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**ARTICLE DETAILS**

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Cardiovascular and non-cardiovascular hospital admissions associated with atrial fibrillation: a Danish nationwide study</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTHORS</td>
<td>Christiansen, Christine Benn; Olesen, Jonas; Hansen, Morten; Gislason, Gunnar; Torp-Pedersen, Christian</td>
</tr>
</tbody>
</table>

**VERSION 1 - REVIEW**

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Dr Christopher X. Wong</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Research Fellow</td>
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<tr>
<td></td>
<td>Centre for Heart Rhythm Disorders</td>
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<td>University of Adelaide and Royal Adelaide Hospital</td>
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<td>REVIEW RETURNED</td>
<td>12-Aug-2012</td>
</tr>
</tbody>
</table>

**THE STUDY**

Substantial improvement in writing required. More recent studies relevant to paper should be included:


**RESULTS & CONCLUSIONS**

Manuscript requires substantial improvement in writing. Similarly, a more thorough discussion of possible reasons underlying their findings needs to be included.

**GENERAL COMMENTS**

In the present manuscript, Dr Christiansen and colleagues retrospectively analyze Danish registries to characterize admissions and re-admissions associated with atrial fibrillation over a 13 year time period. They report that patients with atrial fibrillation have a significantly higher rate of re-admission than do patients without atrial fibrillation. They also describe the variety of non-cardiovascular conditions that patients with atrial fibrillation are re-admitted with.

This is paper that adds to the body of evidence suggesting that atrial fibrillation represents an increasing burden on health care systems. Whilst the data and message is interesting, the readability and subsequent impact of the manuscript could be substantially improved by careful re-writing. The authors’ institution may have resources to be able to assist in this regard.
1. The authors should make the title more descriptive; for example, key characteristics could be included that would make it more informative – e.g. cardiovascular and non-cardiovascular hospital admissions associated with AF, nation-wide study, Denmark, trends.

2. It would be helpful if a careful review of the paper is undertaken to correct language and grammatical errors. The following are a few examples found in the abstract alone. Improving the writing would substantially improve the readability and subsequent impact of the paper.

Page 1, Line 12: AF is duplicated.
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Methods: the methods section needs to state that the study looked at admissions associated with AF.

Results: It seems odd that some of the results are presented in parentheses. Relative risk is also defined in the results section, but is already used earlier in the methods section.

Page 2, Line 10: confirms, not confirm.
Page 2, Line 11: Consider rewording last sentence; “these findings stress the importance”. “Clinical and pharmacological means” seems broad. There is no full stop.

3. The authors should quote more recent studies looking at trends in hospitalizations for AF. There are a number of studies that report on data after 2000, some examples are below.


4. Tables: there is no need to include both mean and median ages. The appropriate one should be used according to whether the distribution of ages is normal or not.

5. Was mortality data (inpatient and long-term) available?

6. Were temporal trends in AF admission/readmission rates assessed (i.e. did these change over the study period).

7. The authors should speculate on the reasons underlying their findings in the discussion section.

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**REVIEWER**

Lars Frost, MD, PhD, DMSc
Associate Professor
Head of Cardiology
Department of Medicine
Silkeborg Hospital
Denmark
THE STUDY

The authors counted the number of patients admitted with and/or for atrial fibrillation (AF) to Danish hospitals. They also found that AF was associated with excess subsequent hospital admissions compared to patients without AF.

I have some reservations to the findings. It is not clear to me what the comparator was, when estimating excess risk of hospitalization among patients with AF. I also had difficulties in figuring out when analyses were adjusted.

In a public health perspective I recommend the purpose of the study to be changed to: Excess risk of re-hospitalization in patients with incident AF. A nation-wide study.

The source population would then be the Danish population, i.e. all civil registration numbers in Denmark.

Age should be restricted to 40-99 years.

Design: Case-control design. Parallel cohorts.

Study sample: All subject, aged 40-99 years, with an incident AF diagnosis during the study period. Controls: 1 control for each case matched for age and sex. Each control should start “time at risk” at the index date for AF. This creates 2 parallel cohorts.

Effect measures:
1. Hazard ratio for hospitalization after the index date.
2. Cumulated hospitalizations and cumulated number of hospitalizations including counting multiple hospitalizations in AF patients versus matched population controls.

Adjust or stratify for comorbid conditions. (Information on comorbidity such as hypertension and diabetes in subjects never hospitalized can be obtained from the Danish Prescription Registry).

The sampling of controls and the statistical analyses have pit falls. Collaboration with an epidemiologist trained in case-control studies and a statistician is recommended.

Be careful not to state that hospitalization of an AF patient is an economic burden to society per se. What drives cost of AF is primarily costs due to stroke (70.000 € per stroke) (1). We do not know if the omission of a hospitalization equals the omission of oral anticoagulation.

Please discuss evidence based intervention for reduction of readmissions (and mortality), for example structured hospital service to AF patients (2).


RESULTS & CONCLUSIONS

The authors counted the number of patients admitted with and/or for atrial fibrillation (AF) to Danish hospitals. They also found that AF was associated with excess subsequent hospital admissions compared to patients without AF.
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Please discuss evidence based intervention for reduction of readmissions (and mortality), for example structured hospital service to AF patients (2).


Dr Christopher X. Wong comment #1:

Substantial improvement in writing required.

Our reply:

We have revised the manuscript carefully, and given special attention to checking for errors in spelling and grammar. The manuscript has also been edited for correct English usage by a scientific editor who is a native English speaker. All changes are tracked in the revised manuscript with marked changes; major changes, such as rephrasing of sentences, moving of paragraphs and adding references, appear in this document.

Dr Christopher X. Wong comment #2:

More recent studies relevant to paper should be included:


Our reply:

We thank the reviewer for bringing these studies to our attention. We have included the suggested references in the revised manuscript. See changes below.
Changes made to the manuscript (Introduction page 3, line 9):

“AF prevalence increases with age as shown in the Framingham Heart Study.”

has been changed to

“AF prevalence increases with age, as shown in the Framingham Heart Study and other studies. (Charlemagne A, Blacher J, Cohen A, et al.)”

