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ORIGINAL ARTICLE

Body Weight Variability and Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus

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BACKGROUND: Some studies have shown that body weight variability is a risk factor for cardiovascular events, but this has not been studied in subjects with diabetes mellitus.

METHODS AND RESULTS: We measured intraindividual variations in body weight from baseline and follow-up visits in 6408 subjects with type 2 diabetes mellitus from 3 clinical trials. The primary end point, any coronary event, was a composite of coronary heart disease death, myocardial infarction, resuscitated cardiac arrest, coronary revascularization, and unstable or new-onset angina. After adjustment for risk factors, baseline lipid levels, mean body weight, and weight change, each increase of 1 SD in body weight variability, measured as average successive variability and used as a time-dependent covariate, was associated with an increase in the risk of any coronary event (hazard ratio, 1.08; 95% CI, 1.01–1.14; *P*=0.017), major coronary event (hazard ratio, 1.12; 95% CI, 1.04–1.20; *P*=0.002), any cardiovascular event (hazard ratio, 1.08; 95% CI, 1.03–1.14; *P*=0.0015), and death (hazard ratio, 1.16; 95% CI, 1.10–1.22; *P*<0.0001). Among patients in the quintile with the highest variation in body weight compared with the lowest, the risk of any coronary event was 59% higher; the risk of a major coronary event, 82% higher; any cardiovascular event, 75% higher; death, 82% higher; myocardial infarction, 99% higher; and stroke, 92% higher in adjusted models. The results were consistent in a number of sensitivity analyses.

CONCLUSIONS: Among subjects with type 2 diabetes mellitus, fluctuation in body weight was associated with higher mortality and a higher rate of cardiovascular events, independent of traditional cardiovascular risk factors.

CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifier: NCT00327691 and NCT00327418.

Key Words: body weight ■ heart arrest ■ humans ■ risk factors ■ stroke

https://www.ahajournals.org/journal/circoutcomes

WHAT IS KNOWN

- In overweight and obese patients with type 2 diabetes mellitus, sustained weight loss provides clinically meaningful reductions in blood pressure, improvements in lipid parameters, and glycemic control.
- Recent studies have shown that body weight fluctuation is a risk factor for cardiovascular events, but this has not been studied in subjects with diabetes mellitus.

WHAT THE STUDY ADDS

- Among subjects with type 2 diabetes mellitus, fluctuation in body weight was associated with higher mortality and a higher rate of cardiovascular events, independent of traditional cardiovascular risk factors, mean body weight, and weight change.

Most patients with type 2 diabetes mellitus are overweight or obese, and weight loss is recommended as part of their treatment. In fact, the American Diabetes Association recommends high-intensity diet, physical activity, and behavioral strategies to achieve short-term weight loss, followed by long-term comprehensive weight maintenance programs.[1] Studies have shown that in overweight and obese patients with type 2 diabetes mellitus, sustained weight loss provides clinically meaningful reductions in blood pressure, improvements in lipid parameters, and glycemic control.[2–4] The effect on reduction in cardiovascular outcomes is, however, controversial. In the randomized Look Action for Health in Diabetes trial, an intensive lifestyle intervention focusing on weight loss did not reduce the rate of cardiovascular events in overweight or obese adults with type 2 diabetes mellitus.[2]

Lifestyle interventions often result in only temporary weight loss, and repeated attempts to diet and exercise may result in weight fluctuations. A study entitled "Does Dieting Make You Fat? A Twin Study" concluded that dieting itself may induce a small subsequent weight gain, independent of genetic factors.[5]

In studies of populations not selected for diabetes mellitus, weight variations have been associated with an increased risk of future cardiovascular events.[6–8] Other studies have not found this association.[9–11] The purpose of this study was to examine the relationship between weight variability and cardiovascular events in patients with type 2 diabetes mellitus from 3 structured randomized clinical trials.

