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Inverse relation of body weight and weight change with mortality and morbidity in patients with type 2 diabetes and cardiovascular co-morbidity: An analysis of the PROactive study population

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ABSTRACT

Context: Although weight reduction is a recommended goal in type 2 diabetes mellitus (T2DM), weight loss is linked to impaired survival in patients with some chronic cardiovascular diseases.
Objective: To assess the association of weight and weight change with mortality and non-fatal cardiovascular outcomes (hospitalisation, myocardial infarction and stroke) in T2DM patients with cardiovascular co-morbidity and the effect of pioglitazone-induced weight change on mortality.
Setting and participants: We assessed in a post hoc analysis body weight and weight change in relation to outcome in 5202 patients from the PROactive trial population who had T2DM and evidence of pre-existing cardiovascular disease. Patients were randomized to treatment with pioglitazone or placebo in addition to their concomitant glucose-lowering and cardiovascular medication. Mean follow up was 34.5 months.
Main outcome measure: The impact of body weight and body weight change on all-cause mortality, cardiovascular mortality, on non-fatal cardiovascular events and on hospitalisation.
Results: The lowest mortality was seen in patients with BMI 30–35 kg/m^2 at baseline. In comparison to this (reference group), patients in the placebo group with BMI <22 kg/m^2 (Hazard Ratio (95% confidence intervals) 2.96 [1.27 to 6.86]; $P=0.012$) and BMI 22 to 25 kg/m^2 (HR 1.88 [1.11 to 3.21]; $P=0.019$) had a higher all-cause mortality. Weight loss was associated with increased total mortality (HR per 1% body weight: 1.13 [1.11 to 1.16]; $P<0.0001$), with increased cardiovascular mortality, all-cause hospitalisation and the composite of death, myocardial infarction and stroke. Weight loss of ≥7.5% body weight (seen in 18.3% of patients) was the strongest cut-point to predict impaired survival (multivariable adjusted HR 4.42 [3.30 to 5.94]. Weight gain was not associated with increased mortality. Weight gain in patients treated with pioglitazone (mean + 4.0 ± 6.1 kg) predicted a better prognosis (HR per 1% weight gain: 0.96 [0.92 to 1.00] $P=0.037$) compared to patients without weight gain.
Conclusion: Among patients with T2DM and cardiovascular co-morbidity, overweight and obese patients had a lower mortality compared to patients with normal weight. Weight loss but not weight gain was associated with increased mortality and morbidity. There may be an "obesity paradox" in patients with type 2 diabetes and cardiovascular risk.
The original PROactive trial is registered as an International Standard Randomized Controlled Trial (Number ISRCTN NCT00174993).

1. Introduction

Overweight is an established risk factor for increased cardiovascular morbidity and mortality [1–5]. Overweight is closely associated with other metabolic risk factors such as impaired glucose metabolism and

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type 2 diabetes mellitus (T2DM). Weight control and, if possible, weight reduction are therefore recommended treatment goals in T2DM patients [6]: any weight gain associated with anti-diabetic therapy such as glitazones might be regarded as an unwanted effect.

However, obesity is not associated with a worse outcome in all patient populations. There is a survival benefit in being overweight or moderately obese for patients with overt chronic cardiovascular disease. In patients with chronic heart failure (CHF), overweight is associated with decreased mortality [7–10]. In patients with acute heart failure, a higher BMI is associated with lower in-hospital mortality [11]. Further, despite the known role of obesity as a risk factor for ischemic cardiovascular events [12–14], mortality following acute myocardial infarction is not *higher* in overweight and obese patients compared with normal weight patients [15]: indeed, in a systematic review of 40 studies including a total of more than 250,000 patients with coronary artery disease, there was a better outcome in the overweight and mildly obese patients compared with normal weight patients [16].

In addition to single time point assessment of body weight, weight loss during the course of the disease is strongly related to worse prognosis. In heart failure patients [17, 18] as well as in patients with coronary artery disease [19] weight loss is an independent marker of reduced survival.

The significance of weight change on patients with T2DM and cardiovascular co-morbidity in association with outcome has not been studied in detail. In the PROactive study (PROspective pioglitAzone Clinical Trial In macroVascular Events), pioglitazone reduced the combined endpoint of all-cause mortality, non-fatal infarction and stroke [20]. This effect was observed despite significant weight gain due to pioglitazone therapy. The aim of the present analysis was to assess the effects of body weight, weight loss and weight gain on mortality and non-fatal cardiovascular outcomes (hospitalisation, myocardial infarction and stroke) in the patients with Diabetes and cardiovascular co-morbidity. We hypothesised that in patients with T2DM and cardiovascular co-morbidity overweight is associated with better outcome and weight loss but not weight gain is associated with worse outcome.

