

May 14, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 2256-R1.doc).

Title: Ibutilide and novel indexes of ventricular repolarization in patients with persistent atrial fibrillation

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers

Reviewer 1 (00227622)

1. We agree with reviewer that the study population was small. We mention that limitation in the section of 'Limitations'.
2. In this study we did not include a control group since our purpose was to investigate the effect of ibutilide on the ECG indexes in patients undergoing elective electrical cardioversion. In this type of study a control group is not essential since each parameter in each patient is compared before and after ibutilide administration in the same patient. In other words, every patient serves as control of himself. For that reason we used the paired t-test or the non parametric Wilcoxon signed-rank test for the comparisons.
3. The reviewer mentions that "Measurements need to be made by investigators blinded to whether ibutilide or placebo was administered". However, no placebo was used in this study. All patients received ibutilide. In the Methods section (page 5) we clearly state that the investigator who performed the measurements "was unaware of the clinical characteristics of the study participants".

Reviewer 2 (00211908)

We would like to thank the referee for his positive comment on our paper.

We corrected the indicated minor grammar error according to his suggestion (Page 4).

Reviewer 3 (00214267)

We would like to thank the reviewer for his comments. There is no any recommendation for corrections.

Reviewer 4 (00214291)

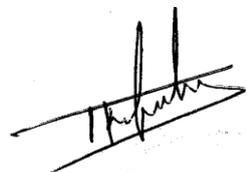
We would like to thank the reviewer for his helpful and constructive comments.

1. We concur with this limitation that the study population is rather small. We acknowledge this limitation in the Limitations section.

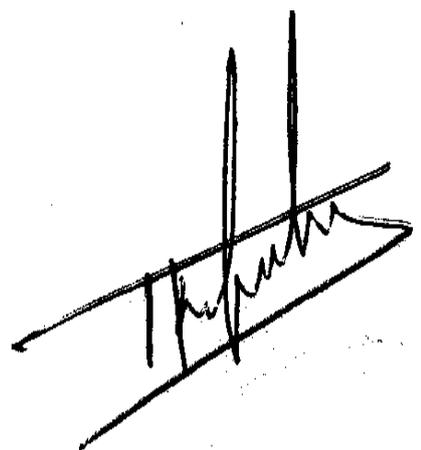
2. We agree that “it is difficult to assess the QTc interval because of the high variability of the RR intervals during AF”. As we mention in the methods section “The measurements were obtained in 5 consecutive complexes of each lead and the resulting average value was finally accepted”. This methodology was used to ameliorate the high variability in the setting of AF. In the revised manuscript we also added a relative limitation in the Limitations section: “Finally, although we measurements of the ECG were obtained in 5 consecutive complexes of each lead and the resulting average value was finally accepted, we have to acknowledge that the high variability of the RR intervals during AF pose specific problems in the accuracy of measurements.”
3. Unfortunately, we do not have ECG data on ECG parameters 30, 60 or 90 minutes after ibutilide administration.
4. We concur with the referee’s comment that “Ibutilide does not play a major role in the treatment of AF...”. However, in the latest update of ESC guidelines regarding AF (European Heart Journal 2012;33, 2719-2747) ibutilide is one of the first choices for the pharmacological cardioversion of recent-onset AF. Secondly, as we stress in our article, ibutilide pretreatment significantly increases the success rate of electrical cardioversion of persistent AF, as applied in our protocol. Thirdly, this model as well as measurement of the novel indexes of ventricular repolarization may prove significant tools in the study of drug-induced proarrhythmia in general. We stress that view clearly in our article(Eg. See Discussion, and Conclusions).

3 References and typesetting were corrected

ALL CHANGES ARE INDICATED THROUGHOUT TEXT IN YELLOW FONT.



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P.S.: We would like to declare that our revised manuscript has reached Grade A regarding language evaluation.