

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Comparative thromboembolic risk in atrial fibrillation with and without a secondary precipitant– a Danish nationwide cohort study
<b>AUTHORS</b>	Gundlund, A; Kümier, Thomas; Bonde, Anders; Butt, Jawad; Gislason, Gunnar; Torp-Pedersen, Christian; Køber, Lars; Olesen, Jonas; Fosbøl, Emil

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Prof John D Horowitz University of Adelaide Australia
<b>REVIEW RETURNED</b>	03-Jan-2019

<b>GENERAL COMMENTS</b>	<p>This is a very interesting manuscript, centred on the possibility that atrial fibrillation should be categorised as either "primary" or "secondary", depending on whether or not there is an obvious precipitant. This distinction is questionable: after all, there is always a precipitant, at least from a theoretical point of view. The authors need to concede that their bases for categorisation are somewhat arbitrary, and that, biochemically speaking, AF arises essentially because of inflammatory activation within atria, largely reflecting neutrophil-derived release/activation of myeloperoxidase, as well as impairment of nitric oxide availability/signalling. However, the main point made by the investigation is that thrombo-embolic risk is substantial for secondary AF, so that AF in the context of acute infection (the main form of "secondary" AF studied) should not be considered in any way a low-risk condition. This is quite important.</p> <p>In this context, the authors may be interested in the work of Procter et al, showing that acute onset of AF (often in patients with concomitant infection) have impaired nitric oxide signaling, and that the standard scoring systems for thrombo-embolic risk in patients with AF partially parallel plasma concentrations of the NO synthase inhibitor ADMA (Horowitz et al, JACC 2018).</p> <p>From a more practical point of view, limitations to the study include not only the lack of mechanistic data (eg measurement of blood glucose levels, myeloperoxidase and ADMA levels), but also the fact that the "secondary AF" data are substantially driven by cases with concomitant infections. Furthermore, not all patients were anticoagulated, and not all anticoagulants are equi-effective.</p>
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<b>REVIEWER</b>	Eitaro Kodani Department of Internal Medicine and Cardiology, Nippon Medical School Tama-Nagayama Hospital, Tokyo, Japan.
<b>REVIEW RETURNED</b>	19-Jan-2019

<b>GENERAL COMMENTS</b>	<p>This protocol manuscript by Gundlaud al. focused on the risk of thromboembolic events and death in patients with any trigger (defined as secondary AF including alcohol intoxication, thyrotoxicosis, myocardial infarction, surgery, and infection) and without it (defined as primary AF). Authors demonstrated the secondary AF was associated with the same thromboembolic risk as primary AF. Since physicians generally hesitate to prescribe anticoagulant to the patients with secondary AF, the concept of this study is understandable. Although overall manuscript seems written well, this reviewer has several questions for statistical methods. Authors may want to consider several issues as below.</p> <p>Major comments;</p> <p>1) It is unclear whether the main focus of this study was the comparison between primary AF and secondary AF or the effect of oral anticoagulant (OAC). Figure 2 did not show the comparison between primary AF and secondary AF.</p> <p>2) Although secondary outcome was defined as AF re-hospitalization and death, results showed only death. There was no results of re-hospitalization.</p> <p>3) Matching procedure was undescribed. Did authors use propensity score matching?</p> <p>4) Authors should clarify the definition of the crude model and adjusted model. Since both the matching and the variable adjustment were performed in this study, it difficult to understand it. In general, after matching two groups, no further adjustment is required. Was multivariate adjustment performed in the matched population? In other words, did the crude model mean the unadjusted model in unmatched population or in the matched population without further adjustment? Did the adjustment model mean the multivariate adjustment model in unmatched population or the further adjustment in the matched population?</p> <p>Minor comments;</p> <p>1) Abbreviations of AF and OAC should be described using full spelling at the first time of use, even in the abstract.</p> <p>2) Are the terms of “primary AF” and “secondary AF” popular?</p>
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<b>REVIEWER</b>	Keitaro Senoo Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Department of Cardiac Arrhythmia, JAPAN
<b>REVIEW RETURNED</b>	22-Jan-2019

<b>GENERAL COMMENTS</b>	<p>Authors investigated long-term outcomes in patients with secondary and primary AF, in which they pointed out two major findings.</p> <p>First, different subtypes of secondary AF were in general associated with the same thromboembolic risk as primary AF. Second, OAC therapy vs. no OAC therapy were associated with no significant risk-reduction for patients with AF secondary to almost all precipitants.</p> <p>I agree with first point you mentioned, but second point needs to be corrected.</p>
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	<p>First, different subtypes of secondary AF were in general associated with the same thromboembolic risk as primary AF.  &gt;&gt; I'm very surprised by this unexpected result that there were similar thromboembolism rate among secondary and primary AF although there was less AF re-hospitalization in secondary AF after matching OAC use.  It is a very important result and I believe this result will cast a stone in the future discussion.</p> <p>Second, OAC therapy vs. no OAC therapy were associated with no significant risk-reduction for patients with AF secondary to almost all precipitants according to Figure 2A.  &gt;&gt; This might be affected by the persistence of OAC and TTR (if warfarin users).  In general, secondary AF rarely recur after controlling precipitants. This was supported from less AF re-hospitalization in secondary AF in your result.  Therefore, physicians often hesitate to prescribe OAC during follow-up.  Even though physicians give OAC for patients at the index date (so, categorized as OAC+ group), some of them tend to discontinue OAC because of the absence of AF.  Did you chase the persistence of OAC during follow-up in OAC+ group?</p> <p>In addition to that, almost all anticoagulated patients must be warfarin users in this era.  Warfarin control, such as TTR, could affect validity of comparison of thromboembolism risks between OAC users and non OAC users.  Could you discuss this matter on your manuscript?</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Prof John D Horowitz

