

The Obesity Paradox or Vulnerability of the Underweight

To the Editor:

In response to the interesting articles from Zamora¹ and Artham,² we would like to comment on the controversial issue of the obesity paradox.

Advances in pharmacological treatments have been the main reason for the reduction in mortality associated with acute myocardial infarction (AMI) between 1975 and 1995.³ It is therefore surprising that the studies reporting on different aspects of reverse epidemiology, within the context of polypharmacy and haemodynamic instability, as well as acute coronary syndrome (ACS) and acute cardiac failure (ACF), all under-utilise pharmacological variables and are limited to a general analysis of the percentage of drugs used.^{1,4}

Another element to be highlighted is the high percentage of patients excluded from these researches since their weight and/or size is not provided.⁴ This would seem to suggest that, in particular during the first stages of a cardiological emergency, there are failures in taking the patient's anthropometric measurements, which may lead to an incorrect pharmacological dose.⁴

Unfortunately, drugs which have proven to be beneficial in reducing cardiovascular morbimortality can also have very serious adverse effects if the correct dose is not given.⁵ In this way, subjects with reduced body mass have greater "pharmacological susceptibility,"⁵ which is perhaps related to older age^{1,6} and comorbidity, as well as a reduced "therapeutic window."

Therapeutic intervals are directly and proportionately related to body mass index (BMI) and are influenced by multiple factors, such as age, sex, and renal function. This relationship is not taken into account in the exclusive analysis of the percentage of drugs used. Fonarow recently recognised the need to include more complex pharmacological variables such as: dose, tolerability and adverse effects.⁷

It is also to be noted that the insufficiencies indicated have been concluded from studies based on hospital records^{4,5} and that the situation in practice may be much more critical.

Moreover, markers should not be confused with risk factors.² The obesity paradox does not fit the causality criteria, since on analysing the strength of the association, severe obesity does not yield better outcomes, in particular when compared to overweight and slightly obese patients.² While the paradox is not detected or even

disappears ("reversal of the reversal epidemiology")⁸ in situations where the importance of quantifying the acute pharmacological management is "reduced," as is the case of sudden death^{1,2,6} (in particular where this occurs outside the hospital), stable coronary heart disease,⁹ long-term monitoring (>5 years) of heart failure^{6,8} or heart failure with ejection fraction >40%^{1,2} and heart transplant.⁸

Finally, we believe that the risk factors can never be separated from the constant of cardiovascular risk, rather they are associated with ACS and ACF in a much more complex maze of causality than we have been able to quantify and in which medical treatment plays a leading role.⁴

In conclusion, we have put forward a theory that pharmacological variables are the main confounding factors in reverse epidemiology and suggest caution on accepting the validity of the obesity paradox, until more evidence is acquired.

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REFERENCES

- Zamora E, Lupón J, Urrutia A, González B, Mas D, Pascual T. ¿El índice de masa corporal influye en la mortalidad de los pacientes con insuficiencia cardíaca? *Rev Esp Cardiol*. 2007;60:1127-34.
- Artham SM, Ventura HO. Insuficiencia cardíaca y la «paradoja de la obesidad»: la historia continúa. *Rev Esp Cardiol*. 2007;60:1113-7.
- Heidenreich PA, McClellan M. Trends in treatment and outcomes for acute myocardial infarction: 1975-1995. *Am J Med*. 2001;110:165-74.
- Morales A, Lopez G, Ramos R. Replay. *Am Heart J*. 2008;155:e1.
- Curtis JP, Alexander JH, Huang Y, Wallentin L, Verheugt F, Armstrong PW, et al. Efficacy and safety of two unfractionated heparin dosing strategies with tenecteplase in acute myocardial infarction (results from Assessment of the Safety and Efficacy of a New Thrombolytic Regimens 2 and 3). *Am J Cardiol*. 2004; 94:279-83.
- 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;38:789-95.
- Fonarow G. Reply. *Am Heart J*. 2007;154:e21.
- Kalantar-Zadeh K, Block G, Horwich T, Fonarow GC. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. *J Am Coll Cardiol*. 2004;43:1439-44.
- Domanski MJ, Jablonski KA, Murguia-Rice M, Fowler SE, Braunwald E. Obesity and cardiovascular events in patients with established coronary disease *Eur Heart J*. 2006;27:1416-22.