2. Methods

We assessed in a post hoc analysis the association of body weight and weight change with mortality and non-fatal outcome in the patient cohort of the PROactive study.

2.1. Patients and protocol

The PROactive study was a randomized, double-blind, placebo-controlled trial (ISRCTN NCT00174993) investigating the effect of pioglitazone on mortality and cardiovascular events in 5238 patients with T2DM and pre-existing cardiovascular co-morbidity aged 35 to 75 years with an HbA_{1c} level >6.5% despite anti-diabetic therapy. The study conformed to the Declaration of Helsinki, the protocol was approved by the local Ethics Committees and written informed consent was obtained from all study participants. The design and the results of the study have been published previously [20, 21]. Briefly, evidence of macrovascular disease was defined by one or more of the following: (1) history of myocardial infarction or stroke; (2) percutaneous coronary intervention or coronary artery bypass surgery at least 6 months before enrolment; (3) acute coronary syndrome at least 3 months before enrolment; or (4) objective evidence of coronary artery disease or obstructive artery disease of the legs. Patients were excluded if they had type 1 diabetes, were taking only insulin, were planned to have coronary or peripheral revascularization, had New York Heart Association class II heart failure or worse, had ischemic ulcers or gangrene, leg pain at rest, or were on haemodialysis. Patients were randomized 1:1 to receive pioglitazone (target dose 45 mg/day) or matching placebo in addition to their usual medication. Patients were treated for at least 30 months and mean follow-up was 34.5 months. Vital signs including weight and oedematous status were assessed monthly for the first 2 months, then every 2 months for the first year and every 3 months thereafter.

2.2. Covariates and outcomes

All information on covariates including demographics, height and weight, cardiovascular risk factors, and concomitant medications was recorded at enrolment of the patient [21]. The presence of oedema was meticulously monitored during the study: Oedema was recorded as mild, moderate or severe and classified as serious or non-serious. To avoid the confounding effects of oedema on weight change, only those weights recorded when the patients were free of *any* degree of oedema were included in the present analysis. Body mass index (BMI) was calculated as body weight divided by height squared (kg/m^2). Only patients with at least one valid follow-up weight measurement were included in the weight change analysis. The outcomes analyzed in the present study were all-cause death, cardiovascular death, all-cause death or hospitalization for all causes, the composite of all-cause death or myocardial infarction (excluding silent MI) or stroke (which is identical with the principal secondary endpoint of the PROactive study), and cardiovascular death or hospitalization for worsening heart failure (the primary composite outcome of the CHARM trial program [9] and of the SHIFT trial [22].

2.3. Statistical analysis

All analyses were performed according to an a priori defined analysis plan. Baseline BMI and weight change were analyzed in the total study population adjusted for treatment and in the placebo arm and in the pioglitazone treatment arm separately. Weight loss and weight gain were considered independently of each other. Baseline characteristics of patients are displayed as means (±standard deviation) for continuous variables and by frequency (percentage) for categorical variables.

We evaluated BMI both as a continuous (for every 1-kg/m^2 change) and as a categorical variable (below 22 kg/m^2, 22 to <25 kg/m^2, 25 to <30 kg/m^2, 30 to <35 kg/m^2, and ≥35 kg/m^2). The BMI categories were defined as normal body weight if BMI was below 25 kg/m^2, overweight if BMI was 25 to <30 kg/m^2, mild obesity if BMI was 30 to <35 kg/m^2 and severe obesity if BMI was 35 or greater [23]. The subgroup with the lowest mortality was used as the reference group. The effect of proportional weight change (as% change from baseline) on outcome was assessed as a continuous, time-dependent variable. The association of baseline BMI and weight change with all endpoints was assessed by Cox proportional hazard analysis; hazard ratios (HR) and 95% confidence intervals are presented. One-year weight change during the first year of follow-up was used in Cox analysis to predict subsequent survival. To identify the best competitive cut-point for weight loss to predict prognosis, we compared model fit statistics of pre-specified cut-points within a range of 5% to 15% of weight loss (using the criterion of the lowest negative likelihood ratio) in a model adjusted for treatment and in a multivariable model.

