Reviewer's report

Title: Beta-2 adrenergic receptor gene polymorphisms Gln27Glu, Arg16Gly and Thr164Ile in patients with heart failure

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Reviewer: Cinzia Forleo

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The Authors evaluated the polymorphisms Arg16Gly, Gln27Glu, and Thr164Ile of the beta2-adrenergic receptor gene with regard to clinical features as well as prognosis in a cohort of 501 patients with heart failure of different etiologies. The data show that body mass index was significantly different in patients with heart failure according to the genotype distribution of the Arg16Gly polymorphism. The Arg16Gly and Gln27Glu polymorphisms were not associated with a different outcome in patients with heart failure when the studied population was on the whole evaluated. Nevertheless, the Gln27Glu polymorphism may have a possible prognostic role in subjects older than 65 years of age.

In reviewing this manuscript, I have the following questions and comments.

Major Compulsory Revisions

1) Page 5, lines 21-23 and page 9, lines 12-15: Why body mass index was available in 362 (72%) out of 501 patients? Why body mass index was not considered as a continuous variable and, consequently, it was not evaluated by using analysis of variance?

2) Page 6, line 2: Why the cardiac rhythm was not retrieved in 74 (15%) out of 501 patients? According to the recent guidelines on heart failure (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. EHJ 2008; 29:2388-2442), an electrocardiogram should be performed in every patient with suspected heart failure. Was the present a retrospective or a prospective study?

3) Page 6, lines 4-5: Why about 34% of patients were not receiving angiotensin converting enzyme inhibitors? Why no patients were taking angiotensin II receptor blockers?

4) Page 6, line 6: The percentage of patients receiving beta-blocker therapy was 20%. Why about 80% of patients who were not taking a beta-blocker? Were these drugs added to the pharmacological treatment of patients during follow-up? In case of affirmative answer, what proportion of patients received beta-blockers during follow-up? Among 188 (37.5%) patients who died during follow-up, how many patients were not taking beta-blockers? In fact, it is well known that beta-blockers modify heart failure outcome and their effects could be influenced
by beta2-adrenergic receptor polymorphisms. Therefore, the Cox regression model evaluated by the Authors (page 7, line 16-17) should be adjusted considering beta-blocker use.

5) Page 9, lines 22-23: The authors described an association between etiology of heart failure and survival of patients. Which is the heart failure etiology characterized by the worse outcome?

6) Page 11, line 6: It may be useful to know the percentage of patients who were older than 65 years.

7) Page 18, Table 1: As shown in Table 1, only a number of patients had clinical and laboratory characteristics analysable by the Authors. Furthermore, the number of patients with known clinical and laboratory parameters was differently changeable for each considered variable. In particular, left ventricular diastolic diameter was estimated in 444 (89%) patients, left ventricular systolic diameter in 338 (67%) patients, and left ventricular ejection fraction (LVEF) was calculated in 397 (79%) patients. How the Authors could explain the heterogeneous number of patients with regard to the recorded measurements? How the missing values were handled by the Authors in the statistical analysis?

8) Page 18, Table 1: Whether LVEF was assessed in 79% of patients, how heart failure was diagnosed in the other (21%) patients?

9) Page 18, Table 1: How the authors explain, on one side, the relatively preserved LVEF (mean 45%) and, on the other side, the severe New York Heart Association (NYHA) functional class III or IV of the patients enrolled in their study?

10) Results – Outcome section. Due to the high percentage (37.5%) of mortality during a mean follow-up of 12.6 months and to the different etiologies underlying heart failure, it may be interesting to know the cause of death (worsening heart failure, sudden death or non-cardiac causes). The number of patients underwent cardiac transplant and those who received an implantable cardioverter defibrillator should be also indicated in the “Results – Outcome” section.

Minor Essential Revisions

1) Page 2, line 14: The number “Thr163Ile” should be substituted with “Thr164Ile”.

2) Page 9, lines 7-9: Within the following sentence “The frequency of polymorphisms Gln27Glu and Arg16Gly were in accordance with Hardy Weinberg equilibrium”, the verb “were” should be replaced with “was” or the word “frequency” should be changed with “frequencies”.

3) Page 10, lines 11-12: In the following phrase “… a potential subgroup of heart failure patients were B2 adrenergic genotype might be of predictive value”, I think that the verb “were” should be substituted with the adverb “where”.
4) Page 11, lines 12-13: The word “individuals that” should be replaced with “individuals who”.

5) Page 11, lines 14-15: The word “patients that” should be changed with “patients who”.

6) Page 12, line 17: The word “Agr16” should be changed with “Arg16”.

7) Page 13, line 14: The word “homozygosis” should be substituted with “homozygosis”.

8) Page 13, line 18: The word “studues” should be replaced with “studies”.

9) Within the Table 1, the unities of measure of heart rate and LVEF are missing. Please, add the unities of measure of the aforementioned parameters. Moreover, please, show the values of LVEF as percentage.

10) Page 22, Figure 2: The Figure 2A refers to heart failure patients with age >65 years and the Figure 2B shows the Kaplan-Meier survival curves according to the genotypes of the Gln27Glu polymorphism in patients having age <65 years. Consistently with the following sentence (page 11, lines 5-6) “a clear difference was observed when only individuals older than 65 years were analyzed” the age “<65 years” should be replaced with the age “>65 years”.

Level of interest: An article of importance in its field

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests.