Body mass index and all-cause mortality in heart failure patients with normal and reduced ventricular ejection fraction - a dose-response meta-analysis

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**Abstract**

**Background**

For patients with heart failure, there is an inverse relation between body mass index (BMI) and mortality, sometimes called the obesity-paradox. However, the relationship might be either U- or J-shaped and might differ between patients with reduced (HFrEF) or preserved left ventricular ejection fraction (HFpEF). We sought to investigate this further in a dose-response meta-analysis of published studies.

**Methods**

PubMed and Embase from June 1980 to April 2017 were searched for prospective cohort studies evaluating associations between BMI and all-cause mortality in patients with HFrEF (LVEF <40%) or HFpEF (LVEF ≥ 50%). Summary estimated effect sizes were obtained by using a random effects model. Potential non-linear relationships were evaluated by using random effects restricted cubic spline models.

**Results**

Ten studies were identified that included 96,424 patients of whom 59,263 had HFpEF (mean age 68 years of whom 38% were women) and 37,161 had HFrEF (mean age 60 years of whom 17% were women). For patients with HFpEF, the summary hazard ratio (HR) for all-cause mortality was: 0.93 (95%CI: 0.89-0.97) per 5 units increase in BMI (I-squared = 75.8%, p for heterogeneity = 0.01 and Begg’s test, p = 1.0, Egger’s test, p = 0.29) but the association was U-shaped (p for nonlinearity <0.01) with the nadir of risk at a BMI of 32-33 kg/m². For patients with HFrEF, the summary HR for all-cause mortality was: 0.96 (95%CI: 0.92-0.99) (I-squared=95%, p for heterogeneity < 0.001 and Begg’s test, p=0.45, Egger’s test, p=0.01). The relationship was also U-shaped (p < 0.01), although ‘flatter’ than for HFpEF, with the nadir at a BMI of 33 kg/m².

**Conclusions**

For patients with heart failure, the relation between BMI and mortality is U-shaped with a similar nadir of risk for HFpEF and HFrEF at a BMI of 32-33 kg/m². Whether interventions that alter weight in either direction can alter risk is unknown.

**Introduction**

Many studies have shown that mild-to-moderate obesity is associated with a lower mortality amongst patients with heart failure: the so-called obesity-paradox. 1-5 The possible causes of the paradox are controversial. There is no doubt that BMI declines as heart failure (HF) becomes more severe: some believe that a low BMI simply reflects more advanced disease. Adherents of this view suggest that interventions to reduce a high BMI will benefit patients symptomatically and perhaps prognostically, by reducing pro-inflammatory visceral adiposity and perhaps haemodynamic stress as well as improving glycaemic control.6 Others believe that a higher BMI may provide a metabolic reserve as disease progresses or even be intrinsically beneficial, in which case efforts should be made to increase rather than reduce BMI. Indeed, one of the great successes of heart failure therapy, beta-blockers, increases BMI.7

A recent study from the MAGGIC8, 9 collaboration, based on individual patient data, reported that there was a U-shaped relationship between BMI and all-cause mortality both for patients with HFpEF and those with HFrEF with the nadir of risk at a BMI of 30-34.9 kg/m². In order to investigate this observation further, we conducted a systematic review and dose-response meta-analysis to quantify and better understand the potential non-linear relation between BMI and prognosis in prospective cohort studies of patients with HFpEF and HFrEF.

**Methods**

**Search Strategy**

The study was designed according to the Meta-analysis of Observational Studies in

Epidemiology (MOOSE) Groupand the PRISMA 2009 guidelines.10, 11 We searched for all prospective cohort and other related studies that evaluated the associations between BMI and all-cause mortality in patients either with heart failure and a reduced (HFrEF; LVEF <40%) or preserved left ventricular ejection fraction (HFpEF; LVEF ≥ 50%). Only studies with at least three categories of BMI were considered.12 Studies13-15 with patients with a mean left ventricular ejection fraction (LVEF) close to 45% were not included as the patients could not be reliably classified as having predominantly HFpEF or HFrEF. To reduce bias, only prospective cohort studies were included, including an individual patient-data meta-analysis.8