For multivariable analysis, those of the 25 prospectively defined baseline variables were included that were significantly related to outcome in the original publication of the PROactive study [21]. This included age, creatinine, LDL, HbA1c, previous MI, previous stroke, previous PCI or CABG, peripheral obstructive artery disease, smoking status, Insulin use, diuretic use, and statin use. All analyses were performed in the intention-to-treat population. Statistical tests were two-sided and P values of <0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

From the original PROactive study population, 5202 patients (99.3%) had sufficient weight measurements to be included in the analysis. The mean age was 62 ± 8 years and the mean follow-up was 34.5 months. 2592 of the included patients were randomly allocated to pioglitazone and 2610 patients to placebo. Treatment groups were well matched for baseline characteristics (Table 1). Co-morbidity, clinical characteristics, and drug regimen were similar between groups and not different from the main analysis of the PROactive study (data not shown). Distribution of BMI by subgroups is shown in Fig. 1A.

3.2. Mortality by BMI category

During follow-up, 174 patients died in the pioglitazone group and 173 patients died in the placebo group. The lowest all-cause mortality risk was seen in patients with a baseline BMI 30 to <35 kg/m^2 both in the total study population adjusted for treatment group and in each treatment group tested separately. Patients with BMI 22 to <25 kg/m^2 had a significant higher mortality (Table 2A). In the placebo group, any BMI <25 kg/m^2 was associated with significantly worse survival (Fig. 2A). By contrast, in the pioglitazone group there was no increase in mortality with lower BMI (Table 2A). The association of low BMI with increased mortality in the placebo arm remained after multivariable adjustment (Supplementary Table 1).

Cardiovascular mortality followed the same pattern, being lowest in patients with BMI 30 to 35 kg/m^2. Patients with BMI <22 kg/m^2 without pioglitazone treatment had the highest mortality risk

(crude: HR 3.27 95%CI 1.29–8.26, $P=0.012$; multivariable model: HR 2.73, 95%CI 1.06–7.04, $P=0.037$).

3.3. Hospitalization by BMI category

The composite endpoint of hospitalization for any cause or all-cause mortality was lowest in the BMI category 30 to 35 kg/m^2 (Fig. 2B). Patients with a BMI lower than 25 kg/m^2 had a higher risk (Table 2B; Fig. 3) but this effect was not seen in the pioglitazone treatment arm. After multivariable adjustment BMI below 25 kg/m^2 remained independently predictive of increased risk for hospitalisation (Supplementary Table 1). All-cause hospitalization as a single endpoint followed a similar pattern in both treatment-adjusted and fully adjusted models (Supplementary Table 2).

3.4. Weight change and mortality

Of 76,351 weight measurements taken during the study, more than 97% were made when patients were free of oedema. In patients treated with pioglitazone, mean weight gain was $+3.1\pm4.4$ kg, $+3.7\pm5.6$ kg and $+4.0\pm6.1$ kg at 12 months, 24 months and at 36 months, respectively (all $P<0.0001$ compared to baseline Fig. 1B). In the placebo arm, there was a small but significant weight loss during the study (-0.4 ± 4.4, -0.4 ± 4.9, -0.6 ± 5.1 kg mean weight change at 12, 24, and 36 months, respectively; vs baseline: $P<0.0001$; vs pioglitazone: $P<0.0001$). When patients who died during the study were excluded, there was a similar pattern of weight gain and loss (pioglitazone arm $+3.1$ kg, $+3.8$ kg and 4.0 kg at 12, 24, and 36 month, respectively; placebo arm: -0.3, -0.4, and -0.6 kg at 12, 24, and 36 month, respectively.

Weight loss during the study was associated with increased mortality. Weight loss of 1% body weight was associated with a 13% increase in all-cause mortality (Table 3). The association of weight loss with increased mortality held true for each treatment arm separately (placebo group: HR 1.15; 95%CI 1.11–1.18; $P<0.0001$; pioglitazone group: HR 1.12; 95%CI 1.09–1.15; $P<0.0001$). Weight gain was not significantly associated with increased mortality in the placebo arm. Weight gain whilst on pioglitazone treatment was associated with improved survival (HR 0.96; 95%CI 0.92–1.00; $P<0.037$). Multivariable adjustment confirmed the association of weight loss but not weight gain with increased all-cause mortality (Table 3 and Supplementary Fig. 1 A to C).

A similar pattern was observed for cardiovascular mortality, with an increased risk in patients with weight loss, but not in patients with weight gain. Weight gain in the pioglitazone group was associated with significant lower risk of cardiovascular death (Table 3).

3.5. Weight change and composite outcomes

Further outcome measures were (a) the composite of all-cause death or myocardial infarction or stroke, (b) the composite of all-cause death or all-cause hospitalization, and (c) the composite of cardiovascular death or hospitalization for heart failure. Weight loss was predictive for increased risk of these composite outcomes (Supplementary Table 3). These effects were, again, not seen in the pioglitazone treatment group considered separately.