Changes made to the manuscript (Introduction page 4, line 3):

We now refer to Charlemagne A, Blacher J, Cohen A, et al. after the following sentence: “The majority of direct costs related to AF are caused by hospitalisations and in-hospital procedures.”

Changes made to the manuscript (Discussion page 8, line 3):

We also refer to Charlemagne A, Blacher J, Cohen A, et al. after this sentence:

“Even though several studies have found that heart failure and ischemic heart disease to be among the most common comorbidities in AF patients, data are scarce on the relative risk of admission for these diagnoses for AF patients.”

“However, even though several studies have found that heart failure and ischemic heart disease are among the most common comorbidities in AF patients, data are scarce regarding the relative risk of admission for these diagnoses for AF patients.”
Changes made to the manuscript (Introduction page 4, line 14):

We now refer to Wong CX et al. after this sentence.

“In Denmark the incidence of AF as a hospital diagnosis more than doubled from 1980-1999 and similar trends are seen in the UK, Scotland and in Iceland.”

has been revised and is now written as follows:

“In Denmark the incidence of AF as a hospital diagnosis more than doubled from 1980-1999, and similar trends have been observed in the United States, the United Kingdom, Scotland, Australia, and Iceland.(1-6)”

Changes made to the manuscript (Discussion page 8, line 21):

We have added a sentence with reference to Wong et al.:

The increase is most obvious after 1990-1991, which may be explained by changes in the threshold for hospitalisations, as several trials were published demonstrating the efficacy of antithrombotic therapy for stroke prevention in individuals with AF.(4) A recent study supports these findings: the number of bed days associated with AF in Australian hospitals increased by 125% from 1993 through 2007. This finding reflects an even steeper 155% increase in the prevalence of AF hospitalisations and a reduction in the mean length of hospital stay for AF from 4.0 to 3.1 days.(7) Although we did not calculate the temporal pattern of length of hospital stay or the total number of bed days, these are relevant topics for further investigation.

Changes made to the manuscript (Introduction page 4 line 25):

We now refer to Wong et al. and McDonald et al. in the following sentence:

“Although several studies have explored the increase in AF-related hospital admissions,(1, 3, 6, 8-11) no nationwide study has investigated to which degree admissions as a whole are related to AF, or specified the types of diagnoses that are related to AF-associated hospital admissions.”

Dr Christopher X. Wong comment #3:

As above - manuscript requires substantial improvement in writing.

Our reply:
We agree, and we have revised the manuscript accordingly.

**Dr Christopher X. Wong comment #4:**

Similarly, a more thorough discussion of possible reasons underlying their findings needs to be included.

**Our reply:**

We acknowledge reviewer’s request to expand the discussion with likely explanations for our findings. To elaborate on the subject further, we have made the following changes and additions to the Discussion:

**Changes made to the manuscript (Discussion page 8, line 28):**

“Our study shows that AF admissions is associated with similar high cardiovascular admission rates across age groups, which means that AF in younger patients leads to ageing in terms of cardiovascular admissions.”

has been revised as follows:

“Our study shows that AF admissions are associated with similarly high cardiovascular admission rates across age groups; hence, patients 65 years of age or younger hospitalized for AF and AF patients older than 75 years of age are equally burdened by cardiovascular comorbidity. This finding may indicate that patients with early AF onset represent a group of patients with a particularly high prevalence of cardiovascular risk factors, and therefore an increased risk of subsequent cardiovascular morbidity.”

**Changes made to the manuscript (Discussion page 8, line 36):**

Non-cardiovascular admission rates varied more between age groups, which means that AF has less of an effect on non-cardiovascular comorbidity with regard to ageing. However, within each age group AF patients experienced higher rates of cardiovascular and non-cardiovascular admissions than non-AF patients. This less pronounced impact of AF on the rate of non-cardiovascular admissions most likely reflects the interplay between AF and risk factors for AF (i.e., certain non-cardiovascular admissions, such as admissions related to thyroid disease, overlap, while other non-cardiovascular admissions not associated with increased risk of AF, such as orthopaedic surgery, are not associated with AF). Furthermore, this finding may also suggest that the clinicians’ threshold for admitting
patients is influenced by the complexity of the disease entity and by additional comorbidity, such as AF.

**Dr Christopher X. Wong comment #5:**

In the present manuscript, Dr Christiansen and colleagues retrospectively analyze Danish registries to characterize admissions and re-admissions associated with atrial fibrillation over a 13 year time period. They report that patients with atrial fibrillation have a significantly higher rate of re-admission than do patients without atrial fibrillation. They also describe the variety of non-cardiovascular conditions that patients with atrial fibrillation are re-admitted with.

This is paper that adds to the body of evidence suggesting that atrial fibrillation represents an increasing burden on health care systems. Whilst the data and message is interesting, the readability and subsequent impact of the manuscript could be substantially improved by careful re-writing. The authors’ institution may have resources to be able to assist in this regard.

**Our reply:**

Thank you for the positive comments about the data and the message of the paper. We agree that the readability required improvement. In addition to substantially revising the manuscript, we took the extra step of having it edited by a scientific editor whose native language is English. Larger changes all appear in this document in the relevant paragraphs, as well as in the revised manuscript using Track Changes. Minor grammatical revisions only appear in Track Changes mode in the revised manuscript.

**Dr Christopher X. Wong comment #6:**

1. The authors should make the title more descriptive; for example, key characteristics could be included that would make it more informative – e.g. cardiovascular and non-cardiovascular hospital admissions associated with AF, nation-wide study, Denmark, trends.

