

Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study

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Summary

Background Weight loss in chronic heart failure is linked to impaired survival. We aimed to assess the frequency of weight loss in patients with this disease, whether the degree of weight loss predicts mortality, and whether weight loss can be prevented by angiotensin-converting-enzyme (ACE) inhibitors.

Methods We investigated weight changes in 1929 patients from the SOLVD trial who had chronic heart failure, were free of oedema at baseline, and survived for at least 4 months after trial entry. Mean follow-up was 35 months (SD 13). We analysed the effect of weight loss at cutpoints of 5%, 7.5%, 10%, 15% (a priori), and 6% (post hoc) to identify which one best predicted outcome. To validate results, we analysed data for 619 patients in the V-HeFT II trial.

Findings 817 (42%) patients in the SOLVD trial had weight loss from baseline of 5% or more. At 8 months follow-up, all cutpoints for weight loss were significantly associated with impaired survival after adjustment for age, sex, New York Heart Association class, left ventricular ejection fraction, and treatment allocation. Weight loss of 6% or more at any time during follow-up was the strongest predictor of impaired survival (adjusted hazard ratio 2.10, 95% CI 1.77–2.49; $p < 0.0001$). Patients on the ACE inhibitor enalapril had a lower hazard of 6% or more weight loss than did those not taking the drug (adjusted reduction 19%, $p = 0.0054$). Results from analyses of V-HeFT II data lent support to our findings.

Interpretation Weight loss occurs frequently in patients with chronic heart disease, its reversal is rare, and when present, it is independently linked to impaired survival. Weight loss of more than 6% should be used to define the presence of cachexia in patients with chronic heart failure. In chronic heart failure, treatment with an ACE inhibitor reduces the risk of weight loss.

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Introduction

Cachexia is a serious complication of several chronic diseases, including heart failure, malignant cancer, acquired immunodeficiency syndrome, thyrotoxicosis, and rheumatoid arthritis, and is suggestive of a poor outlook for patients. In a previous single-centre prospective study of 171 patients, we reported that weight loss in chronic heart failure is linked to impaired survival independent of other well recognised risk factors.¹ The definition of cardiac cachexia that we used in that study (ie, >7.5% loss of bodyweight from baseline) was arbitrary, and the study was done in a sole tertiary referral centre with patients who were potentially highly selected; thus our results left several questions unanswered.

Angiotensin-converting-enzyme (ACE) inhibitors are a well studied and widely available treatment that ameliorates symptoms, reduces morbidity, and improves survival in patients with chronic heart failure. The benefits of ACE inhibitors cannot be explained solely by a haemodynamic mode of action; other effects of ACE inhibitors include modification of the neurohormonal axis and of endothelial function.² ACE inhibitors are most successful in preventing deaths in patients who have raised catecholamines,^{3,4} which are closely related to the presence of cardiac cachexia.⁵

We reanalysed data from patients who participated in the SOLVD trial⁶ to assess the frequency of substantial weight loss in patients with chronic heart failure, to ascertain whether the degree of weight loss predicts mortality, and whether ACE inhibitors can reverse or prevent weight loss. We did similar analyses with data from the V-HeFT II database.⁷

Methods

Patients

SOLVD

The SOLVD treatment study⁶ was a randomised, double-blind, placebo-controlled trial investigating the effects of enalapril treatment in 2569 clinically stable patients who had a left ventricular ejection fraction (LVEF) of 35% or less and evidence of overt congestive heart failure. To avoid the confounding effect of weight loss caused by reduction of oedema, we included patients from this study who (in the opinion of the local investigator and as documented in the case report form) had been free of oedema at entry to the study, had survived for at least 4 months after study entry), had weight measurements at baseline, and at least one follow-up visit at 4 months or later. Height was not recorded in the SOLVD study.