Table 1
Baseline characteristics of the study population.

Patient characteristics	Pioglitazone	Placebo
	$n=2592$	$n=2610$
Male (n, %)	1725 (66.6)	1712 (62.6)
Race (white%)	2552 (98.5)	2578 (98.8)
Age (years)	61.9 ± 7.6	61.6 ± 7.7
Time since diagnosis of DM (years, median; IQR)	8.0 (4–13)	8.0 (4–14)
Systolic blood pressure (mmHg)	144 ± 18	143 ± 18
Diastolic blood pressure (mmHg)	83 ± 10	83 ± 9
Weight (kg)	87.5 ± 15	88.6 ± 16
BMI (kg/m^2)	30.7 ± 4.7	31.0 ± 4.8
Waist circumference (cm)	104.9 ± 11.7	105.6 ± 12.1

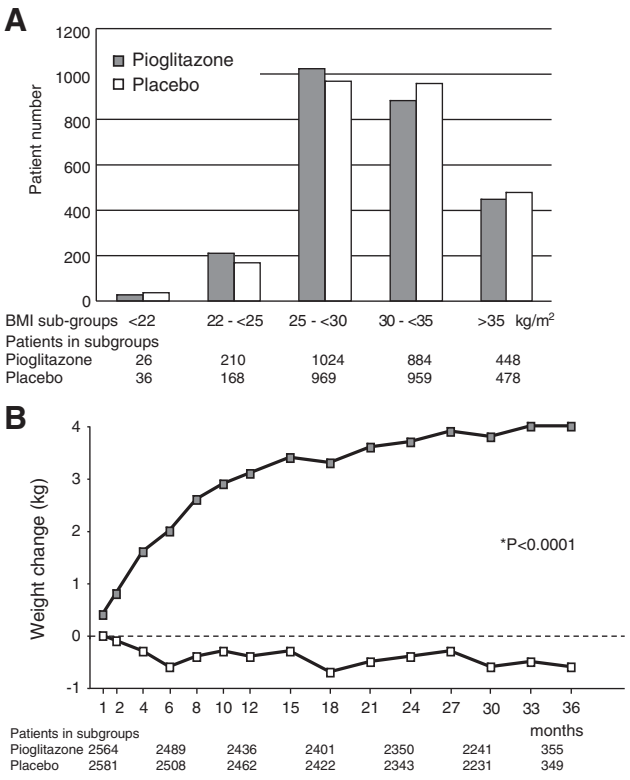

Fig. 1. A: Body mass distribution at baseline in treatment arms of the PROactive study population. B: Weight change in the PROactive population in treatment arms, *P between treatment arms.

We assessed the prognostic value of weight change during the first year of follow-up as a predictor of subsequent survival. Patients who died in first year of the study were excluded from this analysis. The results are consistent with the previous analysis for the entire study duration showing an increased risk for patients with one-year weight loss but no increased risk for patients with weight gain being observed in either treatment group (Table 4).

During follow-up 957 patients in the placebo arm (36.7%) lost at least 5% of body weight, 728 patients (27.9%) lost at least 6%, 478 patients (18.3%) lost at least 7.5%, 237 patients (9.1%) lost at least 10%, and 85 patients (3.3%) lost at least 15% (Fig. 4). 14.2% of patients in the placebo group gained ≥5% and 4% gained at least 10%.

All predefined cut-points for observed weight loss (≥5%, ≥6%, ≥7.5%, ≥10%, ≥15% of body weight) were associated with increased mortality. The hazard ratios in the treatment-adjusted models increased from 3.58 (for ≥5% weight loss) to 9.42 (weight loss ≥15%, Table 5). Using the criterion of the lowest negative likelihood ratio weight loss of ≥7.5% was the strongest predictor of impaired survival in treatment-adjusted analysis and in multivariable analysis.

We assessed the impact of incident malignancy on weight change analysis. During the study, 97 patients in the pioglitazone group (3.7%) and 98 patients (3.8%) in the placebo group had an incident malignancy. Malignant disease was associated with greater weight loss in the placebo group (mean weight change -3.2 ± 8.2% vs -0.3 ± 5.3% in patients without malignancy: $P<0.0001$); and was associated with less weight gain in the pioglitazone group (mean weight gain 2.4 ± 7.4% in patients with incident malignancy vs 4.3 ± 6.3% in patients without: $P=0.0113$). Excluding patients with incident malignancies did not affect the significant relation between weight loss and increased mortality in univariable and multivariable adjusted analysis (data not shown).