**Our reply:**

Thank you for pointing this out. We have changed the title to: “Cardiovascular and non-cardiovascular hospital admissions associated with atrial fibrillation: a Danish nationwide study”.
Dr Christopher X. Wong comment #7:

2. It would be helpful if a careful review of the paper is undertaken to correct language and grammatical errors. The following are a few examples found in the abstract alone. Improving the writing would substantially improve the readability and subsequent impact of the paper.

Page 1, Line 12: AF is duplicated.

Page 1, Line 17: there is an extra space at the beginning.

Page 1, Line 27: there is a comma missing

Page 1, Line 34: cardiovascular is spelt wrong. Age- and sex- stratified should be hyphenated. Non-cardiovascular should be hyphenated.

Page 1, Line 38: as well is not required twice.

Page 2, Line 10: confirms, not confirm.

Page 2, Line 11: Consider rewording last sentence; “these findings stress the importance”. “Clinical and pharmacological means” seems broad. There is no full stop.

Our reply:

We have carefully revised the manuscript, and we believe that it has been significantly improved. We have corrected all of the above-mentioned misspellings and grammatical errors in the abstract, and the entire manuscript has been edited for clarity and English usage. Most rephrasing appears in this document and in the revised manuscript. Minor rephrasings and grammatical revisions only appear in Track Changes mode in the revised manuscript.

Dr Christopher X. Wong comment #8:

Methods: the methods section needs to state that the study looked at admissions associated with AF.

Our reply:

We acknowledge the reviewers comment and agree that this is an important point. We have therefore made the following changes to the manuscript:
Changes made to the manuscript (Methods page 4, line30):

“All data was retrieved from nationwide Danish registries. Data on admissions was found in the Danish National Patient Registry that holds information on all admissions since 1978.”

has been revised as follows:

After: This study is a nationwide registry-based cohort study investigating hospital admissions associated with AF and their influence on later cardiovascular and non-cardiovascular hospitalizations. All data was retrieved from registries on the entire Danish population. Admissions data was found in the Danish National Patient Registry, which contains information on all admissions since 1978.

Dr Christopher X. Wong comment #9:

Results: It seems odd that some of the results are presented in parentheses. Relative risk is also defined in the results section, but is already used earlier in the methods section.

Our reply:

Thank you for pointing that our results should not be presented in parentheses. We have corrected this in the revised manuscript. We also removed excess parentheses from the Results section of the Abstract (these changes appear in Track Changes mode in the revised manuscript). In the revised manuscript, relative risk is defined at its first use in the Abstract and at its first use in the main manuscript text.

Changes made to the manuscript (results page 5, line 2):

"After exclusion remained 4,602,264 individuals, 49.1% (2,259,118) were men and 50.9% (2,343,146) women. From 154,671 (3.4%) with AF, 82.3 (53.2%) were male and 72.418 (46.8%) were female, the overweight of men was significant (p <0.0001)."

has been revised as follows:

"After exclusion, 4,602,264 individuals remained: 2,259,118 (49.1%) men and 2,343,146 (50.9%) women. Of 154,671 (3.4%) with AF, 82,253 (53.2%) were male and 72,418 (46.8%) were female; men were significantly overrepresented in the study population (p<0.0001)."
Dr Christopher X. Wong comment #10:

The authors should quote more recent studies looking at trends in hospitalizations for AF. There are a number of studies that report on data after 2000, some examples are below.


Our reply:

These are indeed interesting studies, and we have included all of them in our revision. Please see our reply to Dr Christopher X. Wong comment #2 regarding specific changes made to the text.

Dr Christopher X. Wong comment #11:

Tables: there is no need to include both mean and median ages. The appropriate one should be used according to whether the distribution of ages is normal or not.

Our reply:

We agree that there is no need to include both median and mean. We have only included the median age in the revised manuscript, as the age distribution is not normal. We have made this revision in the text, as well as in Table 1. In the previously submitted manuscript, the median age referred to the median age of patients at admission; however, in the new manuscript it refers to the median age at the index date.
**Changes made to the manuscript (Table 1):**

Table 1. Baseline characteristics for patients according to Atrial Fibrillation. *= p value <.0001

<table>
<thead>
<tr>
<th></th>
<th>Overall study population (n=4,602,264)</th>
<th>Non-AF (n=4,447,593)</th>
<th>AF patients (n=154,671)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>2,270,728 (51.06%)</td>
<td>72,418 (46.82%)</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>2,176,865 (48.94%)</td>
<td>82,253 (53.18%)</td>
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<tr>
<td>Age ≤ 65</td>
<td>3,758,673</td>
<td>43,147</td>
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<tr>
<td>Age 66-75</td>
<td>312,205</td>
<td>39,033</td>
<td></td>
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<tr>
<td>Age &gt; 75</td>
<td>376,715</td>
<td>85,034</td>
<td></td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>42.88 (19.60)</td>
<td>66.98 (13.32)</td>
<td></td>
</tr>
<tr>
<td>Median age (IQR)</td>
<td>41.13 (14.08-78.21)</td>
<td>69.05 (42.88-85.38)</td>
<td></td>
</tr>
</tbody>
</table>

has been changed as follows:

Table 1 Baseline characteristics for patients according to the presence or absence of atrial fibrillation

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>Female, n (%)*</td>
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<td>312,205</td>
<td>35,126</td>
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</tr>
<tr>
<td>Age &gt; 75</td>
<td>376,715</td>
<td>80,529</td>
<td></td>
</tr>
<tr>
<td>Median age (SD)</td>
<td>41.30 (20.17)</td>
<td>75.65 (12.76)</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.0001

**Dr Christopher X. Wong comment #12:**

Was mortality data (inpatient and long-term) available?

**Our reply:**

Although it is possible to gain access to mortality data through Danish registries, we have chosen not to in the current study. The reason for this decision is that the objective of this study is to communicate data regarding the burden of the disease related to admissions, rather than the risk of death related to the disease. The inclusion of mortality data would also confuse the issue. We are presenting Poisson regression analyses, which include ALL hospitalisations, and presenting an additional analysis with a single endpoint would introduce the risk of a loss of clarity.

