Absence of obesity paradox in patients with chronic heart failure and diabetes mellitus: a propensity-matched study

Chris Adamopoulos¹, Philippe Meyer², Ravi V. Desai³, Kyparissi Karatzidou¹, Fernando Ovalle³, Michel White⁴, Inmaculada Aban³, Thomas E. Love⁵, Prakash Deedwania⁶, Stefan D. Anker^{7,8}, and Ali Ahmed^{3,9*}

¹Papageorgiou General Hospital, Thessaloniki, Greece; ²University Hospital of Geneva, Geneva, Switzerland; ³University of Alabama at Birmingham, 1530 3rd Ave South, CH-19, Ste-219 Birmingham, AL 35294-2041, USA; ⁴Montreal Heart Institute, Montreal, Quebec, Canada; ⁵Case Western Reserve University, Cleveland, OH, USA; ⁶University of California, San Francisco, Fresno, CA, USA; ⁷Charite Medical School and Campus Virchow-Klinikum, Berlin, Germany; ⁸Centre for Clinical and Basic Research, IRCCS San Raffaele, Rome, Italy; and ⁹VA Medical Center, Birmingham, AL, USA

Received 3 May 2010; revised 15 June 2010; accepted 18 June 2010; online publish-ahead-of-print 7 October 2010

See page 130 for the editorial comment on this article (doi:10.1093/eurjhf/hfq237)

Aims

Obesity is paradoxically associated with survival benefit in patients with chronic heart failure (HF). However, obesity complicates the management of diabetes mellitus (DM), which is common in HF. Yet, little is known about the impact of obesity in HF patients with DM. Therefore, we examined the association between obesity and outcomes in propensity-matched cohorts of HF patient with and without DM.

Methods and results

Of the 7788 participants with chronic mild to moderate HF in the Digitalis Investigation Group trial, 7379 were non-cachectic [body mass index (BMI) ≥ 20 kg/m²] at baseline. Of these, 2153 (29%) had DM, of whom 798 (37%) were obese (BMI ≥ 30 kg/m²). Of the 5226 patients without DM, 1162 (22%) were obese. Propensity scores for obesity were used to separately assemble 636 pairs of obese and non-obese patients with DM and 770 pairs of obese and non-obese patients without DM, who were balanced on 32 baseline characteristics. Among matched patients with DM, all-cause mortality occurred in 38 and 39% of obese and non-obese patients, respectively [hazard ratio (HR) when obesity was compared with no obesity 0.99; 95% confidence interval (CI) 0.80–1.22; $P = 0.915$]. Among matched patients without DM, all-cause mortality occurred in 23 and 27% obese and non-obese patients, respectively (HR associated with obesity 0.77; 95% CI 0.61–0.97; $P = 0.025$).

Conclusion

In patients with chronic mild to moderate HF and DM, obesity confers no paradoxical survival benefit. Whether intentional weight loss may improve outcomes in these patients needs to be investigated in future prospective studies.

Keywords

Heart failure • Obesity • Diabetes • Mortality • Hospitalization • Propensity score

Introduction

Obesity is associated with increased risk of incident heart failure (HF).¹ In contrast, several contemporary studies suggested that obesity may confer a survival benefit in patients with established HF, a phenomenon termed the ‘obesity paradox’.^{2–5} These findings raise concerns about the current wisdom of weight loss in obese patients with HF. Owing to its close links to obesity and HF, DM is highly prevalent among obese patients with chronic HF and is associated with poor outcomes.^{6–8} Furthermore,

obesity increases the risk of cardiovascular complications and mortality in DM and weight loss is strongly recommended for all obese individuals who have DM as it improves glycaemic control and other risk factors for cardiovascular disease.⁹ Yet, it is unknown if the obesity-associated survival benefit in general HF populations also exists in HF patients with DM. Therefore, the objective of the present study was to examine the association between obesity and outcomes in HF patients with and without DM using propensity-matched design.

* Corresponding author. Tel: +1 205 934 9632, Fax: +1 205 975 7099, Email: aahmed@uab.edu

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2010. For permissions please email: journals.permissions@oxfordjournals.org.