Table 2
Hazard ratios for comparison between BMI categories to predict all-cause mortality and for all-cause death or hospitalisation; BMI category 30 to <35 kg/m^2 as reference group.

(A) All-cause death	HR	95% CI	*P*
All patients, adjusted for treatment			
BMI <22 kg/m^2	1.93	0.90–4.14	0.093
BMI 22 to <25 kg/m^2	**1.53**	**1.04–2.25**	**0.031**
BMI 25 to <30 kg/m^2	1.14	0.89–1.47	0.30
BMI 30 to <35 kg/m^2	1.00 (referent)		
BMI ≥35 kg/m^2	1.33	0.99–1.79	0.057
Placebo arm			
BMI <22 kg/m^2	**2.96**	**1.27–6.87**	**0.012**
BMI 22 to <25 kg/m^2	**1.88**	**1.11–3.21**	**0.019**
BMI 25 to <30 kg/m^2	1.29	0.90–1.81	0.17
BMI 30 to <35 kg/m^2	1.00 (referent)		
BMI ≥35 kg/m^2	1.18	0.77–1.81	0.46
Pioglitazone arm			
BMI <22 kg/m^2	0.64	0.09–4.61	0.66
BMI 22 to <25 kg/m^2	1.24	0.71–2.16	0.46
BMI 25 to <30 kg/m^2	1.02	0.71–1.46	0.94
BMI 30 to <35 kg/m^2	1.00 (referent)		
BMI ≥35 kg/m^2	1.49	0.99–2.23	0.054
B) All-cause death or all-cause hospitalization	HR	95% CI	*P*
All patients, adjusted for treatment			
BMI <22 kg/m^2	**1.49**	**1.07–2.06**	**0.017**
BMI 22 to <25 kg/m^2	**1.21**	**1.03–1.41**	**0.018**
BMI 25 to <30 kg/m^2	1.026	0.93–1.13	0.59
BMI 30 to <35 kg/m^2	1.00 (referent)		
BMI ≥35 kg/m^2	1.090	0.97–1.22	0.14
Placebo arm			
BMI <22 kg/m^2	**1.872**	**1.19–2.67**	**0.005**
BMI 22 to <25 kg/m^2	**1.410**	**1.13–1.76**	**0.002**
BMI 25 to <30 kg/m^2	1.094	0.96–1.25	0.18
BMI 30 to <35 kg/m^2	1.00 (referent)		
BMI ≥35 kg/m^2	1.14	0.97–1.33	0.11
Pioglitazone arm			
BMI <22 kg/m^2	1.14	0.66–1.98	0.64
BMI 22 to <25 kg/m^2	1.04	0.84–1.30	0.71
BMI 25 to <30 kg/m^2	0.96	0.84–1.09	0.51
BMI 30 to <35 kg/m^2	1.00 (referent)		
BMI ≥35 kg/m^2	1.04	0.88–1.23	0.67

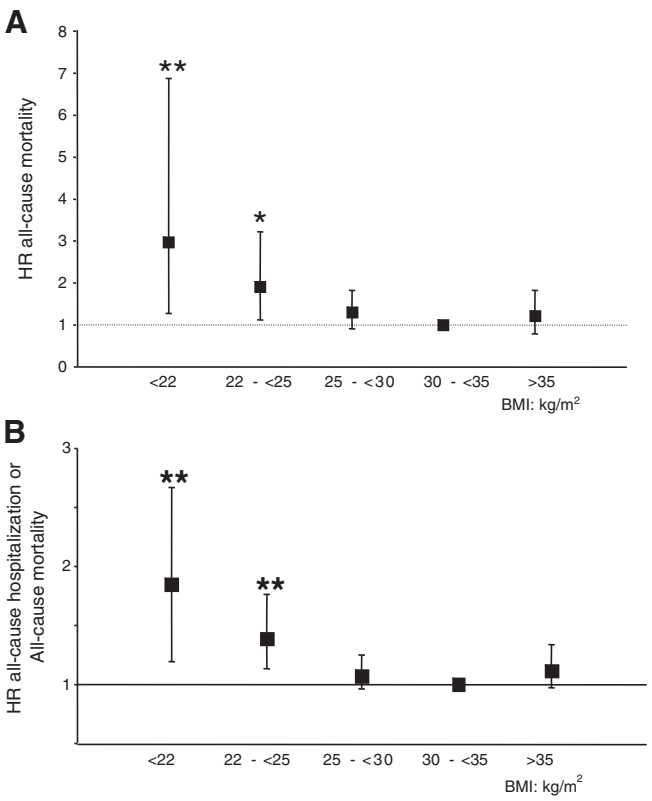

Fig. 2. Risk of all-cause mortality (A) and composite of all-cause mortality or all-cause hospitalization (B) by BMI categories in patients of the PROactive population (placebo arm). Bars indicate 95%CI * $P<0.05$; ** $P<0.01$.

