Weight loss and mortality risk in patients with chronic heart failure in the candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM) programme

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Aims

The curiosity that leanness is associated with poor survival in patients with chronic heart failure (CHF) needs further insight by investigating the impact of weight loss on prognosis in a large sample of patients across a broad spectrum of both reduced and preserved left ventricular (LV) systolic function.

Methods and results

We investigated the change in weight over 6 months in 6933 patients in the Candesartan in Heart failure: Reduction in Mortality and morbidity (CHARM) programme, and its association with subsequent mortality (1435 deaths) over a median 32.9 months follow-up using Cox proportional hazard models to account for the impact of body mass index and other risk predictors. We then used time-updated Cox models to relate each patient’s ongoing data on annual weight change to their mortality hazard. The percentage weight loss over 6 months had a highly significant monotonically increasing association with excess mortality, both for cardiovascular and for other causes of death. Patients with 5% or greater weight loss in 6 months had over a 50% increase in hazard compared with those with stable weight. Weight loss carried a particularly high risk in patients who were already lean at study entry. Findings were similar in the presence of dependent oedema, preserved or reduced LV ejection fraction, and treatment with candesartan, although weight loss was significantly less common on candesartan. The time-updated analyses revealed an even stronger link between weight loss and short-term risk of dying, i.e. risk increased more than four-fold for patients whose last recorded annual weight loss exceeded 10%. Weight gain had a more modestly increased short-term mortality risk. Weight loss accelerates in the year prior to death.

Conclusions

Weight loss and leanness are important predictors of poor prognosis in CHF. Being lean and losing weight is particularly bad. The detection of weight change, and particularly weight loss, should be considered as an adverse sign prompting further evaluation.

Keywords

Chronic heart failure • Clinical trial database • Weight loss • Mortality

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Introduction

Several studies of heart failure (HF) populations have shown that leaner patients have a poor survival and obese patients with chronic HF (CHF) have no excess mortality risk.1–10 This had led to the term ‘the obesity paradox’11 and claims that it is driven in truth by the deleterious effects of cachexia in HF patients.

There have been previous informative studies of weight loss and mortality in HF patients.12,13 CHARM was a large international programme of three trials including patients from a broad spectrum of HF, including both reduced and preserved left ventricular (LV) systolic function, where the effect of the angiotensin-receptor blocker candesartan was compared with placebo for mortality and morbidity. The main aim of this analysis in the CHARM programme was to assess and quantify the effect of weight loss on mortality.

Methods

Previous publications describe the design and results of the CHARM programme.14,15 In CHARM, 7599 patients with CHF were randomized to candesartan or placebo.

Body mass and weight changes over time

Patients in the CHARM programme had regular visits and each patient’s weight was recorded according to each centre’s usual practice. These were planned to be at baseline, 2, 4, 6 weeks, 6 months, and then every 4 months thereafter until a maximum of 42 months.

Actual timing of visits varied and was assigned to the planned visit when within 1 week of the intended visit (first two visits), within 1 week before or 5 weeks after (third visit) or within 2 months of intended timing for the 6 month visit onwards. Height was recorded at baseline, enabling body mass index (BMI) to be calculated.

Other patient characteristics

Prognostic models have previously determined which baseline variables in this population are significantly related to mortality, and details of such variables are described therein.16

Mortality

Over a median 37.7 months follow-up time (range 24–48 months), 1831 of the total 7599 patients in CHARM died. Causes of death were determined by an independent adjudication committee using pre-specified criteria. A death was considered cardiovascular (CV) unless a specific non-CV cause was identified.

Statistical methods

For each patient, weights at 6 months and baseline visits were used to calculate the percentage change in weight at 6 months. A total of 305 patients died, five were lost to follow-up before 6 months, and a further 356 patients did not have a recorded weight at 6 months, which left 6933 patients (1435 deaths) for analysis relating 6 month mortality.

The associations of percentage weight change and mean BMI with those baseline variables previously shown to predict mortality,16 are presented in Table 1. More than 5% weight loss within 6 months appeared more commonly in patients who were older, female, NYHA class IV, and with dependent oedema. Patients on candesartan gained a mean 0.71 kg at 6 months compared with placebo (95% CI, 0.48–0.94 kg, P < 0.0001), and hence there were fewer patients with over 5% weight loss within 6 months on candesartan (6.1% vs. 9.2% in candesartan and placebo groups, respectively, P < 0.0001).