V-HeFT II

This study⁷ was a randomised, double-blind trial in 804 patients with chronic heart failure to compare the effects on mortality of enalapril (20 mg, daily) with a

	Original trial (n=2569)	Reanalysis (n=1929)
Age (years)	60.9 (9.9)	60.2 (9.9)
Weight (kg)	79.8 (16.7)	78.9 (15.9)
Men	2065 (80%)	1583 (82%)
NYHA class*		
I	283 (11%)	243 (13%)
II	1457 (57%)	1144 (59%)
III	783 (31%)	524 (27%)
IV	45 (2%)	18 (>1%)
LVEF*		
>25%	1256 (49%)	954 (50%)
≤25%	1312 (51%)	975 (51%)
Taking diuretic	2196 (86%)	1614 (83%)
Cause of heart failure		
Ischaemic	1832 (72%)	1375 (71%)
Non-ischaemic	737 (29%)	554 (29%)
Alive	1607 (63%)	1313 (68%)
Dead	962 (37%)	616 (32%)

Data are mean (SD) or number (%). *NYHA Class and LVEF for one patient in SOLVD treatment trial not known.

Table 1: Baseline characteristics of patients in the SOLVD treatment study

combination of 300 mg hydralazine and 160 mg of isosorbide dinitrate, daily. In V-HeFT II, patients with substantial weight changes during the stabilisation period were excluded. We included patients who had (as documented in the case report form) no oedema at baseline, had survived at least 6 months, and had weight measurements at baseline and at 6 months.

Procedures

We used analysis of data from the V-HeFT II study to validate results of our findings derived from the SOLVD database with respect to frequency of weight loss in patients with chronic heart failure and the prognostic value of weight loss of more than 6%.

In both studies, bodyweight at baseline and during follow-up was assessed per protocol (during all visits). Weight was measured while the patient was wearing light clothes and no shoes. The study protocols did not prescribe a time of day for measurements to be taken. Weight loss was defined as loss of bodyweight from baseline. We did not adjust for the development of oedema during follow-up.

Statistical analysis

We compared means and proportions between groups in the SOLVD study with an unpaired *t* test and χ^2 test, respectively. We used a priori weight loss cutpoints of 5.0% or more, 7.5% or more, 10.0% or more, and 15.0% or more for analyses. The effect of weight loss on survival was assessed with Cox's proportional hazards model, with weight loss as a continuous, time-dependent variable. We tried several non-linear transformations, including quadratic terms ($p=0.78$), which produced non-significant results (all $p>0.10$). When information on bodyweight was not available at a specific time point, we carried forward the previous measurement.

To address the question of whether ACE inhibitors can affect the risk of first occurrence of substantial weight loss, we compared the hazards of weight loss in the two treatment groups using the log-rank statistic. In the analysis of first occurrence of weight loss, missing information is treated as censored (ie, it was judged not to have occurred at this visit). Primary analysis was by intention to treat.

To identify the best cut-point for weight loss to predict prognosis (adjusted for age, treatment, sex, New

York Heart Association [NYHA] class, and LVEF), we identified in the SOLVD treatment study the best competitive cutpoint within a prespecified range of 5–10% weight loss (with the criterion of the highest *z* value). We used weight loss at any time during follow-up as a time-dependent variable. As much as possible, we validated this selected cutoff in the V-HeFT II study using the weight loss assessment at 9 months, and we adjusted for covariates and did quadratic transformations ($p=0.41$) in much the same way as for SOLVD data.

We judged *p* values less than 0.05 (two-sided) as significant. In assessment of the effect of weight loss on survival, we adjusted for age, sex, NYHA functional class, LVEF ($\leq 25\%$ or $>25\%$), and treatment status (enalapril *vs* placebo).

We based our analyses of V-HeFT II data on the results of the SOLVD database analysis. The cutpoint of 6.0% or more for weight loss was considered for analyses. In exploratory analyses, the effect of weight loss on subsequent survival (and of treatment allocation on the risk of the first occurrence of $\geq 6\%$ weight loss) was assessed with Cox's proportional hazards analysis. For univariate analyses, the log-rank statistic is reported, and for multivariable analyses, we provide results of the Wald test. Because the sample size in the V-HeFT II study was smaller than that in SOLVD, we did not expect to have adequate power to investigate the differential effect of the different treatments used in each study on weight loss.

Results

SOLVD

We included 1929 patients from SOLVD—75% of the original trial population. Apart from oedema status, baseline clinical characteristics of these patients did not differ from those of the total study population (table 1). 993 of the included patients were randomly allocated enalapril (2.5 to 20 mg daily) and 936 patients received placebo. Mean follow-up was 35 months (SD 13), during which time 757 (39%) participants died.

During follow-up, 817 patients (42%) had weight loss of 5% or more, 549 (28%) lost 7.5% or more, 348 (18%) lost 10% or more, and 129 (7%) lost 15% or more during follow-up (figure 1). Between month 24 and 36 of follow-up, the cross-sectional frequency of cachexia in patients

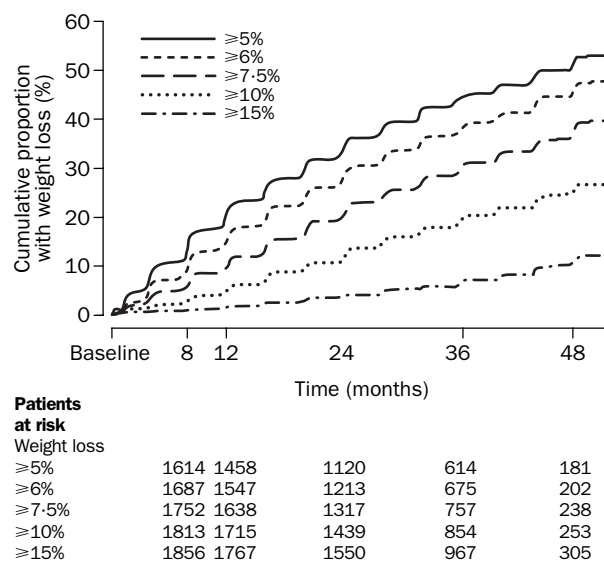


Figure 1: Cumulative incidence of weight loss in patients with chronic heart failure in the SOLVD treatment study

	Weight loss \geq 7.5%		Weight loss \geq 6.0%	
	No (n=1380)	Yes (n=549)	No (n=1227)	Yes (n=702)
Age (years)	59.8 (10.1)	61.1 (10.1)*	59.5 (10.2)	61.2 (9.3)*
Weight (kg)	77.9 (15.4)	81.4 (16.8)*	77.9 (15.5)	80.5 (16.4)*
Women	229 (17%)	117 (21%)†	194 (16%)	152 (22%)‡
Men	1151 (83.4)	432 (78.7)	1033 (84%)	550 (78%)
NYHA class				
I	185 (13%)	58 (11%)	163 (13%)	80 (11%)
II	832 (60%)	312 (57%)	744 (61%)	400 (57%)
III	351 (25%)	173 (32%)	308 (25%)	216 (31%)
IV	12 (<1%)	6 (1%)	12 (1%)	6 (<1%)
LVEF				
>25%	678 (49%)	276 (50%)	605 (49%)	349 (50%)
\leq 25%	702 (51%)	273 (50%)	622 (51%)	353 (50%)
Taking diuretics	1140 (83%)	474 (86%)‡	1010 (82%)	604 (86%)‡
Cause of heart failure				
Ischaemic	974 (71%)	401 (73%)	864 (70%)	511 (73%)
Non-ischaemic	406 (29%)	148 (27%)	363 (30%)	191 (27%)

Data are mean (SD) or number (%). * $p < 0.001$. † $p < 0.05$. ‡ $p < 0.01$.

Table 2: Baseline characteristics of patients with or without subsequent weight loss (SOLVD)

with heart failure was stable. For weight loss of 7.5% or more, it was between 10% and 14% in the enalapril group, and between 13% and 15% for patients on placebo. Patients who lost 7.5% or more of their bodyweight during follow-up were on average 1.3 years older ($p < 0.05$) and had a mean initial weight that was 3.5 kg higher than in other patients ($p < 0.0001$, table 2).