**Dr Christopher X. Wong comment #13:**

Were temporal trends in AF admission/readmission rates assessed (i.e. did these change over the study period).

**Our reply:**

We know from previous studies that the prevalence and incidence of atrial fibrillation is increasing (1,2). Thus, our main objective was to focus on the general healthcare burden associated with AF relative to patients without AF.
Dr Christopher X. Wong comment #14:

The authors should speculate on the reasons underlying their findings in the discussion section.

Our reply:

We agree with this suggestion and have elaborated further in the Discussion section. Revisions in the text are shown in response to comment #4.

Reviewer: Lars Frost, MD, PhD, DMSc

Associate Professor

Head of Cardiology

Department of Medicine

Silkeborg Hospital

Denmark

The authors counted the number of patients admitted with and/or for atrial fibrillation (AF) to Danish hospitals. They also found that AF was associated with excess subsequent hospital admissions compared to patients without AF.

Lars Frost, MD, PhD, DMSc comment #1:

I have some reservations to the findings. It is not clear to me what the comparator was, when estimating excess risk of hospitalization among patients with AF.
Our reply:

We acknowledge the referees request to explain the definition of the reference population more clearly. The examined study population included patients with first admission for AF during the study period, and the inclusion date of the first AF admission was defined as the inclusion (index) date. For the simplistic Kaplan-Meier curves, we provided the rest of the population with a date in the middle of the study period, excepting individuals who died before that date, and were therefore given a date at the start of the observation time. For the Poisson regression models, we entered all patients from the start of the observation period, and time was split whenever atrial fibrillation status changed and at 1-year intervals thereafter. This method resulted in a model in which the reference to the atrial fibrillation patients is all patients who do not have atrial fibrillation at the same calendar time.

Changes made to the manuscript (Methods, Statistical analysis page 5, line18):

“For univariate comparisons of admissions, AF patients were followed from an index date, which was the date of the first AF admission. As patients with AF were included throughout the study period and therefore contributed with different number of days, the index date for patients without AF was set in the middle of the study period (January 1st 2004). Patients without AF that died before the index date were followed from January 1st 1997.

For comparisons of hospitalizations per observation time and multivariable comparisons of risk of hospitalizations, all patients were followed from 1st of January 1997 and allocated to the non-AF population until a first hospitalization for AF.

Multivariate comparisons of numbers of hospitalizations were performed with Poisson regression models. Follow up ended 31st of December 2009 or at the time of the death of the patient. All hospitalizations were counted in the models.”

has been revised as follows:

“The study began on 1 January 1997. For univariate construction of Kaplan-Meier curves, AF patients were followed from an index date, which was the date of the first AF admission. Thus, patients with AF were included throughout the study period and therefore contributed different numbers of days. Therefore the index date for patients without AF was set in the middle of the study period, 1 January 2004. Patients without AF that died before 1 January 2004 were given an alternative index date of 1 January 1997.

For comparisons of hospitalisation rates and multivariable comparisons of risks of hospitalisation, all patients were followed from 1 January 1997 and allocated to the non-AF population until a first hospitalisation for AF.
Technically, time was split at the time of first admission with a diagnosis of AF, and further split at 1-year intervals. Multivariate comparisons of numbers of hospitalisations were performed using Poisson regression models. Follow-up ended 31 December 2009 or at the death of the patient. For estimation of admission rates and risk of admission, all admissions for all patients were included in the calculations.

Lars Frost, MD, PhD, DMSc comment #2:
I also had difficulties in figuring out when analyses were adjusted.

Our reply:
The univariate Kaplan-Meier curves are unadjusted. The admission rates are shown unadjusted as well as stratified for sex and age. Relative risks of admission (Table 2) are adjusted for age, sex, and year. Mean lengths of hospital stay (Table 3) are unadjusted. We have made revised the manuscript for clarification. Changes are shown below.

Changes made to the manuscript (Results page 6, line 11):
“Figure 1 shows the accumulated share of patients admitted to hospital for cardiovascular or non-cardiovascular reasons according to atrial fibrillation as well as readmissions for atrial fibrillation.” has been revised as follows:
“Figure 1 shows the unadjusted accumulated share of patients admitted to hospital for cardiovascular or non-cardiovascular reasons related to AF, as well as readmissions for AF.”

Changes made to the manuscript (Results page 6, line 20):
“Figure 2 shows the incidence rates for cardiovascular admissions and readmissions for AF each year after inclusion stratified by age groups.” has been revised as follows:
“Admission rates were adjusted for age, sex, and epoch. Figure 2 shows the admission rates for cardiovascular admissions and readmissions for AF each year after inclusion, stratified by age group.”

Lars Frost, MD, PhD, DMSc comment #3:
In a public health perspective I recommend the purpose of the study to be changed to: Excess risk of re-hospitalization in patients with incident AF. A nation-wide study.

**Our reply:**

We completely agree that this more accurately describes the objective and method. We have rephrased the objective and the design as shown below.

**Changes made to the manuscript (Abstract, Objective page 2, line 2):**

“To examine the burden of atrial fibrillation AF (AF) in terms of admissions.”

has been revised as follows:

“To examine the excess risk of re-hospitalisation in patients with incident atrial fibrillation (AF).”

**Changes made to the manuscript (Abstract, Design page 2, line 4):**

“A retrospective cohort study.”

has been revised as follows:

“A nationwide, retrospective cohort study.”

**Lars Frost, MD, PhD, DMSc comment #4:**

The source population would then be the Danish population, i.e. all civil registration numbers in Denmark.

Age should be restricted to 40-99 years.

Design: Case-control design. Parallel cohorts.

Study sample: All subject, aged 40-99 years, with an incident AF diagnosis during the study period. Controls: 1 control for each case matched for age and sex. Each control should start “time at risk” at the index date for AF. This creates 2 parallel cohorts.

Effect measures:

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2. Cumulated hospitalizations and cumulated number of hospitalizations including counting
multiple hospitalizations in AF patients versus matched population controls.

