PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Non-withdrawal of beta-blockers in acute decompensated chronic and de-novo heart failure with reduced ejection fraction in a prospective multicenter study of patients with acute heart failure in the Middle East
AUTHORS	Abi Khalil, Charbel; Suliman, Kadhim; Mahfoud, Ziyad; Singh, Rajvir; Asaad, Nidal; AlHabib, Khalid; Alsheikh-Ali, Alawi; Al-Jarallah, Mohammed; Bulbanat, Bassam; Al Mahmeed, Wael; Ridha, Mustafa; Bazargani, Nooshin; Amin, Haitham; Al-Motarreb, Ahmed; AlFaleh, Husam; Elasfar, Abdelfatah; Panduranga, Prashanth; Al Suwaidi, Jassim

VERSION 1 - REVIEW

REVIEWER	Andrew Ambrosy Duke University Medical Center/Duke Clinical Research Institute (USA)
REVIEW RETURNED	24-Jan-2017

GENERAL COMMENTS	The present study is a post-hoc analysis of the Gulf CARE registry which enrolled 5,005 patients with AHF in 7 Middle Eastern Countries. The study looked at survival in patients with ADHF based on beta-blocker withdrawal status. The investigators found non-withdrawal of beta-blockers in ADHF was associated with lower short-term mortality. The manuscript is well-written but the major limitation is that the results are highly confounded. Major Comments: 1.) How does a beta-blocker withdrawal rate of 10% compare to the prior literature. 2.) The major limitation is that the patient in whom beta-blockers were withdrawn were much sicker confounding the results. Please comment. How would you conduct a prospective study. 3.) Any data regarding beta-blocker dose? 4.) Should take a stab at what future prospective studies might look like. 5.) Conclusion is one sentence and very weak. Minor Comments: 1.) Abstract should start by presenting some basic descriptive statistics of patient population (i.e. age, etiology of HF, EF). 2.) Introduction don't forget the most important beta-blocker trials with carvedilol (i.e. U.S. carvedilol study and COPERNICUS). 3.) Might consider adding IMPACT-HF study by Gheorghiade et al. which showed in-hospital initiation of beta-blocker was safe compared to post-discharge. 4.) Results should report percentage of patients with EF <40% on beta-blocker. Hard to tell but seems lower than most registries?

	5.) Limitations section says "didn't". Shouldn't use contractions in formal writing.

REVIEWER	Gianna Fabbri, Cardiology Consultant ANMCO Research Center Florence Italy
REVIEW RETURNED	30-Jan-2017

GENERAL COMMENTS	The aim of the manuscript “Non-withdrawal of beta-blockers in acute decompensated chronic and de-novo heart failure: Findings from the Gulf aCute heart failure (GULF-CARE) registry was to describe use of beta-blockers in patient admitted with acute heart failure and to assess the prognostic impact of withdrawal or continuation of beta blockers in these patients. Comments 1. Abstract, section “Outcome measures”. The paper studies the effects of betablocker not-withdrawal, this section should be changed. 2. The reduction in mortality seems to be limited to in-hospital death so in the conclusion “short term” should be changed in “in hospital”. The adjustment for markers of disease severity could be incomplete(etiology, past medical history, comorbidities) Data on timing of death could be interesting to know how many withdrawal influences in hospital mortality 3. Table 3 reports multivariate analysis for in hospital and three months mortality by beta blockers at admission, a logistic regression with end point mortality by withdrawal could be interesting. 4. The limitations of the study are well described and seem very reasonable as the conclusion that the results should be validated in ad hoc randomized clinical trial

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

The present study is a post-hoc analysis of the Gulf CARE registry which enrolled 5,005 patients with AHF in 7 Middle Eastern Countries. The study looked at survival in patients with ADHF based on beta-blocker withdrawal status. The investigators found non-withdrawal of beta-blockers in ADHF was associated with lower short-term mortality. The manuscript is well-written but the major limitation is that the results are highly confounded.

Dear Reviewer,

Thank you for carefully reading our manuscript. We have substantially modified the manuscript to respond to all your comments and we hope that you will find the manuscript suitable for publication.

Major Comments:

1.) How does a beta-blocker withdrawal rate of 10% compare to the prior literature.

In older studies, beta-blockers were withdrawn in over 20% of patients in the OPTIME-CHF study. In our study, beta-blockers were withdrawn in 9% of patients with ADCHF and 13.8% of patients with ADNHF. Those numbers are almost similar to the Italian Survey on Acute Heart Failure in which Orso et al reported a withdrawal rate of 9% in all AHF patients with beta-blockers on admission. However, Bohm et al reported a lower rate (6.8%) in the retrospective analysis of the SURVIVE study.