346 (18%) of included patients were female. During follow-up, women with chronic heart failure were more likely to have had weight loss of 7.5% or higher than were men (34% *vs* 27%, respectively; $p = 0.08$). A comparison of patients who had weight loss of 7.5% or more (or $\geq 6\%$) and those who did not, showed that NYHA class, LVEF, and disease cause were much the same in the two groups (table 2). In patients with weight loss of 7.5% or more at any time point ($n = 549$), only ten (2%) had subsequent weight measurements equal to or higher than the baseline weight (six on enalapril, four on placebo). These ten patients all had a weight gain of 7.5% or more from their baseline weight after being diagnosed as cachectic. Information on the development of oedema was missing for these patients.

Weight loss was independently related to reduced survival (table 3). At 8 months, weight loss at all cutpoints (5%, 7.5%, 10%, and 15%) was associated with increased mortality. The hazard ratios (HR) increased from 1.38 (for weight loss of $>5\%$) to 2.71 ($>15\%$) and were independent of age, sex, NYHA class, LVEF, and treatment allocation (table 4). Weight loss of 6.0% was the strongest predictor of impaired survival in crude and

adjusted analyses. In crude analysis, the z value was 8.7 with a hazard ratio of 2.1 (95% CI 1.80–2.52), adjusted for age, treatment, sex, NYHA class, and LVEF the z value was 8.5 (HR 2.1 [1.77–2.49], both $p < 0.0001$). For these analyses, weight loss at any time during follow-up was treated as a time-dependent variable. Weight loss of 6% or more occurred in 702 patients (36%). Weight loss of 6% or more at 4, 8, or 12 months was also associated with impaired survival (tables 3 and 4).

During follow-up, patients who were allocated enalapril had a lower risk of weight loss ($\geq 5\%$, HR 0.83 [0.72–0.95], $p = 0.0079$; $\geq 6.0\%$, 0.80 [0.69–0.93], $p = 0.0039$; $\geq 7.5\%$, 0.85 [0.72–1.01], $p = 0.060$). These findings remained after adjustment for age, sex, NYHA class, and LVEF (weight loss $\geq 5\%$, 0.83 [0.72–0.96], $p = 0.0088$; $\geq 6\%$, 0.81 [0.70–0.94], $p = 0.0054$ (figure 2); $\geq 7.5\%$; 0.86 [0.72–1.01], $p = 0.071$). However, treatment with enalapril did not reduce the hazard of severe cachexia with weight loss of 10% or more ($p = 0.28$), or 15% or more ($p = 0.26$). After 18 months, the effect of enalapril on cachexia became large (table 5, figure 2). The association between enalapril and delay in weight loss was such that a 30% cumulative proportion of patients with weight loss of 6.0% or more was reached after 24 months in the placebo group, and 32 months in the enalapril group.

Results from the SOLVD study⁶ have shown that treatment allocation to enalapril had a beneficial effect on survival. Patients might have died before development of cachexia—ie, they prematurely left the risk set.

	Hazard ratio	95% CI	p
Weight loss \geq 7.5%	2.073	(1.728, 2.487)	<0.0001
Age (years)	1.015	(1.007, 1.024)	0.0004
Treatment (placebo vs enalapril)	1.12	(0.96, 1.31)	0.16
Gender (male vs female)	1.50	(1.20, 1.88)	0.0004
NYHA II*	1.29	(0.98, 1.72)	0.07
NYHA III*	1.85	(1.38, 2.49)	<0.0001
NYHA IV*	2.88	(1.47, 5.66)	0.0021
LVEF ($\leq 25\%$ vs $>25\%$)	1.49	(1.27, 1.75)	<0.0001
Weight loss \geq 6.0%	2.102	(1.772, 2.493)	<0.0001
Age (years)	1.015	(1.006, 1.023)	0.0008
Treatment (placebo vs enalapril)	1.10	(0.94, 1.29)	0.23
Gender (male vs female)	1.50	(1.20, 1.88)	0.0004
NYHA II*	1.32	(0.997, 1.76)	0.052
NYHA III*	1.87	(1.39, 2.51)	<0.0001
NYHA IV*	3.05	(1.55, 5.99)	0.0012
LVEF ($\leq 25\%$ vs $>25\%$)	1.48	(1.26, 1.74)	<0.0001

Cachexia has been treated as a time-dependent covariate. *vs NYHA I.

