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# Comparative thromboembolic risk in atrial fibrillation patients with and without a concurrent infection

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Abbreviated title: Outcomes in secondary atrial fibrillation

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Background: The aim of this study was to compare long-term thromboembolic risk in infection-related and non-infection-related atrial fibrillation (AF).

Methods: Using Danish nationwide registries, we identified patients with first-time AF from 1996 – 2015 and performed a retrospective cohort study. We did a 1:1 match (upon sex, age, calendar year, and oral anticoagulation (OAC) status at the beginning of follow-up) of patients with infection-related (concurrent discharge diagnosis code for infection) and non-infection-related AF. Long-term outcomes were examined using multivariable Cox regression analyses.

Results: Our study population comprised 48,644 patients equally distributed on infection-related and non-infection-related AF. In both groups, those initiated on OAC therapy were younger than those not initiated on OAC therapy (median age 77 years, interquartile range 69-83 versus median age 79 years, interquartile range 71-86). During the 1st year of follow up, infection-related AF was associated with an increased risk of thromboembolic events compared with non-infection-related AF: adjusted hazard ratio (HR) 1.44 (95% confidence interval (CI) 1.16-1.78) for those initiated on OAC therapy and HR 1.17 (95% CI 1.06-1.28) for those not initiated on OAC therapy. In both groups, OAC therapy was associated with better outcomes than no OAC therapy (HR of thromboembolic events 0.75 (95% CI 0.68- 0.83) and HR 0.70 (95% CI 0.63- 0.78) for patients with infection-related and non-infection-related AF, respectively).

Conclusion: Infection was associated with an increased thromboembolic risk in patients with first-time AF. OAC therapy was associated with a similar risk-reduction in AF patients with and without a concurrent infection.

Key words: Stroke, atrial fibrillation, infection, longitudinal population-based cohorts, anticoagulation therapy

## Highlights

- Infection-related and non-infection-related AF was at least equal in thromboembolic risk
- Infection-related AF had lower rates of AF re-hospitalizations
- OAC therapy was associated with a lower thromboembolic risk in infection-related AF

## Introduction

Atrial fibrillation (AF) occurring secondary to infection is common, yet little data exist on long-term outcomes for patients in this setting.[1] European and American guidelines from 2011 stated that AF occurring secondary to another precipitant (e.g. pneumonia, myocardial infarction, pericarditis etc.) usually will terminate without recurrence.[2] This recommendation was, however, retracted in current guidelines, where no such recommendations regarding oral anticoagulation (OAC) therapy for patients with AF in this setting exist.[3, 4] Further, the randomized controlled trials regarding OAC therapy as stroke prophylaxis in AF patients excluded patients with AF due to reversible conditions.[5–9] When it comes to thromboembolic risk, it is unknown whether AF secondary to reversible precipitants differs from AF in general. Recently, Lubitz et al. found a 42% five-years recurrence rate of AF among patients with first-detected AF at the same time as a reversible secondary precipitant.[1] Since AF without a precipitating cause is associated with a high risk of thromboembolism, and since this thromboembolic risk is unknown when a precipitating cause is present, it is important for clinical decision making to seek further knowledge of the risk of thromboembolism when a precipitating cause of AF is present with and without the use of OAC therapy.[4, 10]

We compared the long-term risk of thromboembolic events, AF re-hospitalization, and death among patients presenting with first-time AF with and without a concurrent infection.

## Methods

*Data sources*

We linked data on an individual level across four nationwide registries. The Danish Civil Registration System holds information about date of birth and death, sex, and emigration.[11] The Danish national patient registry holds information about all hospital contacts and includes diagnosis codes and dates of hospital visits.[12] Diagnoses are registered in terms of the International Classification of Diseases (ICD) system (ICD-8 until 1994, ICD-10 thereafter). The Danish Register of Causes of Death [13] holds information about causes of death and the Danish National Registry of Medicinal Statistics holds information about all filled prescriptions in Denmark.[14]

*Infection-related AF*

Among all Danish residents, patients with first-time AF and infection during the same hospital admission from January 1, 1996 to September 30, 2015 were defined as having infection-related AF. The very young and old patients (<18 years or >100 years), those who had emigrated before the inclusion, and those with valvular AF were excluded (Figure 1). To ensure exclusion of patients with previously diagnosed AF (e.g. at a general practitioner), we excluded those treated with OAC therapy 100 days prior to their AF hospital admission and patients treated with antiarrhythmic and rate-controlling drugs at any time before their AF hospital admission. See Online Table 1 for specification of diagnosis codes and anatomical therapeutic chemical codes.