From a Cox proportional hazards model adjusting for all baseline predictors, we show that, compared with patients with <1% weight change, there was a clear monotonic increase in mortality hazard with increasing weight loss, with a 62 and 50% increase in hazard for those experiencing over 7% weight loss and 5–7% weight loss, respectively (Figure 1). There was no clear evidence that weight gain is associated with an increase in mortality risk.

Mean BMI over this 6 month period showed an inverse association with mortality at the leaner end of the spectrum, i.e. from BMI 27.5 kg/m² downwards (Figure 1). Patients with BMI < 20 kg/m² had a 95% increase in hazard compared with the middle category of BMI, 25–27.5 kg/m². Note that patients who were obese (BMI > 30 kg/m²) have a mortality risk similar to this middle category.
A further model fitted percentage weight loss as a continuous covariate: for every 1% weight loss over 6 months, there was 5.0% increase in mortality hazard (95% CI: 3.3–6.6%).

**Subgroup analyses**

Figure 2 shows the association between weight loss and mortality for several patient subgroups. We explored whether the link between weight loss and mortality risk was different for patients with and without dependent oedema: no such interaction was found. Similarly, the impact of weight loss on mortality was not related to BMI or LV ejection fraction, but appeared more pronounced in patients not on angiotensin-converting enzyme (ACE) inhibitors (interaction $P = .011$). The link between weight loss and mortality risk was similar in patients on candesartan and on placebo, though weight loss was less common in candesartan patients.

We also explored whether the link between weight loss and mortality varied with the cause of death (Figure 2). The results...
<table>
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<th>Baseline variables</th>
<th>n</th>
<th>Mean percentage weight change (SEM)</th>
<th>Mean BMI (SEM)</th>
<th>No. (%) with &gt;5% weight loss</th>
<th>No. (%) with BMI &lt; 22.5 kg/m²</th>
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Continued
were similar for CV deaths ($n = 1116$), and specifically for deaths due to HF ($n = 359$) and sudden deaths ($n = 490$), and also for non-CV deaths ($n = 319$).

Six month weight loss appeared to have a greater impact on mortality in the next year, and then the effect diminished somewhat over time (Figure 2). That is, for every 1% weight loss over 6 months the mortality hazard increased by 7.1, 4.4, and 2.0%, respectively, in the next year, the year after, and two or more years after the weight change was measured, test for trend $P = 0.013$.

Table 2 explores how the link between the percentage weight change and mortality depends on BMI. The highest risk increase, over 150%, is in the small group of patients who are both lean (BMI $< 22.5 \text{ kg/m}^2$) and experiencing more than 5% weight loss. Patients who are either lean or experiencing such weight loss (but not both) have around 50% increase in hazard. Weight gain and/or being overweight has no evident increase in mortality risk. Overall, there is no evidence of a statistical interaction between percentage weight change and mean BMI.

All the above analyses were repeated for percentage weight change from baseline to the 10 month visit, and findings were very similar (data not shown).

Exploratory analyses with hospitalization for HF as the outcome show no evidence of an association of percentage weight change with subsequent risk of HF hospitalization (data not shown).
Figure 3 shows 10 categories of annual percentage weight change, with extremes of 10% or more weight loss to 7% or more weight gain. Starting from the 10 month visit date, each patient’s follow-up time was broken down into 4 monthly periods, with each period assigned to the estimated annual percentage weight change at its commencement. Figure 3 gives the crude death rate per 100 person-years that patients spent in each annual percentage weight change category.
There is a marked monotonic trend towards higher death rates with increasing weight loss and also a weaker trend to higher death rates with increasing weight gain. Patients missed some planned visits over time, so that for 7.5% of follow-up time the time-updated annual percentage weight change was unknown. The death rate was higher during this time, which suggests that patients close to death may be especially prone to miss visits.

Figure 3 also shows how the mortality hazard relates to last recorded percentage weight change, based on a Cox model with percentage annual weight change and mean BMI as time-updated covariates and known baseline predictors as fixed covariates. Patients with stable weight have the lowest risk. There is a highly significant monotonic increase in risk with increasing weight loss; patients with a last recorded weight loss over 10% have hazard ratio 4.4 (95% CI: 3.5–5.6) compared with patients with currently stable weight, after adjusting for other covariates. Patients with last recorded weight gain exceeding 7% also have a significantly higher mortality risk than those with stable weight: hazard ratio 1.6 (95% CI: 1.2–2.1).

Fitting linear terms to the trends in Figure 3, we obtain an 11.2% increase in short-term mortality risk per 1% weight loss (P < 0.0001) and a 3.4% increase per 1% weight gain (P = 0.001). In this time-updated Cox model, findings for time-updated mean BMI were similar to those in the fixed Cox model (Figure 1) and hence are not shown.

