Reviewer's report

**Title:** Comparison of the rhythm control treatment strategy versus the rate control strategy in patients with permanent or long-standing persistent atrial fibrillation and heart failure treated with cardiac resynchronization therapy - rationale and design of a pilot study of the randomized controlled Cardiac Resynchronization in Atrial Fibrillation Trial (Pilot-CRAfT).

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**Reviewer:** riccardo PROIETTI

**Reviewer's report:**

The CRAFT trials presented by Ciszewski et al will be welcomed by the EP community, considering the paucity of literature available on CRT in patients with atrial fibrillation. The topic is increasingly relevant since the incidence of atrial fibrillation in patients with congestive heart failure is high and connected to the NYHA functional class.

Notably, the major endpoint of the study is the percentage of Biventricular pacing in both arms of the study that compare a rhythm control versus a rate control strategy in patients undergoing CRT with atrial fibrillation. Prior studies focused on mortality, morbidity and CRT response defined by echocardiographic parameters as major outcomes. The goal to assess the percentage of biventricular pacing by Ciszewski et al is clever and addresses a clear clinical challenge. However, the paper submitted presents a few major concerns that should be further assessed:

1) All prior studies on this topic should be cited in the introduction and commented on in the discussion. There are at least two meta-analysis regarding patients with CRT and Afib.

2) In the rhythm control strategy the option for an Afib ablation should be clearly indicated and commented on. Analyzing a subset of patients with CRT undergoing AFib ablation could be highly relevant, considering that until now only one study on PABA-CF has assessed the outcome of AFib ablation in patients with congestive heart failure. Please consider changing the phrase “ablation AF substrate” or define what you mean by that.

3) The major concern for the analysis proposed is that comparing overall percentage of pacing in both arms could be biased by the time the patients in the rate control will maintain sinus rhythm. This bias should be considered and commented on. Clinically, I would be interested in analyzing the improvement in the percentage of pacing in both arms of treatment pre- and post enrollment in the study, using each arm as its own reference. The improvement in Biv pacing in both arms could also be compared.

4) Perhaps a paragraph in the discussion on the influences of CRT on Afib could
be added and would be helpful in identifying additional bioumoral markers that could be evaluated in the trial and intervene in CRT response.

5) Please QoL is meaningless. Many trials assess these outcomes without understanding that it is a very subjective parameter and not completely reliable. Moreover, in patients with AFib cognitive deterioration is relevant and amply discussed. Cognitive performance should be assessed in order to provide a correct evaluation in improvement of NYHA functional class and QoL after CRT. For reference please see Proietti et al PACE 2014.

6) Patients with congestive heart failure can present inter-atrial block that can predict occurrence of atrial fibrillation. However, incidence of inter-atrial block in patients with congestive heart failure is unknown. It would be interesting to assess the occurrence of IAB in the rhythm control arm during the follow-up. Some authors even hypothesized atrial resynchronization with pacing in the inter-atrial septum in patient undergoing CRT..