Author's response to reviews

Title: Incidence of Atrial Fibrillation in Patients with either Heart Failure or Acute Myocardial Infarction and Left Ventricular Dysfunction: A Cohort Study

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Author's response to reviews: see over
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Editorial Assistant
BMC Cardiovascular Disorders
Hayley Hewitt

Regarding the manuscript MS: 2159720595128559, “Incidence of Atrial Fibrillation in Patients with either Heart Failure or Acute Myocardial Infarction and Left Ventricular Dysfunction: A Cohort Study”

Dear Hayley Hewitt

We thank you for the constructive criticism of our manuscript. In the following we have thoroughly gone through all critique points made by the reviewers (see below). We believe, that we have taken all comments into account, and we hope that our revised manuscript is acceptable for the BioMed Central Cardiovascular Disorders.

In the following reply, the reviewer’s comments are formatted in Italic, black colour and numbered (reviewer’s comments). The comments are followed by our reply in normal, green colour (our reply). When changes to the manuscript are made, we have printed the previous version in normal, black colour (previous version). In the following new version text added to the manuscript is clearly marked by use of normal, blue colour (inserted text), whereas text removed from the manuscript is in normal, strikethrough, red colour (removed text). In addition, typographical and grammatical changes have been made throughout the manuscript and are clearly indicated by use of purple colour (inserted text, removed text)

All authors have seen and approved the final version of the manuscript.

Kind regards
Michelle Schmiegelow, MB
Reviewer #1, Chris Arden

Minor essential revisions;

Reviewer #1, q1) Background (p2) - need to clarify is symptomatic HF, as otherwise reader may see LVSD as synonymous as HF and not be able to distinguish between the two

Author’s reply: We accept the comment and have clarified the patient selection.

The following change has been made:

Previous version: Abstract section, Background:

We examined the incidence of new-onset atrial fibrillation in patients with left ventricular dysfunction and either a recent myocardial infarction or symptomatic heart failure with and without treatment with the class III antiarrhythmic drug dofetilide over 36 months.

New version:

We examined the incidence of new-onset atrial fibrillation in patients with left ventricular dysfunction. Patients either had a recent myocardial infarction (with or without clinical heart failure) or symptomatic heart failure (without a recent MI). Patients were with and without treatment with the class III antiarrhythmic drug dofetilide over 36 months.

Reviewer #1, q2) Conclusion (p2) - Rx significantly reduced risk of developing AF 'only in the HF group' compared with placebo
Author’s reply:

The total number of events in patients with myocardial infarction was quite low, and we probably had a statistically lack of power to gain significant results in this population. However, we tested for interaction in between the two studies in order to investigate, whether the effect of dofetilide had a differential impact of the incidence of AF in patients with heart failure compared with patients with myocardial infarction. We found no interaction between dofetilide and study (p=0.89 for interaction). Therefore we feel it is appropriate to conclude that dofetilide prevented development of AF in patients with heart failure as well as in patients with myocardial infarction. However, we have modified the wording to make it clear that the significance was only seen in the subgroup of heart failure patients. The following changes have been made:

Previous version: Abstract section, Conclusion:

Dofetilide significantly reduced the risk of developing atrial fibrillation compared to placebo.

New version:

Dofetilide significantly reduced the risk of developing atrial fibrillation compared to placebo in the entire study group and in the subgroup of patients with heart failure. The reduction in the subgroup with recent MI was not significant, but the hazard ratio was similar to the hazard ratio for the heart failure patients, and there was no difference between the effect in the two studies (p=0.89 for interaction).

Reviewer #1, q3) Backgroud (p3) - last para 'group of interest to benefit from...'

Author’s reply:
This paragraph has been rewritten due to comments made by reviewer #2 (q1), and we have therefore inserted the new version of this paragraph, which we believe also takes the comment into account.

**Previous version: Background section, 2nd paragraph:**

We used data from these two studies to examine the incidence of AF with and without treatment with dofetilide, and explored the risk factors for the development of new-onset AF to specify the patient group of interest to benefit of prophylactic anticoagulation or potentially antiarrhythmic treatment.