Adjust or stratify for comorbid conditions. (Information on comorbidity such as hypertension and diabetes in subjects never hospitalized can be obtained from the Danish Prescription Registry).

The sampling of controls and the statistical analyses have pit falls. Collaboration with an epidemiologist trained in case-control studies and a statistician is recommended.

Our reply:

The first part of this comment is a suggestion to restrict the included population with respect to age. We wish to present to total burden of AF in the Danish population, and are therefore somewhat unwilling to restrict the included population in this manner.

The suggestion to change to a case-control design is at odds with the purpose of the study. We wish to present the total burden, and therefore rates that include ALL hospitalisations, including repeated hospitalization of each patient, are important. This information would be completely lost if a case-control design were used. Although we agree with the reviewer that a case-control design can provide estimates of risk of first hospitalisation, we present the total risk in a cohort design, which is more appropriate for the purpose of this study.

Regarding the suggested effect measures:

- The suggestion to use hazard rates reduces the follow-up hospitalisation to the first hospitalisation, which is not the purpose of the study.
- We are indeed presenting cumulative hospitalisation rates for both AF patients and the rest of the population without AF (at the same time).
- Adjustments: We have adjusted for a wide range of diagnoses and find the included adjustments suitable for the purpose of the paper.
- The final suggestion to seek statistical advice has been followed during the development of this project.

Lars Frost, MD, PhD, DMSc comment #5:

Be careful not to state that hospitalization of an AF patient is an economic burden to society per se. What drives cost of AF is primarily costs due to stroke (70.000 € per stroke) (1). We do not know if the omission of a hospitalization equals the omission of oral anticoagulation.

Our reply:
This is a good point. We aimed to communicate that hospitalisations related to AF constitute the largest direct expense related to AF, which is a reason for us to investigate admissions. The cost associated with ischemic stroke related to low warfarin initiation in AF is also a major health care burden, and we have rephrased the following to include this point.

Changes made to the manuscript (Introduction page 4, line 3):
“The majority of costs related to AF are caused by hospitalizations and in-hospital procedures.” has been revised as follows:

The majority of direct costs related to AF are caused by hospitalisations and in-hospital procedures.(3, 4) In the United States costs directly linked to AF accumulate to 6.65 billion dollars annually, and 73% of these arise from in-patient care with AF as a primary or comorbid diagnosis.(5) Thus, the key to lessening the economic strain is to reduce the number of hospitalisations.(4) The economic burden of AF is enhanced by the cost of complications, particularly costs related to stroke.(6) (Ericson et al.)"

Lars Frost, MD, PhD, DMSc comment #6:
Please discuss evidence based intervention for reduction of readmissions (and mortality), for example structured hospital service to AF patients (2).

Our reply:

We have included the suggested reference, and we think that the manuscript has been improved. The revisions are shown below.

**Changes made to the manuscript (Clinical implications, Discussion page 9, line 2):**

“Our study is nationwide and covers all admissions in a thirteen-year period ending with the end of 2009. Data are solid and prove that AF-related costs require large amounts of health care resources. Furthermore, our study explores the diagnoses particularly frequent for AF patients and temporal patterns for admissions for AF patients versus non-AF patients. This knowledge is valuable when planning better clinical accommodation of AF patients.”

has been revised as follows:

“Our study is nationwide and covers all admissions in a 13-year period ending with the end of 2009. Data are solid and prove that AF admissions are associated with increased rates of subsequent cardiovascular and non-cardiovascular admissions. Furthermore, our study explores which diagnoses are particularly frequent for AF patients, and which temporal patterns are pertinent for admissions of AF patients versus non-AF patients. The implications of this study are that both non-cardiovascular and particularly cardiovascular admissions add to the economic burden associated with AF. Thus, the health care system should organize the care of AF patients in order to reduce rate of admissions. A recent study of outpatient care shows that nurse-led care leads to better adherence to guidelines, which significantly lowers the rates of cardiovascular admissions and cardiovascular death.(40) This finding suggests that with the current guidelines, there is the potential to reduce admission rates and cardiovascular death if the care of AF patients is reorganised in a manner that ensures better adherence to guidelines.”

We chose to move the following from the Conclusion to the Introduction (page 3 line 17) because this is a contributing factor to why we chose to perform this study, rather than a conclusion of the study.

**Changes to the manuscript:**

“In clinical trials, hospitalisation is a relevant endpoint in itself, as it provides a direct measure of costs associated with AF; however, it is also a relevant surrogate endpoint for death. The association between cardiovascular-related hospitalisations and death is also highly significant.(19) However, to
better accommodate care for AF patients, it is essential to define cardiovascular as well as non-
cardiovascular hospitalisations, and thereby understand the associated comorbidities. (19-24)

Other changes to the manuscript:

We have also chosen to move the entire Limitations and Strengths paragraph to the end of the
Discussion section. This means that the Clinical Implications paragraph directly follows the discussion
of the results in order to improve the overall flow of the Discussion section of the manuscript.

VERSION 2 – REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Dr Christopher X. Wong</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Research Fellow</td>
</tr>
<tr>
<td></td>
<td>Centre for Heart Rhythm Disorders</td>
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<td>University of Adelaide and Royal Adelaide Hospital</td>
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<tr>
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<td>11-Oct-2012</td>
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</table>

- The reviewer completed the checklist but made no further comments.

<table>
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<tr>
<th>REVIEWER</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Department of Medicine</td>
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<td></td>
<td>Silkeborg Hospital &amp; Institute of Clinical Medicine, Aarhus University Hospital</td>
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<td>Silkeborg Hospital</td>
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<td>Denmark</td>
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<tr>
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<td>17-Oct-2012</td>
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</tbody>
</table>

THE STUDY

The authors studied excess risk of re-hospitalization in patients with an incident hospital diagnosis of atrial fibrillation (AF) in Denmark. The risk reference group was subjects hospitalized for other reasons than AF.

