-weight measurements, excluded patients with a history of heart failure, excluded months 3 and 9 in the calculation of variability, or used other measures of variability (SD, coefficient of variation, and variability independent of the mean) yielded largely similar results (Tables S4 through S9 in the Supplementary Appendix). In addition, sensitivity analyses that were computed with measurement of variability in the first 2 years and that were used to evaluate outcomes after 2 years showed largely similar results (Table S10 in the Supplementary Appendix). Moreover, sensitivity analyses computed with measurement of variability in the first 18 months and used to evaluate the primary outcome after 18 months showed a consistent increase in the risk of any coronary event in both unadjusted models (hazard ratio, 1.05; 95% CI, 1.02 to 1.09; P=0.002) and adjusted models (hazard ratio, 1.04; 95% CI, 1.01 to 1.08; P=0.03). Similar results were seen with a cutoff point of 30 months (unadjusted hazard ratio, 1.07; 95% CI, 1.03 to 1.11; P<0.001; adjusted hazard ratio, 1.06; 95% CI, 1.01 to 1.10; P=0.009).

BODY WEIGHT AND PROGNOSIS

In the primary analyses, mean body weight was a predictor of any coronary event, any cardiovascular event, myocardial infarction, and new-onset diabetes independent of body-weight variability and treatment effect (Table S2A through S2F in the Supplementary Appendix). However, in the fully adjusted model, mean weight was a predictor of new-onset diabetes but not of other outcomes. Similarly, weight change (from baseline to final) was a predictor of new-onset diabetes but not of other outcomes. Figure S3 in the Supplementary Appendix shows the example of a patient from the trial with high body-weight variability and worse prognosis.

DISCUSSION

In this post hoc analysis involving patients with established coronary artery disease who partici-

Figure 1. Quintiles of Body-Weight Variability and Rates of Coronary and Cardiovascular Events.

A coronary event was defined as a composite of death from coronary heart disease, nonfatal myocardial infarction, resuscitated cardiac arrest, revascularization, or angina. A cardiovascular event was defined as a composite of any coronary event or cerebrovascular event, peripheral vascular disease, or heart failure. ASV denotes average successive variability.

pated in the TNT trial, fluctuations in body weight were strongly associated with the risk of cardiovascular events and even death. Moreover, body-weight variability was associated with the risk of new-onset diabetes. The associations observed were independent of the mean body weight and appeared to be independent of traditional risk factors.

In patients without cardiovascular disease, obesity is a major risk factor for insulin resistance, diabetes, hypertension, dyslipidemia, heart

failure, and coronary heart disease.[2,21] In addition, weight gain is associated with an increased risk of illness and death.[4,5] Dramatic weight loss, as seen after bariatric surgery, has been shown to produce clinically significant improvements related to the risk of cardiovascular disease, including reductions in the risk of hypertension, hypercholesterolemia, and diabetes.[6-8] As such, weight loss is an important lifestyle intervention.

However, in patients with established cardiovascular disease, an obesity paradox has been described in which some adverse findings occur less frequently among those who are overweight or obese than among those of normal weight. In an analysis of the International Verapamil SR-Trandolapril (INVEST) study, a trial involving 22,576 patients with known coronary artery disease, mortality was 30% lower among overweight and obese patients, despite the fact that they had less effective blood-pressure control than a comparative group of patients of normal weight.[9] Similar findings have been described in patients with heart failure[22,23] and those with coronary artery disease.[11-13] The concept of an obesity paradox has been debated, and the findings that support it have been attributed to selection bias and confounding. Indeed, weight loss as a lifestyle intervention is recommended in obese patients, even for those with established cardiovascular disease.

Although weight loss is recommended, the usual pattern for most patients attempting intentional weight loss is weight loss followed by weight gain. The question of whether such fluctuation is detrimental to health is controversial. In an analysis from the Framingham Heart Study involving patients without known cardiovascular disease, highly variable body weights were associated with higher mortality and morbidity related to coronary heart disease.[15,24] However, other cohort studies have failed to confirm these findings.[16-18]