PubMed and Embase from June 1980 to April 2017 were searched evaluating associations between BMI and all-cause mortality in patients with HFrEF or HFpEF. There were no language restrictions. Search terms included: HFpEF, HFrEF, HFnEF, reduced, normal or preserved EF, reduced, normal or preserved ejection fraction, BMI, body mass index, mortality and death. We also searched reference lists of the retrieved articles to identify other eligible studies. Two investigators independently reviewed all titles and abstracts from the search results to identify articles that met the inclusion criteria. Selected studies were compared, and disagreement was resolved by discussion and consensus. If any of the eligibility criteria were not met, the article was excluded. If results were incomplete or unclear, attempts were made to contact the study authors. Articles finally selected for review were checked to avoid inclusion of data published in duplicate. Relevant information was collected on baseline characteristics, such as age, sex, New York Heart Association (NYHA) functional classification, HF phenotype, heart rhythm at baseline, mean follow-up and events.

**Statistical Analysis**

The hazard ratio (HR) with 95% confidence intervals for all-cause mortality in each baseline BMI category obtained from multivariable models for all studies was used as the effect size. A dose-response association between BMI and all-cause mortality was assessed by the methods described by Greenland and Longnecker16 and Orsini17 based on a generalized least squares regression model using STATA version 14.2. We assumed that the reference category was the lowest BMI category for each study. For studies in which the reference group was not the lowest category, we transformed it to the lowest category using the method proposed by Orsini.18 We used the mid-point of the corresponding range of BMI as the exposure value. When upper and lower categories were open-ended, we used the width of the adjacent category to calculate an upper or lower bound.

For studies that did not report the number of person-years by BMI category, we used approximated values based on follow-up period, number of subjects provided and number of BMI categories. One study19 reported results for peak oxygen uptake ≤14 and >14 ml.kg-1.min-1 separately; we combined the estimated hazard ratios using a fixed effect model to obtain an overall estimate. A potential non-linear relationship between BMI and mortality was evaluated by modelling BMI dose with the use of restricted cubic splines with 4 knots at fixed centiles (5%, 35%, 65% and 95%) based on all categories of BMI for all studies, and examined by testing the hypothesis that the regression coefficients of the spline transformations were all equal to zero. We produced a dose-response curve with a re-scaled reference category of BMI of 23.8 kg/m2, which we took as a value within the normal weight range. Summary estimated effect sizes were obtained using a random effects model based on each study calculated using the method of Orsini et al.20 Heterogeneity was assessed using Q test and I-squared statistics.21 Forest plots were used to represent graphically the results generated from the random-effects meta-analysis. The pooled HR and the degree of heterogeneity are presented. Publication-bias was minimized by comprehensive literature searching. In addition, Begg’s test22 and Egger’s test23 were used to investigate publication bias.

**Results**

The selection process and results are shown in **Figure 1**. Of 622 articles found by the initial search, 47 were retrieved for more detailed evaluation. Ten studies were identified with 96,424 patients, for whom the mean age was 64 years; 28% were women. The biggest study contained 47,866 patients24 and the smallest study 446 patients.25 Where NYHA class was reported, most patients were in class III or IV. One study included only women26 and one study included predominantly (96%) men.3

Most studies were conducted in the United States of America (**Table 1**). Patients with a higher BMI were more likely to have a history of diabetes and hypertension, especially for patients with HFpEF. Patients with a BMI in the normal range were more likely to have IHD. (**Table 2**). Patients with HFrEF were more likely to take digoxin (**Table 3**). Of the ten studies, nine reported all-cause mortality, three reported cardiovascular (CV) mortality and one reported death/urgent heart transplant/or ventricular assist device.19

**HFpEF**

Four studies3, 8, 24, 27 including one individual patient data meta-analysis8 included 59,263 patients of whom 6,061 died. The average patient age was 68 years, and 38% were women. In multivariable analysis, the variables most commonly adjusted for were: age, sex, LVEF, diabetes, blood pressure, NYHA class, ischaemic aetiology and hypertension (**Table 4**). The summary HR per 5 unit increment in BMI was 0.93 (95%CI: 0.89-0.97) (I-squared = 75.8%, p for heterogeneity=0.01 (**Figure 2A**)), with an inverse association between BMI and all-cause mortality. There was no evidence of publication bias (Begg’s test, p=1.0 or Egger’s test, p=0.29). The dose-response meta-analysis showed a U-shaped association between BMI and all-cause mortality with the lowest mortality at a BMI of 32-33 kg/m2 (p<0.01 for non-linearity, **Figure 3A**). Similar results were found when the MAGGIC meta-analysis8 was excluded (leaving n = 53,210 patients). There were too few studies to investigate an interaction between age and mortality for patients with HFpEF (Table 5).