*Non-infection-related AF*

All Danish residents admitted with AF for the first time from January 1, 1996 to September 30, 2015 without a concurrent infection were identified. We applied the same exclusion criteria as for the group with infection-related AF (Figure 1).

*Study population*

To exclude the most fragile patients, those who had a thromboembolic event or died during a blanking period of 14 days from discharge to a defined index date were excluded. Initiation of OAC therapy was assessed during this blanking period. Among those available for follow up at the index date (alive and not emigrated), we did a one to one match by incidence density sampling according to age, sex, calendar year, and OAC status at the index date of AF patients with and without a concurrent infection. We used a previously described function to perform the match.[15]

*Long-term outcomes*

The outcomes of interest included thromboembolic events (ischemic stroke, transient ischemic attack, and systemic thromboembolism), bleeding events, AF re-hospitalization, and death (of any cause). AF re-hospitalization only included those with AF as the primary diagnosis. Patients were followed from the index date and until an event, death, emigration, end of study period (December 31, 2015), or five years after the index date, whichever came first. AF and ischemic stroke have been validated in the Danish registries with a positive predictive value of 93% and 97%, respectively.[16, 17] There exist no validation study on infection-related AF.

*Statistics*

Patient characteristics were presented for AF patients with and without a concurrent infection according to OAC therapy at the index date and including diagnoses given during the AF hospitalization. Cumulative incidences of long-term outcomes (taking into account the competing risk of death) were calculated using the Aalen Johansen estimator. Differences across groups were tested by using the Log Rank and the Gray's test. Crude and adjusted hazard ratios (HR) (adjusted

for alcohol abuse, cancer, chronic kidney disease, diabetes, heart failure, hypertension, ischemic heart disease, peripheral artery disease, bleeding events, prior thromboembolic events, thyroid disease, and antiarrhythmic and rate-controlling therapy in the analyses on thromboembolic events and further chronic obstructive pulmonary disease and liver disease for the analysis on death) were calculated by Cox regression models comparing the risk of long-term outcomes in AF patients with and without a concurrent infection using unconditional analyses comparing cases and controls within each matching strata and shown by OAC therapy at the index date. We tested for clinically relevant interactions including age, calendar year, and several comorbidities. Since the assumption of proportional hazards was not met in the analyses on thromboembolic events, these analyses were stratified in two time periods. OAC treatment effect was assessed by multivariable Cox regression models including thromboembolic events and death as endpoints. A two-sided P-value <0.05 was considered statistically significant. All statistical analyses were performed by A.G. in SAS statistical software version 9.4 and R Studio.[18]

*Other analyses*

To account for potential changes in OAC therapy status over time, we adjusted for changes in therapy in a sensitivity analysis. To address the validity of the infection diagnosis, we performed analyses on long-term outcomes only including patients with a c-reactive protein level >49 mg/L in the infection-related AF group. Also, long-term outcomes were examined in a non-matched population, including all patients available for matching (see Figure 1). See Supplementary material for further specifications. In a sub analysis, we stratified the infection-related AF group into the following groups according to type of infection: pneumonia, urinary tract infection, gastrointestinal infection, sepsis, and other infections. Long-term thromboembolic risk was assessed for each sub group and compared with non-infection-related AF. To test, whether underlying heart disease or AF

risk factors influenced the results, we did sensitivity analyses on different subgroups of the patients with infection-related defined from underlying ischemic heart disease, heart failure (incl. cardiomyopathies), hypertension, and diabetes.

*Ethics*

Approval from the Research Ethics Committee System is not required in retrospective registry-based studies in Denmark. The Danish Data Protection Agency approved use of data for this study (ret.no: 2007-58-0015 / GEH-2014-013 I-Suite no: 02731).