We added this paragraph in the discussion section

2.) The major limitation is that the patient in whom beta-blockers were withdrawn were much sicker confounding

We completely agree with you. It is a major limitation that we acknowledged and disussed in the article.

3.) Any data regarding beta-blocker dose?

Unfortunately, we don't have data on beta-blockers dose.
We have acknowledge this in the limitations section and in the section "Strengths and limitations of this study"

4.) Should take a stab at what future prospective studies might look like.

We added in the conclusion section that our findings could only be validated in randomized controlled trials designed to show the superiority of non-withdrawal of beta-blockade therapy and also determine whether beta-blocker dose should be reduced or kept unchanged compared to a withdrawal strategy.

5.) Conclusion is one sentence and very weak.

We changed the conclusion and expanded it.
Minor Comments:

1.) Abstract should start by presenting some basic descriptive statistics of patient population (i.e. age, etiology of HF, EF).

We presented basic descriptive statistic of patients per your request

2.) Introduction don't forget the most important beta-blocker trials with carvedilol (i.e. U.S. carvedilol study and COPERNICUS).

The US Carvedilol Heart failure and COPERNICUS trials were added in the introduction

3.) Might consider adding IMPACT-HF study by Gheorghiade et al. which showed in-hospital initiation of beta-blocker was safe compared to post-discharge.

We added IMPACT-HF in the discussion

4.) Results should report percentage of patients with EF <40% on beta-blocker. Hard to tell but seems lower than most registries?

Beta-blockers were prescribed in 44.2% of patients with a LVEF <40%.We reported this in the results and compared it to other studies in the discussion section.

5.) Limitations section says "didn't". Shouldn't use contractions in formal writin

Contractions have been removed and the manuscript has been corrected by a Native English speaker.

Reviewer 2

The aim of the manuscript “Non-withdrawal of beta-blockers in acute decompensated chronic and de-novo heart failure: Findings from the Gulf aCute heart failure (GULF-CARE) registry was to describe use of beta-blockers in patient admitted with acute heart failure and to assess the prognostic impact of withdrawal or continuation of beta blockers in these patients.

Dear Reviewer,

Thank you for your reviewing our paper and providing us with helpful comments. We have changed the manuscript to answer your specific comments.

1. Abstract, section “Outcome measures”. The paper studies the effects of betablocker not-withdrawal, this section should be changed.

We changed this section and indicated that we’re stydying beta-blocker’s non-withdrawal.

2. The reduction in mortality seems to be limited to in-hospital death so in the conclusion “short term” should be changed in “in hospital”. The adjustment for markers of disease severity could be incomplete(etiology, past medical history, comorbidities) Data on timing of death could be interesting to know how many withdrawal influences in hospital mortality.

- We changed “short-term” to “intra-hospital” per your request.

- We totally agree that markers of for disease severity such as etiology, past-medical history and comorbidities are major predictors of mortality. However, many of those variables were not statistically different when we compared the baseline characteristics of each heart failure sub-type per the status of beta-blockers withdrwawl (supplementary table 1 and 2). Our model , in each heart failure sub-type, included all variables that were significantly different according to supplementary tables 1 and 2, in addition to age and gender. We are afraid that adding all variables would make our model over-adjusted, which could distort associations. However, we added the following sentence in limitations: Despite the correction on available cofounding factors, we could have missed other markers of disease severity that were not recorded in the cohort.

- Regarding time of death: Unfortunately, those were not recorded by the investigators in the CRF. We are only in possession of death/alive status (and other cardiovascular endpoints) at the end of

hospitalization, at 3 and 12 months.

3. Table 3 reports multivariate analysis for in hospital and three months mortality by beta blockers at admission, a logistic regression with end point mortality by withdrawal could be interesting.

We added the the odds of mortality by beta-blockers withdrawal status in multivariate analysis.

4. The limitations of the study are well described and seem very reasonable as the conclusion that the results should be validated in ad hoc randomized clinical trial

Thank you for your positive feedback. We even enhanced the limitations and conclusion sections per Dr Ambrosy's suggestions (reviewer 1).