Institution and Country: University of Adelaide

Australia

This is a very interesting manuscript, centered on the possibility that atrial fibrillation should be categorised as either "primary" or "secondary", depending on whether or not there is an obvious precipitant. This distinction is questionable: after all, there is always a precipitant, at least from a theoretical point of view. The authors need to concede that their bases for categorisation are somewhat arbitrary, and that, biochemically speaking, AF arises essentially because of inflammatory activation within atria, largely reflecting neutrophil-derived release/activation of myeloperoxidase, as well as impairment of nitric oxide availability/signalling.

However, the main point made by the investigation is that thrombo-embolic risk is substantial for secondary AF, so that AF in the context of acute infection (the main form of "secondary" AF studied) should not be considered in any way a low-risk condition. This is quite important.

In this context, the authors may be interested in the work of Procter et al, showing that acute onset of AF (often in patients with concomitant infection) have impaired nitric oxide signaling, and that the standard scoring systems for thrombo-embolic risk in patients with AF partially parallel plasma concentrations of the NO synthase inhibitor ADMA (Horowitz et al, JACC 2018).

Answer: We agree that the findings in this study are very important, since AF during an infection in general is considered a rather benign condition. Thank you for making us aware of the studies mentioned. We have added a discussion of the subjects suggested:

Changes made to the manuscript (p. 6, line 2-4):

The etiology of atrial fibrillation (AF) remains partly unknown. Studies have shown, that an inflammatory reaction inside the atria always precipitate AF.(1) However, in clinical practice, AF may occur as an isolated event or together with a secondary precipitant

And (p. 16, line 5-9):

Previous studies have shown an association between an impaired platelet nitric oxide response and recent onset AF and that disturbances in nitric oxide function are associated with outcomes (including thromboembolic events, bleeding events, and death) in AF. Unfortunately, we did not have any information on nitric oxide levels in our study cohort.(27,28)

From a more practical point of view, limitations to the study include not only the lack of mechanistic data (eg measurement of blood glucose levels, myeloperoxidase and ADMA levels), but also the fact that the "secondary AF" data are substantially driven by cases with concomitant infections. Furthermore, not all patients were anticoagulated, and not all anticoagulants are equi-effective.

Answer: We agree with the reviewer on most points. However, all results are stratified according to type of secondary AF, and therefore we cannot agree that secondary AF are driven by cases with concomitant infection. We have added the following to the limitation section:

Changes made to the manuscript (p. 16, line 4-5):

Also, no data were available with regard to the physicians' considerations when choosing between OAC therapy and no OAC therapy, patients compliance, and measurements of international normalized ratio (INR) and time in therapeutic range for warfarin users.

Reviewer: 2

Reviewer Name: Eitaro Kodani

Institution and Country: Department of Internal Medicine and Cardiology, Nippon Medical School Tama-Nagayama Hospital, Tokyo, Japan.

This protocol manuscript by Gundlaud al. focused on the risk of thromboembolic events and death in patients with any trigger (defined as secondary AF including alcohol intoxication, thyrotoxicosis, myocardial infarction, surgery, and infection) and without it (defined as primary AF). Authors demonstrated the secondary AF was associated with the same thromboembolic risk as primary AF. Since physicians generally hesitate to prescribe anticoagulant to the patients with secondary AF, the concept of this study is understandable. Although overall manuscript seems written well, this reviewer has several questions for statistical methods. Authors may want to consider several issues as below.

Major comments;

1) It is unclear whether the main focus of this study was the comparison between primary AF and secondary AF or the effect of oral anticoagulant (OAC). Figure 2 did not show the comparison between primary AF and secondary AF.

Answer: The main focus of this study is the comparison between primary and secondary AF and not the effect of OAC. We have changed the order of the figures to make this more clear. Now Figure 2 is the figure showing Number of events, incidence rates, and crude and adjusted hazard ratios of long-

term outcomes in patients with secondary vs. primary AF and Figure 3 is the figure showing Cumulative incidence of long-term outcomes by secondary precipitant and OAC therapy at the index date.

2) Although secondary outcome was defined as AF re-hospitalization and death, results showed only death. There was no results of re-hospitalization.

Answer: We have added the results of AF re-hospitalization to Figure 2.

