Response to:
Medical journals and editorial quality control by Erviti et al.

We want to thank Erviti J. et al. for their interest in our paper. We answer their questions point by point.

**Question:**
Why are there mortality data included in the baseline characteristics? If patients died during follow-up, it is not clear what the duration of the follow-up was, and how the time ‘before’ and ‘after’ in Table 2 was defined. Why did patients not die in the time defined in Table 2 but only thereafter? What does ‘before’ and ‘after’ in Table 2 denote? Were patients discontinued in taking sacubitril/valsartan ‘after’?

**Answer:**
We apologize for the possible misunderstandings of including mortality in the table of baseline characteristics.

During the study, 13 subjects died, and for 11 subjects, the 6MWT was not available after the beginning of the treatment. However, in the statistical analysis, all the subjects in which the outcome variables were available (6MWT) were included before the end of the study, or before their death. We apologize for the possible misunderstanding due to the lack of clarity in the definition of evaluation times. ‘Before’ refers to the baseline assessment, before the start of treatment with sacubitril/valsartan, and ‘after’ refers to the control assessment at the end of the study time.

The mean follow-up time of the patients during the study was 282 days (range between 21 and 560 days). The mean follow-up time for patients who died during the study was 198 days (range between 55 and 491 days).

**Question:**
A statement of inclusion of patients with ejection fraction ‘somewhat greater than 35%’ is not sufficient and requires more precision. What was the range of included patients’ ejection fraction?

**Answer:**
Subjects with an average ejection fraction of 37% (range between 15% and 40%) were included.

**Question:**
There are many other methodology aspects to be pointed out like misreporting of side effects (not registered).

**Answer:**
Regarding the side effects, we appreciate the clarification because it allows us to reinforce, as stated in the paper, that we have not observed side effects. The side effect that most limits the use of this treatment is hypotension. As specified in the text, more than half of the sample (56%) tolerated the dose of 24/26 mg every 12 h. Despite the relatively low dose, a significant improvement in the functional capacity of the patients has been observed.

**Question:**
Why is the percentage of patients with ‘preuse ACEI/ARB’ comparatively small? Were patients started outright on sacubitril/valsartan? If so, what was the rationale in these patients given that ESC guidelines advocate initiation only after the start of ACEI or ARB if patients remain symptomatic?

**Answer:**
Due to the observational design of the study, we have not included patients who have not tolerated this medication due to hypotension, and we have not included the subjects who could benefit from this treatment but who were not indicated for other reasons. It was not the aim of this study to compare the subjects who have tolerated this treatment with those who have not tolerated it for any reason. As reported in Table 1, 22 patients did not take ACEI/ARB at the time of indication for treatment with sacubitril/valsartan. These patients took ACEI/ARB at some time during their clinical history, but the reason that they were suspended has not been recorded. After readjustment of the treatment, sacubitril/valsartan could be started.

In relation to the treatment prior to the sacubitril–valsartan regimen, this is an observational real-life study, so possible confounding factors have not been evaluated.

In complex patients, sometimes aggressive treatment is ruled out due to the presence of co-morbidities. In our unit, this type of difficult-to-handle patient is treated, in which...
other treatments have been ruled out, but they are patients with symptoms that limit daily life a lot (such as dyspnoea and asthenia).³

This study presents some limitations: being an observational study, possible confounding factors have not been evaluated. Second, we have not evaluated the quality of life with validated scales. Despite this, patients reported rapid and substantial functional improvement, as observed in another study.⁶

Regardless of these limitations, our study has several points of strength. The first is that it is a real-life study in a co-morbidity unit. Second, an increase in the distance walked in the 6MWT has been observed. Probably, this improvement does not represent a clinically significant improvement, but it shows that patients improved their exercise tolerance already in the short term, and therefore, they can develop a physically active life.

Question:
The point raised with regard to ethics approval and informed consent is considered highly important and crucial by the editorial office. If informed consent for participation in this observational study was waived based on the inclusion into a registry, we would like to see more information or correspondence with regard to these points.

Answer:
The patients included in this study are included in the National Registry of Heart Failure (RICA registry) of the Spanish Society of Internal Medicine. The main objective of this registry is to know the clinical characteristics and evolution of patients with heart failure, especially the mortality and morbidity (readmissions) of these patients.

The information sheet of the patients as well as the informed consent signed by the participants in the study have been approved by the Ethics Committee of the Reina Sofia University Hospital of Córdoba.

Question:
Payments received by the authors that could create even a potential (f) conflict of interest should be acknowledged with great attention to detail.

Answer:
We apologize for not having included this information before. Since the study was not funded, and considering that the payments received are not related to the present study, we believed that they were not necessary. At the time of the study, the three authors were dependent on the Government of Navarra, as well as Erviti J. et al.

The Conflict of interest statement is as follows:

None of the three authors have received fees (direct or indirect) to perform this study. R.R.F. has received lecture fees, educational grant, and/or honoraria from Rovi, Novartis, Pfizer, Bristol-Myers Squibb, Daiichi-Sankyo, Esteve, Vifor Pharma, Lilly, and Novo Nordisk. V.M. has received lecture fees, educational grant, and/or honoraria from Rovi, Lacer, Novartis, Nestlé Health Care, Abbott Nutrition, Nutricia, Zambon, Grünenthal, Pfizer, and Bristol-Myers Squibb and research grants from Nutricia. G.T.L. has received lecture fees and educational grant from Recordati, Mylan, Novartis, Lacer, Ferrer, Bayer, Sanofi, and MSD.

Future studies should evaluate the clinical evolution of subjects with heart failure with reduced ejection fraction who tolerate sacubitril–valsartan compared with subjects who cannot tolerate it due to hypotension.

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