VERSION 2 – REVIEW

REVIEWER	Andrew Ambrosy Duke University Medical Center/Duke Clinical Research Institute (USA)
REVIEW RETURNED	09-Feb-2017

GENERAL COMMENTS	I recommend the authors create a consort diagram for Figure 1 and remove this information from the abstract. Otherwise, all of my comments have been fully addressed.

REVIEWER	Gianna Fabbri, Cardiology Consultant ANMCO Research Center Florence, Italy
REVIEW RETURNED	20-Feb-2017

GENERAL COMMENTS	Thank you the carefully revision and for the clarification provided.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1

I recommend the authors create a consort diagram for Figure 1 and remove this information from the abstract. Otherwise, all of my comments have been fully addressed.

Dear Reviewer,

Thank you for carefully reading our manuscript. We created a consort diagram for figure 1.
We hope that you will find the manuscript suitable for publication.

Reviewer 2

Thank you the carefully revision and for the clarification provided

Dear Reviewer,

Thank you for your reviewing again our paper and recommending acceptance of the manuscript.

VERSION 3 – REVIEW

REVIEWER	Muaamar Al-Gobari Institute of social & preventive medicine (IUMSP) and Cochrane Switzerland, Lausanne University Hospital (CHUV), Lausanne, Switzerland.
REVIEW RETURNED	11-May-2017

GENERAL COMMENTS	Dear Authors, Dear Editor, Thank you for being given the opportunity to review this paper. The current study evaluted the effects of betablokers non-withdrawal on mortality for HFrEF patients. The study is interesting enough due to the design and multinational setting and the importance of the research question. I have some remarks: 1- The title is somewhat “misleading” because the analysis concerns only heart failure patients with reduced ejection fraction (HFrEF). So. I suggest that the term “ with reduced ejection fraction” is added after “heart failure” in the first mention in the title. 2- Statistically, I could not know which variables were adjusted for in addition to gender and age. In the abstract in particular, the result of multivariable logistic regression is reported but no idea which variables were adjusted for. I do not ask to adjust for all variables in the cohort. Selection of variables is made upon search in the literature and expert opinion. 3- Similarly, The result of propensity score matching is reported as OR, CIs and P-value. Stating the selected independent variables will make your result reproducible and comparable to other studies. 4- The conclusion in the abstract does not seem complete. I may have appreciated that you mention that you found no effects or no decrease in hospitalization and/or duration of stay. Also if 3 month or 12 month mortality were significant or insignificant. 5- Strengths and Limitations of this study: I am not sure if the placement of this section after the abstract is required by BMJ open. 6- In page 7: please replace the word numeric by continuous for clarity. 7- In page 7: please mention after/or before 5% level that statistical testing is two-tailed test. 8- BBs may be withdrawn due to side effects. Have you been able to investigate that? How might this influence the result? Here is the importance to know the variables you adjusted for to get the result. 9- Bivariate analysis you made showed also a reduction in intra-hospital mortality. However, 10- Is there any patients with preserved ejection fraction (or >40 %) you identified and had been withdrawn from BBs? This is perhaps another study but could give more information to what is presented in your study. 11- In page eleven and nineteen, you report that 10% withdrawn from ADCHF. However, you mention almost every where else that the percentage is 9 %. Is this merely a typos?

	12- Page 14 : even after correcting for all parameters. Which parameters? This get me back to the previous remarks, namely 2 and 3. 13- Discussion is interesting and interpretation is plausible. 14- In the conclusion: you might consider the remark number 4. Some more minor remarks: 1- Please add SD for age in the abstract as: Mean age was 71 (SD 12). This is to avoid misunderstating with standard error. In the tables: you have already mentioned that in the legend. That is ok, I guess. 2- Please add (days) after "length of stay" in the tables for clarity (not to understand otherwise, hours, months,.etc) . Thank you

VERSION 3 – AUTHOR RESPONSE

We are sorry for the long period of time that your revision has been under review. We identified a number of concerns with the statistical aspects of the paper and as a result we secured a specialist statistical review. We would be willing to offer publication if you can satisfactorily address the concerns raised by reviewer 3 and our comments/ requests below:

Thank you for checking our manuscript with scrunity
We do hope however that the 3rd revision would be handled quicker than the previous one

Please find attached an answer to your questions

- Please carefully check again the reporting of your p values. In the Abstract >> Results section you say "p<0.006 for both". Do you mean p<0.001? Please check that you are reporting p values appropriately/ accurately throughout the paper.

Thank you for bringing this to our attention.

We don't think that there were was a typo but some confusion.