Changes made to the manuscript (p. 12, line 4-6):

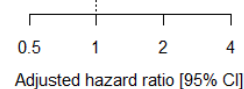
All subgroups of AF with a secondary precipitant were associated with a significantly lower risk of AF re-hospitalization compared with AF without a secondary precipitant (Figure 2). In multivariable Cox regression models the risk of AF re-hospitalizations in patients with secondary vs. primary AF were: HR 0.40, 95% confidence interval 0.28-0.58 (alcohol intoxication), HR 0.66, 95% CI 0.59-0.73 (thyrotoxicosis), HR 0.73, 95% CI 0.65-0.82 (myocardial infarction), HR 0.52, 95% CI 0.48-0.57 (surgery), HR 0.61, 95% CI 0.59-0.64 (infection), and HR 0.46, 95% CI 0.42-0.51 (>1 precipitant)).

And:

Figure 2: Number of events, incidence rates, and crude and adjusted hazard ratios of long-term outcomes in patients with secondary vs. primary AF according to secondary precipitant and OAC therapy at the index date

Groups	Events	Person Years	IR*	Crude hazard ratio [95% CI**]	Adjusted hazard ratio [95% CI**]
<b>Thromboembolic event, OAC therapy</b>					
Primary AF	819	33939	24.1	1.00 [1.00-1.00]	1.00 [1.00, 1.00]
Secondary AF					
Alcohol intoxication	<5	<150	17	1.16 [0.07-18.59]	1.00 [1.00, 1.00]
Thyrotoxicosis	75	4267	17.6	0.88 [0.64-1.21]	0.92 [0.67, 1.26]
Myocardial infarction	130	4051	32.1	0.88 [0.70-1.12]	0.98 [0.69, 1.41]
Surgery	103	3342	30.8	1.42 [1.06-1.91]	1.18 [0.86, 1.62]
Infection	544	16710	32.6	1.39 [1.22-1.58]	1.35 [1.19, 1.54]
>1 precipitant	72	3126	23	1.07 [0.77-1.48]	1.05 [0.72, 1.53]
<b>Thromboembolic event, no OAC therapy</b>					
Primary AF	3464	92142	37.6	1.00 [1.00-1.00]	1.00 [1.00, 1.00]
Secondary AF					
Alcohol intoxication	23	1051	21.9	1.60 [0.84-3.05]	1.53 [0.78, 2.99]
Thyrotoxicosis	121	5166	23.4	0.79 [0.62-1.00]	0.78 [0.61, 0.99]
Myocardial infarction	399	10221	39	1.01 [0.88-1.16]	1.10 [0.90, 1.34]
Surgery	427	11891	35.9	1.02 [0.89-1.16]	0.99 [0.86, 1.13]
Infection	1818	38270	47.5	1.17 [1.10-1.25]	1.11 [1.04, 1.18]
>1 precipitant	381	10518	36.2	1.02 [0.89-1.17]	1.04 [0.90, 1.21]
<b>AF re-hospitalization</b>					
Primary AF	10777	100840	106.9	1.00 [1.00-1.00]	1.00 [1.00, 1.00]
Secondary AF					
Alcohol intoxication	53	1051	50.4	0.43 [0.31-0.60]	0.40 [0.28, 0.58]
Thyrotoxicosis	667	7508	88.8	0.66 [0.60-0.73]	0.66 [0.59, 0.73]
Myocardial infarction	977	12303	79.4	0.72 [0.66-0.78]	0.73 [0.65, 0.82]
Surgery	791	13825	57.2	0.51 [0.47-0.56]	0.52 [0.48, 0.57]
Infection	3300	49119	67.2	0.61 [0.58-0.64]	0.61 [0.59, 0.64]
>1 precipitant	634	12670	50	0.48 [0.43-0.52]	0.46 [0.42, 0.51]
<b>Death, OAC therapy</b>					
Primary AF	2382	35103	67.9	1.00 [1.00-1.00]	1.00 [1.00, 1.00]
Secondary AF					
Alcohol intoxication	5	120	41.7	1.71 [0.41-7.14]	1.00 [1.00, 1.00]
Thyrotoxicosis	208	4369	47.6	0.92 [0.77-1.12]	0.94 [0.78, 1.14]
Myocardial infarction	398	4244	93.8	1.18 [1.02-1.37]	1.04 [0.84, 1.28]
Surgery	304	3477	87.4	1.45 [1.22-1.72]	1.29 [1.07, 1.56]
Infection	2098	17295	121.3	1.73 [1.62-1.85]	1.64 [1.53, 1.76]
>1 precipitant	291	3217	90.5	1.41 [1.18-1.68]	1.30 [1.06, 1.59]
<b>Death, no OAC therapy</b>					
Primary AF	11350	96757	117.3	1.00 [1.00-1.00]	1.00 [1.00, 1.00]
Secondary AF					
Alcohol intoxication	96	1094	87.8	3.04 [2.06-4.48]	3.37 [2.23, 5.09]
Thyrotoxicosis	461	5294	87.1	1.06 [0.93-1.21]	1.07 [0.94, 1.22]
Myocardial infarction	1674	10796	155.1	1.37 [1.27-1.47]	1.40 [1.26, 1.56]
Surgery	1793	12377	144.9	1.41 [1.31-1.51]	1.25 [1.17, 1.35]
Infection	9610	39883	241	1.80 [1.75-1.86]	1.66 [1.61, 1.71]
>1 precipitant	2073	10928	189.7	1.77 [1.66-1.90]	1.66 [1.55, 1.79]

\* Incidence rate per 1000 person years  
\*\* Confidence interval



3) Matching procedure was undescribed. Did authors use propensity score matching?

