



SDI Review Form 1.6

Journal Name:	<u>Cardiology and Angiology: An International Journal</u>
Manuscript Number:	Ms_CA_32001
Title of the Manuscript:	Dronedarone as a New Option for Hybrid Therapy after Catheter Ablation of Atrial Fibrillation
Type of the Article	

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.

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PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Compulsory REVISION comments	The paper presents the results of an open-label randomized study comparing treatment success for reducing AF recurrence after AF catheter ablation in 3 groups of patients - 1) dronedarone treated patients, 2) patients receiving conventional AADs (mostly flecainide and amiodarone) and 3) a control group (no AADs). Randomization occurred after the ablation, AADs were discontinued at 6 months, and patients were followed for 12 months total. The results demonstrate that both dronedarone and conventional AAD groups significantly reduce AF recurrence at 6 months compared to no treatment, conventional AADs were still better than no treatment at 9 months, but there was no difference in the effectiveness between the 3 groups at 12 months. MAJOR COMMENTS: 1. The Introduction should end with the study aim. The last 2 sentences should be replaced in the Methods section ("<i>The strategy consisted of a circumferential pulmonary vein ablation in combination with a potential-guided segmental approach to achieve complete pulmonary vein isolation plus further linear left atrial lesions as needed. After completion of the ablation procedure patients received either dronedarone (novel hybrid therapy or NAAT), a conventional Vaughan-Williams class I or III AAD (conventional hybrid therapy or CAAT), or no AAD therapy (control group) in a randomized fashion.</i>"). 2. Considering the methodology of the study there are	Thank you for these excellent remarks. We have made changes in the manuscript accordingly. We've integrated the last two sentences from the Introduction into the Methods section.



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	several concerns: (1) Considering that patients were randomized to receive dronedarone, one of the exclusion criteria MUST HAVE included NYHA class III or IV heart failure (HF) at randomization, or recently decompensated HF, in accordance with practice guidelines. As presented in the results, mean NYHA class of the dronedarone group was 2 ± 1, so it could be inferred that AF patients with HF were randomized to dronedarone. The authors need to clarify the study protocol regarding patients with overt/recent HF at randomization. (2) The exact timing of randomization to AADs following the ablation procedure should be stated (e.g how many days after the ablation?). (3) The study protocol did not include uniform discontinuation of AAD treatment at 6 months ("The hybrid antiarrhythmic treatment (i.e. dronedarone, flecainid, propafenone, or amiodarone) was discontinued after 6 months as long as no signs of AF recurrence were found"). A significant proportion of patients (24% receiving dronedarone and 30% receiving convectional AADs) continued to receive AADs beyond the 6 months (mean duration of AAD treatment, dronedarone group 7.25 months; conventional AAD group 7.72 months). The authors need to report whether there was a statistical difference in a number of patients treated beyond the 6 months, and whether there was a statistically significant difference in treatment duration between the dronedarone and conventional AAD arms, as these differences might pertain to the 9-month outcomes. Also, the authors need to report whether there was a	Thank you for this comment. We've clarified the exclusion criteria. We've made changes to the Methods section accordingly. We have changed the manuscript to account for these good remarks.
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	statistically significant difference in the number of repeated ablative procedures between the 3 groups. (4) Since the study results at 12 months show no difference in the efficacy to prevent AF recurrence, it could be concluded that AAD treatment is effective as long as it is applied, but approx. 6 months after AAD discontinuation, prior treatment does not demonstrate "remote" effectiveness, probably due to a lack of influence on AF substrate and remodeling (a speculation...). The study outcomes also included measures of symptom burden (e.g. EHRA class) and the quality of life (QoL). Considering EHRA class, the authors report a significant difference in symptom burden before and after the procedure, but there are no statistical analyses reported. As for the QoL outcome, the tool (test) used for the assessment of QoL MUST BE reported if a validated tool was used. Otherwise, the study might become subjected to the copyright breach claims!	This is an excellent comment. We agree with this speculation. Indeed, to our knowledge there is no evidence that AAD have an effect on AF substrate and atrial remodeling. Statistical data on EHRA class and QoL are stated in Table 1. We have added arrows to mark statistical differences for EHRA class and QoL in the table.
Minor REVISION comments	Text editing is strongly recommended. Ethical issue:The authors have not stated whether the local Ethics Committee approved the study protocol.	We've reviewed the manuscript again and done some editing. The local EC was consulted and approved this study.
Optional/General comments		