Methods

Study data and patients

We conducted a secondary analysis of the public-use copy of the Digitalis Investigation Group (DIG) trial data set obtained from the National Heart, Lung and Blood Institute. The rationale, design, and results of the DIG trial have been previously reported.¹⁰ Briefly, this prospective randomized clinical trial involved 7788 patients with HF who were randomly assigned to digoxin or placebo between February 1991 and September 1993 at clinical sites in the USA (186) and Canada (116).

Digitalis Investigation Group participants were ambulatory chronic HF patients in normal sinus rhythm with reduced ($\leq 45\%$, $n = 6800$) or preserved ($> 45\%$, $n = 988$) left ventricular ejection fraction (LVEF). Most patients were receiving angiotensin-converting enzyme (ACE) inhibitors ($> 90\%$) and diuretics ($> 80\%$). Data on beta-blocker use were not collected as these drugs were not approved for HF at the time of the DIG trial.

Diabetes mellitus and body mass index

The presence of baseline DM as a co-morbid condition was ascertained by investigators based on chart documentation of DM and data on baseline DM were available for all 7788 participants.^{6,10} Of the 7788 DIG participants with chronic mild to moderate HF, 7379 were non-cachectic at baseline, defined as baseline body mass index (BMI) ≥ 20 kg/m². Considering the poor prognosis associated with cardiac cachexia in HF, we used a cutoff of BMI < 20 kg/m² to define cardiac cachexia.¹¹ Of the 7379 non-cachectic HF patients, 2153 (29%) had DM, of whom 798 (37%) were obese (BMI ≥ 30 kg/m²). Of the 5226 non-cachectic HF patients without DM, 1162 (22%) were obese. Obesity was defined as BMI ≥ 30 kg/m² according to the World Health Organization (WHO) BMI classification criteria.¹²

Study outcomes

The primary outcome of the current analysis was all-cause mortality, which was also the primary endpoint of the DIG trial during 38 months of median follow-up (range, 0.03 to 59 months). We also studied several other secondary DIG outcomes. Outcomes data were complete for 99% of the patients.¹³

Study design: propensity-score matching

Owing to significant imbalances in baseline characteristics between obese and non-obese patients before matching (Table 1 and Figure 1), we used propensity-score matching to assemble a cohort of patients whereby obese and non-obese patients would be well balanced on all measured baseline characteristics.^{14–18} Propensity score is the conditional probability of receiving an exposure (e.g. being obese) given a set of measured baseline characteristics.^{15,16} Propensity-score matching makes it possible to design observational studies like randomized clinical trials in several key ways. First, it allows investigators to assemble retrospectively a study cohort, in which patients are well balanced on all measured covariates. Second, it allows investigators to measure objectively the achieved balance (i.e. bias reduction) in the study cohort. Finally, and perhaps most importantly, propensity-score matching makes it possible to do both of these procedures without the knowledge of, or access to, outcomes data, as investigators of a randomized clinical trial would not know the outcomes of the trial during its design. Although, propensity-score matching is often used to balance two treatment groups, the method can also be used to balance patients across non-treatment exposures.^{6,14,18}

Assembly of study cohorts

Patients with diabetes mellitus

Of the 2153 non-cachectic (BMI ≥ 20 kg/m²) HF patients with DM, 798 were obese (BMI ≥ 30 kg/m²). We estimated propensity scores for obesity for each of the 2153 patients using a non-parsimonious multi-variable logistic regression model. In the model, obesity was the dependent variable and all measured baseline patient characteristics shown in Figure 1 were included as covariates. The efficacy of the propensity-score model was assessed by estimating absolute standardized differences of covariates between the two groups, after matching. An absolute standardized difference of 0% on a covariate indicates no residual bias for that covariate, and an absolute standardized difference below 10% suggests inconsequential residual bias.^{6,14,18} We used a greedy matching protocol to match each obese patient with a non-obese patient who had similar propensity scores to five, four, three, two, and one decimal places in five repeated steps.^{6,14,18} In all, we matched 636 (80%) of the 798 obese patients with HF and DM with 636 non-obese patients with HF and DM.