Answer: The matching procedure used was incidence density sampling, matching on specific matching criteria. We did not use propensity score matching. The two groups were matched according to their age at the AF diagnosis, the calendar year at the AF diagnosis, their sex, and their CHA<sub>2</sub>DS<sub>2</sub>-VASc group. We have tried to make this more clear in the manuscript.

Changes made to the manuscript (p. 8, line 3-9):

Patients with AF with and without a secondary precipitant were matched 1:1 by incidence density sampling according to age (allowing a difference of up to two years), sex, calendar year (allowing a difference up to two years), CHA<sub>2</sub>DS<sub>2</sub>-VASc group (0, 1-2, >2) and OAC therapy status at the index date. Consequently, each case was matched with a control diagnosed at the same time and in the same age with AF. Further, the control had the same sex and was categorized in the same CHA<sub>2</sub>DS<sub>2</sub>-VASc group as the case.

4) Authors should clarify the definition of the crude model and adjusted model. Since both the matching and the variable adjustment were performed in this study, it difficult to understand it. In general, after matching two groups, no further adjustment is required. Was multivariate adjustment performed in the matched population? In other words, did the crude model mean the unadjusted model in unmatched population or in the matched population without further adjustment? Did the adjustment model mean the multivariate adjustment model in unmatched population or the further adjustment in the matched population?

Answer: Thanks a lot. We could have explained this better. All analyses were performed on the matched population. The crude models were without any adjustments while the multivariable models adjusted for several other potential confounders than the matching criteria (please see below for full list of covariates in the model).

Changes made to the manuscript (p. 9, line 5-12):

Cox regression analyses were performed to calculate hazard ratios (HR) of long-term outcomes in patients with AF with and without a secondary precipitant according to OAC therapy at the index date. All analyzes were performed on the matched population. The multivariate models were adjusted for other potential confounders than the matching criteria (incl. comorbidities at the index date (incl. peripheral artery disease, heart failure, hypertension, prior thromboembolic event, ischemic heart disease, chronic kidney disease, diabetes, prior bleeding event, cancer) and antiarrhythmic and rate-controlling therapy during the blanking period (amiodarone, digoxin, flecainide)).

Minor comments;

1) Abbreviations of AF and OAC should be described using full spelling at the first time of use, even in the abstract.

Answer: Thanks, this has been corrected.

2) Are the terms of “primary AF” and “secondary AF” popular?

Answer: This is a good point. The terms are “popular”, but are not used in atrial fibrillation guidelines. We have changed the naming of the groups to patients with atrial fibrillation with and without a secondary precipitant. We hope the reviewer finds this more suitable. The changes are made throughout the entire manuscript as well as in tables and figures. Hence, they are not shown here.

Reviewer: 3

Reviewer Name: Keitaro Senoo

Institution and Country: Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Department of Cardiac Arrhythmia, JAPAN

Authors investigated long-term outcomes in patients with secondary and primary AF, in which they pointed out two major findings.

First, different subtypes of secondary AF were in general associated with the same thromboembolic risk as primary AF.

Second, OAC therapy vs. no OAC therapy were associated with no significant risk-reduction for patients with AF secondary to almost all precipitants.

I agree with first point you mentioned, but second point needs to be corrected.

First, different subtypes of secondary AF were in general associated with the same thromboembolic risk as primary AF.

>> I'm very surprised by this unexpected result that there were similar thromboembolism rate among secondary and primary AF although there was less AF re-hospitalization in secondary AF after matching OAC use.

It is a very important result and I believe this result will cast a stone in the future discussion.

Answer: Thanks a lot, and we definitely agree.

Second, OAC therapy vs. no OAC therapy was associated with no significant risk-reduction for patients with AF secondary to almost all precipitants according to Figure 2A.

>> This might be affected by the persistence of OAC and TTR (if warfarin users).

In general, secondary AF rarely recur after controlling precipitants. This was supported from less AF re-hospitalization in secondary AF in your result.

Therefore, physicians often hesitate to prescribe OAC during follow-up.

Even though physicians give OAC for patients at the index date (so, categorized as OAC+ group), some of them tend to discontinue OAC because of the absence of AF.

Did you chase the persistence of OAC during follow-up in OAC+ group?

Answer: Dr. Senoo has some good points. Unfortunately, we did not have any information about patient compliance and INR/TTR. Information on OAC use were collected from dispensed prescriptions, and we had information about type of drug, dosage, and package size. We have added a sensitivity analysis, not stratifying the patients in those initiated on OAC/no OAC, but instead adjusting for OAC therapy as a time-dependent variable and thereby taking discontinuations and new initiations into account.

Changes made to the manuscript (p. 9, line 21-23 to p. 10, line 2):

Other analyses

Analyses of long-term outcomes were also performed on a non-matched population including all patients available before the matching (Figure 1). To account for changes in OAC therapy status over time, we did a sensitivity analysis not stratifying patients with regard to their OAC therapy status at the index date, but instead adjusting for OAC therapy status as a time-dependent variable. Consequently, new initiations and discontinuations were taking into account. The method used, has been used and described previously (14-16).