**New version:**

We used retrospectively analyzed data from the DIAMOND studies to investigate these two studies to examine the incidence of AF in placebo-treated patients with left ventricular dysfunction and either heart failure or recent myocardial infarction. Secondarily we examined the potential benefit of treatment with dofetilide in these populations. Additionally, we assessed risk factors that may contribute to new-onset AF in these two cohorts in order to identify a population that would benefit from treatment with prophylactic anticoagulation or antiarrhythmic agents, with and without treatment with dofetilide, and explored the risk factors for the development of new-onset AF to specify the patient group of interest to benefit of prophylactic anticoagulation or potentially antiarrhythmic treatment.

**Reviewer #1, q4) p4 (3rd para) - diagnosis of AF left 'to' the discretion**

**Author’s reply:**

We have made following change:

**Previous version: Method section, 3rd paragraph:**

The diagnosis of AF was left on the discretion of the investigator.
New version:

The diagnosis of AF was left on to the discretion of the investigator.

Reviewer #1, q5) p8 (top) - need to re-phrase 'of AF in patients, who cannot die' does not make sense

Author’s reply:

We agree and have made the following changes:

Previous version: Discussion section, 3rd paragraph:

As the populations being studied in general have a high mortality, the results of other studies can be difficult to interpret, as they study the cumulative incidence of AF in patients, who cannot die.

New version:

As the populations being studied in general have a high mortality, the results of other studies can be difficult to interpret, as they study the cumulative incidence of AF in patients, who cannot die without taking the competing risk of mortality of atrial fibrillation development into account.

Simple Kaplan Meier graphs with censoring for death assumes a similar risk of atrial fibrillation in patients that die to those remaining in the analyses. This can cause distorted interpretations when the risk of death is high.

Reviewer #1, q6) p8 (3rd para) - useful to acknowledge that diagnosis of AF is probably underestimated by not using ARM (ambulatory rhythm monitoring) as part of the study, but would probably use alternative to (or omit) 'punctiliously'

Author’s reply:

Absolutely correct. Continuous Holtermonitoring was used when feasible at the day prior to inclusion as well as the day following treatment initiation, but Holter monitoring were not used
throughout the study period and only for a few patients. However, we have chosen to follow the point made by the reviewer and we have omitted “punctiliously”.

**Previous version; Discussion section, 5th paragraph:**

However, we cannot exclude that AF is underestimated in our study, as we did not punctiliously examine for AF with Holter monitoring.

**New version:**

However, we cannot exclude that AF is underestimated in our study, as we did not punctiliously examine for AF with continuous Holter monitoring.

**Reviewer #1, q7) p9 (para 5) - to identify patients 'at' high risk of developing AF**

**Author’s reply:**

We have made following change:

**Previous version; Discussion section, Risk factors of new-onset AF, 3rd paragraph:**

Furthermore, LVEF was confirmed as a predictor of new-onset AF, which makes it easier to identify patients in high risk of developing AF in the daily clinical life as the role of echocardiography is increasing.

**New version:**

Furthermore, LVEF was confirmed as a predictor of new-onset AF, which makes it easier to identify patients in at high risk of developing AF in the daily clinical life as the role of echocardiography is increasing.

**Reviewer #1, q8) p10 'Reduction of the AF burden has not been shown to improve survival in AF patients' am not sure this makes sense, what is the AF burden? if risk factors are actively managed, stroke risk reduced then mortality, admissions and morbidity will improve**
Author’s reply:

All though the high risk of mortality and morbidity in patients with AF intuitively should be reduced by restoration of sinus rhythm, previous studies have not found rhythm control to be superior to rate control.[1]

A study of the PRIME-II (Prospective Randomized study of Ibopamine on Mortality and Efficacy) found the increased mortality and morbidity in patients with severe heart failure and atrial fibrillation to be due to risk factors closely associated with AF, and neither new-onset AF nor baseline AF were found to be independent predictors of mortality and morbidity[2].

Several studies have however found correct management of risk factors and anticoagulation treatment to improve the outcome of these patients. As discussed in the paragraph “The prognostic impact of AF”, dronedarone has been found to reduce the admission rate and death of any cause [3], which makes us suggest that prevention of new-onset AF by use of dofetilide might improve the prognosis of patients in high risk of developing AF.

We have made the following changes, and we have added a reference to support our statements.

Previous version: Discussion section, The prognostic impact of AF, 1st paragraph:

Reduction of the AF burden has so far not been shown to improve survival in AF patients.