Table 3: Cox proportional hazard analysis for the effect of covariates on survival in patients with chronic heart failure (SOLVD)

Weight loss cutpoint	Assessed at 4 months		Assessed at 8 months		Assessed at 12 months	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
≥5.0%						
Crude	1.36 (1.08–1.73)	0.0098	1.32 (1.08–1.62)	0.0063	1.27 (1.05–1.54)	0.0131
Adjusted	1.42 (1.12–1.79)	0.0039	1.38 (1.13–1.69)	0.0018	1.31 (1.08–1.59)	0.0056
≥6.0%						
Crude	1.47 (1.12–1.92)	0.0051	1.40 (1.12–1.75)	0.0031	1.39 (1.13–1.71)	0.0018
Adjusted	1.52 (1.16–1.99)	0.0023	1.44 (1.15–1.81)	0.0014	1.40 (1.14–1.72)	0.0015
≥7.5%						
Crude	1.70 (1.23–2.34)	0.0012	1.59 (1.22–2.07)	0.0005	1.44 (1.13–1.84)	0.0034
Adjusted	1.88 (1.36–2.59)	0.0001	1.69 (1.30–2.20)	0.0001	1.51 (1.18–1.92)	0.0011
≥10.0%						
Crude	1.41 (0.83–2.39)	0.21	1.41 (0.95–2.09)	0.09	1.67 (1.23–2.28)	0.0012
Adjusted	1.40 (0.82–2.38)	0.21	1.51 (1.02–2.24)	0.0404	1.72 (1.26–2.35)	0.0006
≥15.0%						
Crude	3.21 (1.43–7.17)	0.0045	2.48 (1.28–4.78)	0.0070	2.17 (1.25–3.76)	0.0057
Adjusted	3.34 (1.49–7.47)	0.0033	2.71 (1.40–5.24)	0.0031	2.31 (1.33–4.01)	0.0030

Hazard ratios adjusted for age, treatment, sex, NYHA, and LVEF.

Table 4: Effect of weight loss on survival in patients with chronic heart failure (SOLVD)

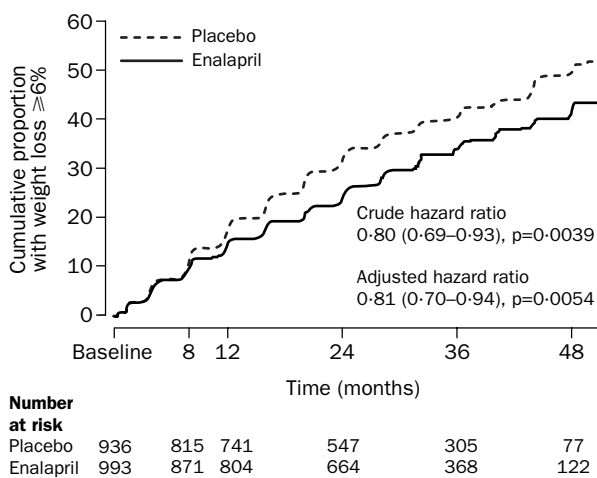


Figure 2: Cumulative incidence of weight loss $\geq 6\%$ in patients with chronic heart failure treated with enalapril or placebo in the SOLVD treatment study

Therefore, we analysed the effect of enalapril on the combined end-point of death or development of cachexia. Compared with placebo, enalapril reduced the combined risk of death or cachexia by 13% (for weight loss $\geq 7.5\%$; $p=0.036$) to 16% (for weight loss $\geq 6\%$; $p=0.0031$).

V-HeFT II

We included 619 patients from the V-HeFT II study, which was 77% of the original trial population; 322 were randomly allocated enalapril, and 297 had the hydralazine and isosorbide dinitrate combination.

SOLVD	V-HeFT II	
	Enalapril	Hydralazine plus ISDN
Follow-up (months)		
6	6.8%	7.1%
12	14.8%	13.8%
18	19.1%	18.2%
24	23.8%	23.2%
30	29.6%	29.0%
36	33.7%	33.3%

ISDN=Isosorbide dinitrate.