**HFrEF**

Seven studies were identified8, 19, 25, 26, 28-30 with 37,161 patients of whom 12,429 died. The average patient age was 60 years and 17% were women. In multivariable analysis, the variables most commonly adjusted for were: age, sex, LVEF, diabetes, blood pressure, NYHA class, ischaemic aetiology and hypertension (**Table 4**). The summary HR per 5 unit increment in BMI was 0.96 (95%CI: 0.92-0.99) (I-squared = 95%, p for heterogeneity<0.001 (**Figure 2B**)). There was no evidence of publication bias (Begg’s test, p=0.45, Egger’s test, p=0.01). The dose-response meta-analysis showed a ‘flatter’ U-shaped association than for HFpEF with the lowest mortality at a BMI of 32 kg/m2 (p<0.01) (**Figure 3B**). Similar results were found excluding the MAGGIC meta-analysis8 (leaving n= 21,205 patients). The negative relationship was statistically significant for patients with HFrEF who were aged >60 years (HR: 0.95 (0.92-0.97), p<0.05), but not for patients aged <60 years (HR: 0.97 (0.91-1.03), p>0.05), and the p-values for heterogeneity were different for each group (Table 5). One study30 showed a negative relation between BMI and CV deaths in patients with HFrEF without giving detailed data. Another study28 provided detailed data, and found a ‘flatter’ U-sharped relation between BMI and CV deaths than between BMI and all-cause mortality amongst patients with HFrEF (**Table 2**).

**Discussion**

This analysis confirms, in part, the existence of an obesity-paradox for patients with heart failure. However, rather than a linear relationship between greater BMI and longevity, we observed, as anticipated, a U-shaped relationship; very low body weight and extreme obesity are both known to be dangerous. Previous studies have reported a U-shaped relationship between BMI and mortality with a nadir anywhere between 30 kg/m2 26 and 42 kg/m2.31 Our analysis provides a considerably narrower range for the nadir of risk both for HFpEF and HFrEF at a BMI of 32-33 kg/m2 although the U-shaped relationship was ‘flatter’ for HFrEF.

There are many possible explanations for the ‘obesity-paradox’ in patients with heart failure. Obesity may be a risk factor for developing heart failure at an earlier age; younger patients generally have a better prognosis.32-35 Thus, so called “reverse-causation” could account for the relationship between obesity and prognosis. Obesity might induce symptoms, such as breathlessness on exertion or lying down, leading to earlier diagnosis of heart failure or even misdiagnosis. Obesity might indicate less advanced disease. Weight loss is an ominous sign in patients with heart failure even before patients become notably cachectic.35-37 A recent report38 suggested that patients with heart failure and a greater waist-hip ratio had a worse prognosis. This may reflect the pro-inflammatory response to accumulation of visceral/omental fat. Obesity is also associated with the development of type 2 diabetes that is associated with an adverse prognosis in patients with heart failure. The proportion of patients with diabetes increases with BMI regardless of HF phenotype in all studies.

Alternatively, obesity might be protective. Fat might provide an energy reserve that helps a patient cope with the metabolic costs of illness, protecting muscle and bone from the catabolic effects of worsening heart failure. Fat might also provide protection against endotoxins.39,40,41,42,8, 43,44,45 Treatment with beta-blockers causes BMI to rise and improves the prognosis of patients with HFrEF, although it is unclear whether this relationship is causal. However, ESC guidelines on heart failure no longer advise weight loss in moderately obese in patients.46

Many reports suggest an obesity-paradox for patients aged >50 years with established cardio-metabolic disease. This is true for hypertension47, type-2 diabetes mellitus48, 49, atrial fibrillation50, 51 and ischaemic heart disease52 as well as heart failure53-55. Reverse-causation could explain each instance. On the other hand, from a clinical perspective it is the prognosis of the patient who they are caring for that is important rather than the patient’s prior medical history, which cannot be altered. Accordingly, knowing that a patient with heart failure who is slightly obese has a better prognosis might be helpful for making decisions about management. Patients might be advised to lose weight (and take more exercise) to improve symptoms and exercise capacity but whether this will have a beneficial or deleterious effect on longevity is unknown.

