

Statins in Heart Failure



Estatinas en la insuficiencia cardiaca

To the Editor,

We have read with the utmost interest the letter by Ramirez et al,¹ published in *Revista Española de Cardiología*. In their report, the authors retrospectively evaluate the prognostic effect of lipophilic statins in 270 patients admitted to a single center for acute heart failure. After multivariable analysis, which included at least 10 covariates, they conclude that lipophilic statins were not associated with cardiovascular mortality risk (odds ratio = 1.12; 95% confidence interval, 0.22-5.64; $P = .88$) or all-cause mortality (odds ratio = 4.94; 95% confidence interval, 0.90-27.11; $P = .06$), or with readmissions for cardiovascular causes (odds ratio = 0.91; 95% confidence interval, 0.63-1.34; $P = .66$) or all-cause readmissions (odds ratio = 1.06; 95% confidence interval, 0.82-1.38; $P = .61$).

First, we appreciate the publication of reports of this type that attempt to clarify the role of statins in the treatment of heart failure, which continues arouse strong debate.

With respect to the findings presented here, we would like to discuss certain issues, mostly methodological, which we feel should be taken into account in the interpretation of the reported results:

1. The text does not provide the absolute number of adverse events recorded, the length of follow-up, or the multivariable model performance measures.²
2. Although we do not know the length of follow-up, we understand that, in analyses of the time to the first event, as in this case, the use of a Cox regression model would be much more appropriate than logistic regression,² especially with irregular follow-ups, which are very common in studies of this type.
3. Although the total number of events is not reported, we understand that, being a small study, the accuracy of the risk estimates is vague (demonstrated very clearly by the width of the confidence interval for the odds ratio corresponding to all-cause mortality). Moreover, the probability of overfitting of the multivariable model is quite high (because of the inclusion of more than 10 covariates). The latter aspect is particularly important, as it has a highly significant effect on the external validation of the results.²
4. The prediction of the time to the first readmission requires the use of survival analyses that take into account competing adverse events.³ In the case of heart failure, adjustment for mortality as a competing adverse event appears to be necessary, given the high rate of mortality following hospital admission. It is well-known that standard techniques for survival analysis overestimate the risk of interim adverse events, such as readmissions, in contexts with a high mortality rate.³

5. Given that hospital admissions are usually recurrent, limiting the analysis to the time of the first readmission is a simplification that impedes a more detailed analysis of the disease course. In this respect, in recent years, a number of professionals have argued in favor of replacing analyses of time to first readmission with longitudinal analyses that include all the events that occurred during follow-up.⁴ A clear example is the case of statins in heart failure. The randomized clinical trial, CORONA, which evaluated the impact of rosuvastatin on prognosis in patients with heart failure and systolic dysfunction, demonstrated that the drug had a discrete protective effect, bordering on statistical significance, on the first readmission for heart failure (hazard ratio = 0.91; 95% confidence interval, 0.82-1.02; $P = .105$); however, a post hoc analysis taking into account repeated hospitalizations demonstrated that rosuvastatin was associated with a greater reduction (from 14%-18%, depending on the type of statistical method employed) that was statistically significant ($P < .05$ for all the comparisons) in the risk of repeated hospital admission.⁵
6. The lack of data on natriuretic peptides and the inflammatory status makes it impossible to define the clinical profile of the study population in greater detail.

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Statins in Heart Failure. Response



Estatinas en la insuficiencia cardiaca. Respuesta

To the Editor,

We have read with interest the comments by Núñez et al, which contribute to the interpretation of the results of our work, published in *Revista Española de Cardiología*.¹ We acknowledge

the inherent limitations due to our not using Cox proportional hazards regression or Cox regression. With an absolute number of 34 cardiovascular deaths and 113 readmissions for heart failure, in the absence of follow-up time, the study design did not permit calculation of the incidence of events. For this reason, we decided on multivariable logistic regression for the analysis. To include the confounding variables and effect modifiers when building the logistic regression model, we first performed an analysis to identify those that could have an influence on the final event. We agree

with Núñez et al that, as a consequence of the limited number of patients included in the study and the large number of variables that we ultimately considered introducing in the multivariable model, the results presented could have affected the external validity of the study. Consequently, the statistical model used may partly be responsible for our not corroborating in our patient population either the benefits in terms of a reduction in new hospital admissions among the heart failure patients treated with rosuvastatin, observed in the post hoc analysis of the CORONA trial,² or the benefits in terms of survival, mainly with lipophilic statins (97% atorvastatin), observed in the real world.³ As occurred in the latter study,³ in our study, access to levels of the amino-terminal fraction of pro-brain natriuretic peptide was limited to only a small number of patients, which may have prevented us from examining whether those with higher values benefit less from statin therapy, as appears to occur with both hydrophilic⁴ and lipophilic⁵ statins.

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Heart Failure and Age

Insuficiencia cardíaca y edad

To the Editor,

We read with interest the article by Crespo-Leiro et al. on treatment adherence in outpatients with heart failure (HF). The article highlighted at least 2 important points: the high standard of prescribing in this area by cardiologists and, most notably, the good treatment adherence in the patients studied,¹ with figures much better than those reported in previous publications.²

Our comments and objections relate to the patients' age, a detail that was not mentioned in the discussion, even in the section on limitations. The mean age of the patients was 65 years, and no patients were older than 73 years. This was surprising and seriously calls into question the representativeness of the whole study.

The age at which HF presents is increasingly older. The incidence and prevalence of the syndrome double every decade from the age of 45 years.³ Over the last 40 years, the age at first episode has increased by some 15 years, and 70% of patients admitted for heart failure are older than 70 years.^{4,5}

Epidemiological data are in line with the literature on the subject, such as the successive NHANES reports and the PRICE study in Spain.⁴ In a study of close to 6000 patients carried out in Spanish emergency departments, the mean patient age was 79.4 years, and only 8.5% were younger than 65 years.⁵ The Rotterdam study reported a HF prevalence of 0.9% in 55 to 64-year-olds, and 17.4% in those older than 85 years; the incidence was 1.4/1000 in 55 to 59-year-olds and 47.4/1000 in those older than 90 years.⁶ The Swedish HF hospital registry is very significant, due to the number of patients included: it spanned 12 years and included 156 919 patients with a primary discharge diagnosis of HF (295 425 if secondary diagnoses are included); only 8% of the men and 5% of the women were younger than 65 years.⁷



An explanation is required. One, very weak, explanation is that the authors concentrated on outpatients; a more convincing explanation is that the study was carried out only by cardiologists in cardiology clinics, when in reality HF is managed by many other specialties (such as general practice, health care for the elderly, and general medicine). One registry, spanning an entire year of data from *Hospital Clínico San Carlos*, Madrid, showed that, of almost 1000 diagnoses of HF appearing in discharge reports that year, fewer than 200 were from the cardiology department. The mean age of those cardiology patients was 70.9 years, while patients from general medicine had a mean age of 80 years, and those from health care for the elderly, 88 years.⁸

Although some progress has been made, there is more ground to be covered by the official scientific societies that represent cardiology in Europe and in Spain. Complex and highly prevalent syndromes such as HF must be studied from a broader perspective and should not be limited to cardiologists in order to eliminate significant biases such as that found in the study prompting these comments.

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