We reported in the results section that the OR of beta-blockers withdrawal after correcting for variables that remained significantly different in the new model was OR=0.084, 95% CI: 0.015-0.468, p=0.005 for ADCHF (page 15) and OR=0.047, 95% CI: 0.013-0.169, p<0.001 for ADNHF (page 18), so we used p <0.006 for both

However, to avoid any confusion:
- We did add in the abstract the sentence: "even after correcting for variables that remained significantly different in the new model" to differentiate from the p<0.001 for both that is only applicable before correcting for variables in the new model.
- We replaced the "p<0.006 for both" by the exact p after the 2 ORs.

- Table 3: what do the asterisks in this table signify?: one asterisk is used for both p<0.001 and p=0.002. Is this an error? Please make it clear what the asterisk refers to in the table's footnotes.

We do apologize for this error.
The asterisks have been removed (it was previously left by the statistician to indicate significant results and we removed all asterisk in all the tables)

- Table 1: a number of p values are given as 0.001. Should this be <0.001 (as presented in the other tables)? Please clarify.

We doubled-checked with our statistical team the p values in table 1.
The ones given as 0.001 are accurate and there were no p values <0.001in table 1.

- Table 4: what does 'NE' stand for?

NE stands for not estimable.
We clarified that at the bottom of table 4.
- There appears to be discrepancies between the abstract and results sections in the reporting of the odds ratios and confidence intervals. Why are two decimal places used in the abstract whilst three decimal places are used in the results? It also looks like you have not rounded your figures up/ down correctly. In the abstract it would be helpful to consistently use the equals sign when reporting ORs as you have done in the results section (i.e. OR=0.047 etc.)

As you suggested above, we double-checked all the ORs and the p value with our statistician.We also made sure we copied the same exact numbers with 3 decimals

- Data sharing statement: please amend this statement to make it clear how other researchers could access the dataset analysed in the study, or what restrictions are in place to accessing the dataset.

The data sharing agreemet was amended to: " The data includes human data. To protect participant privacy, the data is available on request from the corresponding author".

Reviewer 3

Thank you for being given the opportunity to review this paper. The current study evaluted the effects of betablokers non-withdrawal on mortality for HFrEF patients. The study is interesting enough due to the design and multinational setting and the importance of the research question.

Dear Reviewer,

Thank you for carefully reading our manuscript. We have substantially modified the manuscript to respond to all your comments and we hope that you will find the manuscript suitable for publication

1- The title is somewhat "misleading" because the analysis concerns only heart failure patients with reduced ejection fraction (HFrEF). So. I suggest that the term " with reduced ejection fraction" is added after "heart failure" in the first mention in the title.

We added " with reduced ejection fraction" after "heart failure".

2- Statistically, I could not know which variables were adjusted for in addition to gender and age. In the abstract in particular, the result of multivariable logistic regression is reported but no idea which variables were adjusted for. I do not ask to adjust for all variables in the cohort. Selection of variables is made upon search in the literature and expert opinion.

Thank you for the comment. We added in the section methods the variables choosen in the model.

The following sentence was added: “The model included age, gender, non-compliance to medication, systolic blood pressure (SBP), diastolic blood pressure (DBP), left ventricular ejection fraction (LVEF), creatinine, aspirin, statins and inotropes for ADCHF; and age, gender, ACE-inhibitors and inotrops for ADNHF”.

We would like to note the following:
- The models are different for ADCHF and ADNHF because the baseline characteristics (supplementary tables) are different in both conditions when beta-blockers were withdrawn or continued
- Unfortunately, we could not add the variables in the abstract because of characters/words limitation. The current structure of the abstract and all included data were recommended by the 2 previous reviewers.However, we changed the conclusion per your suggestion (suggestion number 4) but we had to delete the sentence “Ischemic heart disease was the precipitating factor in 20% of the ADCHF group and 45% in the ADNHF” to accommodate those changes in terms of words count.
3- Similarly, The result of propensity score matching is reported as OR, CIs and P-value. Stating the selected independent variables will make your result reproducible and comparable to other studies.

We already mentioned in the methods section the variable used for propensity score matching in the following sentence: “Moreover, propensity score matching using the most influential variable (inotropes) was used and the main comparison between the two groups was assessed with and without adjustment to variables that were still significantly different between the two groups even after matching”.

Inotropes were used because they were the most predictive mortality variable in the multivariable model (OR 20.369, 95%CI [8.241-50.337] in ADCHF and 172.272, 95%CI [16.002-1854.600] in ADNHF, and represent clinically an indication to stop beta-blockers in patients.