New version:

Reduction of the AF burden has so far not been shown to improve survival in AF patients with severe heart failure nor has rhythm control been found to be superior to rate control in these patients[1, 2].

Reviewer #1, q9) p10 (1st para) - patients' who have had a myocardial infarction'

Author’s reply:
The following change has been made:

**Previous version; Discussion section, The prognostic impact of AF, 1st paragraph:**
These results suggest that prevention of new-onset AF may have favourably impact on outcome, but further studies are needed, especially when it comes to patients with an MI.

**New version:**
These results suggest that prevention of new-onset AF may have favourably impact on outcome, but further studies are needed, especially when it comes to patients, who have had, with an MI.

**Reviewer #1, q10) p10 (2nd para) - paroxystic should read 'paroxysmal'**

**Author’s reply:**
We have changed the grammatical mistake.

**Previous version; Limitations section, 1st paragraph:**
On the other hand, many of the patients might have undiagnosed paroxystic AF at baseline.

**New version:**
On the other hand, many of the patients might have undiagnosed paroxysmal AF at baseline.

**Reviewer #1, q11) p10 (2nd para) - when 'managing' not handling...patients with LVSD**

**Author’s reply:**
The following change has been made:

**Previous version; Limitations section, 1st paragraph:**
However, the message of this paper remains unchanged, that is, the relatively high incidence of AF should be kept in mind, when handling patients with left ventricular dysfunction and, especially, new or worsening
heart failure, and if symptomatic, rhythm control can be achieved effectively through administration of dofetilide.

**New version:**

However, the message of this paper remains unchanged, that is, the relatively high incidence of AF should be kept in mind, when handling patients with left ventricular dysfunction and, especially, new or worsening heart failure, and if symptomatic, rhythm control can be achieved effectively through administration of dofetilide.

*Reviewer #1, q12) p10 (2nd para) - was this really an assessment of a rhythm control strategy as patients were in SR when started on active Rx at the beginning of the trial, and had no prior Hx of AF, there is no evidence to support the statement that Dofetilide was more effective at converting patients in AF to SR, or maintaining them in SR once cardioverted?*

**Author’s reply:**

We agree fully with the reviewer that this study does not support the statement that dofetilide was more effective at converting patients in AF to sinus rhythm or maintaining them in sinus rhythm once cardioverted. However, we have previously published that dofetilide in these patients is more effective at converting patient in AF to sinus rhythm, and in maintaining them in sinus rhythm once cardioverted [4].

The primary message of this study was that patients hospitalized with left ventricular dysfunction and either new or worsening heart failure or an MI and no AF at baseline have a very high risk of developing AF, and this risk can be reduced by use of prophylactic treatment with dofetilide. The patients were randomized to either dofetilide or placebo and the baseline characteristics in the two groups were similar.
Reviewer #1, q13) Conclusion - incidence of AF 'at' 42 months in patients with 'symptomatic' HF

Author’s reply:

We have made following changes:

Previous version; Conclusion section, 1st paragraph:

In patients with left ventricular dysfunction the incidence of AF in 42 months was 9.6% in patients with heart failure and 2.9% in patients with a recent MI, and these results were based on a competing-risk analysis, that is, the estimated risk of developing AF, when the competing risk of death is taken into account.

New version:

In patients with left ventricular dysfunction the incidence of AF in 42 months was 9.6% in patients with new or worsening heart failure and 2.9% in patients with a recent MI, and these results were based on a competing-risk analysis, that is, the estimated risk of developing AF, when the competing risk of death is taken into account.

Reviewer #1, q14) does this particular study really show that dofetilide is indicated for restoring SR?

Author’s reply:

We agree with the reviewer that this study did not investigate the effect of dofetilide in the acute setting of AF, and from these data we cannot conclude that dofetilide is indicated for converting patients with AF to sinus rhythm as previously published [4]. This has been moved from the conclusion.

We have made the following changes to the conclusion:
The administration of dofetilide reduced the incidence of new-onset AF significantly by a mean of 41% compared to placebo, and is indicated for restoration of sinus rhythm in symptomatic patients.