METHODS

On request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the United States and European Union or (2) in programs that have been terminated (ie, development for all indications has been discontinued). The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

Patient Material

Patients with type 2 diabetes mellitus at baseline, who were enrolled in the below 3 clinical trials of statins, were included in this analysis if they had at least 2 postbaseline measurements of body weight.

In the CARDS (Collaborative Atorvastatin Diabetes Study), 2838 patients with type 2 diabetes mellitus, no history of cardiovascular disease, but with at least one other risk factor (among retinopathy, albuminuria, current smoking, and hypertension) were randomized to atorvastatin 10 mg/day or placebo and were followed for a median of 3.9 years.[12] CARDS was terminated earlier than expected because of benefit.

In the ASPEN (Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus), 2410 patients with type 2 diabetes mellitus were randomized to atorvastatin 10 mg/day or placebo and were followed for a median of 4 years.[13] The trial began as a secondary prevention trial, and 505 of the enrolled patients had previous myocardial infarction (MI) or an interventional procedure. When guidelines advanced and recruitment floundered, the entry criteria were changed to patients without known coronary disease, and an additional 1905 patients were enrolled. Overall, no significant difference between the treatment groups was seen for the primary outcome.

In the TNT trial (Treating to New Targets), 10 001 patients with documented coronary disease, including 1501 with type 2 diabetes mellitus at baseline, were randomized to atorvastatin 10 or 80 mg/day and were followed for a median of 4.9 years.[14,15] The primary end point was significantly reduced in the 80-mg group both in the overall population and in those with diabetes mellitus at baseline. The 3 trials were approved by the institutional review boards of the participating centers, and patients provided written informed consent before participating in the trial.

Follow-Up Visits

In all 3 trials, patients were seen at 3, 6, and 12 months after randomization and every 6 months thereafter. In TNT, patients were also seen at 9 months and in CARDS and ASPEN, at 1 and 2 months. In addition to trial-specific recommendations at each follow-up visit and body weight measurements, lifestyle counseling, including weight loss counseling in overweight or obese subjects, was recommended in each of the trials.

Study Design and End Points

Intraindividual body weight variability between visits was measured using average successive variability (ASV), defined as the average absolute difference between successive values;

postbaseline weight measurements (starting from month 3) were used to compute ASV.

The primary and secondary end points of CARDS, ASPEN, and TNT differed. For this analysis, we used 3 end points, any coronary event (the primary end point), major coronary event, and any cardiovascular event. Any coronary event was a composite of coronary heart disease death, MI, resuscitated cardiac arrest (except in CARDS), coronary revascularization, and unstable or new-onset angina (defined slightly differently in each trial; Table I in the Data Supplement). Major coronary event comprised coronary heart disease death, MI, and resuscitated cardiac arrest (except in CARDS). Any cardiovascular event was any coronary event plus fatal or nonfatal stroke, transient ischemic attack, peripheral vascular disease, or heart failure. In addition, death, MI, and stroke were tabulated separately.

Statistical Analysis

The relation between body weight variability (as measured by ASV) and the risk of outcomes was evaluated with the use of body weight variability as both a continuous and a categorical variable. Subjects with events before the visit at 3 months were excluded from the analysis because weight variability was calculated from month 3 onward. For the time-dependent analysis, we excluded events in the first 6 months because the first variability measure would be the month 6 to month 3 measure, and in the time-dependent analysis, we used the variability measure before the event. The primary analyses evaluated body weight variability as a time-dependent covariate. Secondary analyses used time-independent 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 (HR) 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, 10 mg of atorvastatin, and placebo) and study; model 3 adjusting model 2 for mean body weight and change in weight (with sensitivity analysis based on percentage change in weight from baseline), taking directionality into account (continuous variable); and model 4 adjusting model 3 for age, sex, race, hypertension, and smoking status; chronic kidney disease and baseline levels of LDL (low-density lipoprotein) cholesterol, total cholesterol, HDL (high-density lipoprotein) cholesterol, and triglycerides; and time between initial and final weight measurement (for time-independent variable models). The proportional-hazards assumptions were tested and confirmed for these 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 4 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 HR, 1.0). Kaplan-Meier curves were plotted to assess the relationship between quintiles of weight variability measures and the risk of any coronary event. Further analyses were performed to explore the relation between body weight variability and outcomes on the basis of baseline body mass index (BMI). 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 1 of 3 categories: normal weight (BMI, <25), overweight (BMI, 25 to <30), or obese (BMI, ≥30). For each of these 3 groups, patients were further divided into 2 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 3 BMI categories. All analyses were performed with the use of SAS Software, version 9.0 (SAS Institute). A P value of <0.05 (2 sided) was considered to indicate statistical significance. Given the exploratory nature of the analyses, no adjustment was made for multiple testing.