And (p. 12, line 21 to p. 13, line 6):

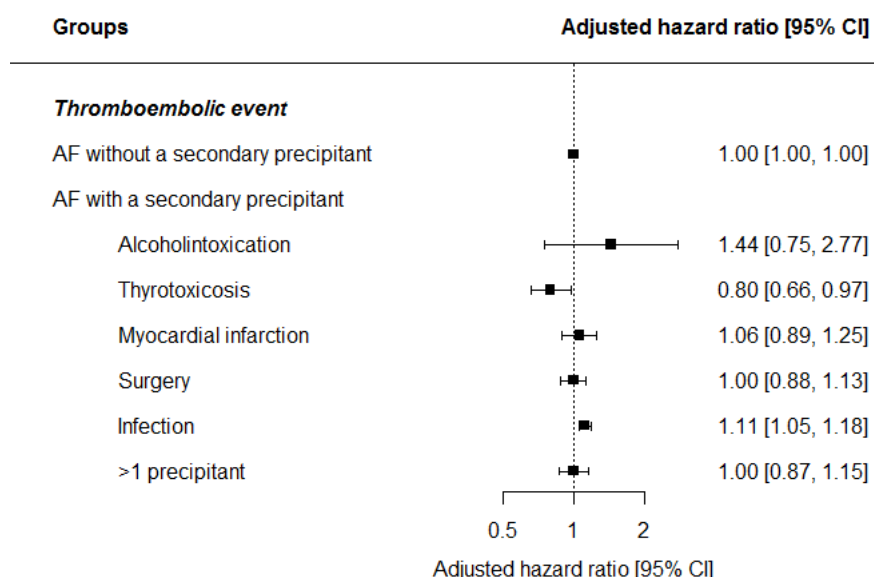
### Other analyses

The long-term risk of thromboembolic events for patients with AF with and without a secondary precipitant in the non-matched population were comparable to the risks found in the main analysis, except that AF with thyrotoxicosis reached statistical significance and hence was associated with a significantly lower risk of thromboembolic events (HR 0.75, 95% CI 0.60-0.95 for those initiated on OAC therapy and HR 0.77, 95% CI 0.64-0.92 for those not initiated on OAC therapy). Further, among those initiated on OAC therapy, AF after surgery was associated with an increased risk of thromboembolic events (HR 1.23, 95% CI 1.01-1.50).

The sensitivity analysis, adjusting for OAC therapy status as a time-dependent variable, revealed result similar to those found in the main analysis (Online Figure 1).

And:

Online Figure 1: Adjusted Hazard ratios of long-term outcomes in patients with AF with and without a secondary precipitant. Adjustments: age groups, peripheral artery disease, heart failure, hypertension, prior thromboembolic event, ischemic heart disease, chronic kidney disease, diabetes, prior bleeding event, cancer, antiarrhythmic therapy (amiodarone, digoxin, flecainide) at the index date and OAC therapy status as a time-dependent variable.



In addition to that, almost all anticoagulated patients must be warfarin users in this era.

Warfarin control, such as TTR, could affect validity of comparison of thromboembolism risks between OAC users and non OAC users.

Could you discuss this matter on your manuscript?

Answer: As mentioned above, we did not have information about INR and were therefore not able to calculate TTR for those in warfarin therapy. We have added this matter to the limitations section.

Changes made to the manuscript (p. 16, line 3-5):

Also, no data were available with regard to the physicians' considerations when choosing between OAC therapy and no OAC therapy, patients compliance, and measurements of international normalized ratio (INR) and time in therapeutic range for warfarin users.



## VERSION 2 – REVIEW

<b>REVIEWER</b>	Prof John D Horowitz Queen Elizabeth Hospital, University of Adelaide, Australia
<b>REVIEW RETURNED</b>	27-Jun-2019

<b>GENERAL COMMENTS</b>	<p>The authors have addressed all of the issues which I previously raised, and I am happy with these responses. There is one residual issue, and I apologise for not raising it with my initial review. It is the nature of AF secondary to the presence of other disorders (such as acute myocardial infarction) to be a transient problem in most cases, and therefore it might be expected that the associated thrombo-embolic risk would also be limited by the duration of AF. I would ask the authors to consider this point, as they have provided no relevant data thus far. For example, do they know what proportion of the cases of AF triggered by intercurrent illnesses were, in fact, transient? Further to this, if the thrombo-embolic risk is, indeed, comparable to that of "primary" AF, despite a theoretically smaller period of vulnerability to thrombo-embolism, these findings would tend to reinforce those of Procter et al about the implications of loss of platelet anti-aggregatory response to nitric oxide associated with the acute stages of AF, and perhaps that could be briefly discussed.</p> <p>There are a few minor spelling/grammatical errors.</p>
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<b>REVIEWER</b>	Eitaro Kodani Nippon Medical School Tama-Nagayama Hospital, Tokyo, Japan.
<b>REVIEW RETURNED</b>	08-May-2019