Response

To the Editor:

We would like to express our thanks to Alberto Morales Salinas for his letter. In our response, we wish to discuss his comments and our manuscript without entering into a debate on the specifics of “reverse epidemiology” described in different pathologic situations. Clearly, in our series incidence of mortality is higher among low weight patients. This is not surprising and there may well be no single factor to justify it. While therapeutic intervals can have a direct, proportionate association with body mass index (BMI) and, in turn, be influenced by multiple factors such as age, gender or kidney function—as Morales Salinas affirms—we are unaware of any study of mortality in heart failure with beta-blockers or ACE inhibitors—the drugs that have most influenced these patients’ survival—that has shown an association between the benefits obtained and dosage adjustment for patient BMI or body surface area. Furthermore, we know that mortality in patients with heart failure has been seen to be related to greater blood concentrations of some drugs.¹ Consequently, although we cannot affirm that some patients may not have exhibited this susceptibility, we do not feel we can consider the greater mortality among low-weight patients in our series may have been favored by a relative excess of the treatment received (“the vulnerability of the low-weight patient”). On the other hand, in no case could we consider this phenomenon a confounding factor to the finding that overweight and obese patients had a better prognosis than normal weight patients did. At no point in our manuscript do we affirm the existence of a causal relation between obesity and better prognosis. We simply state that, in a strict 2-year follow-up, overweight and obese patients presented lower mortality. Nor do we have an explanation for this. Although some series report³ finding a *U* shaped mortality curve—ie, greater mortality in patients with outlying weights (low- or over-weight)—and that, therefore, severe obesity did not provide patients with greater protection than being overweight or slightly obese, we did not observe this phenomenon. In fact, as we comment in our study, no patients with morbid obesity (BMI >40) died in the 2-year follow-up although, as we are dealing with a small number of patients, we cannot generalize from our conclusions.

We agree that it is difficult to accept the obesity paradox in patients with heart failure, even though it has been identified in studies with thousands of patients.³⁻⁵ It would be easier to do so if we could find an explanation as to

why this paradox arises that did not need to depend—exclusively—on pharmacologic variables.

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REFERENCES

1. Rathore S, Curtis J, Wang Y, Bristol M, Krumholz H. Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA*. 2003;289:871-8.
2. Habbu A, Lakkis NM, Dokainish H. The obesity paradox: fact or fiction? *Am J Cardiol*. 2006;98:944-8.
3. Curtis JP, Selzer JG, Wang Y, Rathore SS, Jovin IS, Jadbabaie F, et al. The obesity paradox: body mass index and outcomes in patients with heart failure. *Arch Intern Med*. 2005;165:55-61.
4. Ciccoira M, Maggioni AP, Latini R, Barlera S, Carretta E, Janosi A, et al. Body mass index, prognosis and mode of death in chronic heart failure: Results from the Valsartan Heart Failure Trial. *Eur J Heart Fail*. 2007;9:397-402.
5. Kenchaiah S, Pocock SJ, Wang D, Finn PV, Zornoff LA, Skali H, et al; CHARM Investigators. 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;116:627-36.

Response

To the Editor:

With great interest, we read Dr Alberto Morales Salinas¹ comments in which he questions the paradoxical association between obesity and prognosis in heart failure.² Throughout the last decade, numerous cohort studies have been published which detail the so-called “obesity paradox” in the context of both acute and chronic heart failure.³⁻⁵ Body mass index (BMI) is not the only conventional cardiovascular (CV) risk factor that has a favorable influence in patients with heart failure, given that high concentrations of low density lipoproteins and total cholesterol, as well as high blood pressure, have also been associated with a survival advantage in heart failure.⁶⁻⁸

We agree with Dr Salinas’s ideas and point of view on this controversial topic and recognize the interest of his new hypothesis in as much as most of these studies lack an element of control of the pharmacologic agents used, which could introduce confusion into the final results. We agree that documenting patient height, weight, BMI and kidney function forms part of providing top quality attention and that we need this documentation to avoid dosage errors and unfavorable clinical course.⁹

This new hypothesis may be more applicable to studies conducted in the acute context—when patients are attended while presenting acute decompensated heart failure or acute coronary syndrome—because this is when

medication dosage tends not to be proportionate to weight, height and BMI. However, even in these acute situations, a vast amount of data points to the existence of an inverse relation between obesity and prognosis.^{3,10,11} In contrast, the opposite occurs in patients with stable coronary disease (CD), or with other chronic conditions—eg, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, and terminal kidney disease (TKD)—and the “obesity paradox” phenomenon, or in older patients, in whom this new hypothesis is less likely to play a role in “reverse epidemiology.”^{12,13}

One specific reason that could explain why the “obesity paradox” is observed in such a wide range of diseases—CD, heart failure, arterial hypertension, and dyslipidemia—could be the more energetic treatment administered to obese patients. In one study of patients with CD, the highest BMI values were associated with better administration of CD treatment according to established guidelines, and led to lower rates of in-hospital mortality.¹⁴

