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## **Clinical characteristics and prognostic impact of atrial fibrillation in patients with chronic heart failure**

### **RESPONSES TO THE REVIEWERS**

We appreciate the kind comments and insightful critiques from the reviewers, which have helped us to significantly improve our manuscript. Here we reply point-by-point to the raised issues, highlighted in bold.

#### **Reviewer's code: 00227470**

**The authors investigated the correlation between AF and long-term all-cause mortality. I have several comments:**

**1. How did you assess atrial fibrillation? At first visit? Or do you mean permanent AF? The manuscript contains confusing information on this point.**

We thank the reviewer for giving us the opportunity through this revision to better clarify the definition of AF in our study population. A diagnosis of permanent AF was assigned at first study visit based on a documented history of AF that had persisted for more than 6 months and was confirmed by a surface ECG at first visit. This point has been better explained throughout the manuscript and particularly in the methods section (see at page 7: "Permanent AF (subsequently indicated solely as AF) was defined as a documented history of AF that had persisted for more than 6 months and was confirmed by a surface ECG at first visit").

**2. How did you assess mortality? Was follow-up complete in all 903 patients?**

This process has also been better detailed in the revised version of the manuscript, as requested by the reviewer (see page 6: "Mortality was ascertained by consulting hospital and administrative databases and death registers. Follow-up was censored at June 30, 2015; survival status was not retrievable in five patients, leaving a final study sample of 903 patients.").

**3. Did you aim for rhythm control in this population? Were electrocardioversions done? Please comment and add to the analyses.**

We thank the reviewer for giving us the opportunity to better clarify this point. As mentioned above, we diagnosed permanent AF at first study visit based on medical history and on the presence of AF at the baseline ECG. Unfortunately prospective clinical information were only available in a minority of patients, thus we were not able to perform a longitudinal analysis accounting for the persistence of the arrhythmia or potential interventions aimed at restoring a regular sinus rhythm (e.g. electrical cardioversion) or at further controlling heart rate (e.g. AV node ablation). We therefore assigned a diagnosis of permanent AF during the first study visit at our clinic, and performed statistical analysis testing all potential predictors of mortality evaluated at the same time (i.e. baseline), including AF. This is a common method in retrospective cohort studies, which surely have important intrinsic limitations, as correctly highlighted by the reviewer. We acknowledged this further limitation in the discussion of the manuscript (see page 15: "Our analysis has several limitations that should be acknowledged. First, this is a retrospective analysis, thus our findings can only be interpreted with the intrinsic limits of this methodology. Second, cardiac rhythm was defined at first study visit, and we cannot exclude subsequent rhythm modifications").

**4. Please delete duplicate sentence in Methods: "This retrospective analysis ..... board approval"**

The duplicate sentence has been deleted.

**Reviewer's code: 00227654**

**This interesting study by Gigli and colleagues examined the impact of atrial fibrillation on outcomes in patients with chronic heart failure. The authors conclude that AF did not have an independent impact on mortality, but beta blockade use appeared to affect this relationship. It would be useful to analyze the data separating HFpEf and HFrEF patients. Effect of beta blockade would also be impacted by whether the patient has HFrEF or HFpEF. It may be better to use LVEF of  $\geq 50\%$  for diagnosis of HFpEF.**

We thank the reviewer for raising this important issue. The study population mainly included HF patients with HFrEF, with only a small percentage of patients with a LVEF  $>45\%$  (149 patients, 16.5%), as shown in Table 1 and underscored at page 12 in the discussion. This percentage decrease to 14.7% when considering the more reasonable LVEF cutoff of 50% recommended by the reviewer, in accordance with the most recent European guidelines. This low number of cases did not allow us to particularly explore the prognostic impact of AF separately in HFrEF and HFpEF patients.

This stratification would result in a very low number of cases of AF with HFpEF (50 patients with LVEF>45%, vs. 123 with LVEF≤45%). For the same reason, we decided not to investigate the interaction between LVEF and AF on mortality. This limitation has been underlined in the revised discussion (see page 15: “Finally, due to the low number of patients with preserved LVEF, we could not explore the interaction between LVEF and AF on mortality.”)