4. Discussion

We have found that in patients with type 2 diabetes mellitus and cardiovascular co-morbidity, all-cause mortality and hospitalization are lower in overweight and mildly obese patients and are significantly increased in patients with BMI <25 kg/m^2. Weight loss was an independent predictor of increased all-cause mortality. Further, weight loss was associated with an increased risk of cardiovascular mortality and morbidity as indicated by increased hospitalization, myocardial infarction and stroke. By contrast, weight gain was not associated with increased all-cause mortality or cardiovascular mortality or morbidity. Indeed, weight gain associated with pioglitazone treatment predicted improved survival independent of other established predictors.

Our findings run counter to common ideas about T2DM. Overweight and obesity significantly worsen metabolic control and hence are thought to promote the development and progression of disease. Accordingly, weight control and, whenever possible, weight reduction are firmly established targets in the therapy of diabetes, with the aim of preventing cardiovascular disease [6, 24]. Such targets are, however, based on epidemiological studies of the general population from a primary prevention perspective, which have identified obesity as an independent risk factor for the development of cardiovascular disease and for death [1-5]. In contrast, the PROactive population includes T2DM patients who already have established cardiovascular disease, that is, a population for whom *primary* prevention is no longer a concern.

The present results are fully in line with previous studies showing a protective effect of overweight in patients with pre-existing cardiovascular disease. The term "obesity paradox" has been coined to describe the association. Substantial evidence has accumulated in patients with chronic heart failure that overweight and obesity are associated with improved survival [7–10, 25]. In studies of other cardiovascular conditions, such as in acute heart failure [11], acute myocardial infarction [26], bypass surgery [27], hypertension, and coronary artery disease, [28] being overweight is protective. One of these, the INVEST study, [28] investigated more than 22,500 patients who had an advanced cardiovascular risk profile (hypertension plus documented coronary artery disease) similar to the patients in the PROactive study population.

Our study adds to the accumulating evidence that there is an obesity paradox in patients with cardiovascular disease. The important novel finding is that the paradox is also present in patients with diabetes and cardiovascular co-morbidity. The association between obesity and an increased metabolic and cardiovascular risk seems to be overridden once cardiovascular illness has become established.

We found that weight loss of ≥7.5% body weight occurs in 18.3% of the patients in the PROactive population not treated with pioglitazone. This was the best cut-point for the relation between weight loss and mortality. Malignancy often accounts for weight loss (and contributes to poor survival) thus potentially confounding the association of weight loss and mortality. However, only 3.8% of patients included in the present analysis developed a malignancy; their exclusion did not affect the relation between weight loss and mortality.

Pioglitazone consistently induces weight gain, which is generally regarded as an unwanted consequence from the metabolic viewpoint. Our analysis showed that weight gain in the placebo arm was not associated with increased mortality and pioglitazone-induced weight gain is associated with improved survival independent of other risk

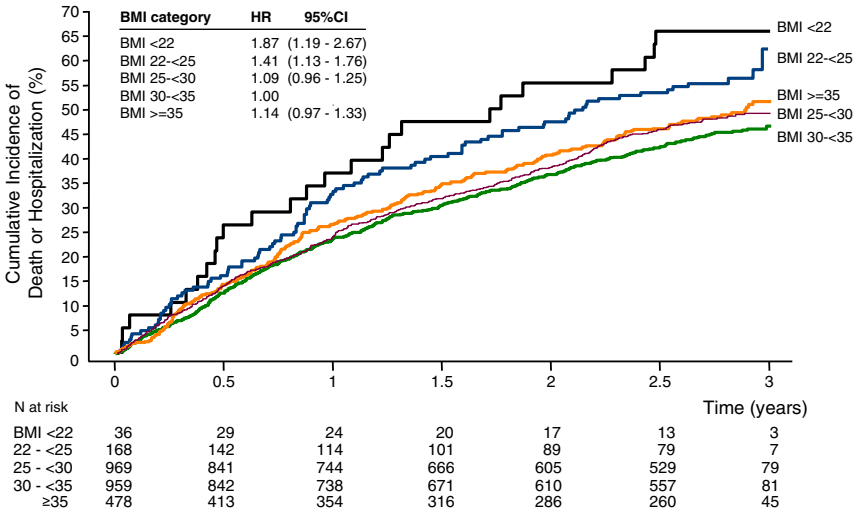

Fig. 3. Cumulative incidence of death or first all-cause hospitalization in BMI categories in patients (placebo arm).