Patients without diabetes mellitus

Of the 5226 non-cachectic (BMI ≥ 20 kg/m²) HF patients without DM, 1162 were obese (BMI ≥ 30 kg/m²) and 4064 (78%) were non-obese. To ensure that our non-DM cohort would have a sample size similar to that of our DM cohort, we selected a random subset of 798 obese patients (which is the same as the number of obese patients in the DM group) from the 1162 non-DM obese patients. Thus, our pre-match cohort of non-DM patients consisted of 4862 (798 obese + 4064 non-obese) patients. Using methods described above, propensity scores were estimated and used to assemble a matched cohort of 770 pairs of obese and non-obese HF patients without DM.

Statistical analysis

For descriptive analyses, we used Pearson χ^2 and Wilcoxon rank-sum tests for the pre-match, and McNemar's test and paired sample t-test for the post-match comparisons of baseline covariates between obese and non-obese patients, as appropriate, and separately for the DM and non-DM groups. Pre- and post-match absolute standardized differences for DM and non-DM patients were estimated and displayed as Love plots (Figure 1). Kaplan–Meier survival analyses and Cox regression models stratified by matching were used to estimate associations between obesity and outcomes among patients with and without DM. We confirmed the assumption of proportional hazards by a visual examination of the log (minus log) curves. All statistical tests were evaluated using two-tailed 95% confidence levels, and data analyses were performed using SPSS for Windows, Rel. 15. 2009 (SPSS, Inc., Chicago, IL, USA).

Results

Baseline characteristics

There were significant imbalances in the distribution of many baseline characteristics between obese and non-obese HF patients with DM, all of which were balanced after matching (Table 1). Post-match absolute standardized differences for all measured baseline characteristics were $< 10\%$ (most were $< 5\%$) in both cohorts with and without DM, suggesting substantial covariate balance across the groups (Figure 1).

Obesity and mortality

Among matched non-cachectic HF patients with DM, all-cause mortality occurred in 243 (38%) and 246 (39%) obese and non-

Table 1 Baseline characteristics for heart failure patients with diabetes mellitus, by body mass index, before and after propensity-score matching

Variable, n (%) or mean ($\pm$ SD)	Before matching			After matching		
	BMI <30 kg/m ² (n = 1355)	BMI $\geq$ 30 kg/m ² (n = 798)	P-value	BMI <30 kg/m ² (n = 636)	BMI $\geq$ 30 kg/m ² (n = 636)	P-value
Age (years)	65 $\pm$ 9	62 $\pm$ 10	<0.001	63 $\pm$ 9	63 $\pm$ 9	0.892
Age $\geq$ 65 year	795 (59)	335 (42)	<0.001	308 (48)	296 (47)	0.500
Female	352 (26)	268 (34)	<0.001	192 (30)	1992 (30)	1.000
Non-white	226 (17)	147 (18)	0.302	119 (19)	114 (18)	0.717
Duration of HF (months)	29 $\pm$ 37	31 $\pm$ 38	0.355	32 $\pm$ 41	31 37	0.887
Primary cause of HF						
Ischaemic	1049 (77)	541 (68)	<0.001	449 (71)	470 (74)	0.630
Hypertensive	128 (9)	132 (17)		86 (14)	76 (12)	
Idiopathic	119 (9)	96 (12)		73 (12)	65 (10)	
Others	59 (4)	29 (4)		28 (4)	25 (4)	
Prior myocardial infarction	932 (69)	472 (59)	<0.001	391 (62)	418 (66)	0.116
Current angina	401 (30)	248 (31)	0.469	197 (31)	201 (32)	0.809
Hypertension	734 (54)	546 (68)	<0.001	400 (63)	406 (64)	0.727
Chronic kidney disease	685 (51)	374 (47)	0.098	284 (45)	311 (49)	0.129
Medications						
Pre-trial digoxin use	645 (48)	284 (36)	<0.001	268 (42)	270 (43)	0.910
Trial use of digoxin	685 (51)	378 (47)	0.153	308 (48)	301 (47)	0.694
ACE-inhibitors	1271 (94)	756 (95)	0.371	593 (93)	602 (95)	0.290
Diuretics	1126 (83)	692 (67)	0.025	544 (87)	542 (85)	0.330
Symptoms and signs of HF						
Dyspnoea at rest	345 (26)	225 (28)	0.265	186 (29)	170 (27)	0.318
Dyspnoea on exertion	1010 (75)	647 (81)	0.001	495 (78)	500 (79)	0.734
Jugular venous distension	219 (16)	122 (15)	0.592	91 (14)	101 (16)	0.434
Third heart sound	360 (27)	166 (21)	0.003	156 (25)	147 (23)	0.554
Pulmonary râles	267 (20)	150 (19)	0.607	131 (21)	118 (19)	0.358
Lower extremity oedema	323 (24)	307 (39)	<0.001	203 (32)	207 (33)	0.810
NYHA functional class						
Class I	169 (13)	90 (11)	0.827	69 (11)	75 (12)	0.932
Class II	700 (52)	411 (52)		340 (54)	331 (52)	
Class III	448 (33)	275 (35)		210 (33)	214 (34)	
Class IV	38 (3)	22 (3)		17 (3)	16 (3)	
Heart rate (per minute)	80 $\pm$ 13	82 $\pm$ 12	0.028	82 $\pm$ 12	81 $\pm$ 12	0.706
Blood pressure (mmHg)						
Systolic	128 $\pm$ 20	134 $\pm$ 21	<0.001	131 $\pm$ 21	132 $\pm$ 21	0.572
Diastolic	74 $\pm$ 11	78 $\pm$ 12	<0.001	76 $\pm$ 11	76 $\pm$ 11	0.650
Chest radiograph findings						
Pulmonary congestion	246 (18)	117 (15)	0.037	95 (15)	99 (16)	0.755
Cardiothoracic ratio >0.5	824 (61)	540 (68)	0.001	417 (66)	416 (65)	0.659
Serum creatinine (mg/dL)	1.34 $\pm$ 0.42	1.28 $\pm$ 0.38	<0.001	1.29 $\pm$ 0.48	1.30 $\pm$ 0.39	0.655
Serum potassium (mEq/L)	4.4 $\pm$ 0.5	4.3 $\pm$ 0.4	0.026	4.4 $\pm$ 0.5	4.4 $\pm$ 0.4	0.752
Estimated glomerular filtration rate (mL/min/1.73 m ²)	60 $\pm$ 21	63 $\pm$ 21	0.009	63 $\pm$ 21	62 $\pm$ 21	0.273
Left ventricular ejection fraction (%)	31 $\pm$ 11	34 $\pm$ 13	<0.001	33 $\pm$ 12	33 $\pm$ 12	0.606

obese patients, respectively [matched hazard ratio (HR), when obesity was compared with non-obesity 0.99; 95% confidence interval (CI) 0.80–1.22; $P = 0.915$; Table 2 and Figure 2A]. When BMI was used as a continuous variable and adjusted for propensity

score, BMI still had no association with mortality (adjusted HR, 1.00; 95% CI, 0.98–1.02; $P = 0.975$).

Among matched non-cachectic HF patients without DM, all-cause mortality occurred in 179 (23%) and 209 (27%) obese

Figure 1 Absolute standardized differences (%) for measured baseline characteristics between patients with body mass index <30 and ≥ 30 kg/m^2 , before and after propensity-score matching (ACE, angiotensin-converting enzyme; NYHA, New York Heart Association). Data for heart failure patients with (left panel) and without (right panel) diabetes.

and non-obese patients, respectively (matched HR 0.77; 95% CI 0.61–0.97; $P = 0.025$; Table 2 and Figure 2B). When BMI was used as a continuous variable and adjusted for propensity score, every kg/m^2 of BMI increase was associated with 2% significant reduction in mortality risk (adjusted HR, 0.98; 95% CI, 0.97–0.99; $P = 0.002$). Associations of obesity with cause-specific mortalities for patients in both the DM and non-DM groups are displayed in Table 2.

Obesity and hospitalization

All-cause hospitalization occurred in 477 (75%) and 471 (74%) obese and non-obese HF patients with DM, respectively (matched HR when obesity was compared with non-obesity 1.05; 95% CI 0.89–1.24; $P = 0.582$; Table 3). Associations of obesity with cause-specific hospitalization for patients with and without DM are displayed in Table 3.