Sensitivity analyses were performed to evaluate whether the relationship between weight variability and outcomes differed by treatment group (atorvastatin versus placebo), BMI, sex, and race, by introducing a weight variability×variable interaction terms. In addition, we also generated a spline plot using natural cubic spline in the logistic regression model. We tested linearity of weight variability for outcomes, and the relationship was linear for ASV <7. However, for ASV >7 (<1% of patients), the distribution was nonlinear. The spline plots for all weight variability values and for weight variability ≤7 are included in Appendix in the Data Supplement. We computed LDL variability and systolic blood pressure variability using ASV and examined the correlation between ASV for SBP and LDL and ASV for weight, and although the P values were statistically significant (P <0.001 for both), the correlations were weak (Pearson correlation between LDL and weight variability, 0.08; and between SBP and weight variability, 0.05). Therefore, the effect of weight variability is not driven by variability in LDL or SBP.

RESULTS

The clinical features of the patients in each of the 3 trials and the overall population are listed in Table 1. Mean age was 61.7 years; approximately one-third were women, two-thirds had a history of hypertension, one-third had chronic kidney disease, and 16% were current smokers. The mean baseline body weight was 85 kg with a mean BMI of 29. Body weight increased on average from month 3 to the end of the trials by 0.9±5.2 kg.

Subjects had a median of 12 (range, 2–15) measurements of body weight during follow-up. The median body weight variability as measured by ASV was 1.72 kg (maximum was 19.5 and the 99th percentile was 6.46). The characteristics of patients with body weight variability below the median versus body weight variability greater than or equal to the median are listed in Table 2. Patients with body weight variability above, compared with below the median tended to be younger, to be smokers, and to have a history of hypertension, as well as to have higher BMI, lower HDL cholesterol, and higher triglyceride levels.

Table 1. Clinical Features of the Patients in Each Trial

	CARDS (n=2727)	ASPEN (n=2283)	TNT (1398)	Total (n=6408)
Age, y	61.6±8.1	61.0±8.2	63.1±7.9	61.7±8.1
Women	873 (32.0%)	775 (33.9%)	384 (27.5%)	2032 (31.7%)
Current smokers	606 (22.2%)	285 (12.5%)	146 (10.4%)	1037 (16.2%)
BMI	28.8±3.6	28.9±3.8	30.4±5.3	29.2±4.1
Chronic kidney disease	931 (34.1%)	699 (30.6%)	539 (38.6%)	2169 (33.8%)
Cerebrovascular disease	5 (0.2%)	110 (4.8%)	117 (8.4%)	232 (3.6%)
History of hypertension	2169 (79.5%)	1248 (54.7%)	985 (70.5%)	4402 (68.7%)
Baseline				
Body weight, kg	83.6±13.0	84.6±14.2	88.9±17.5	85.1±14.7
Systolic BP, mm Hg	143.8±15.9	133.2±16.5	134.4±17.5	138.0±17.3
Diastolic BP, mm Hg	82.7±8.4	78.9±9.2	77.0±9.7	80.1±9.3
LDL-C, mg/dL	118.2±30.4	113.3±25.5	96.1±18.1*	111.6±27.7
HDL-C, mg/dL	54.5±13.5	46.8±13.3	44.9±10.2*	49.7±13.4
Triglycerides, mg/dL	170.1±102.8	169.3±100.2	169.4±79.5*	169.7±97.2
Weight change,† kg	1.3±5.6	1.1±5.8	–0.3±2.8	0.9±5.2