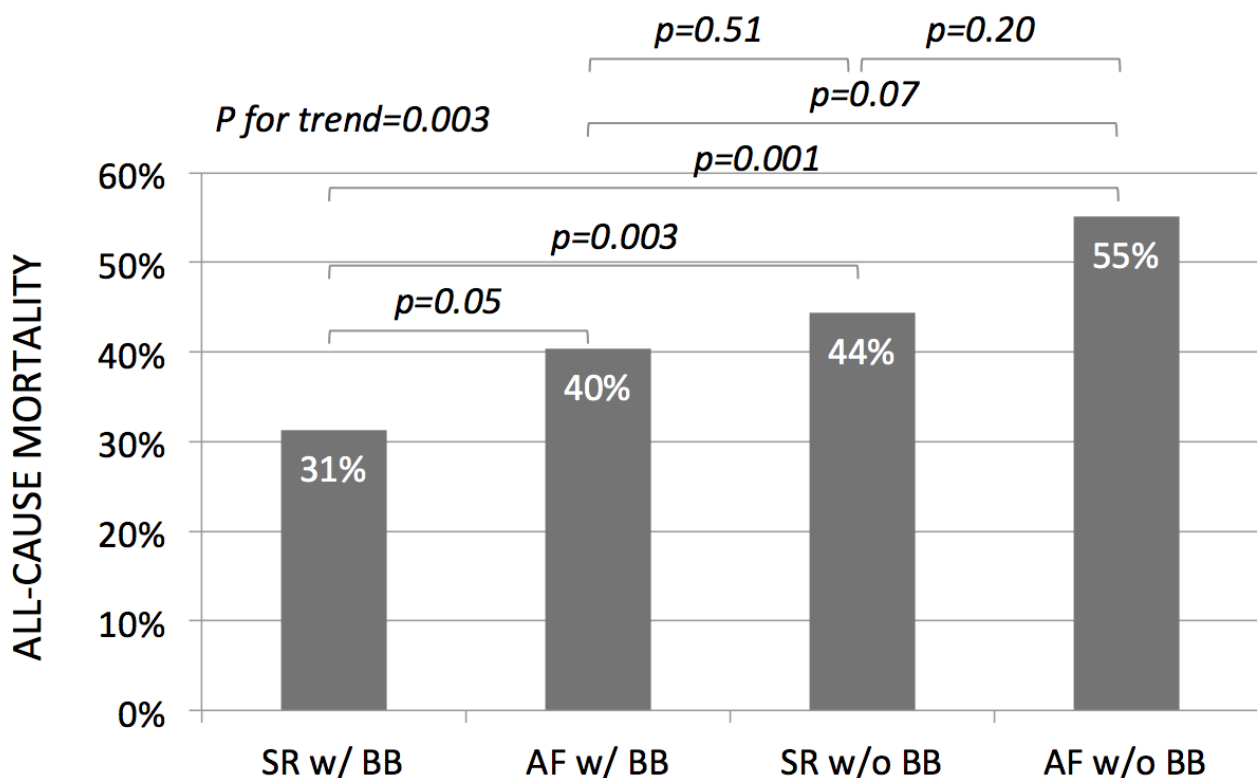
### **Reviewer's code: 02446043**

A useful informative paper that should be accepted after authors addresses 2 matters.

1. In figure 3, comparison as presently shown is not logical. Comparison should be between like groups ie SRwBB vs AFwBB, SRwoBB vs AFwoBB, then SRwBB vs SRwoBB and AFwBB vs AFwoBB.

Figure 3 has been modified according to the request of the reviewers, and it now includes the statistics for all the multiple comparisons, as shown below.

**Figure 3.** All-cause mortality in patients with atrial fibrillation (AF) as compared to patients with sinus rhythm (SR) based on the use of beta-blocker (BB) medications.



The text referring to this figure has also been updated (see page 11: “Patients with AF not receiving BB treatment were found to have the worst prognosis, followed by patients with SR not receiving BB therapy and patients with AF receiving BB therapy, who both had similarly worse survival when compared to patients with SR receiving BB therapy (Figure 3).” and at page 13 “Although the use of BB in the setting of CHF has recently been disputed [9], we observed the worst prognosis in AF patients not receiving BB medications, while patients with AF receiving BB presented a significant survival benefit similar to those with SR not receiving BB but still lower than those with SR receiving BB treatment (see Figure 3 and 4).”.

**2. Table 2 has too many univariate/multivariate corrections and is very confusing to read.**

**Authors should simplify the table and their message**

We thank the reviewer for this comment. The style of the table has been improved, and the content has been a bit cleaned. The complexity of this table reflects the complexity of elderly patients with CHF seen in our center located in northern Italy and probably in most developed countries with an increasingly aged population. These patients frequently have important non-cardiovascular comorbidities with an independent impact on prognosis. This is clearly shown in our multivariate analysis, in which among other variables, diabetes mellitus, COPD, anemia and a history of cancer are all independent predictors of mortality at long-term follow-up. The contribution of AF to prognosis becomes negligible after accounting for these variables, as previously shown in other studies. This message has been better clarified in this new version of the manuscript (see at page 13: “However, after adjusting for other significant predictors (including older age, male sex, systolic blood pressure, NYHA class II-III, ischemic etiology, pacemaker implanted, diabetes mellitus, history of cancer, COPD, anemia), AF did not show an independent impact on overall mortality (see Table 2).”)