Discussion

The findings of the current analysis demonstrate that in chronic HF patients with DM, obesity had no independent association with

mortality. However, in those without DM, obesity had a significant independent association with mortality reduction. These findings are important as DM is common in HF patients and is associated with poor prognosis.^{6,8} While obesity is a risk factor for DM it has been shown to paradoxically improve outcomes in HF, which may confound management of obese HF patients with DM. However, findings from the current analysis suggest that non-obese HF patients with DM may not have worse outcomes as has been shown to be true for non-obese HF patients in general, or those without DM in particular.

Multiple hypotheses have been proposed to explain the counterintuitive absence of an adverse effect or even a beneficial effect of obesity on outcomes in patients with established HF which was also observed in our cohort of HF patients without DM. However, there is currently no definite explanation for this phenomenon and its clinical significance remains an open question.¹⁹ The lack of association between obesity and mortality in HF patients with DM is intriguing. Recent evidence suggests that obesity may not be an independent predictor of mortality but its effects are mediated through variables such as DM and

Table 2 Association between obesity and mortality in propensity-matched heart failure patients with and without diabetes

	Events (%)		Hazard ratio (95% confidence interval)	P-value
	BMI <30 kg/m ²	BMI ≥30 kg/m ²		
Patients with diabetes	n = 636	n = 636		
All-cause	246 (39)	243 (38)	0.99 (0.80–1.22)	0.915
Cardiovascular	187 (29)	188 (30)	1.02 (0.80–1.29)	0.903
Progressive heart failure	80 (13)	84 (13)	1.00 (0.69–1.44)	1.000
Patients without diabetes	n = 770	n = 770		
All-cause	209 (27)	179 (23)	0.77 (0.61–0.97)	0.025
Cardiovascular	157 (20)	140 (18)	0.81 (0.62–1.04)	0.102
Progressive heart failure	54 (7)	53 (7)	0.87 (0.56–1.33)	0.513

Figure 2 Kaplan–Meier plots for all-cause mortality by body mass index <30 and ≥30 kg/m², among chronic heart failure patients (A) with and (B) without diabetes mellitus (CI, confidence interval; HF, hazard ratio).

hypertension which are on the biological pathway of obesity and cardiovascular disease.²⁰ Therefore, it is possible that the presence of DM is a much stronger predictor of outcome than obesity *per se* and largely offsets any effect of obesity, even a protective one. This hypothesis is further corroborated by the striking difference in mortality between obese patients with and without DM (38 vs. 24%, respectively) in our analysis.

In patients with HF, the presence of DM is associated with a higher burden of comorbidity and poor outcomes.^{6–8} Generally, subgroups of high-risk patients with poor outcomes are more likely to benefit from beneficial interventions or exposures, and less likely to be affected by those that are harmful.²¹ Considering the poor prognosis of HF patients with DM, it would be expected that the obesity-associated survival benefit would be more pronounced in these patients. Therefore, the observed lack of an association between obesity and mortality may reflect a true association. Of note, to avoid sample size and power disparity between patients with and without DM, we restricted our analysis of non-DM patients to a sample size similar to that of DM patients. Yet, despite the sample size parity and fewer events in the non-DM cohort, we observed a significant association between obesity and decreased mortality in those without DM. This suggests a strong association that was independent of 32 measured baseline characteristics.

Several studies have demonstrated a paradoxical association between obesity and mortality reduction in chronic HF.^{2–4,22–24} A recent meta-analysis of nine observational HF studies also demonstrated mortality reduction associated with obesity.⁵ In contrast, two other recent studies of HF patients failed to demonstrate any such survival benefit.²⁵ The findings of the current study are distinct from those prior studies due to our use of a robust propensity-score matching design, which is the likely the best study design short of randomized clinical trials, and allowed us to assemble balanced cohorts. Traditional regression-based multivariable risk adjustment models used in other studies may lead to biased conclusions as confounders may not be balanced at baseline, thus leading to extrapolations beyond the data.²⁶ The current study is principally distinctive as we separately examined the association between obesity and mortality in HF

Table 3 Association between obesity and hospitalization in propensity-matched heart failure patients with and without diabetes