This is the first study using a dose-response meta-analysis to evaluate the association between BMI and all-cause mortality in patients with HFrEF and HFpEF. The advantage of using the method is that it provides estimates that better quantify the potential non-linear relation between BMI and all-cause mortality. Another advantage of the approach is that it does not require the use of the same cut points for BMI in all studies, which means that all the BMI data can be used.

One problem in interpreting the data is the definition of HFpEF. Many people have “abnormal” features of diastolic function in association with increasing age and obesity. In the absence of conclusive evidence of cardiac dysfunction (such as atrial dilatation or raised plasma concentrations of natriuretic peptides), the diagnosis of heart failure is in doubt. Amongst the studies of HFpEF that we have included, only one (Haass et al.27) reported plasma concentrations of natriuretic peptides which, although raised, were much lower than typically seen in clinical trials of patients with HFrEF.

The study has several other limitations. Some patients with an LVEF of 40-49% (HFmrEF) will have been misclassified as either HFrEF or HFpEF. We did not include studies where the mean value for LVEF was around 45%13, 15, 56 because it was not clear what proportion of these patients would have HFrEF or HFpEF. The characteristics and treatment of patients varied across cohorts as might be expected and differed in adjusted variables and follow-up time. We used a random effect model and most studies were controlled for age, sex, left ventricular ejection fraction, diabetes, blood pressure, NYHA class, ischemic aetiology and hypertension. We only included studies with BMI given in more than 2 categories, which potentially limits the number of studies. However, it makes more efficient for dose-response meta-analysis. In addition, weight changes in patients with heart failure, but the data are not available from the studies included in our meta-analysis to investigate the relation between weight change and outcome.

The relation between BMI and outcome might depend on the end-point chosen. Patients with HFpEF are more likely to die from non-cardiovascular causes than are patients with HFrEF57 but cause-specific mortality data were not available. Furthermore, no data are available to allow us to explore the effect of inflammation or dysglycaemia on the relation between BMI and survival.

Conclusion

Both for patients with HFpEF and HFrEF, the relationships between BMI and mortality are U-shaped with a similar nadir of risk at a BMI of 32-33 kg/m2. Whether interventions to change BMI alter risk is unknown. Further research is required to discover the reasons underlying the obesity-paradox in heart failure and other cardio-metabolic diseases and to provide guidance on whether and how patients should attempt to lose or gain weight.

**Figure legend**

Figure 1: Flowchart of search process.

Figure 2: Adjusted relative risk (HR) for all-cause mortality per 5 units increment in BMI. (A): HFpEF; B): HFrEF). HR and 95% CI are represented by the black dot and horizontal line, respectively; the area of the grey square is proportional to the specific-study weight to the overall meta-analysis.

Figure 3: Association between BMI and all-cause mortality. A reference is set at BMI=23.8 (the top (A): HFpEF; the bottom (B): HFrEF). The middle boxes show the range of BMI for which the relative risk is <1.0 compared to the reference BMI.

References

1. 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**(3):789-95.

2. Osman AF, Mehra MR, Lavie CJ, Nunez E, Milani RV. The incremental prognostic importance of body fat adjusted peak oxygen consumption in chronic heart failure. J Am Coll Cardiol 2000;**36**(7):2126-31.

3. Kapoor JR, Heidenreich PA. Obesity and survival in patients with heart failure and preserved systolic function: a U-shaped relationship. Am Heart J 2010;**159**(1):75-80.

4. 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**(1):13-22.

5. Zamora E, Lupon J, Urrutia A, Gonzalez B, Mas D, Pascual T, Domingo M, Valle V. [Does body mass index influence mortality in patients with heart failure?]. Rev Esp Cardiol 2007;**60**(11):1127-34.

6. Shah RV, Murthy VL, Abbasi SA, Blankstein R, Kwong RY, Goldfine AB, Jerosch-Herold M, Lima JA, Ding J, Allison MA. Visceral adiposity and the risk of metabolic syndrome across body mass index: the MESA Study. JACC Cardiovasc Imaging 2014;**7**(12):1221-35.

7. Clark AL, Coats AJS, Krum H, Katus HA, Mohacsi P, Salekin D, Schultz MK, Packer M, Anker SD. Effect of beta-adrenergic blockade with carvedilol on cachexia in severe chronic heart failure: results from the COPERNICUS trial. J Cachexia Sarcopenia Muscle 2017;**8**(4):549-556.