Whether weight fluctuation affects prognosis in patients with coronary artery disease — for whom there is emphasis on lifestyle intervention — is not known. We reviewed data from more than 9000 patients with coronary artery disease
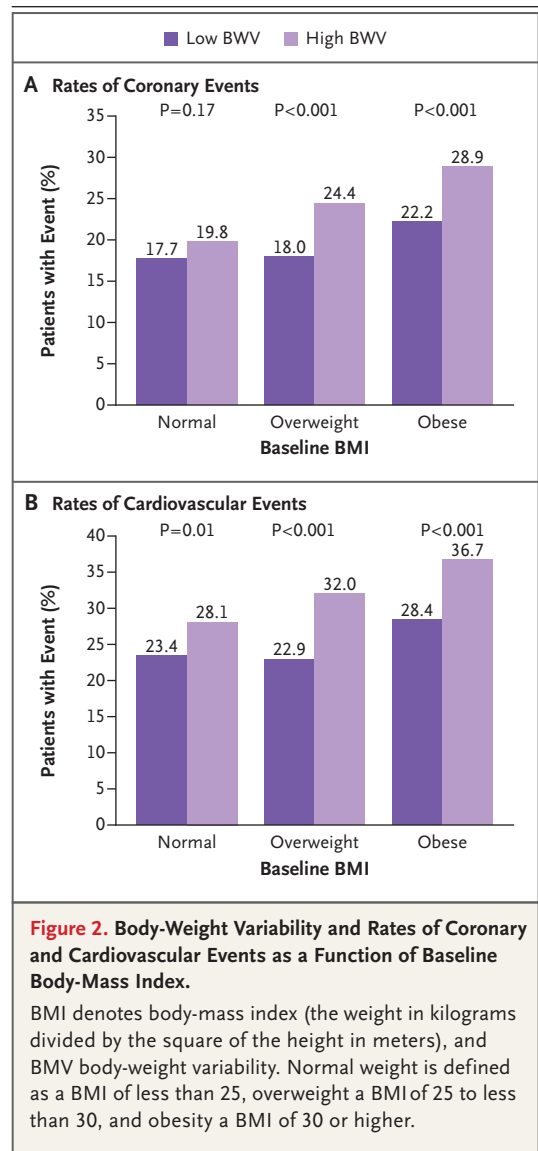

Figure 2. Body-Weight Variability and Rates of Coronary and Cardiovascular Events as a Function of Baseline Body-Mass Index.

BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters), and BMV body-weight variability. Normal weight is defined as a BMI of less than 25, overweight a BMI of 25 to less than 30, and obesity a BMI of 30 or higher.

Table 3. Multivariable Models and Risk of Outcomes in the Highest versus the Lowest Quintile of Variability in Body Weight.

Outcome	Adjusted Hazard Ratio (95% CI)*	P Value
Any coronary event	1.64 (1.41–1.90)	<0.001
Any cardiovascular event	1.85 (1.62–2.11)	<0.001
Death	2.24 (1.74–2.89)	<0.001
Myocardial infarction	2.17 (1.59–2.97)	<0.001
Stroke	2.36 (1.56–3.58)	<0.001
New-onset diabetes	1.78 (1.32–2.40)	<0.001

* Results were adjusted for age, sex, race, diabetes, hypertension, and smoking; mean weight and weight change (taking directionality into account); treatment (80 mg of atorvastatin vs. 10 mg); baseline levels of LDL cholesterol, HDL cholesterol, total cholesterol, and triglycerides; chronic kidney disease and chronic heart failure; and time between initial and final weight measurements.

and found that body-weight variability was associated with a significant increase in the risk of cardiovascular events and death. We also observed a graded relation, such that greater degrees of body-weight fluctuation were associated with higher event rates. We also found that high versus low body-weight variability was associated with a greater absolute increase in the risk of any coronary event among overweight and obese persons than among persons of normal weight. Finally, our data indicate that body-weight variability was strongly and independently associated with new-onset diabetes mellitus.

The associations observed in our study may be due to reasons other than causality. Higher body-weight variability may be a marker of serious preexisting illnesses that have worse prognoses. However, our study used data from a randomized trial that excluded patients with a poor prognosis. Moreover, the worse prognosis was also seen in cause-specific outcomes, such as coronary events, myocardial infarction, and stroke. Patients with systolic heart failure can have swings in body weight based on the status of their body-fluid volume. However, patients with New York Heart Association class IIIB and IV heart failure were excluded from the trial. Thus, volume changes would seem to be less likely to contribute to weight changes in our study. Moreover, our sensitivity analyses (excluding patients with a history of heart failure at baseline) yielded largely similar results. The fluctuations in body weight may be a consequence of — not the cause of — nonfatal end points. However, a sensitivity analysis in which we calculated body-weight variability at different cutoff points and evaluated outcomes beyond those cutoff points yielded largely similar results.

The present study has certain limitations. It tests association, not causation. Furthermore, the study did not assess whether the body-weight fluctuations were intentional or unintentional, factors that can have different effects on prognosis.[25] In addition, the study did not assess measures of obesity other than BMI. The sensitivity analyses that assessed outcomes beyond a certain cutoff point were underpowered. Although the approach of calculating body-weight variability until a certain cutoff point and then evaluating its effects on events beyond that time frame offers a potential "causal" hypothesis, the disadvantage is that the body-weight variability calculated may not remain the same in the follow-up phase, resulting in misclassification.

In this large cohort of patients with coronary artery disease, body-weight fluctuation was associated with a significant increase in the risk of cardiovascular events and death. The magnitude of this risk increased with greater variability in body weight and among those who were overweight or obese at baseline and was independent of traditional factors related to cardiovascular risk.

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