Control of confounding.
The main results presented in the abstract were not adjusted for age and sex. The age difference between AF and non-AF patients was very large (median age 76 vs. 41 years) and is not accounted for in the main result. Please present a condensed and adjusted effect measure, for example incidence rate ratios or hazard ratios adjusted for age, sex and comorbidity. The authors used broad age band for age stratification. This potentially leads to severe residual confounding because the mean age in each age band very likely differ between AF and non-AF patients, AF patients being oldest. Please use age as a continuous variable to fully adjust for age in the main result.

Follow-up period
It seems like the authors picked 1, 3 and 6 months for the follow-up period for the abstract because results were most impressive at that point of time. Please give good arguments for not using all available information in the study, which is using the total follow-up time.
Statistics
Specify if sex and age were controlled for in Poisson regression analyses. Specify how age was entered into regression analyses.

Nomenclature
Please make a sharp distinction between first admission and re-admission. When readmission is on the agenda please use readmission throughout the manuscript including the study title. The study title could then be: CV and non-CV hospital re-admissions after a first hospital admission with AF: a Danish nationwide study.

Result section
First paragraph gives very detailed unadjusted results. These results are not interesting due to heavy confounding from age. Please shorten, and omit detailed reference to unadjusted findings.
Second paragraph: “Admission rates were adjusted for age, sex and epoch”.
This is far from the truth. Age was not fully adjusted for because the only adjustment for age was by stratification of age in broad age groups. What is epoch?

Health economics vs. national economy.
In the limitation section, please consider to comment that the excess use of hospital beds among AF patient may not imply that the total national cost from cradle to grave is higher in AF patients, because AF patients have a shorter live span due to excess risk of heart failure, dementia, and stroke which lead to excess mortality. A shorter life span will shorten the pension period.

AF patients seen as outpatients
Please add to the limitations that study findings cannot be extended to AF patients managed as outpatient. This could support arguments for establishing and testing highly specialized outpatient clinics for selected patients with AF.

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The authors studied excess risk of re-hospitalization in patients with an incident hospital diagnosis of atrial fibrillation (AF) in Denmark. The risk reference group was subjects hospitalized for other reasons than AF.

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**VERSION 2 – AUTHOR RESPONSE**

Reviewer: Dr Christopher X. Wong
Research Fellow
Centre for Heart Rhythm Disorders
University of Adelaide and Royal Adelaide Hospital

(There are no comments.)

Reviewer: Lars Frost, Associate professor, MD, PhD, DMSc
Department of Medicine
Silkeborg Hospital & Institute of Clinical Medicine, Aarhus University Hospital
Silkeborg Hospital
Denmark
Dr Lars Frost, Associate professor, MD, PhD, DMSc comment #1:

Control of confounding.

The main results presented in the abstract were not adjusted for age and sex. The age difference between AF and non-AF patients was very large (median age 76 vs. 41 years) and is not accounted for in the main result. Please present a condensed and adjusted effect measure, for example incidence rate ratios or hazard ratios adjusted for age, sex and comorbidity.

Our reply:

This is a good point and in our revision of the manuscript we have included adjusted relative risks for admission for cardiovascular and non-cardiovascular admissions in the abstract as well as in the Results section. We also included relative risk for cardiovascular and non-cardiovascular admissions in Table 2.

Changes made to the manuscript (Results section, Abstract page 6 line 5):

“Of 10,779,945 hospital admissions, 729,088 (6.8%) were associated with AF. Admissions for cardiovascular reasons after 1, 3, and 6 months occurred for 6.0%, 14.3%, and 28.4% of AF patients versus 0.2%, 0.6%, and 1.8% of non-AF patients. Admissions for non-cardiovascular reasons after 1, 3, and 6 months comprised 6.8%, 16.1%, and 33.3% of AF patients and 1.2, 3.2%, and 9.7% of non-AF patients. AF is associated with similar cardiovascular admission rates across all age groups, while non-cardiovascular admission rates are higher in older patients. Within each age group and for both cardiovascular and non-cardiovascular admissions, AF was associated with higher rates of admission. For all diagnoses, AF patients had a higher RR of admission and a longer duration of admissions.”

Was changed to

“Of 10,779,945 hospital admissions, 729,088 (6.8%) were associated with AF. Admissions for cardiovascular reasons after 1, 3, and 6 months occurred for 6.0%, 14.3%, and 28.4% of AF patients versus 0.2%, 0.6%, and 1.8% of non-AF patients. Admissions for non-cardiovascular reasons after 1, 3, and 6 months comprised 6.8%, 16.1%, and 33.3% of AF patients and 1.2, 3.2%, and 9.7% of non-AF patients. When stratified for age, AF was associated with similar cardiovascular admission rates across all age groups, while non-cardiovascular admission rates were higher in older patients. Within each age group and for both cardiovascular and non-cardiovascular admissions, AF was associated with higher rates of admission. When adjusted for age, sex and time period patients with AF had a relative risk of 8.6 (95 % confidence interval (CI) 8.5-8.6) for admissions for cardiovascular reasons and 4.0 (95 % CI 4.0-4.0) for admission for non-cardiovascular reasons.”

Changes made to the manuscript (Results, Relative risk of admission and length of hospital stay page 7 line 6)
For all diagnoses, AF patients were more likely to be admitted to hospital than patients without AF. Overall, patients with AF had a RR of admission for cardiovascular reasons of 8.6 (95% CI 8.5-8.6 p < 0.001) and 4.0 (4.0-4.0 p < 0.001) for non-cardiovascular reasons.