factors. The latter may be seen as an indirect effect of improved lipid and glucose homeostasis. However, weight change (controlled for oedema) in patients fitting the PROactive profile should be viewed differently from people without overt cardiovascular disease. Catabolism and weight loss is a key feature of advanced illness, such as cardiovascular disease, that affects both storage tissue (i.e. fat) and lean tissues (i.e. muscle). Weight loss in the presence of chronic illness is often associated with advanced symptoms and a worse prognosis compared to patients with stable weight. Under these circumstances, weight gain may be a reflection of reduced catabolic activity and restored anabolic capacity. This may also explain that in the pioglitazone arm lower BMI was not associated with increased mortality as seen in the placebo arm.

Therapies that are highly effective in prolonging survival in patients with heart failure have been shown to prevent weight loss, such as ACE inhibitors [17] or to induce weight gain such as beta-blocker treatment [29]. The weight gain in those patients may, in fact, be an indicator of effective therapy by neutralizing catabolic dominance [30].

The study did not include the small proportion of patients who died or withdrew from the study during the first month of treatment (<1%), for whom no measure of weight change was available. We think this does not have major implications for the results observed. From the associations of weight and weight change with outcome no causal effect of body weight per se may be concluded. Weight change as a global (and easy to measure) variable may be the net effect of multiple pathophysiologic factors to reflect disease progression or treatment effect.

5. Conclusions

In a large cohort of patients with diabetes and with cardiovascular co-morbidity, overweight and mild obesity were associated with improved survival compared to patients with normal weight. Weight loss predicted impaired outcome on all-cause mortality, cardiovascular mortality and hospitalisation. Weight loss of ≥7.5% body weight occurred in 18% of the patients and was the best cut-point to predict impaired prognosis. Weight gain, in contrast, did not confer increased mortality risk. Weight gain following pioglitazone treatment was an independent predictor of improved outcome. These data suggest the presence of an obesity paradox in T2DM patients with advanced cardiovascular risk.

Supplementary materials related to this article can be found online at doi:10.1016/j.ijcard.2011.09.039.

Table 3
Impact of weight gain and weight loss on all-cause mortality (A) and on cardiovascular mortality (B). Hazard ratios for 1% weight change.

Outcome	Bivariable model[a]			Multivariable model[b]		
(A) All cause mortality	HR	95%CI	*P*	HR	95%CI	*P*
All patients, adjusted for treatment						
Weight gain (1%)	0.97	0.94–1.01	0.14	0.97	0.94–1.01	0.14
Weight loss (1%)	**1.13**	**1.11–1.16**	<**0.0001**	**1.13**	**1.10–1.15**	<**0.0001**
Placebo arm						
Weight gain (1%)	1.02	0.95–1.08	0.61	1.01	0.95–1.08	0.70
Weight loss (1%)	**1.15**	**1.11–1.18**	<**0.0001**	**1.13**	**1.10–1.17**	<**0.0001**
Pioglitazone arm						
Weight gain (1%)	**0.96**	**0.92–1.00**	**0.037**	**0.96**	**0.92–1.00**	**0.035**
Weight loss (1%)	**1.12**	**1.09–1.15**	<**0.0001**	**1.12**	**1.09–1.16**	<**0.0001**
(B) Cardiovascular mortality	HR	95%CI	*P*	HR	95%CI	*P*
All patients, adjusted for treatment						
Weight gain (1%)	0.97	0.93–1.01	0.15	0.97	0.93–1–01	0.11
Weight loss (1%)	**1.08**	**1.04–1.11**	<**0.0001**	**1.07**	**1.03–1.10**	**0.0003**
Placebo arm						
Weight gain (1%)	1.00	0.93–1.08	0.89	1.00	0.93–1.08	0.94
Weight loss (1%)	**1.08**	**1.04–1.13**	**0.0003**	**1.06**	**1.01–1.11**	**0.015**
Pioglitazone arm						
Weight gain (1%)	0.96	0.91–1.00	0.075	**0.95**	**0.90–1.00**	**0.042**
Weight loss (1%)	**1.07**	**1.02–1.13**	**0.004**	**1.07**	**1.02–1.13**	**0.0008**

[a] Bivariable model included weight loss and weight gain as separate variables.
[b] Multivariable model included age, creatinine, LDL, HbA1c, previous MI, previous stroke, previous PCI or CABG, peripheral obstructive artery disease, smoking status, Insulin use, diuretic use, and statin use.