8. Padwal R, McAlister FA, McMurray JJ, Cowie MR, Rich M, Pocock S, Swedberg K, Maggioni A, Gamble G, Ariti C, Earle N, Whalley G, Poppe KK, Doughty RN, Bayes-Genis A, Meta-analysis Global Group in Chronic Heart F. The obesity paradox in heart failure patients with preserved versus reduced ejection fraction: a meta-analysis of individual patient data. Int J Obes (Lond) 2014;**38**(8):1110-4.

9. Somaratne JB, Berry C, McMurray JJ, Poppe KK, Doughty RN, Whalley GA. The prognostic significance of heart failure with preserved left ventricular ejection fraction: a literature-based meta-analysis. Eur J Heart Fail 2009;**11**(9):855-62.

10. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;**283**(15):2008-12.

11. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. Open Med 2009;**3**(3):e123-30.

12. Organization WH.Principles for modelling dose-response for the risk assessment of chemicals: Geneva : World Health Organization; 2009.

13. Shah R, Gayat E, Januzzi JL, Jr., Sato N, Cohen-Solal A, diSomma S, Fairman E, Harjola VP, Ishihara S, Lassus J, Maggioni A, Metra M, Mueller C, Mueller T, Parenica J, Pascual-Figal D, Peacock WF, Spinar J, van Kimmenade R, Mebazaa A, Network G. Body mass index and mortality in acutely decompensated heart failure across the world: a global obesity paradox. J Am Coll Cardiol 2014;**63**(8):778-85.

14. Bozkurt B, Deswal A. Obesity as a prognostic factor in chronic symptomatic heart failure. Am Heart J 2005;**150**(6):1233-9.

15. Hamaguchi S, Tsuchihashi-Makaya M, Kinugawa S, Goto D, Yokota T, Goto K, Yamada S, Yokoshiki H, Takeshita A, Tsutsui H, Investigators J-C. Body mass index is an independent predictor of long-term outcomes in patients hospitalized with heart failure in Japan. Circ J 2010;**74**(12):2605-11.

16. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 1992;**135**(11):1301-9.

17. Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am J Epidemiol 2012;**175**(1):66-73.

18. Orsini N. From floated to conventional confidence intervals for the relative risks based on published dose–response data. Computer Methods and Programs in Biomedicine 2009;**88**(1):90-93.

19. Clark AL, Fonarow GC, Horwich TB. Impact of cardiorespiratory fitness on the obesity paradox in patients with systolic heart failure. Am J Cardiol 2015;**115**(2):209-13.

20. Orsini N BR, Greenland S. Generalized least squares for trend estimation of summarized dose–response data. Stata J. 2006;**6**:40–57.

21. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;**21**(11):1539-58.

22. Begg CB MM. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;**50**:1088–1101.

23. Egger M DSG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;**315**:629–634.

24. De Schutter A, Lavie CJ, Kachur S, Patel DA, Milani RV. Body composition and mortality in a large cohort with preserved ejection fraction: untangling the obesity paradox. Mayo Clin Proc 2014;**89**(8):1072-9.

25. Wu AH, Eagle KA, Montgomery DG, Kline-Rogers E, Hu YC, Aaronson KD. Relation of body mass index to mortality after development of heart failure due to acute coronary syndrome. Am J Cardiol 2009;**103**(12):1736-40.

26. Vest AR, Wu Y, Hachamovitch R, Young JB, Cho L. The Heart Failure Overweight/Obesity Survival Paradox: The Missing Sex Link. JACC Heart Fail 2015;**3**(11):917-26.

27. Haass M, Kitzman DW, Anand IS, Miller A, Zile MR, Massie BM, Carson PE. Body mass index and adverse cardiovascular outcomes in heart failure patients with preserved ejection fraction: results from the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. Circ Heart Fail 2011;**4**(3):324-31.

28. Curtis JP, Selter JG, Wang Y, Rathore SS, Jovin IS, Jadbabaie F, Kosiborod M, Portnay EL, Sokol SI, Bader F, Krumholz HM. The obesity paradox: body mass index and outcomes in patients with heart failure. Arch Intern Med 2005;**165**(1):55-61.