ASPEN indicates Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus; BMI, body mass index; BP, blood pressure; CARDS, Collaborative Atorvastatin Diabetes Study; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and TNT, Treating to New Targets.

*Patients in TNT had been taking atorvastatin 10 mg/d for 8 wk at baseline.

†Weight change from month 3 of follow-up until the end of the trial.

Body Weight Variability as a Continuous Variable and Outcomes

Excluding events within the first 3 months of follow-up, 861 patients experienced any coronary event (13.4%), 368 experienced a major coronary event (5.7%), 1222 had any cardiovascular event (19.1%), 359 died (5.6%), including 178 cardiovascular deaths (2.8%), 286 had an MI (4.5%), and 177 experienced a stroke (2.8%).

When body weight variability was used as a time-dependent covariate in the fully adjusted model (model 4), each increase in body weight variability of 1 SD increased the risk of any coronary event (HR, 1.08; 95% CI, 1.01–1.14; P=0.017), major coronary event (HR, 1.12; 95% CI, 1.04–1.20; P=0.002), any cardiovascular event (HR, 1.08; 95% CI, 1.03–1.14; P=0.0015), death (HR, 1.16; 95% CI, 1.10–1.22; P<0.0001), and cardiovascular death (HR, 1.13; 95% CI, 1.03–1.25; P=0.012). For MI and stroke, an increase in body weight variability did not significantly increase the risk.

When body weight variability was used as a covariate in the time-independent fully adjusted model (model 4), each increase in body weight variability of 1 SD increased the risk of any coronary event (HR, 1.14; 95% CI, 1.08–1.20; P<0.0001), major coronary event (HR, 1.20; 95% CI, 1.12–1.29; P<0.0001), any cardiovascular event (HR, 1.15; 95% CI, 1.10–1.21; P<0.0001), death (HR, 1.19; 95% CI, 1.11–1.28; P<0.0001), cardiovascular death (HR, 1.13; 95% CI, 1.00–1.27; P=0.055), MI (HR, 1.17; 95% CI, 1.07–1.27; P=0.0005), and stroke (HR, 1.21; 95% CI, 1.10–1.34; P=0.0002).

Quintiles of Body Weight Variability and Outcomes

As shown in Figure 1, the rates of any coronary event and any cardiovascular event increased in increasing quintiles of mean body weight variability as measured by ASV. The rates also increased for major coronary events, death, MI, and stroke (not shown). The rate of cardiovascular death did not increase, perhaps because of the smaller number of events and fewer weight measurements in patients who died.

For quintile 5 compared with quintile 1 in a fully adjusted model, the risk was 59% higher for any coronary event, 82% higher for a major coronary event, 75% higher for any cardiovascular event, 82% higher for death, 99% higher for MI, and 92% higher for stroke (Table 3). The Kaplan-Meier curves for the relationship between weight variability measures and any coronary event are shown in Figure I in the Data Supplement.