Table 5: Cumulative frequency of weight loss of 6% or more in the SOLVD treatment study and in V-HeFT II

The cumulative frequency of weight loss of 6% or more was 15% at 12 months, 24% at 24 months, 31% at 36 months, and 34% at 48 months. Of the 603 patients who were alive at 9 months, weight loss of 6% or more was present in 71 patients (12%). These patients had similar baseline characteristics to those who did not have this degree of weight loss (table 6).

At 9 months, 181 patients (30%) had died. We noted that survival after 9 months (treated as a new baseline) was worse in patients who had lost 6% or more of their bodyweight, compared with patients without such weight loss (HR 1.85 [95% CI 1.25–2.72], $p=0.0019$, figure 3). In multivariable analysis, weight loss of 6% or more at 9 months predicted subsequent survival (HR 2.00 [95% CI 1.34–2.99]; $p=0.0007$) independent of LVEF ($p=0.0001$), age ($p=0.31$), baseline bodyweight ($p=0.43$), NYHA class ($p=0.22$), and treatment group (enalapril *vs* hydralazine and isosorbide dinitrate combination, $p=0.27$). When weight loss of 6% or greater was noted at 12 months ($n=569$, cachexia present in 89 patients, 166 deaths during subsequent follow-up), the prognostic value of this weight loss cutpoint was similar in univariate (HR 1.65, $p=0.009$) and multivariate analysis (1.75, $p=0.005$).

Patients in the enalapril group had weight loss of 6% or more at about the same rate as those on hydralazine and isosorbide dinitrate (HR for enalapril group 0.92 [95% CI 0.70–1.20], $p=0.52$, table 5). Likewise, the frequency of the combined endpoint of weight loss of 6% or more, or death did not differ between the groups (0.94 [0.75–1.17, $p=0.56$]).

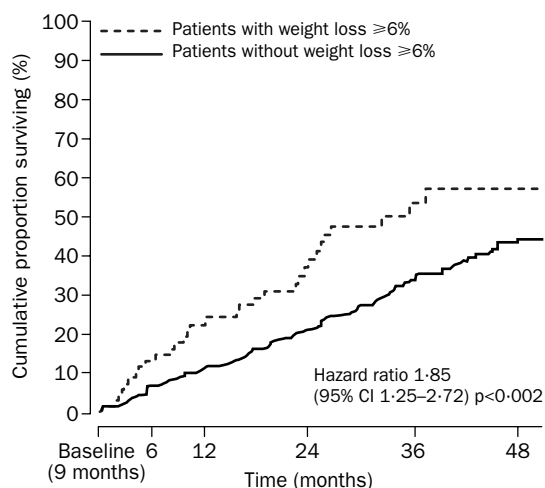
Discussion

Our results show that substantial weight loss is a common event in patients with chronic heart failure. Spontaneous reversal of substantial weight loss was a rare event, and

	Weight loss $\geq 6\%$ (n=71)	No weight loss, or weight loss $< 6\%$ (n=532)
Age (years)	58.8 (9.5)	60.4 (8.2)
Weight (kg)	83.4 (16.8)	80.4 (13.3)
LVEF (%)	31 (12)	29 (11)
NYHA class	2.48	2.34
Coronary artery disease and medication use*	31 (44%)	252 (47%)

Data are mean (SD) or number (%). All $p>0.05$. *Antiarrhythmics, vasodilators, or diuretics.

Table 6: Baseline characteristics of patients in V-HeFT II with or without weight loss of 6% or more at 9 months follow-up



Number at risk	Baseline (9 months)	6	12	24	36	48
Patients with weight loss $\geq 6\%$	71	60	48	30	15	4
Patients without weight loss $\geq 6\%$	532	459	404	280	161	50

Figure 3: **Weight loss 6% or more (assessed at 9 months) and subsequent cumulative survival in patients with chronic heart failure in the V-HeFT II study**

was noted for fewer than 2% of cases. Weight loss was independently linked to impaired survival of patients with chronic heart failure. Treatment with an ACE inhibitor, enalapril, in addition to conventional treatment reduced the risk of weight loss of 6% or more by 19%.