<b>GENERAL COMMENTS</b>	<p>This revised manuscript by Gundlaud al. focused on the risk of thromboembolic events and death in patients with any trigger (defined as AF with a secondary precipitant including alcohol intoxication, thyrotoxicosis, myocardial infarction, surgery, and infection) and without it (defined as AF without a secondary precipitant). Authors have revised the manuscript appropriately according to the most of the reviewers' comments. It appears to be better. This reviewer still has a comment on statistical method. Authors may want to consider it as below.</p> <p>Major comments;</p> <p>1) Since heart failure, hypertension, diabetes mellitus, prior thromboembolic event (including stroke and transient ischemic attack), and vascular diseases (including ischemic heart disease and peripheral artery disease) are the components of CHA2DS2-VASc score, these variables should not be included in covariates for further adjustment on multivariate analysis after matching with CHA2DS2-VASc score to avoid multicollinearity.</p>
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<b>REVIEWER</b>	Keitaro Senoo Kyoto Prefectural University of Medicine, Department of Cardiac Arrhythmia Research and Innovation, Kyoto, JAPAN
<b>REVIEW RETURNED</b>	17-May-2019

<b>GENERAL COMMENTS</b>	I have reviewed again this article, the answer that given have addressed the queries. I would recommend the article to be accepted.
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## VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Prof John D Horowitz

Institution and Country: Queen Elizabeth Hospital, University of Adelaide, Australia

The authors have addressed all of the issues which I previously raised, and I am happy with these responses. There is one residual issue, and I apologise for not raising it with my initial review. It is the nature of AF secondary to the presence of other disorders (such as acute myocardial infarction) to be a transient problem in most cases, and therefore it might be expected that the associated thrombo-embolic risk would also be limited by the duration of AF. I would ask the authors to consider this point, as they have provided no relevant data thus far. For example, do they know what proportion of the cases of AF triggered by intercurrent illnesses were, in fact, transient? Further to this, if the thrombo-embolic risk is, indeed, comparable to that of "primary" AF, despite a theoretically smaller period of vulnerability of thrombo-embolism, these findings would tend to reinforce those of Procter et al about the implications of loss of platelet anti-aggregatory response to nitric oxide associated with the acute stages of AF, and perhaps that could be briefly discussed.

Answer: This is a very good point. Unfortunately, we did not have any information about duration of AF or even heart rhythm at discharge. However, we have information about new hospital admissions, oral anticoagulation therapy, and antiarrhythmic therapy. We have added some of this information to the manuscript. We are very sorry, but we are not sure what study Prof. Horowitz refers to.

Changes made to the manuscript (p. 11, line 2 to p. 12, line 2):

On the other hand, they were more likely to suffer from stroke risk factors (incl. diabetes, heart failure, ischemic heart disease, and hypertension) than those not initiated on OAC therapy.

During the first year after the index date, 9.9% and 17.3% of patients with AF with and without a secondary precipitant, respectively, had a new hospital admission with AF. One year after the index date, 19.8% and 32.7% of the patients with AF with and without a secondary precipitant, respectively, were in OAC therapy and 22.3% and 21.8% of the patients with AF with and without a secondary precipitant, respectively, were in antiarrhythmic therapy.

And (p. 16, line 7-13):

Our definition of AF with a secondary precipitant was based on diagnosis codes from hospital admissions with AF and a reversible precipitant. Both diagnoses were registered at the discharge date, and therefore we may have included patients in the group of AF with a secondary precipitant who developed AF before the secondary precipitant (e.g. patients admitted with AF who developed infection during their hospital stay), and thereby should have been classified as patients with AF without a secondary precipitant. Moreover, we had no access to patient files, and we did not know the duration of AF or whether the patients were discharged in sinus rhythm or with AF.

There are a few minor spelling/grammatical errors.

Answer: Thanks, we have checked the manuscript for spelling and grammatical errors.

Reviewer: 2

Reviewer Name: Eitaro Kodani

Institution and Country:

Nippon Medical School Tama-Nagayama Hospital,

Tokyo, Japan.

This revised manuscript by Gundlund al. focused on the risk of thromboembolic events and death in patients with any trigger (defined as AF with a secondary precipitant including alcohol intoxication, thyrotoxicosis, myocardial infarction, surgery, and infection) and without it (defined as AF without a secondary precipitant). Authors have revised the manuscript appropriately according to most of the reviewers' comments. It appears to be better. This reviewer still has a comment on statistical method. Authors may want to consider it as below.