**Changes made to the manuscript (Table 2)**

**Table 2 Relative risk (RR) and 95% confidence interval (95% CI) for admissions for most common diagnoses adjusted for sex, age, and year**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>RR (95% CI)</th>
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<tbody>
<tr>
<td>Cardiovascular diagnoses</td>
<td>8.6 (8.5-8.6)</td>
</tr>
<tr>
<td>Non-cardiovascular diagnoses</td>
<td>4.0 (4.0-4.0)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>20.1 (19.8-20.3)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>13.9 (13.7-14.1)</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>11.5 (11.1-11.8)</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.2 (4.1-4.2)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>11.0 (10.9-11.1)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>6.8 (6.8-6.8)</td>
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<tr>
<td>Diabetes</td>
<td>5.7 (5.7-5.8)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>5.2 (5.2-5.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5.0 (5.0-5.1)</td>
</tr>
<tr>
<td>Embolus</td>
<td>5.0 (4.8-5.2)</td>
</tr>
<tr>
<td>Syncope</td>
<td>4.3 (4.2-4.4)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4.1 (4.1-4.1)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>3.8 (3.7-3.8)</td>
</tr>
<tr>
<td>Other</td>
<td>3.2 (3.2-3.2)</td>
</tr>
</tbody>
</table>

The term arrhythmia refers to arrhythmias other than atrial fibrillation (AF). AF patients had higher risks for all diagnoses. For all RR, p < 0.0001.

**Dr Lars Frost, Associate professor, MD, PhD, DMSc comment #2:**

The authors used broad age band for age stratification. This potentially leads to severe residual confounding because the mean age in each age band very likely differ between AF
and non-AF patients, AF patients being oldest. Please use age as a continuous variable to fully adjust for age in the main result.

Our reply:

Mean age for age groups consisting of patients >75 years and 65-75 years are comparable. However, as the mean age in the age group with age <65 years differed between the groups with and without AF, we chose to change the age band to ≤50 years and >50-65 years, which resulted in comparable mean ages in the AF and non-AF groups in the age group >50-65 years. We made following additions to Table 1 to illustrate this and changed Figures 2-7 accordingly (Figures not shown in this document).

Changes made to the manuscript (Table 1)

<table>
<thead>
<tr>
<th></th>
<th>Overall study population (n=4,602,264)</th>
<th>Non-AF (n=4,447,593)</th>
<th>AF patients (n=154,671)</th>
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</thead>
<tbody>
<tr>
<td>Female, n (%)*</td>
<td>2,270,728 (51.06%)</td>
<td>72,418 (46.82%)</td>
<td></td>
</tr>
<tr>
<td>Male, n (%)*</td>
<td>2,176,865 (48.94%)</td>
<td>82,253 (53.18%)</td>
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<tr>
<td>Age &lt;65 years</td>
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<td>Age 66-75 years</td>
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<td>Age &gt;75 years</td>
<td>376,715</td>
<td>80,529</td>
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</tr>
<tr>
<td>Median age (SD)</td>
<td>41.30 (20.17)</td>
<td>75.65 (12.76)</td>
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</table>

*p<0.0001

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<td>75.65 (12.76)</td>
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<tr>
<td>Median age for age ≤50 (SD)</td>
<td>31.05 (11-09)</td>
<td>43.50 (7.23)</td>
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<tr>
<td>Median age for age &gt;50-65</td>
<td>56.05 (4.31)</td>
<td>59.68 (4.07)</td>
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<tr>
<td>Median age for age &gt;65-75</td>
<td>69.71 (2.87)</td>
<td>70.58 (2.87)</td>
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<tr>
<td>Median age for age &gt;75</td>
<td>82.05 (5.55)</td>
<td>82.71 (5.37)</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.0001

Dr Lars Frost, Associate professor, MD, PhD, DMSc comment #3:

Follow-up period

It seems like the authors picked 1, 3 and 6 months for the follow-up period for the abstract because results were most impressive at that point of time. Please give good arguments for not using all available information in the study, which is using the total follow-up time.

Our reply:

As patients are included continuously, follow-up time varies between extremely short to approximately ten years.

We gave results from 1, 3 and 6 months for the follow-up period to give a broad view of the impact of the AF diagnosis on risk of admission. Friberg et al have taken a similar approach (Friberg L, Rosenqvist M. Cardiovascular hospitalization as a surrogate endpoint for mortality in studies of atrial fibrillation: report from the Stockholm Cohort Study of Atrial Fibrillation. Europace. 2011;13:626-33). However, we are very much willing to present data from the total follow-up time in the abstract as already presented in the Results section if this is advised.

Dr Lars Frost, Associate professor, MD, PhD, DMSc comment #4:

Statistics

Specify if sex and age were controlled for in Poisson regression analyses. Specify how age was entered into regression analyses.

Our reply:

Yes, sex and age were controlled for in the Poisson regression. Age was entered in 5-year intervals.

Furthermore the time period was subdivided into the following four time periods from 1997-June 30
changes made to the manuscript (methods, statistical analysis page 5 line 28) 

“multivariate comparisons of numbers of hospitalisations were performed using poisson regression models”

was changed to

“multivariate comparisons of numbers of hospitalisations were performed using poisson regression models adjusted for sex, age and time periods. The study period was divided in four time periods to adjust for improvement or changes in care. Age was entered in the model in five-year intervals.”

Dr Lars Frost, Associate professor, MD, PhD, DMSc comment #5:

Nomenclature

Please make a sharp distinction between first admission and re-admission. When readmission is on the agenda please use readmission throughout the manuscript including the study title. The study title could then be: CV and non-CV hospital re-admissions after a first hospital admission with AF: a Danish nationwide study.

Our reply:

We have in our revision of the manuscript made sure that readmissions for AF are referred to as such. All patients in the AF group are defined by having an index AF admissions, thus in a sense all subsequent admissions are ‘readmissions’ although not necessarily for the same diagnosis (AF). However, we find that the language becomes artificial and suffers a loss of fluency if we compare ‘readmissions’ in the AF group with ‘admissions’ in the non-AF group, and have chosen to refer to subsequent admissions as ‘admissions’ both in the AF and the non-AF group. Nevertheless, we are very much willing to listen to the editor’s advice on this matter.