The development of weight loss is not a sudden event, but a gradual and graded process. In chronic heart failure, the wasting process affects not only muscle, fat, and bone,⁸ but also the heart.⁹ The key event in a wasting disease—ie, cachexia—is general weight loss, and it seems logical to define cardiac cachexia on this basis.¹⁰ We assessed various degrees of weight loss for incorporation in a definition of cachexia. All definitions yielded similar results; although in SOLVD, weight loss of 6% or greater was the strongest predictor of impaired survival. The value of this cutoff was confirmed in V-HeFT II. We suggest that weight loss of more than 6% should be the cutpoint to define presence of cachexia in chronic heart failure.

Weight loss during follow-up could be caused by reduction of oedema that was present at baseline, because reliable quantification of oedema is almost impossible. To avoid this potentially confounding effect, we restricted our reanalyses of SOLVD and V-HeFT II to patients who had been free of any degree of oedema at baseline. Nevertheless, in the SOLVD treatment study baseline body weight was 2.6 kg higher in patients who subsequently became cachectic (with weight loss of 6% or more).

The reliable quantification of oedema is difficult, and to avoid biases inherent in estimation of weight loss in patients who could also have developed oedema, we did not adjust for the development of oedema during follow-up. Therefore, the data presented are conservative estimates, because if newly developed oedema were taken into account, our estimates of weight loss would always be underestimates. Additionally, at baseline, symptom status, LVEF, and disease cause did not differ between patients with and without subsequent weight loss (table 2). Therefore, we believe that unrecognised fluid retention at baseline in patients who subsequently lost weight could not explain their weight loss, which on average was more than 10 kg.

For clinical purposes, the search for useful cutoff values is important. In exploratory analysis, we noted that patients with weight loss of 6% or more at 9 months or 12 months had a 75–100% higher subsequent mortality rate than patients who did not lose this much weight.

Plasma hormone concentrations and cytokines are related to the presence of cardiac cachexia^{5,8,11} and they are related to survival in patients with chronic heart failure.^{12,13} These associations could explain why the presence of weight loss in heart failure is an independent predictor of impaired survival. The intensity of hormonal and immunological alterations in patients with heart failure varies substantially. The onset of weight loss might be a sensitive indication that hormonal and immunological abnormalities have reached clinically relevant concentrations, and that the subsequent outlook of the patient is impaired.

In the SOLVD study population, 29% of all deaths occurred on the background of newly developed weight loss of 7.5% or more, and 38% of people who died had weight loss of 6% or more. These deaths were in a population of patients judged clinically stable and non-cachectic at baseline. We have estimated that in our previous population¹ with 16.4% prevalence of cardiac cachexia at baseline (defined as $\geq 7.5\%$ weight loss, body-mass index $< 24 \text{ kg/m}^2$), nearly half of deaths in 18 months were related to the presence of body wasting. No specific treatment for cardiac cachexia exists and spontaneous reversal of weight loss seems rare. In our previous experience with 60 patients who had cardiac cachexia, we recorded only one case of spontaneous weight gain and long-term survival, and 6 cases of long-term weight stability and survival (> 4 years). Clinical experience suggests that cardiac cachexia can be reversed after heart transplantation, but this has never been studied in detail. Whether there is a future in treating patients with cardiac cachexia with anticytokine drugs, anabolic growth factors, or both is not clear.^{14,15}

In this reanalysis of the SOLVD study, enalapril delayed the development of cardiac cachexia by about 8 months during the first 3 years of follow-up, and delayed death by 5.5 months.⁶ The proportion of the survival benefit conferred by enalapril that was mediated through its effect on body wasting is impossible to estimate. Absence of a difference in weight loss between enalapril and the hydralazine and isosorbide dinitrate combination could be attributable to a lack of statistical power, or because two active drugs were compared.