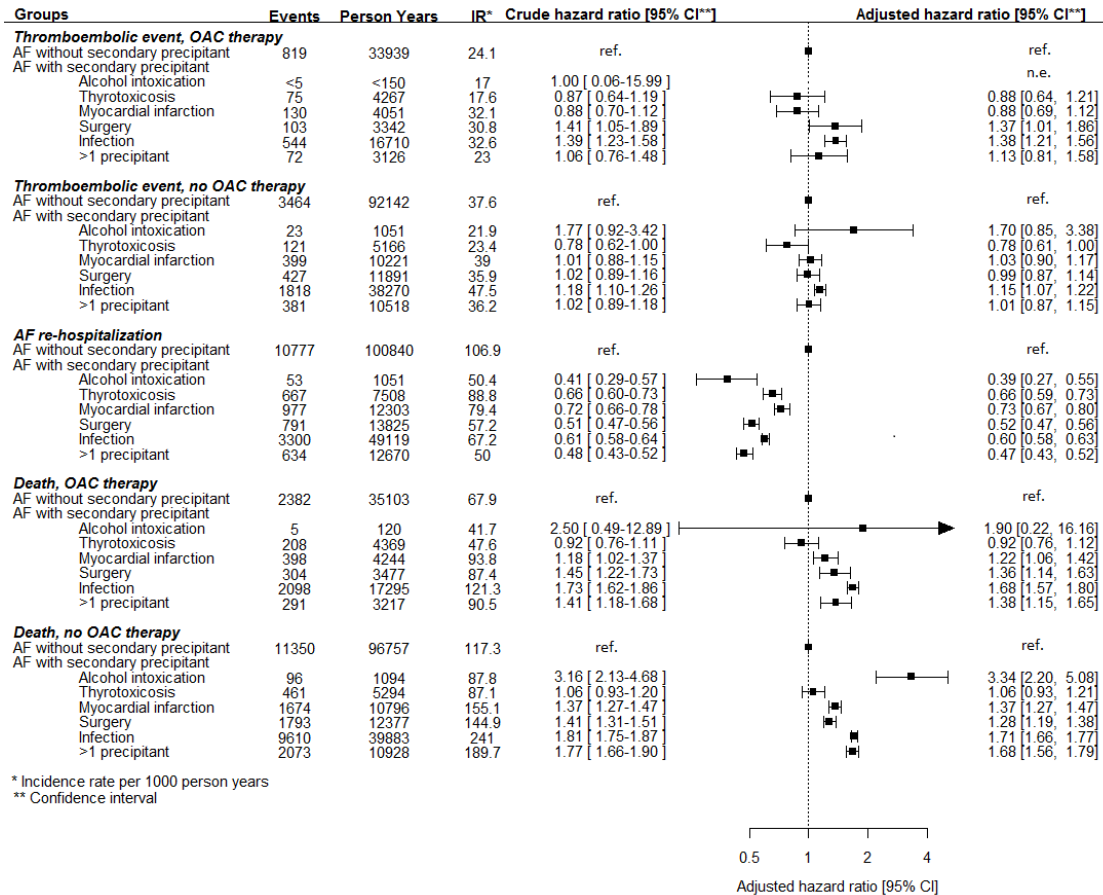
Major comments;

1) Since heart failure, hypertension, diabetes mellitus, prior thromboembolic event (including stroke and transient ischemic attack), and vascular diseases (including ischemic heart disease and peripheral artery disease) are the components of CHA<sub>2</sub>DS<sub>2</sub>-VASc score, these variables should not be included in covariates for further adjustment on multivariate analysis after matching with CHA<sub>2</sub>DS<sub>2</sub>-VASc score to avoid multicollinearity.

Answer: We appreciate the comment, but respectfully disagree. We match by a crude classification of CHA<sub>2</sub>DS<sub>2</sub>-VASc and to adjust for the fact that different groups may have their CHA<sub>2</sub>DS<sub>2</sub>-VASc for different reasons, we find it important to include the components of CHA<sub>2</sub>DS<sub>2</sub>-VASc in the analysis. The consequences of collinearity is variance inflation and would appear as very wide confidence intervals, and we do not see a major change in confidence intervals with and without the components of CHA<sub>2</sub>DS<sub>2</sub>-VASc.

We respect that the reviewer requests an analysis without the components of CHA<sub>2</sub>DS<sub>2</sub>-VASC and we have therefore included the requested analysis below:

Number of events, incidence rates, and crude and adjusted Hazard ratios of long-term outcomes in patients with AF with and without a secondary precipitant. Adjustments: age groups, chronic kidney disease, prior bleeding event, cancer, antiarrhythmic therapy (amiodarone, digoxin, flecainide).

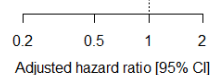


Adjusted hazard ratios of long-term outcomes in patients with AF initiated vs. not initiated on OAC therapy (stratified according to type of AF). Adjustments: age groups, chronic kidney disease, prior bleeding event, cancer, antiarrhythmic therapy (amiodarone, digoxin, flecainide).