## Results

*Study population*

The patient selection is depicted in Figure 1. After exclusions, 24,607 patients with infection-related AF and 68,746 patients with non-infection-related AF were available for matching. Patients with infection-related AF were less likely to receive OAC therapy (24.3% versus 41.7%), they were older, had more comorbid illness, and higher risk scores for stroke and bleeding than patients with non-infection-related AF (Online Table 2).

After matching, the study population comprised 24,607 patients with infection-related AF and 24,607 patients with non-infection-related AF. Infections in the respiratory system were the most common infections (online Table 3). Table 1 shows the baseline characteristics of the matched study population. In general, the patients with infection-related AF had more comorbidities than patients with non-infection-related AF, and in both groups, patients initiated on OAC therapy had less comorbidity compared with patients not initiated on OAC therapy.

*Treatment over time*

Equal proportions of patients with infection-related and non-infection-related AF discontinued OAC therapy over time (Online Figure 1A). Of those on no OAC therapy at the index date, more patients with non-infection-related AF than infection-related AF initiated OAC therapy over time (Online Figure 1B). By six months from the index date, 50.0% and 46.1% of patients with infection-related and non-infection-related AF, respectively, were in antiarrhythmic or rate-controlling therapy.

*Long-term outcomes*

The median follow-up time from the index date to death, study end (5 years after the index date or December 31, 2015), or emigration was 2.5 years (IQR 0.7 –5.0) for patients with infection-related AF and 3.6 years (IQR 1.3 –5.0) for patients with non-infection-related AF. During follow-up, 14.6% of the patients with infection-related AF compared with 27.4% of the patients with non-infection-related AF had a re-admission with AF (adjusted HR 0.60, 95% confidence interval (CI) 0.56–0.64 for patients on OAC therapy at the index date and adjusted HR 0.51, 95% CI 0.48-0.54 for patients on no OAC therapy at the index date). The cumulative incidences of thromboembolic events and death in AF patients with and without a concurrent infection according to OAC therapy at the index date are depicted in Figure 2 (A: thromboembolic events during the 1st year from the index date, B: thromboembolic events one to five years from the index date, C: Kaplan Meier curve for death). Figure 3 illustrates incidence rates and crude and adjusted HRs of long-term outcomes in patients with infection-related AF compared with patients with non-infection-related AF according to OAC therapy status at the index date. During the 1st year from the index date, infection-related AF was associated with an increased risk of thromboembolic events compared with non-infection-related AF. After one year, this risk decreased, and became comparable to the thromboembolic risk in non-infection-related AF. No differences were found in bleeding risk across the two patient

groups when initiated on OAC therapy at the index date. For those not initiated on OAC therapy, infection-related AF was associated with an increased risk of bleeding events. Infection-related AF was associated with a higher risk of death than non-infection-related AF. OAC therapy vs. no OAC therapy was associated with a lower the risk of thromboembolic events and death and a higher bleeding risk for both infection-related and non-infection related AF patients (Figure 4).

*Other analyses*

Adjustments for OAC therapy as a time-dependent variable did not change the results on thromboembolic events in patients with infection-related versus non-infection-related AF (1st year from the index date: adjusted HR 1.40, 95% CI 1.13-1.74 for those on OAC therapy at the index date and adjusted HR 1.16, 95% CI 1.06-1.27 for those not on OAC therapy at the index date). Among patients with infection-related AF and available data on c-reactive protein level, 13.5% had a c-reactive protein level <10 mg/L, 32.1% from 10-49 mg/L, 54.4% >49 mg/L during their hospital admission. The risk of thromboembolic events in patients with infection-related AF and c-reactive protein >49 mg/L compared with patients with non-infection-related AF was: adjusted HR 1.25, 95% CI 0.49-3.18 for those initiated on OAC therapy and adjusted HR 1.17, 95% CI 0.84-1.63 for those not initiated on OAC therapy during the 1st year of follow up. In the non-matched population, infection-related AF was associated with a higher risk of thromboembolic events compared with non-infection-related AF (1st year from the index date: adjusted HR 1.22, 95% CI 1.04-1.43 for those on OAC therapy at the index date and adjusted HR 1.14, 95% CI 1.05-1.24 for those not on OAC therapy at the index date).