	Events (%)		Hazard ratio (95% confidence interval)	P-value
	BMI <30 kg/m ²	BMI ≥30 kg/m ²		
Patients with diabetes	n = 636	n = 636		
All-cause	471 (74)	477 (75)	1.05 (0.89–1.24)	0.582
Cardiovascular	382 (60)	393 (62)	1.08 (0.90–1.28)	0.417
Progressive heart failure	243 (38)	249 (39)	1.13 (0.91–1.39)	0.265
Patients without diabetes	n = 770	n = 770		
All-cause	441 (57)	485 (63)	1.10 (0.93–1.29)	0.269
Cardiovascular	336 (44)	359 (47)	1.05 (0.88–1.26)	0.586
Progressive heart failure	153 (20)	158 (24)	1.14 (0.89–1.46)	0.291

patients with and without DM. These unique features preclude any direct comparison of our study with other prior studies. The apparent lack of a statistically significant association between obesity and cardiovascular mortality for those without DM is likely due to the smaller sample size and smaller number of events in our matched cohort. However, the magnitude of this association (a 19% reduction) is similar to that (an 18% reduction) observed by Curtis *et al.*² in another study using the same DIG database.

Obesity is a major risk factor for DM and complicates its management; a BMI ≥30 is associated with a more than two-fold increase in the prevalence of DM and the total prevalence of DM was increased by 55% over the last three to four decades due to an increasing proportion of the population moving into the obese categories.²⁷ Currently, the European Society of Cardiology and Canadian Cardiovascular Society HF guidelines make class IIa and IIb recommendations, respectively, for weight reduction in obese patients with HF.^{28,29} However, the American College of Cardiology/American Heart Association HF guidelines do not specifically make any such recommendation.³⁰ This lack of uniformity in recommendation is further complicated by the emerging concept of 'obesity paradox' in HF which may confuse clinicians in implementing weight loss strategies in obese HF patients. Most importantly, this issue may raise questions on the management of obese HF patients with DM as purposeful weight loss is the cornerstone of treatment for obese individuals with DM.^{31,32} Although data from this study do not support a change in the existing guidelines and we cannot specifically recommend on weight management policy, our results confirm the dominant negative impact of DM on the outcomes of HF patients and point out that obesity has no additional prognostic value in the presence of DM. The impact of obesity on outcomes in HF patients and whether weight reduction programmes may improve outcomes in obese HF patients with and without DM will need to be examined in future well-designed controlled trials. To ensure the plausibility and the validity of their results, such studies, apart from the prospective design and careful baseline randomization, should consider large sample sizes, long-term

follow-up and data on intentional weight loss, duration of obesity, body composition, and fat distribution in addition to simple BMI measurements.^{33,34}

Several limitations of this study need to be considered. As in all observational studies and despite our rigorous propensity-matching protocol, we cannot completely rule out bias due to imbalances in unmeasured covariates. In this study, as in the majority of other studies,^{2–5} data on duration of obesity, body composition and fat distribution or data for intentionality of weight loss and temporal weight changes, were not collected. However, exclusion of underweight patients (BMI <20 kg/m²) in our analysis limits the unfavourable effect of severe unintentional weight loss and cachexia. Additionally, we did not have data on the duration and control status of DM. Finally, the DIG trial was conducted before the use of the current standard HF therapy including beta-blockers, aldosterone antagonists, and resynchronization devices which may limit the generalizability of these findings to contemporary patients with HF. Even though we do not expect these factors to have an impact on the general nature of the association between obesity and outcomes, our data would need to be confirmed in contemporary patients with HF.

In conclusion, in a wide spectrum of ambulatory patients with chronic mild to moderate systolic and diastolic HF and DM, obesity was not independently associated with mortality or hospitalization. These results suggest that the obesity paradox observed in HF may not be generalized to HF patients with DM. Future well-designed prospective, randomized studies need to investigate whether intentional weight loss may improve outcomes in obese HF patients.

Acknowledgement

This manuscript was prepared using a limited access data set obtained by the NHLBI and does not necessarily reflect the opinions or views of the DIG Study or the NHLBI. The Digitalis Investigation Group (DIG) study was conducted and supported by the NHLBI in collaboration with the DIG Investigators.

Conflict of interest: none declared.

Funding

A.A. is supported by the National Institutes of Health through grants (R01-HL085561 and R01-HL097047) from the National Heart, Lung, and Blood Institute and a generous gift from Ms Jean B. Morris of Birmingham, AL, USA.