Body Weight Variability and Outcomes According to Baseline BMI

Most of the study patients were overweight or obese. BMI at baseline was <25 in 914 patients (14.3%), 25 to 30 in 2820 patients (44.1%), and ≥30 in 2667 (41.7%), whereas 7 patients had missing BMI data. The increased rate of adverse outcomes among patients with body weight variability above the median was more pronounced in overweight and obese patients

Table 2. Clinical Features of the Patients With Low and High Body Weight Variability

	Low Body Weight Variability* (n=3203)	High Body Weight Variability* (n=3205)	*P* Value	Total (n=6408)
Age, y	62.4±8.0	61.1±8.2	<0.0001	61.7±8.1
Women	1045 (32.6%)	987 (30.8%)	0.12	2032 (31.7%)
Current smokers	472 (14.7%)	565 (17.6%)	0.0017	1037 (16.2%)
BMI	28.3±3.8	30.1±4.2	<0.0001	29.2±4.1
Chronic kidney disease	1102 (34.4%)	1067 (33.3%)	0.34	2169 (33.8%)
Cerebrovascular disease	106 (3.3%)	126 (3.9%)	0.18	232 (3.6%)
History of hypertension	2154 (67.2%)	2248 (70.1%)	0.013	4402 (68.7%)
Baseline				
Body weight, kg	81.2±12.8	89.1±15.3	<0.0001	85.1±14.7
Systolic BP, mm Hg	138.4±17.5	137.6±17.0	0.073	138.0±17.3
Diastolic BP, mm Hg	80.0±9.2	80.2±9.4	0.31	80.1±9.3
LDL-C, mg/dL	111.9±27.9	111.3±27.6	0.41	111.6±27.7
HDL-C, mg/dL	50.4±13.6	49.0±13.2	<0.0001	49.7±13.4
Triglycerides, mg/dL	165.6±94.2	173.7±100.0	0.0009	169.7±97.2
Weight change, kg†	0.6±3.4	1.2±6.6	<0.0001	0.9±5.2
Cardiovascular event during follow-up†	504 (15.7%)	718 (22.4%)	<0.0001	1222 (19.1%)
ASV			<0.0001	
Median	1.23	2.43		1.72
Minimum–maximum	0.00–1.70	1.70–19.50		0.00–19.50
Mean (SD)	1.20 (0.34)	2.81 (1.35)		2.00 (1.27)

ASV indicates average successive variability; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

*Low body weight variability is defined as an ASV below the median (1.72 kg), and high body weight variability is defined as an ASV equal to or above the median.

†Weight change or cardiovascular event from month 3 to the end of the trial.

than in normal-weight patients. As depicted in Figure 2, for patients with higher body weight variability, a slight increase in coronary events and cardiovascular events is seen for normal-weight patients; however, for overweight and obese patients, the difference is much larger and statistically significant.

Sensitivity Analyses

A number of analyses were conducted to evaluate the robustness of the results. We evaluated the interaction between weight variability and the following: treatment group, BMI, sex, and race. None of these tests for interactions were statistically significant. The *P* values were 0.23, 0.08, 0.61, and 0.90, respectively. Analysis for any coronary event adjusting for percent change in weight from baseline in the model showed consistent results with significant worse outcomes with higher body weight variability (HR, 1.09; CI, 1.04–1.15; *P*=0.001). We tested linearity of weight variability for outcomes, and the relationship was linear for ASV <7 (Figure II in the Data Supplement). However, for ASV >7 (<1% of patients), the distribution was nonlinear (Figure III in the Data Supplement). The primary analyses were also adjusted for study. In addition, a study×ASV interaction for the primary outcome was not significant (*P*=0.193) suggesting similar relationship across studies.

DISCUSSION

Our results show that higher body weight variability in subjects with diabetes mellitus is associated with an increased risk for coronary events, cardiovascular events, death, cardiovascular death, MI, and stroke. The increased risk persists after adjustment for body weight and traditional cardiovascular risk factors. We also found that high versus low body weight variability was associated with a greater absolute increase in the risk of coronary or cardiac event among overweight and obese persons than among those with a normal BMI.