Multiple physiological and biochemical pathways are altered in patients with chronic heart failure, and initial damage to the heart could result in haemodynamic, endocrine, immunological, and muscular abnormalities. These, in turn, contribute to the clinical picture of heart failure and cardiac cachexia.^{5,16} Furthermore, anorexia, malabsorption, and mental depression might contribute to the development of weight loss.¹⁷ Raised catecholamine concentrations might explain the mechanisms by which ACE inhibitors reduce mortality and weight loss. Catecholamines can contribute to upregulation of resting metabolic rates, which have been noted in patients with chronic heart failure.¹⁸ Cachectic patients often have low peripheral blood flow¹⁹ and a striking increase in vascular resistance.²⁰ ACE inhibitors have a favourable effect on catecholamines and other neurohormones and endothelial function in patients with chronic heart failure,²⁻⁴ which might prevent tissue damage and apoptosis through improved nutritional status of tissues and reduction of ischaemia and oxidative stress.

Immune activation is a well known feature of cardiac cachexia, and cytokines such as tumour necrosis factor α are thought to be causally related to the development of muscle wasting and anorexia.²¹ Bacterial endotoxin might contribute to immune activation in chronic heart failure.^{22,23} With analysis of blood taken during the CONSENSUS study, Eriksson and colleagues²⁴ have shown that enalapril caused a substantial reduction of C-reactive protein, which is a marker of acute inflammation. In an animal model of gut-derived endotoxaemia, enalapril improved survival by reducing bacterial translocation and contributing to a preservation of gastrointestinal functional and structural integrity.²⁵ Through these mechanisms, ACE inhibitors might reduce immune activation in patients with chronic heart failure and prevent weight loss.

Compared with the ACE inhibitor captopril, the angiotensin-II-receptor antagonist losartan does not confer a survival benefit.²⁶ However, captopril does not reduce the frequency of weight loss in patients with chronic heart failure when compared with losartan.²⁷ In patients with severe disease who were treated in the COPERNICUS study,²⁸ weight loss of 6% or more was seen in 14.1% of patients on placebo, but in only 10.2% of patients on carvedilol during a mean follow-up of 10 months ($p=0.005$).²⁹ Treatment with a ventricular assist device does not reverse cardiac cachexia.³⁰

In the past, many clinicians have advised that weight loss is indicated in obese patients with chronic heart failure; however, there is no evidence for this claim. In fact, some results suggest that these patients have a good outlook,^{31,32} and our data show that any weight loss (independent of the patients' weight at baseline) is related to poor survival. A limitation of our study is that it is a retrospective analysis, and we cannot exclude the possibility that weight loss arose for reasons other than heart failure in some patients.

Cardiac cachexia is common in chronic heart failure and predicts poor outcome, especially if a patient loses more than 6% of his or her bodyweight. In view of these findings, the development of specific treatments for cardiac cachexia should be pursued.

Contributors

All authors participated in the design of the study, data analysis, and data interpretation. S Anker wrote the first draft of the manuscript and all authors contributed to its revision. A Negassa and R Afzal did statistical analyses on the SOLVD database.

Conflict of interest statement

S Anker has received grants or honoraria from MSD, Aventis, and AstraZeneca. A Coats has been a consultant for, and received research grants from Roche, Bristol-Myers Squibb, Novartis, AstraZeneca, MSD, and Aventis. P Poole-Wilson has received grants and honoraria from Merck, AstraZeneca, and Bristol Myers Squibb. J Cohn has received grants or honoraria from Novartis, Bristol-Myers Squibb, SmithKline Beecham, AstraZeneca, and Aventis. S Yusuf has received grants and honoraria from Merck, Aventis, AstraZeneca, Bristol-Myers Squibb, and King Pharmaceuticals.

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Clinical picture

Grandma's eyes

Hafiz Syed, Steve Harris, Simon Dubrey



A 69-year-old woman was admitted with features characteristic of Parkinson's disease. A neurological assessment revealed that she had absent upward gaze in both eyes. The diagnosis of a supranuclear gaze palsy was made.

These portraits of the patient, drawn by her 6-year-old granddaughter, were found by the patient's bedside. These images, drawn before a formal diagnosis was made, show the patient looking in all directions except up.

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