References

- Kenchiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB, Vasan RS. Obesity and the risk of heart failure. *N Engl J Med* 2002;**347**:305–313.
- Curtis JP, Selzer JG, Wang Y, Rathore SS, Jovin IS, Jadbabaie F, Kosiborod M, Portnay EL, Sokol SJ, Bader F, Krumholz HM. The obesity paradox: body mass index and outcomes in patients with heart failure. *Arch Intern Med* 2005;**165**:55–61.
- Kenchiah S, Pocock SJ, Wang D, Finn PV, Zornoff LA, Skali H, Pfeffer MA, Yusuf S, Swedberg K, Michelson EL, Granger CB, McMurray JJ, Solomon SD. Body mass index and prognosis in patients with chronic heart failure: insights from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. *Circulation* 2007;**116**:627–636.
- Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH. The relationship between obesity and mortality in patients with heart failure. *J Am Coll Cardiol* 2001;**38**:789–795.
- Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. *Am Heart J* 2008;**156**:13–22.
- Ahmed A, Aban IB, Vaccarino V, Lloyd-Jones DM, Goff DC Jr, Zhao J, Love TE, Ritchie C, Ovalle F, Gambassi G, Dell'Italia LJ. A propensity-matched study of the effect of diabetes on the natural history of heart failure: variations by sex and age. *Heart* 2007;**93**:1584–1590.
- Domanski M, Krause-Steinrauf H, Deedwania P, Follmann D, Ghali JK, Gilbert E, Haffner S, Katz R, Lindenfeld J, Lowes BD, Martin W, McGrew F, Bristow MR. The effect of diabetes on outcomes of patients with advanced heart failure in the BEST trial. *J Am Coll Cardiol* 2003;**42**:914–922.
- MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, Solomon SD, Granger CB, Swedberg K, Yusuf S, Pfeffer MA, McMurray JJ. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur Heart J* 2008;**29**:1377–1385.
- Klein S, Sheard NF, Pi-Sunyer X, Daly A, Wylie-Rosett J, Kulkarni K, Clark NG. Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies: a statement of the American Diabetes Association, the North American Association for the Study of Obesity, and the American Society for Clinical Nutrition. *Diabetes Care* 2004;**27**:2067–2073.
- The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;**336**:525–533.
- Evans WJ, Morley JE, Argiles J, Bales C, Baracos V, Guttridge D, Jatoi A, Kalantar-Zadeh K, Lochs H, Mantovani G, Marks D, Mitch WE, Muscaritoli M, Najand A, Ponikowski P, Rossi Fanelli F, Schambelan M, Schols A, Schuster M, Thomas D, Wolfe R, Anker SD. Cachexia: a new definition. *Clin Nutr* 2008;**27**:793–799.
- The World Health Organization. *The WHO Global Database on Body Mass Index (BMI)*. BMI Classification; 1995. Report No.: 0512-3054 (Print).
- Collins JF, Howell CL, Horney RA. Determination of vital status at the end of the DIG trial. *Control Clin Trials* 2003;**24**:726–730.
- Ahmed MI, White M, Ekundayo OJ, Love TE, Aban I, Liu B, Aronow WS, Ahmed A. A history of atrial fibrillation and outcomes in chronic advanced systolic heart failure: a propensity-matched study. *Eur Heart J* 2009;**30**:2029–2037.
- Rosenbaum PR, Rubin DB. The central role of propensity score in observational studies for causal effects. *Biometrika* 1983;**70**:41–55.
- Rubin DB. Using propensity score to help design observational studies: Application to the tobacco litigation. *Health Serv Outcomes Res Methodol* 2001;**2**:169–188.
- Ahmed A, Husain A, Love TE, Gambassi G, Dell'Italia LJ, Francis GS, Gheorghade M, Allman RM, Meleth S, Bourge RC. Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods. *Eur Heart J* 2006;**27**:1431–1439.
- Ahmed A, Zannad F, Love TE, Tallaj J, Gheorghade M, Ekundayo OJ, Pitt B. A propensity-matched study of the association of low serum potassium levels and mortality in chronic heart failure. *Eur Heart J* 2007;**28**:1334–1343.
- Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol* 2009;**53**:1925–1932.
- Thomas F, Bean K, Pannier B, Oppert JM, Guize L, Benetos A. Cardiovascular mortality in overweight subjects: the key role of associated risk factors. *Hypertension* 2005;**46**:654–659.
- Rothwell PM. Treating individuals 2. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. *Lancet* 2005;**365**:176–186.
- Frankenstein L, Zugck C, Nelles M, Schellberg D, Katus HA, Rempis BA. The obesity paradox in stable chronic heart failure does not persist after matching for indicators of disease severity and confounders. *Eur J Heart Fail* 2009;**11**:1189–1194.
- McMurray JJ, Carson PE, Komajda M, McKelvie R, Zile MR, Ptaszynska A, Staiger C, Donovan JM, Massie BM. Heart failure with preserved ejection fraction: clinical characteristics of 4133 patients enrolled in the I-PRESERVE trial. *Eur J Heart Fail* 2008;**10**:149–156.
- Wu AH, Pitt B, Anker SD, Vincent J, Mujib M, Ahmed A. Association of obesity and survival in systolic heart failure after acute myocardial infarction: potential confounding by age. *Eur J Heart Fail* 2010;**12**:566–573.
- Abdulla J, Kober L, Abildstrom SZ, Christensen E, James WP, Torp-Pedersen C. Impact of obesity as a mortality predictor in high-risk patients with myocardial infarction or chronic heart failure: a pooled analysis of five registries. *Eur Heart J* 2008;**29**:594–601.
- Fitzmaurice G. Confounding: regression adjustment. *Nutrition* 2006;**22**:581–583.
- Gregg EW, Cheng YJ, Cadwell BL, Imperatore G, Williams DE, Flegal KM, Narayan KM, Williamson DF. Secular trends in cardiovascular disease risk factors according to body mass index in US adults. *JAMA* 2005;**293**:1868–1874.
- Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Tendera M, Auricchio A, Bax J, Bohm M, Corra U, della Bella P, Elliott PM, Follath F, Gheorghade M, Hasin Y, Hernborg A, Jaarsma T, Komajda M, Kornowski R, Piepoli M, Prendergast B, Tavazzi L, Vachiera JL, Verheugt FW, Zamorano JL, Zannad F. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail* 2008;**10**:933–989.
- Malcom J, Arnold O, Howlett JG, Ducharme A, Ezekowitz JA, Gardner MJ, Giannetti N, Haddad H, Heckman GA, Isaac D, Jong P, Liu P, Mann E, McKelvie RS, Moe GW, Svendsen AM, Tsuyuki RT, O'Halloran K, Ross HJ, Sequeira EJ, White M. Canadian Cardiovascular Society Consensus Conference guidelines on heart failure—2008 update: best practices for the transition of care of heart failure patients, and the recognition, investigation and treatment of cardiomyopathies. *Can J Cardiol* 2008;**24**:21–40.
- Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009;**119**:e391–e479.
- Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R, Clark JM, Curtis JM, Espeland MA, Foreyt JP, Graves K, Haffner SM, Harrison B, Hill JO, Horton ES, Jakicic J, Jeffery RW, Johnson KC, Kahn S, Kelley DE, Kitabchi AE, Knowler WC, Lewis CE, Maschak-Carey BJ, Montgomery B, Nathan DM, Patricio J, Peters A, Redmon JB, Reeves RS, Ryan DH, Safford M, Van Dorsten B, Wadden TA, Wagenknecht L, Wesche-Thobaben J, Wing RR, Yanovski SZ. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. *Diabetes Care* 2007;**30**:1374–1383.
- American Diabetes Association. Standards of medical care in diabetes—2009. *Diabetes Care* 2009;**32**(Suppl 1):S13–S61.
- Bray GA. Risk factors: the obesity paradox—an artifact of small sample size? *Nat Rev Cardiol* 2009;**6**:561–562.
- Evangelista LS, Heber D, Li Z, Bowerman S, Hamilton MA, Fonarow GC. Reduced body weight and adiposity with a high-protein diet improves functional status, lipid profiles, glycemic control, and quality of life in patients with heart failure: a feasibility study. *J Cardiovasc Nurs* 2009;**24**:207–215.