Table 4
Hazard ratio for 1% weight change during first year of follow-up to predict subsequent all-cause mortality.

Outcome	HR	95% CI	*P*
All-cause mortality			
All patients (adjusted for treatment)			
Weight gain (1%)	0.99	0.95–1.04	0.68
Weight loss (1%)	**1.13**	**1.09–1.17**	<**0.0001**
Placebo arm			
Weight gain (1%)	1.03	0.95–1.13	0.46
Weight loss (1%)	**1.15**	**1.10–1.20**	<**0.0001**
Pioglitazone arm			
Weight gain (1%)	0.98	0.93–1.03	0.35
Weight loss (1%)	**1.11**	**1.04–1.19**	**0.0014**

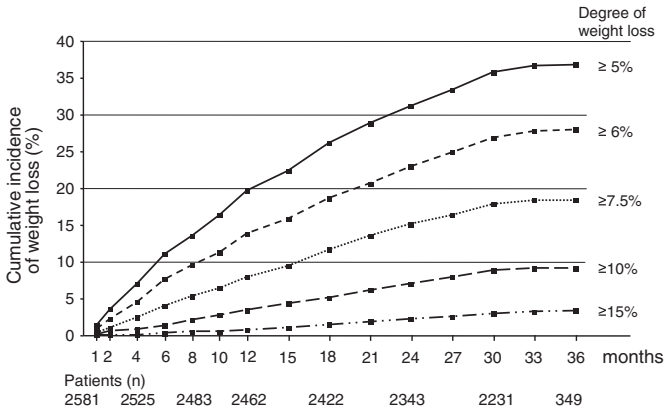

Fig. 4. Cumulative incidence of various degrees of weight loss in the PROactive study population (placebo arm).

Contributors

All authors participated significantly to the work presented in this manuscript. W Doehner and SD Anker designed the analysis plan and are responsible for data interpretation, drafting and final approval of the manuscript. W Doehner takes responsibility for the integrity of the work as a whole, from inception to published article. JA Dormandy, E Ferrannini, and E Erdmann are members of the PROative Steering Committee, granted access to the database and contributed to the analysis plan, data interpretation and write-up. R Cairns is responsible for statistical analysis, data interpretation and contributed to the manuscript draft. R Cairns and W Doehner had full access to all of the data and take responsibility for their integrity and the accuracy of the data analysis. E Ferrannini and A Clark also contributed to the conception of the study, analysis and interpretation of the data and critical revision. All authors read and approved the final version of the manuscript. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [31].

Conflict of interest

The PROacvite study was funded by Takeda Pharmaceutical Company and Eli Lilly and Company. JA Dormandy and E Erdmann are members of the international steering committee of the PROactive study. Both served as consultants and received travel expenses and payments for speaking at meetings from Takeda. R Cairns worked at the Nottingham Clinical Research Group, which was contracted by Takeda for the PROactive study. The sponsors of the PROactive study had no rule in design or mode of this analysis, interpretation of the data, or writing of the report. W Doehner, SD Anker and A Clark have no conflict of interest. The statistical analysis for this study was supported in part by Takeda.

Table 5
Effect of the degree of weight loss on all-cause mortality in the PROactive population using pre-specified cut-points.

Weight loss cut point	HR	95% CI	*P*
≥5% weight loss			
Treatment adjusted	3.58	2.79–4.60	<0.0001
Multivariable adjustment[a]	3.25	2.51–4.21	<0.0001
≥6% weight loss			
Treatment adjusted	4.05	3.11–5.28	<0.0001
Multivariable adjustment[a]	3.56	2.77–4.79	<0.0001
≥7.5% weight loss			
Treatment adjusted	5.03	3.78–6.70	<0.0001
Multivariable adjustment[a]	4.42	3.30–5.94	<0.0001
≥10% weight loss			
Treatment adjusted	6.68	4.79–9.32	<0.0001
Multivariable adjustment[a]	5.60	3.96–7.91	<0.0001
≥15% weight loss			
Treatment adjusted	9.42	5.89–15.07	<0.0001
Multivariable adjustment[a]	7.72	4.73–12.60	<0.0001

[a] Multivariable model included age, creatinine, LDL, HbA1c, previous MI, previous stroke, previous PCI or CABG, peripheral obstructive artery disease, smoking status, Insulin use, diuretic use, and statin use.

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