New version:

The administration of dofetilide reduced the incidence of new-onset AF significantly by a mean of 41% compared to placebo, and there was no interaction between dofetilide and study (p=0.89 for interaction). Dofetilide is indicated for as prophylactic antiarrhythmic treatment of AF in patients with left ventricular dysfunction, and either symptomatic heart failure or myocardial infarction, restoration of sinus rhythm in symptomatic patients.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests: I declare that I have no competing interests.
Reviewer #2, Dimpipatel

Reviewer's report:

Incidence of Atrial Fibrillation in Patients with either Heart Failure or Acute Myocardial Infarction and left Ventricular Dysfunction: A Cohort Study:

General: Schmiegelow et al. question whether the use of dofetilide would reduce the incidence of new-onset AF in patients with a combination of left ventricular dysfunction and heart failure or left ventricular dysfunction and recent myocardial infarction when compared to treatment with placebo. The paper is interesting. Nice job

Background:

Reviewer #2, q1) Minor changes: The thesis is a little awkwardly worded…please see the suggestion below

We retrospectively analyzed data from the DIAMOND studies to investigate the benefit of treatment with dofetilide versus placebo in patients with left ventricular dysfunction with either heart failure or recent myocardial infarction. Additionally, we assessed risk factors that may contribute to new-onset AF in these two cohorts in order to select for a population that would benefit from treatment with prophylactic anticoagulation or antiarrhythmic agents.

Author’s reply

We thank the editor and reviewers for their revision of our manuscript and their positive critique.

We agree that the hypothesis should be more clearly phrased. However, we would like to emphasize that the primary purpose of this study was to examine the risk of new-onset AF in a heart failure population and in a myocardial infarction population, whereas the examination of the potential benefit of the class III antiarrhythmic drug dofetilide was a secondary aim of this study.
We used data from these two studies to examine the incidence of AF with and without treatment with dofetilide, and explored the risk factors for the development of new-onset AF to specify the patient group of interest to benefit of prophylactic anticoagulation or potentially antiarrhythmic treatment.

**New version:**

We used retrospectively analyzed data from the DIAMOND studies to investigate these two studies to examine the incidence of AF in placebo-treated patients with left ventricular dysfunction and either heart failure or recent myocardial infarction. Secondarily, we examined the potential benefit of treatment with dofetilide in these populations. Additionally, we assessed risk factors that may contribute to new-onset AF in these two cohorts in order to select for a population that would benefit from treatment with prophylactic anticoagulation or antiarrhythmic agents, with and without treatment with dofetilide, and explored the risk factors for the development of new-onset AF to specify the patient group of interest to benefit of prophylactic anticoagulation or potentially antiarrhythmic treatment.

**Reviewer #2, q2) Methods:** Minor changes: See below.

We retrospectively analyzed data that was collected by DIAMOND Investigators from (X-X dates of the studies).

**Author’s reply:**

We have added information on time of data collection.

**Previous version; Methods section, 1st paragraph:**

This study was an analysis of data collected in the DIAMOND investigations, which consisted of two separate, randomised, double-blind, multicenter studies investigating the safety and efficacy of
the oral class III antiarrhythmic agent dofetilide in patients with left ventricular systolic dysfunction and either heart failure or a recent MI (DIAMOND-MI).

New version:

We retrospectively analyzed data which was collected by the DIAMOND Investigators from November 1993 to November 1995 (DIAMOND-heart failure), and November 1993 to July 1996 (DIAMOND-MI). The DIAMOND investigations consisted of two separate, randomised, double-blind, and multicentered studies. These investigated the safety and efficacy of the oral class III antiarrhythmic agent dofetilide in patients with left ventricular systolic dysfunction and either heart failure or a recent MI (DIAMOND-MI).

Statistics: Nice Job

Results:

Minor:

Reviewer #2, q3) Did you have left atrial size?

Author’s reply:

Unfortunately we cannot provide data on left atrial size as only left ventricular ejection fraction was registered systematically.

It is interesting that in your baseline characteristic factors such as male gender, DMII, HTN, BMI, age are not significant for new-onset AF. However after adjusting for the variables, I see that age and gender are significant. Do you have a possible idea as to why HTN or DMII is not significant in these populations? It seems odd especially the HTN. It is not surprising to find that heart failure was the strongest predictor!
Author’s reply:

It is a nice point, which we would like to elaborate on.