Figure 4 shows an alternative simple analysis of the extent to which weight loss occurs prior to death. Looking back in time from each death we identified recorded weight changes between 4-monthly visits and grouped them according to their duration from time of death. This shows an interesting pattern of accelerated weight loss in the year prior to death, both for mean weight changes and the percentage of patients with over 5% weight loss in a 4-month period.

**Discussion**

We have found that in a broad spectrum of patients with CHF, there is a strong continuous relationship between weight loss and increased mortality from all causes. This finding is consistent with previous evidence. The more precise estimation achievable with our larger database (1435 deaths in 6933 patients followed for a median 32.9 months after weight change) enables the nature of this relationship to be clarified. We set out to simultaneously assess the effect of both weight loss and weight gain on prognosis, and our study is the first to use the time-updated Cox models to dynamically assess how each patient’s evolving pattern of weight loss (or weight gain) impacts on his or her prognosis.

Anker et al.’s research on weight loss and mortality in the SOLVD trial substantially clarified the prognostic importance of weight loss. They focussed on identifying which level of weight loss gave the strongest discrimination, and proposed 6% weight loss to define cachexia in CHF. Rather than concentrating on any single cut-off value, our approach quantifies the steadily increasing risk of dying as weight loss becomes more marked. The continuous nature this relationship is most striking when relating the time-updated annual weight loss to short-term mortality risk (Figure 3). This is after other known predictors of mortality (e.g. age, diabetes, low LV ejection fraction etc.) have been accounted for.

It is interesting that both recent weight loss and underlying lean-ness are simultaneously associated with an increase in mortality (Figure 1). Thus, patients who are both lean (mean of baseline and 6 month BMI < 22.5 kg/m2) and losing weight (over 5% weight loss in 6 months) have over 150% increase in mortality compared with patients who are heavier and experience little or no weight change (Table 2). In the absence of data on longer term history of weight change in CHF patients, it seems plausible to argue that lower body mass may to some extent be a marker of previous weight loss.

It is difficult to dissect the exact causal explanation for these findings, but it seems reasonable that cachexia causes both weight loss and increased mortality. The precise time course of weight loss in CHF is not known—it has been suggested to be a gradual and graded process, but it could also be a step-wise process where phases of weight stability and weight change are distinct. Our study provides evidence for the latter, as it is shown that mean weight change >12 months before death is small or non-existent, whereas it is steeply increasing in the last 12 months prior to death (Figure 4A).

The presence of weight loss is widely recognized as linked to mortality in elderly and chronic disease populations. In the setting of CHF, the wasting process affects muscle, fat, and bone tissue. At the tissue level, wasting in CHF is due to a complex interplay of catabolic factors and lack of anabolic protection, termed catabolic/anabolic imbalance. Several neurohormones and inflammatory cytokines (that are all prognostic themselves) as well as markers of anaemia are particularly raised in CHF patients with cachexia compared with non-cachetic patients. The degree of neurohormonal activation in CHF patients varies substantially, and it can be argued that the onset of weight loss may indicate, in a very sensitive manner, that these neuro-endocrine and immunological abnormalities have reached a clinically relevant degree and that therefore the mortality risk of these patients is increased. This view assumes that the weight loss itself is not the cause of death but a sensitive marker of poor outcome. Weight loss may also be a specific direct cause of death, but this has not yet been demonstrated.

Weight loss in CHF may also arise from reduced food intake (possibly linked to reduced appetite, increased liver congestion and nausea, increasing fatigue in advanced CHF or even a general sense of hopelessness) or dehydration arising from fluid loss. We did not adjust for the presence of oedema in these weight change analyses. Therefore, the estimates of weight loss may be underestimates of true (non-fluid) weight loss, and overestimates of true (non-fluid) weight gain. This may also explain why we found an adverse impact of weight gain on short-term outcome (Figure 3), but not on long-term outcome (Figure 1A). To some degree the finding of weight gain in the average CHARM patient may document the presence of oedema (or a state of imminent cardiac decompensation) and hence confer the adverse short-term prognosis.