Further, we added in the methods section variables that were used: In ADCHF, variables adjusted after propensity score matching were gender, non-compliance to medication, SBP, DBP, statins and aspirin whereas in ADNHF we only adjusted for ACE-inhibitors as the sample size became small after matching.

4- The conclusion in the abstract does not seem complete. I may have appreciated that you mention that you found no effects or no decrease in hospitalization and/or duration of stay. Also if 3 month or 12 month mortality were significant or insignificant.

Thank you for your suggestion. We amended the conclusion that has become:
In summary, non-withdrawal of beta-blockers in acute decompensated chronic and de-novo heart failure with reduced ejection fraction is associated with lower intra-hospital mortality, but does influence 3- and 12- mortality, re-hospitalization for heart failure, and the length of hospital stay.

5- Strengths and Limitations of this study: I am not sure if the placement of this section after the abstract is required by BMJ open.

This section is required by BMJ open after the abstract

6- In page 7: please replace the word numeric by continuous for clarity.

We replaced the word numeric by continuous.

7- In page 7: please mention after/or before 5% level that statistical testing is two-tailed test.

We mentioned that statistical testing is two-tailed

8- BBs may be withdrawn due to side effects. Have you been able to investigate that? How might this influence the result? Here is the importance to know the variables you adjusted for to get the result.

We were not able to investigate wether beta-blockers were stopped due to their side effects, the etiology of beta-blockers withdrawal is missing in our cohort. However, we added this in the limitations section

9- Bivariate analysis you made showed also a reduction in intra-hospital mortality. However,

Unfortunately, the comment of the reviewer is incomplete. We could not reply to it

10- Is there any patients with preserved ejection fraction (or >40 %) you identified and had been withdrawn from BBs? This is perhaps another study but could give more information to what is presented in your study.

As the reviewer suggested, withdrawal in patients with preserved ejection fraction constitutes another study. The current analysis was designed to test only beta-blockers in heart failure with reduced ejection fraction. We already specified at the beginning of the methods section that “Those patients with preserved left ventricular function and not on beta-blockers at time of admission were excluded from further analysis”

11- In page eleven and nineteen, you report that 10% withdrawn from ADCHF. However, you mention almost every where else that the percentage is 9 %. Is this merely a typos?

We do apologize for the typo. Beta-blockers were withdrawn in 9% of the patients as shown in table 2 (92 over a total of 1018 patients). We corrected this number in page 11 and 19

12- Page 14 : even after correcting for all parameters. Which parameters? This get me back to the previous remarks, namely 2 and 3.

As we previously mentioned in our rebuttal for remarks 2 and 3, we added those parameters (methods section) in this revised version.

13- Discussion is interesting and interpretation is plausible.

We would like to thank the reviewer for his positive comment

14- In the conclusion: you might consider the remark number 4.

We considered the reviewer’s remark and changed the conclusion

Some more minor remarks:

1- Please add SD for age in the abstract as: Mean age was 71 (SD 12). This is to avoid misunderstating with standard error. In the tables: you have already mentioned that in the legend. That is ok, I guess.

2- Please add (days) after “length of stay” in the tables for clarity (not to understand otherwise, hours, months,.etc) .

We added SD after the mean age in the abstract and days for the lengh of stay.

VERSION 4 – REVIEW

REVIEWER	Muaamar Al-Gobari Institute of social & preventive medicine (IUMSP) and Cochrane Switzerland, Lausanne University Hospital (CHUV), Lausanne Switzerland
REVIEW RETURNED	17-May-2017

GENERAL COMMENTS	Thank you for the opportunity again and for having recieved a revised version of this manuscript. To the best of my knowledge, the authors have fully responded to the comments and concerns raised. I do apologize to not proofreading my previous peer review as it contains some spelling mistakes and therefore, ignoring the remark number 9 was justified. Please take into consideration my comments below: 1- If the editor allows you to add the sentence in the conclusion: “Ischemic heart disease was the precipitating factor in 20% of the ADCHF group and 45% in the ADNHF”, if you can, do so. Otherwise, you keep it at the body of the manuscript. 2- In the conclusion: .....but does influence 3- and 12- month mortality, re-hospitalization for heart failure, and the length of hospital stay. I guess you mean does NOT influence. Please correct this serious issue. Not to influence you, I would say: was insignificant for 3-month and 12-month mortality...etc. Please make sure of that.