The primary reason for the differences is that the baseline characteristics are presented for each population, whereas the predictors of new-onset AF were examined in a single model, which included the entire population. That is, the statistical power of the performed calculations increases, and therefore changes in significance level can be expected. This is the case with regard to age, where the differences in between groups are small.

Furthermore, heart failure was the strongest predictor of incident AF. This fact tends to drag the percentages for the categorical values and the mean values of the continuous variables toward the percentages and means in the heart failure population. With regard to gender, 83% of the patients in the combined population were males, whereas only 73% of patients in sinus rhythm were males. Diabetes as a predictor of AF is controversial, and we must conclude that this study did not prove diabetes to predict incident AF.

Hypertension is regarded as an established predictor of AF in most studies, but mainly in populations without heart failure or left ventricular dysfunction. Furthermore, most studies have found a higher prevalence of hypertension than this study did. In this study only 14% (n=174) of the patients with heart failure and 17% (n=234) of the patients with MI had a history of hypertension, which corresponds to 16% of the total population. There is no clear explanation to the low history of hypertension in the DIAMOND-studies, but statistically lack of power can probably explain why this study did not find hypertension to predict incident AF. Secondly, hypertension in these populations mainly consists of patients without a high blood pressure any longer, as they have depressed left ventricular function. Thus, high blood pressure may be a driver of developing AF in other studies, but the high blood pressure is not present in the DIAMOND-populations.

Discussion:
Minor:

Reviewer #2, q4) On page 8 “who cannot die” I would reword this.

Author’s reply:

This comment has been dealt with, and we politely refer to Reviewer #1, q5.

Reviewer #2, q5) On page 8: In our MI group….patients who experience"d"

Author’s reply:

We thank the reviewer for correcting the mistake. The suggested change has been made, and furthermore the whole manuscript has been looked through to make sure all verbs are in the correct forms.

Previous version; Discussion section, 4th paragraph:

In our MI group (DIAMOND-MI) the non-significant effect of dofetilide on the risk of developing AF can be explained by the few number of patients who experiences AF during follow-up (n= 32).

New version:

In our MI group (DIAMOND-MI) the non-significant effect of dofetilide on the risk of developing AF can be explained by the few number of patients who experienced AF during follow-up (n= 32).

Reviewer #2, q6) On page 8: Thus, this study "statistically lacked power" to

Author’s reply:

We thank the reviewer for drawing our attention to the phrase, and we have made the suggested change at page 8 as well as at page 10.
Thus, this study had lack of power to give any clear results of the association between MI and the effect of treatment with dofetilide on new-onset AF.

New version:
Thus, this study statistically lacked power to provide any clear results of the association between MI and the effect of treatment with dofetilide on new-onset AF.

Limitations section, 2nd paragraph:
This was most notable in the MI-group, as the relatively few events in this group resulted in lack of power to show a significant effect of dofetilide on the risk of new-onset AF.

New version:
This was most notable in the MI-group, as the relatively few events in this group resulted in statistical lack of power to show a significant effect of dofetilide on the risk of new-onset AF.

Reviewer #2, q7) On page 10: change paroxystic to "paroxysmal"

Author’s reply:
We politely refer to the reply to Reviewer #1, q10.

Reviewer #2, q8) On page 10: The study was not designed to “evaluate”

Author’s reply:
We have made the suggested change to the manuscript.

Limitations section, 2nd paragraph:
The study was not designed to study the incidence of AF, which might have contributed to some unknown biases although the double-blinded randomization should have minimized biases.
New version:

The study was not designed to study-evaluate the incidence of AF, which might have contributed to some unknown biases although the double-blinded randomization should have minimized biases.

Reviewer #2, q9) On page 11: In the conclusion it is stated as a 41% reduction... in the abstract it is stated as a 42% reduction.

Author’s reply:

We thank the reviewer for pointing out the typing error.

Previous version; Conclusion section, 2nd paragraph:

The administration of dofetilide reduced the incidence of new-onset AF significantly by a mean of 41% compared to placebo, and is indicated for restoration of sinus rhythm in symptomatic patients.

New version:

The administration of dofetilide reduced the incidence of new-onset AF significantly by a mean of 41%42% compared to placebo, and is indicated for restoration of sinus rhythm in symptomatic patients.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: I declare that I have no competing interests
References