29. Zafrir B, Goren Y, Salman N, Amir O. Comparison of body mass index and body surface area as outcome predictors in patients with systolic heart failure. Cardiol J 2015;**22**(4):375-81.

30. McAuley P, Myers J, Abella J, Froelicher V. Body mass, fitness and survival in veteran patients: another obesity paradox? Am J Med 2007;**120**(6):518-24.

31. Alpert MA. Severe Obesity and Acute Decompensated Heart Failure: New Insights Into Prevalence and Prognosis. JACC Heart Fail 2016;**4**(12):932-934.

32. Agarwal SK, Chambless LE, Ballantyne CM, Astor B, Bertoni AG, Chang PP, Folsom AR, He M, Hoogeveen RC, Ni H, Quibrera PM, Rosamond WD, Russell SD, Shahar E, Heiss G. Prediction of incident heart failure in general practice: the Atherosclerosis Risk in Communities (ARIC) Study. Circ Heart Fail 2012;**5**(4):422-9.

33. Miro O, Gil VI, Martin-Sanchez FJ, Jacob J, Herrero P, Alquezar A, Llauger L, Aguilo S, Martinez G, Rios J, Dominguez-Rodriguez A, Harjola VP, Muller C, Parissis J, Peacock WF, Llorens P, Research Group on Acute Heart Failure of the Spanish Society of Emergency Medicine R. Short-term outcomes of heart failure patients with reduced and preserved ejection fraction after acute decompensation according to the final destination after emergency department care. Clin Res Cardiol 2018.

34. Tschope C, Birner C, Bohm M, Bruder O, Frantz S, Luchner A, Maier L, Stork S, Kherad B, Laufs U. Heart failure with preserved ejection fraction: current management and future strategies : Expert opinion on the behalf of the Nucleus of the "Heart Failure Working Group" of the German Society of Cardiology (DKG). Clin Res Cardiol 2018;**107**(1):1-19.

35. Chau K, Girerd N, Magnusson M, Lamiral Z, Bozec E, Merckle L, Leosdottir M, Bachus E, Frikha Z, Ferreira JP, Despres JP, Rossignol P, Boivin JM, Zannad F. Obesity and metabolic features associated with long-term developing diastolic dysfunction in an initially healthy population-based cohort. Clin Res Cardiol 2018.

36. Sze S, Pellicori P, Kamzi S, Anton A, Clark AL. Effect of beta-adrenergic blockade on weight changes in patients with chronic heart failure. Int J Cardiol 2018;**264**:104-112.

37. Oldenburg O, Wellmann B, Bitter T, Fox H, Buchholz A, Freiwald E, Horstkotte D, Wegscheider K. Adaptive servo-ventilation to treat central sleep apnea in heart failure with reduced ejection fraction: the Bad Oeynhausen prospective ASV registry. Clin Res Cardiol 2018.

38. Streng KW, Voors, A. A., Hillege, H. L., Anker, S. D., Cleland, J. G., Dickstein, K., Filippatos, G., Metra, M., Ng, L. L., Ponikowski, P., Samani, N. J., van Veldhusen, D. J., Zwinderman, A. H., Zannad, F., Damman, K., van der Meer, P., and Lang, C. C. Waist-hip ratio and mortality in heart failure. . European Journal of Heart Failure 2018:In press.

39. Ebong IA, Goff DC, Jr., Rodriguez CJ, Chen H, Bertoni AG. Mechanisms of heart failure in obesity. Obes Res Clin Pract 2014;**8**(6):e540-8.

40. Backhaus T, Fach A, Schmucker J, Fiehn E, Garstka D, Stehmeier J, Hambrecht R, Wienbergen H. Management and predictors of outcome in unselected patients with cardiogenic shock complicating acute ST-segment elevation myocardial infarction: results from the Bremen STEMI Registry. Clin Res Cardiol 2018;**107**(5):371-379.

41. Stiermaier T, Santoro F, Graf T, Guastafierro F, Tarantino N, De Gennaro L, Caldarola P, Di Biase M, Thiele H, Brunetti ND, Moller C, Eitel I. Prognostic value of N-Terminal Pro-B-Type Natriuretic Peptide in Takotsubo syndrome. Clin Res Cardiol 2018.

42. Clark AL, Chyu J, Horwich TB. The obesity paradox in men versus women with systolic heart failure. Am J Cardiol 2012;**110**(1):77-82.