Weight loss is recommended for overweight or obese subjects with diabetes mellitus and is associated with improvements in hypertension, dyslipidemia, and glycemic control.[2–4] The effect on reduction in cardiovascular events is controversial,[2] although studies have shown an improvement in functional capacity.[16] Nevertheless, weight gain occurs over time in most individuals with

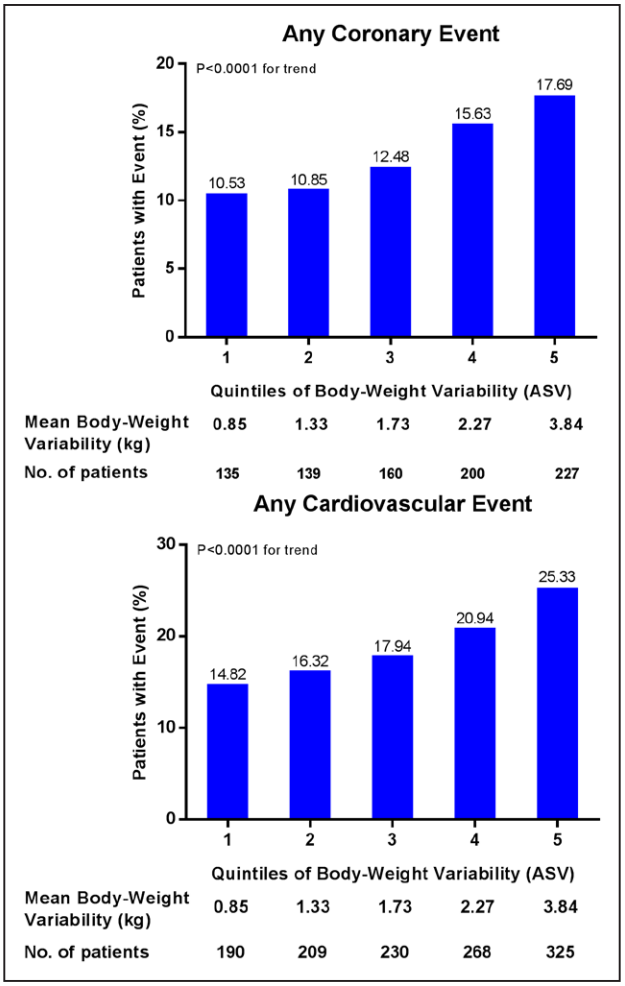

Figure 1. Rates of any coronary event and any cardiovascular event in quintiles of body weight variability as measured by average successive variability (ASV).
Increasing quintiles of body weight variability were associated with increased event rates.

diabetes mellitus, even those motivated enough to participate in a long-term clinical trial. Several hypotheses have been put forth for this weight gain, including metabolic adjustments that occur with weight loss that may contribute to a high rate of weight regain. The metabolic adjustments occur in the form of enhanced metabolic efficiency with reduced resting energy expenditure that is out of proportion to weight loss and alteration in fuel utilization (favoring carbohydrate oxidation).[17] This, combined with an increased drive to eat (hyperphagic response), increases the probability of weight regain when the motivation for restriction of caloric intake reduces.[17] Moreover, in patients with diabetes mellitus, weight loss may conflict with other treatment objectives; for example, in the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes), significantly more weight gain occurred in the first 2 years in the intensive glycemic treatment arm of the trial compared with the standard arm (3.0±7.0 versus 0.3±6.3 kg).[18] Baseline insulin use and initiation of a thiazolidinedione were among the clinical factors independently associated with weight gain.