Groups	Events	Person Years	IR*	Crude hazard ratio [95% CI**]	Adjusted hazard ratio [95% CI**]
<b>Thromboembolic event</b>					
No OAC	6633	169258	39.2	ref.	ref.
AF without secondary precipitant	819	33939	24.1	0.70 [0.65-0.76]	0.69 [0.63, 0.74]
AF and any secondary precipitant	<1000	<3500	29.3	0.75 [0.70-0.81]	0.77 [0.71, 0.83]
AF and alcohol intoxication	<3	<150	17	0.72 [0.14-3.66]	0.68 [0.13, 3.46]
AF and thyrotoxicosis	75	4267	17.6	0.78 [0.58-1.06]	0.81 [0.60, 1.11]
AF and myocardial infarction	130	4051	32.1	0.87 [0.71-1.06]	0.91 [0.74, 1.13]
AF after surgery	103	3342	30.8	0.90 [0.72-1.13]	0.92 [0.73, 1.15]
AF and infection	544	16710	32.6	0.73 [0.66-0.80]	0.74 [0.67, 0.82]
AF and >1 precipitant	72	3126	23	0.64 [0.49-0.83]	0.65 [0.50, 0.85]
<b>Death</b>					
No OAC	27057	177130	152.8	ref.	ref.
AF without secondary precipitant	2382	35103	67.9	0.67 [0.64-0.70]	0.61 [0.59, 0.64]
AF and any secondary precipitant	3304	32722	101	0.56 [0.54-0.58]	0.56 [0.54, 0.58]
AF and alcohol intoxication	5	120	41.7	0.45 [0.18-1.14]	0.43 [0.16, 1.13]
AF and thyrotoxicosis	208	4369	47.6	0.58 [0.49-0.69]	0.55 [0.46, 0.65]
AF and myocardial infarction	398	4244	93.8	0.65 [0.58-0.73]	0.64 [0.57, 0.72]
AF after surgery	304	3477	87.4	0.64 [0.57-0.73]	0.69 [0.61, 0.79]
AF and infection	2098	17295	121.3	0.54 [0.52-0.57]	0.55 [0.52, 0.58]
AF and >1 precipitant	291	3217	90.5	0.50 [0.44-0.57]	0.52 [0.46, 0.59]

\* Incidence rate per 1000 person years

\*\* Confidence interval



Reviewer: 3

Reviewer Name: Keitaro Senoo

Institution and Country: Kyoto Prefectural University of Medicine, Department of Cardiac Arrhythmia Research and Innovation, Kyoto, JAPAN

I have reviewed again this article, the answer that given have addressed the queries.

I would recommend the article to be accepted.

Answer: Thank you very much.

### VERSION 3 – REVIEW

<b>REVIEWER</b>	John D Horowitz University of Adelaide, Australia
<b>REVIEW RETURNED</b>	15-Aug-2019
<b>GENERAL COMMENTS</b>	The overall manuscript reads well and makes the point that AF secondary to intercurrent illness is far from benign. However, in the Discussion, the part related to nitric oxide availability and

	<p>signaling seems completely garbled (I am referring to the part from page 16, line 23 to page 17, line 12.).</p> <p>Perhaps it would be better if the authors were to alter this section to constitute a separate paragraph reading something like the following:- " The retrospective, registry-based nature of the study also precluded consideration of the specific impact of the molecular causes of both acute and chronic AF, including inflammatory activation and impaired nitric oxide (NO) availability and signaling. For example, specific patterns and extent of inflammatory activation associated with intercurrent infection could not be determined, and while impaired NO anti-aggregatory effect occurs in acute AF (27) and increased plasma concentrations of asymmetric dimethylarginine, which inhibits enzymatic generation of NO , predict thrombo-embolic risk in AF (28), neither of these parameters were measured in the current study."</p>
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<b>REVIEWER</b>	Eitaro Kodani Department of Internal Medicine and Cardiology, Nippon Medical School Tama-Nagayama Hospital, Tokyo, Japan.
<b>REVIEW RETURNED</b>	02-Aug-2019

<b>GENERAL COMMENTS</b>	This revised manuscript by Gundlaud al. focused on the risk of thromboembolic events and death in AF patients with and without secondary precipitants (alcohol intoxication, thyrotoxicosis, myocardial infarction, surgery, and infection). Authors have responded satisfactorily to the reviewers' comments. I have no further comment.
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### VERSION 3 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: John D Horowitz

Institution and Country: University of Adelaide, Australia

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

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Answer: Thanks for writing this suggestion, we have implemented it in the Limitation section.

Changes made to the manuscript (p. 16, line 23 to p. 17, line 10):

Previous studies have shown an association between an impaired platelet nitric oxide response and recent onset AF and that disturbances in nitric oxide function are associated with outcomes (including thromboembolic events, bleeding events, and death) in AF. Unfortunately, we did not have any information on nitric oxide levels in our study cohort.(27,28) The retrospective, registry-based nature of this study also precluded consideration of the specific impact of the molecular causes of both acute and chronic AF, including inflammatory activation and impaired nitric oxide (NO) availability and signaling. For example, specific patterns and extent of inflammatory activation associated with intercurrent infection could not be determined, and while impaired NO anti-aggregatory effect occurs in acute AF (27) and increased plasma concentrations of asymmetric dimethylarginine, which inhibits enzymatic generation of NO, predict thromboembolic risk in AF (28), neither of these parameters were measured in the current study.

'Reviewer: 2

Reviewer Name: Eitaro Kodani

Institution and Country: Department of Internal Medicine and Cardiology, Nippon Medical School Tama-Nagayama Hospital, Tokyo, Japan.

Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

This revised manuscript by Gundlaud al. focused on the risk of thromboembolic events and death in AF patients with and without secondary precipitants (alcohol intoxication, thyrotoxicosis, myocardial infarction, surgery, and infection). Authors have responded satisfactorily to the reviewers' comments. I have no further comment.

Answer: Thanks.