43. Fonarow GC, Srikanthan P, Costanzo MR, Cintron GB, Lopatin M, Committee ASA, Investigators. An obesity paradox in acute heart failure: analysis of body mass index and inhospital mortality for 108,927 patients in the Acute Decompensated Heart Failure National Registry. Am Heart J 2007;**153**(1):74-81.

44. Abdin A, Poss J, Fuernau G, Ouarrak T, Desch S, Eitel I, de Waha S, Zeymer U, Bohm M, Thiele H. Revision: prognostic impact of baseline glucose levels in acute myocardial infarction complicated by cardiogenic shock-a substudy of the IABP-SHOCK II-trial. Clin Res Cardiol 2018.

45. Shah M, Patnaik S, Patel B, Ram P, Garg L, Agarwal M, Agrawal S, Arora S, Patel N, Wald J, Jorde UP. Trends in mechanical circulatory support use and hospital mortality among patients with acute myocardial infarction and non-infarction related cardiogenic shock in the United States. Clin Res Cardiol 2018;**107**(4):287-303.

46. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Group ESCSD. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;**37**(27):2129-2200.

47. Shah RV, Abbasi SA, Yamal JM, Davis BR, Barzilay J, Einhorn PT, Goldfine AB, Group ACR. Impaired fasting glucose and body mass index as determinants of mortality in ALLHAT: is the obesity paradox real? J Clin Hypertens (Greenwich) 2014;**16**(6):451-8.

48. Costanzo P, Cleland JG, Pellicori P, Clark AL, Hepburn D, Kilpatrick ES, Perrone-Filardi P, Zhang J, Atkin SL. The obesity paradox in type 2 diabetes mellitus: relationship of body mass index to prognosis: a cohort study. Ann Intern Med 2015;**162**(9):610-8.

49. Sinning C, Ojeda F, Wild PS, Schnabel RB, Schwarzl M, Ohdah S, Lackner KJ, Pfeiffer N, Michal M, Blettner M, Munzel T, Kempf T, Wollert KC, Kuulasmaa K, Blankenberg S, Salomaa V, Westermann D, Zeller T. Midregional proadrenomedullin and growth differentiation factor-15 are not influenced by obesity in heart failure patients. Clin Res Cardiol 2017;**106**(6):401-410.

50. Sandhu RK, Ezekowitz J, Andersson U, Alexander JH, Granger CB, Halvorsen S, Hanna M, Hijazi Z, Jansky P, Lopes RD, Wallentin L. The 'obesity paradox' in atrial fibrillation: observations from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial. Eur Heart J 2016;**37**(38):2869-2878.

51. Abdin A, Poss J, Fuernau G, Ouarrak T, Desch S, Eitel I, de Waha S, Zeymer U, Bohm M, Thiele H. Revision: prognostic impact of baseline glucose levels in acute myocardial infarction complicated by cardiogenic shock-a substudy of the IABP-SHOCK II-trial. Clin Res Cardiol 2018;**107**(6):517-523.

52. Wang ZJ, Zhou YJ, Galper BZ, Gao F, Yeh RW, Mauri L. Association of body mass index with mortality and cardiovascular events for patients with coronary artery disease: a systematic review and meta-analysis. Heart 2015;**101**(20):1631-8.

53. Futter JE, Cleland JG, Clark AL. Body mass indices and outcome in patients with chronic heart failure. Eur J Heart Fail 2011;**13**(2):207-13.

54. Palazzuoli A, Ruocco G, Beltrami M, Nuti R, Cleland JG. Combined use of lung ultrasound, B-type natriuretic peptide, and echocardiography for outcome prediction in patients with acute HFrEF and HFpEF. Clin Res Cardiol 2018.

55. Fu M, Ahrenmark U, Berglund S, Lindholm CJ, Lehto A, Broberg AM, Tasevska-Dinevska G, Wikstrom G, Agard A, Andersson B, All investigators of the HRHFs. Adherence to optimal heart rate control in heart failure with reduced ejection fraction: insight from a survey of heart rate in heart failure in Sweden (HR-HF study). Clin Res Cardiol 2017;**106**(12):960-973.

56. Kenchaiah 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, Investigators C. 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**(6):627-36.

57. Chan MM, Lam CS. How do patients with heart failure with preserved ejection fraction die? Eur J Heart Fail 2013;**15**(6):604-13.