In some studies of patients unselected for diabetes mellitus,[6–8] but not in others,[14,15] high body weight variability has been associated with an increased risk of future cardiovascular events. Similar studies limited to patients with diabetes mellitus are scant. In a report from the Verona Diabetes Study of a cohort of 1319 subjects with type 2 diabetes mellitus followed for 10 years, higher variability in body weight, pulse pressure, and fasting blood sugar were predictive of all-cause mortality in subjects ≥65 but not <65 years of age.[19]

The pathophysiological link between increased body weight variability and adverse cardiovascular events is not known. However, several mechanisms may be put forth. Studies of weight gain after initial weight loss have shown more rapid adipose tissue growth and hyperplasia because of metabolic shifts favoring lipid storage. Adipose tissue is metabolically active, and the increased production of leptin, cytokines, and adiponectin could potentially lead to adverse outcomes.[20] In a study of Japanese men, weight fluctuation was associated with increased risk of developing hyperinsulinemia.[21] Other studies have shown that weight fluctuations lead to higher lipogenic enzyme, higher triglyceride, and cholesterol levels[22,23]; increased risk of hypertension; and metabolic syndrome.[24,25] In our study, patients with body weight variability above median had higher triglyceride levels when compared with those with body weight variability below median. However, other studies have shown no association of body weight variability with changes in blood pressure or lipid profile.[26,27]

Study Limitations

Our study has strengths and limitations. Among the strengths, we studied a large group of well-character-

Table 3. Risk of Outcomes in the Highest vs the Lowest Quintile of Variability in Body Weight

Outcome	Adjusted HR* (95% CI)	*P* Value
Any coronary event	1.59 (1.26–2.00)	<0.0001
Major coronary event	1.82 (1.29–2.56)	0.0006
Any cardiovascular event	1.75 (1.44–2.13)	<0.0001
Death	1.82 (1.31–2.53)	0.0003
Cardiovascular death	1.01 (0.63–1.63)	0.95
MI	1.99 (1.33–2.97)	0.0008
Stroke	1.92 (1.15–3.20)	0.012

HDL indicates high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; and MI, myocardial infarction.

*Adjusted for age, sex, race, hypertension, and smoking; mean weight and weight change (taking directionality into account); study treatment; baseline levels of LDL cholesterol, HDL cholesterol, total cholesterol, and triglycerides; chronic kidney disease and study; and time between initial and final weight measurements.