When dividing the group of patients with infection-related AF according to type of infection, pneumonia-related AF was associated with the highest risk of thromboembolic events. In general, the different subtypes of infection-related AF were associated with the same or an increased

thromboembolic risk as in patients with non-infection-related AF (Online Figure 2). Sub group analyses on different subgroups of the patients with infection-related AF according to underlying cardiac disease and AF risk factors showed similar results for the different groups with regard to thromboembolic events.

## Discussion

We investigated long-term outcomes in patients with AF secondary to infection. The results indicated that infection-related AF is not as benign as previously considered. First, infection-related AF was associated with an increased risk of thromboembolic events during the 1st year of follow-up and hereafter a comparable risk of thromboembolic events compared with non-infection-related AF. These findings were independent of OAC therapy status. Secondly, OAC therapy was associated with a lower risk of thromboembolic events and death compared with no OAC therapy for patients with infection-related AF as well as for patients with non-infection-related AF. Lastly, infection-related AF was associated with a lower risk of AF re-hospitalization than non-infection-related AF.

*Thromboembolic risk and OAC therapy*

Infection-related AF vs. non-infection-related AF was associated with an increased thromboembolic risk during the 1$^{st}$ year of follow up and a comparable thromboembolic risk thereafter. Further, different subtypes of infection-related AF (according to type of infection) were associated with the same or an even higher thromboembolic risk than in patients with non-infection-related AF. With regard to bleeding events, we observed no difference between patients with infection-related vs. non-infection-related AF among those initiated on OAC therapy. However, among those not

initiated on OAC therapy, infection-related AF was associated with an increased bleeding risk. This may indicate that this patient group represents a group of fragile patients.

Previously, Lubitz et al. found no differences in the long-term risk of stroke among AF patients with and without a secondary precipitant. However, the number of patients investigated was low (439 patients with AF secondary to infection) compared with the study population in our study and the analyses were not stratified according to OAC therapy status.[1] In 2014, Gialdini et al. found an association between perioperative AF and the long-term risk of ischemic strokes.[19] Even though surgery is another secondary precipitant to AF than infection, this may reflect, that once AF has occurred, irrespective of the setting it occurs in, the patients carry an increased risk of thromboembolic events. Even though we cannot draw any causal link between infection-related AF and thromboembolic events, we suggest that infection-related AF and non-infection-related AF should be considered at least as equal with regard to thromboembolic risk.

Despite adjustment for several potential confounders in our models, residual confounding cannot be excluded in our administrative registries. Until now, AF secondary to a reversible precipitant has been considered as a temporary event which terminates without recurrence, and therefore, the existence of un-identified confounders could be the explanation for the high long-term risk of thromboembolic events in patients with infection-related AF rather than AF itself. For example, the higher thromboembolic risk observed in patients with infection-related vs. non-infection-related AF during the 1$^{st}$ year of follow up may be explained by a more active anticoagulation system in relation to the acute infection. However, OAC therapy in patients with infection-related AF was associated with the same reduction in thromboembolic risk and death as in non-infection-related AF. This may indicate that at least some of the high risk of thromboembolic events in the patients with infection-related AF were explained by AF. Moreover, the initiation rates of OAC therapy in patients with infection-related AF were markedly lower than for patients with non-infection-related

AF (24.3% vs. 41.7%). These results indicate the need for guidelines regarding OAC therapy for patients with AF secondary to a reversible precipitant, maybe on the same terms as for non-infection-related AF. To support the findings of our study, data regarding AF secondary to other precipitants than infection are warranted.

*AF recurrence*

We found lower AF recurrence rates than those found in previous studies.[1, 20] However, we studied re-hospitalizations and only included primary diagnoses of AF. This was done to avoid bias from the diagnosis coding. Therefore, AF as secondary diagnosis, outpatient hospital contacts with AF, and diagnoses from general practitioners were not included. This is likely to explain the lower recurrence rates in comparison with other studies. In the multivariable analysis, infection-related AF was associated with a significantly lower risk of AF rehospitalizations than non-infection-related AF. This is in accordance with the findings by Lubitz et al. and Walkey et al. examining long-term outcomes in patients with first-detected AF and a secondary precipitant and patients with first-time AF during sepsis, respectively.[1, 20] Siontis et al. recently found an increased risk of cerebrovascular events in patients with silent AF compared with patients with symptomatic AF.[21] Although speculative, it is possible that patients with infection-related AF had more silent episodes of AF not leading to hospitalization. This could explain why the patients with infection-related AF had lower AF re-hospitalization rates but at least as many thromboembolic events as the patients with non-infection-related AF.