Many studies document clear evidence of the fact that low weight patients are not the only ones who present a worse prognosis. Moreover, patients with an ideal weight or even slightly overweight have a worse prognosis than those who are slightly obese,⁴ although many studies have highlighted the fact that prognosis is worse in substantially obese patients than in those who are slightly obese.¹⁵ However, Lavie et al⁵ reported a very good prognosis for patients with intense obesity and those who had a greater quantity of fat—a considerably better prognosis than that of patients with less fat—though it was clear they were far from being considered “cachexic.” Logistic regression analysis found the highest percentage of body fat ($\chi^2=9.1$; $P=.002$) was the most powerful, independent predictive factor for illness-free survival. In this population, for every 1% absolute increase in percentage body fat we found a >13% reduction in major clinical episodes.⁵ Various possible explanations exist for the inverse association between BMI and mortality; it is crucial to investigate the differences in pharmacologic agent dosage, secondary effects and tolerability in relation to BMI. This could provide a partial clue to the explanation and, therefore, we think there is a clear need for new clinical studies to clarify fully the mechanism underlying these paradoxical relations, in the hope they lead to new, definitive treatments.

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REFERENCES

1. Morales-Salinas A. Paradoja de la obesidad o susceptibilidad del bajo peso. *Rev Esp Cardiol*. 2008;61:653.

2. Artham SM, Ventura HO. Insuficiencia cardiaca y la «paradoja de la obesidad»: la historia continúa. *Rev Esp Cardiol*. 2007; 60:1113-7.
3. Fonarow GC, Srikanthan P, Costanzo MR, ADHERE Scientific Advisory Committee and Investigators. An obesity paradox in acute heart failure: analysis of body mass index and in-hospital mortality for 108,927 patients in the Acute Decompensated Heart Failure National Registry. *Am Heart J*. 2007;153:74-81.
4. Curtis JP, Selter JG, Wang Y, Rathore SS, Jovin IS, Jadbabaie F, et al. The obesity paradox: body mass index and outcomes in patients with heart failure. *Arch Intern Med*. 2005;165:55-61.
5. Lavie CJ, Osman AF, Milani RV, Mehra MR. Body composition and prognosis in chronic systolic heart failure: the obesity paradox. *Am J Cardiol*. 2003;91:891-4.
6. Horwich TB, Hamilton MA, Maclellan WR, Fonarow GC. Low serum total cholesterol is associated with marked increase in mortality in advanced heart failure. *J Card Fail*. 2002;8:216-24.
7. Kalantar-Zadeh K, Block G, Horwich T, Fonarow GC. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. *J Am Coll Cardiol*. 2004; 43:1439-44.
8. Uretsky S, Messerli FH, Bangalore S, Champion A, Cooper-Dehoff RM, Zhou Q, et al. Obesity paradox in patients with hypertension and coronary artery disease. *Am J Med*. 2007;120:863-70.
9. Fonarow GC. The relationship between body mass index and mortality in patients hospitalized with acute decompensated heart failure. *Am Heart J*. 2007;15:e21.
10. Gurm HS, Whitlow PL, Kip KE. The impact of body mass index on short- and long-term outcomes in patients undergoing coronary revascularization. Insights from the bypass angioplasty revascularization investigation (BARI). *J Am Coll Cardiol*. 2002; 39:834-40.
11. Gruberg L, Weissman NJ, Waksman R, Fuchs S, Deible R, Pinnow EE, et al. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox? *J Am Coll Cardiol*. 2002;39:578-84.
12. Lavie CJ, Mehra MR, Milani RV. Obesity and heart failure prognosis: paradox or reverse epidemiology? *Eur Heart J*. 2005;26:5-7.
13. Horwich TB, Fonarow GC. Reverse epidemiology beyond dialysis patients: chronic heart failure, geriatrics, rheumatoid arthritis, COPD, and AIDS. *Semin Dial*. 2007;20:549-53.
14. Steinberg BA, Cannon CP, Hernandez AF, Pan W, Peterson ED, Fonarow GC. Medical therapies and invasive treatments for coronary artery disease by body mass: the “obesity paradox” in the Get With The Guidelines database. *Am J Cardiol*. 2007;100: 1331-5.
15. Davos CH, Doehner W, Rauchhaus M, Cicoira M, Francis DP, Coats AJ, et al. Body mass and survival in patients with chronic heart failure without cachexia: the importance of obesity. *J Card Fail*. 2003;9:29-35.