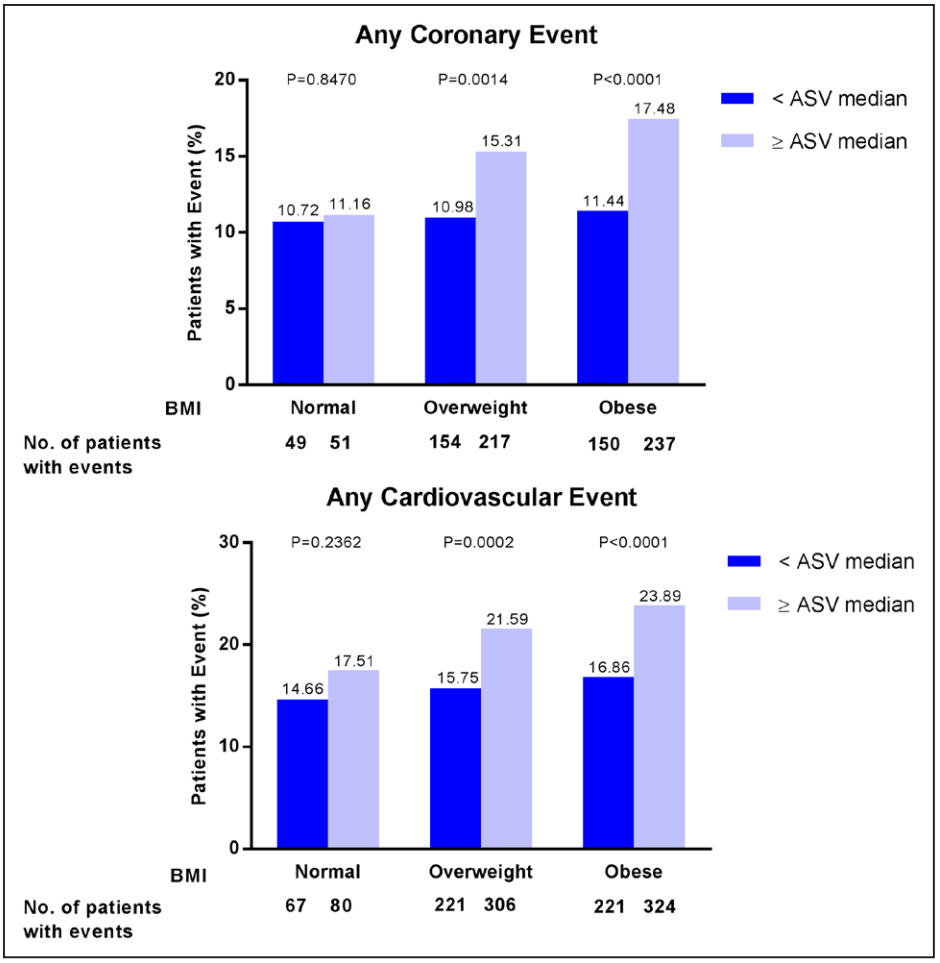

Figure 2. Rates of any coronary event and any cardiovascular event for subjects with body weight below and above the median as measured by average successive variability (ASV), subdivided according to normal body weight, overweight, and obesity.
For subjects with higher body weight variability, a slight increase in events was seen among normal-weight subjects, but for overweight and obese subjects, the difference is much larger and is statistically significant. BMI indicates body mass index.

ized subjects with diabetes mellitus who had been followed within 3 structured clinical trials, with blinded adjudication of end point events. The main limitation of our study is that we are describing an association and cannot infer causation. High body weight variability might increase the risk for cardiovascular events through as yet undefined mechanisms; however, it is also possible that high body weight variability and events do not share a cause-effect relationship. With respect to the former possibility, elevated levels of the inflammatory biomarker C-reactive protein have been reported in Japanese men with high body weight variability.[21] High levels of C-reactive protein have been identified as a risk factor for cardiovascular events in many cohorts.

Another limitation of our study is that we do not know whether weight loss was intentional or unintentional. Intentional weight loss might be associated with a reduction in cardiovascular events, whereas unintentional weight loss might be associated with an increased event rate.[28] We are unable to correlate changes in diabetes mellitus medications to body weight variability. Perhaps the sickest patients experienced more changes in their diabetic medications, resulting in more weight fluctuation.

Conclusions

In summary, in this large cohort of patients with diabetes mellitus, body weight variation was associated with a large and significant increase in the risk of cardiovascular events and death, independent of traditional cardiovascular risk factors. The magnitude of this risk increased with greater variability in body weight and among those who were overweight or obese at baseline.

ARTICLE INFORMATION

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Disclosures

Dr Bangalore belongs to the advisory board/receives honoraria from Abbott Vascular, Pfizer, Amgen, Merck, Medicines Company, and AstraZeneca; reports research grants from Abbott Vascular and National Heart Lung and Blood Institute. Drs Fayyad and DeMicco are employees at Pfizer. Dr Colhoun receives grants (as part of European Union Innovative Medicines Programme Collaborations) from AstraZeneca LP, Boehringer Ingelheim, Eli Lilly & Company, Pfizer, Roche Pharmaceuticals, Sanofi Aventis, Novo Nordisk, and Astra Zeneca; is a shareholder in Bayer and Roche Pharmaceuticals; belongs to the trial steering committees or safety monitoring committees with Eli Lilly, Sanofi, Regeneron, Novartis Pharmaceuticals, and Novo Nordisk and receives remuneration via her institution for this; and speaker fees and travel expenses for presenting trials she has helped design or other research she has led from Pfizer, Eli Lilly, Sanofi, and Regeneron. Dr Waters receives remuneration for participating in clinical trial committees at Commonwealth Serum Laboratories, Ltd, Pfizer, Regeneron, Resverlogix, and Sanofi; honoraria for lectures from Pfizer; and consulting fees from Pfizer.

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