Angiotensin II has repeatedly been shown to relate to the development of skeletal muscle apoptosis, tissue inflammation, and reduced action of insulin-like growth factor-1, an anabolic
and tissue-protective hormone. In experimental studies, angiotensin II infusion caused muscle wasting, and inhibition with an angiotensin II receptor antagonist (losartan) abolished this effect. In CHARM, patients randomized to candesartan treatment had a mean 6 months weight increase of 0.71 kg in 6 months compared with placebo. Although this seems small, this shift in weight did lead to significantly fewer patients on candesartan experiencing substantial weight loss, so that the modest survival benefits of candesartan may be partially mediated through enhanced avoidance of weight loss.

Among the treatments that appear to reduce mortality in CHF, ACE inhibitors, angiotensin receptor blockers, and beta-blockers also seem to help avoid weight loss. These observations need to be considered in an historical perspective, since for most clinicians one key concern in managing patients with CHF has been to avoid inadvertent fluid retention with associated weight gain, and incipient or fulminant symptomatic worsening of CHF requiring hospitalization. Our study suggests that the clinical approach to management of body weight needs some adjustment. From a prognostic standpoint, weight loss is a much more prominent problem.

Figure 4 (A) Mean 4 month percentage weight change (with 95% CI) and (B) percentage of patients with >5% weight loss in 4 months, each shown according to the time prior to each known death.
than weight gain, and this is true regardless of the patients’ body mass. In the context of outpatient care for CHF patients, only limited time is available to educate patients. It appears that among the possible messages one would want to educate patients about, the message to aim for weight loss in moderately obese patients likely is of lesser value than other possible messages including to exercise and to self-manage diuretic medication.

Weight loss is more common in older patients, poor NYHA class, females, and those with dependent oedema and hence it was essential that all our analyses relating weight loss to mortality adjusted for these potential confounders.

We had previously reported that the link between low body mass and increased mortality appeared to be confined to patients without dependent oedema.1 In studying weight loss, the same interaction is not present, i.e. the impact of weight loss on mortality risk exists both for patients with and without dependent oedema at baseline (Figure 2). We also show that the same weight loss/mortality link exists both for patients with preserved and impaired LV function. Also the weight loss/mortality link is observed to be of similar magnitude for deaths from HF, sudden death, other CV deaths, and non-CV deaths.

This study is most innovative in its dynamic assessment of how the ongoing time-updated recordings of weight change are associated with mortality risk. For this purpose, we tracked for each patient over time the ongoing estimate of annual percentage weight change, starting with the change from baseline to the 10 month visit. Each subsequent 4-monthly visit facilitated a new estimate of annual percentage weight change. Linking all deaths and 4-monthly follow-up period to the latest available annual percentage weight change showed a very strong link between recent weight loss and death (Figure 3). Compared with patients with little or no weight change, increasing current weight loss shows a steady and dramatic rise in mortality risk after adjusting for other known predictors in mortality.

Specifically, more than 10% current annual weight loss carried over four times the risk of dying in the next 4 months. The current weight gain was also associated with a steadily increased mortality risk, although less markedly than weight loss. That is, over 5% weight gain led to a 50% excess mortality risk. While careful tracking of body weight is a standard recommendation for HF fluid management, these striking findings provide another reason for systematic weight monitoring—to identify patients at much higher short-term risk of death.

The time-updated analyses of weight change require a different interpretation from the more conventional fixed models in Figure 1. The latter showed that weight gain over 6 months was not linked to increased subsequent mortality in the long run, i.e. over the next 32 months mean follow-up. The former is studying what happens shortly before death and it is evident that some patients gain weight in terminal CHF, probably due to uncontrolled volume overload. The time-updated analyses also revealed a more sharply focussed impact of weight loss on short-term mortality. That is, in some patients, cachexia becomes more dramatically highlighted shortly before death such that substantial weight loss is a strong indicator of imminent death in the next few months. Also, more intensive diuretic therapy may be a contributory factor. Overall, patients with stable weight have the lowest risk of short-term mortality.

Limitations in our investigation include the fact that it is from a clinical trial database that had several exclusion criteria14 that might affect the generalizability. Also, our concentration on overall weight (and BMI) does not distinguish between muscle, fat, fluid, and bone mass and the data provide no means of distinguishing between intentional and unintentional weight loss. We had no other anthropometric measures such as waist to hip ratio or skinfold thickness. Nor did we measure cytokines or any other markers (e.g. neurohormones) that may be in the intermediate causal pathway.

In conclusion, this study shows that weight loss is a clear indicator of poor prognosis in CHF in a broad spectrum of patients regardless of LV ejection fraction or the presence of dependent oedema. Good patient management requires ongoing monitoring of weight change over time, calling for increased vigilance particularly when weight loss >5% is detected as this indicates the presence of cachexia.34

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References