Dr Lars Frost, Associate professor, MD, PhD, DMSc comment #6:

Result section

First paragraph gives very detailed unadjusted results. These results are not interesting due to heavy confounding from age. Please shorten, and omit detailed reference to unadjusted findings.

Our reply:
We agree with the reviewer that the median age between the group with and without AF differ a lot for the population overall as well as for the age group of patients < 65 years. We split the lower age group to two groups of patients aged ≤50 years and patients >50-65 years. We made following additions to the manuscript to stress the fact that we have stratified in age groups as well as changed the figure 2-7 and text accordingly.

Changes made to the manuscript (page 6 line 1)

“Baseline characteristics are shown in Table 1. Data from 4,614,807 subjects were initially included. Of these, data from 12,543 patients were excluded because of a previous diagnosis of AF. After exclusion, 4,602,264 individuals remained: 2,259,118 (49.1%) men and 2,343,146 (50.9%) women. Of 154,671 (3.4%) with AF, 82,253 (53.2%) were male and 72,418 (46.8%) were female; men were significantly overrepresented in the study population (p<0.0001). The median age was 41.3 years (SD 20.17) for individuals without AF and 72.65 years (SD 12.76) for individuals with AF.”

was changed to

“Baseline characteristics are shown in Table 1. Data from 4,614,807 subjects were initially included. Of these, data from 12,543 patients were excluded because of a previous diagnosis of AF. The overall median age was 41.3 years (SD 20.17) for individuals without AF and 72.65 years (SD 12.76) for individuals with AF, whereas the mean age in age groups >50-65, 66-75 and >75 years were comparable (Table 1).”

Changes made to the manuscript (Results page 6 line 22)

“The first year, the rate was slightly higher for patients of 65 years or younger”

Was changed to

“The first year, the rate was slightly higher for patients aged 50-65 years;”

(Results page 6 line 24)

“For patients aged 66-75 years and older than 75 years without AF, the rate of admission increased slightly during the 6-year follow-up; in comparison, the admission rate remained stable during follow-up for non-AF patients 65 years of age or younger.”

Was changed to

“For patients aged >65-75 years and older than 75 years without AF, the rate of admission increased slightly during the 6-year follow-up; in comparison, the admission rate remained stable during follow-up for non-AF patients aged 50-65 years.”

(Results page 6 line 35)

“For non-AF patients, admission rates increased for age groups 66-75 years and >75 years throughout the study period, but remained stable for patients of 65 years of age or younger.”
“For non-AF patients, admission rates increased for age groups >65-75 years and >75 years throughout the study period, but remained stable for patients aged 50-65 years.”

(Discussion, Comorbidity and length of hospital stay page 8 line 35)

“Our study shows that AF admissions are associated with similarly high cardiovascular admission rates across age groups; hence, patients 65 years of age or younger hospitalized for AF and AF patients older than 75 years of age are equally burdened by cardiovascular comorbidity.”

Was changed to

“Our study shows that AF admissions are associated with similarly high cardiovascular admission rates across age groups; hence, patients aged >50-65 years hospitalized for AF and AF patients older than 75 years of age are equally burdened by cardiovascular comorbidity.”

Dr Lars Frost, Associate professor, MD, PhD, DMSc comment #7:

Second paragraph: “Admission rates were adjusted for age, sex and epoch”.

This is far from the truth. Age was not fully adjusted for because the only adjustment for age was by stratification of age in broad age groups. What is epoch?

Our reply:

We agree that this should be rephrased to ensure that the meaning is accurate. We have changed the manuscript as shown below. We divided the study period into four time periods to adjust for changes in care (see also reply to Dr Lars Frost, Associate professor, MD, PhD, DMSc comment #4).

Changes made to the manuscript page 6 line 19)

“Admission rates were adjusted for age, sex and epoch”

was changed to

“Admission rates were stratified for age and sex.”

Dr Lars Frost, Associate professor, MD, PhD, DMSc comment #8:

Health economics vs. national economy.

In the limitation section, please consider to comment that the excess use of hospital beds among AF patient may not imply that the total national cost from cradle to grave is higher in AF patients, because AF patients have a shorter live span due to excess risk of heart failure, dementia, and stroke which lead to excess mortality. A shorter life span will shorten the pension period.
Our reply:

We included this point in our Limitations and strengths section.

**Changes made to the manuscript (Discussions, Limitations and strengths page 9 line 35)**

“The economic burden associated with AF does not rely on admissions alone. A shorter life span of patients with AF due to increased mortality related to heart failure, dementia, and stroke will shorten the pension period and thus reduce expenses related to AF patients. Thus, more aspects need to be considered, when analysing the economic burden of AF. ”

**Dr Lars Frost, Associate professor, MD, PhD, DMSc comment #9:**

**AF patients seen as outpatients**

Please add to the limitations that study findings cannot be extended to AF patients managed as outpatient. This could support arguments for establishing and testing highly specialized outpatient clinics for selected patients with AF.

Our reply:

This is an important limitation and we have made following addition our revision.

**Changes made to the manuscript (Discussions, Limitations and strengths page 9 line 26)**

We added the following sentence (highlighted in blue):

“The AF group in this study only counted patients who were diagnosed with AF during an admission that lasted 24 h or longer. This criterion means that patients who have been diagnosed at their general practitioner’s office or in an outpatient clinic do not contribute to data or are misclassified (i.e., some cases do in fact have AF, but are registered without AF in the hospital setting). This situation could lead to an underestimation of the burden of AF or an incorrect index date, as well as an overestimation of comorbidities and thromboembolic risk, if only the sickest AF patients are registered.(41) Also, the study findings cannot be extended to AF patients managed in outpatient clinics.”
| REVIEWER | Lars Frost, Associate Professor, MD, PhD, DMSc  
          | Head of Cardiology  
          | Department of Medicine  
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          | Denmark |
|----------|--------------------------------------------------|
| REVIEW RETURNED | 06-Dec-2012 |

- The reviewer completed the checklist but made no further comments.