*Limitations*

Our study had several limitations. Most importantly, it was a retrospective registry-based study. We looked at associations, and no causative relations can be drawn. No data on variables such as body

mass index, smoking habits, electrocardiograms, etc. were available. Moreover, the characterization of infection-related and non-infection-related AF was based on discharge diagnosis coding. To minimize the degree of misclassification bias, we restricted the group of patients with non-infection-related AF to patients with AF as the primary diagnosis. Our results showed a notable difference in OAC initiation-rates among the two patient groups. This supports our succeeding in differentiating between patients with infection-related and non-infection-related AF. We had no access to patient files, and therefore, no data regarding physicians' considerations with respect to the individual patient, the AF duration, and clinical presentation. This may have resulted in some degree of confounding by indication. Moreover, we did not know if the patients had sinus rhythm or AF at discharge. However, the proportion of patients in antiarrhythmic or rate-controlling therapy at the index date only differed slightly between the two patient groups. On the other hand, this study was based on nationwide registries from a tax-financed healthcare system with equal availability to health care services regardless of socioeconomic status. Further, these registries enabled long-term follow-up, an unselected study population, and available data on OAC therapy.

## Conclusion

Infection-related AF was associated with at least as high thromboembolic risk as non-infection-related AF. This was despite a lower recurrence rate of AF and the results were independent of OAC therapy status. Our results suggest that infection-related AF should be considered as at least equal to non-infection-related AF with regard to thromboembolic risk. Further, our results indicate that OAC therapy may be considered on the same terms for infection-related and non-infection-related AF—something that currently is unclear in treatment guidelines.

## Conflict of interest

AG: reports grants from Bristol-Myers Squibb, outside the submitted work; TK: reports consulting fees from AstraZeneca, Merck, Bayer, Boehringer-Ingelheim, BMS; JBO: reports personal fees from Bristol-Myers Squibb, personal fees from Boehringer Ingelheim, personal fees from Bayer, personal fees from AstraZeneca, personal fees from Novo Nordisk, outside the submitted work; ANB: none declared; GHG: reports grants from Bayer, grants from AstraZeneca, grants from Bristol Myers Squibb, grants from Boehringer Ingelheim, outside the submitted work; CTP: reports grants and personal fees from Bayer, grants from Biotronic, outside the submitted work; LK: reports personal fees from Novartis honorarium as speaker, outside the submitted work; ELF: reports grants from Janssen Pharmaceuticals, grants from BMS, outside the submitted work.

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**Table 1: Baseline characteristics of the study population**

| | Infection-related AF* N=24,322 | | Non-infection-related AF* N=24,322 | |
|---|---|---|---|---|
| **Demographics** | + OAC[#] N=5981 | - OAC[#] N=18,341 | + OAC[#] N=5981 | - OAC[#] N=18,341 |
| Age, median (IQR[‖]) | 77 (69-83) | 79 (71-86) | 77 (69-83) | 79 (71-86) |
| Female, no. (%) | 2812 (47.0) | 9943 (54.2) | 2812 (47.0) | 9943 (54.2) |
| **Comorbidities, no. (%)** | | | | |
| Alcohol abuse | 201 (3.4) | 1026 (5.6) | 121 (2.0) | 551 (3.0) |
| Cancer | 926 (15.5) | 3947 (21.5) | 852 (14.3) | 3402 (18.6) |
| Chronic kidney disease | 350 (5.9) | 1470 (8.0) | 166 (2.8) | 760 (4.1) |
| Chronic obstructive pulmonary disease | 1227 (20.5) | 3958 (21.6) | 656 (11.0) | 1952 (10.6) |
| Diabetes | 705 (11.8) | 1753 (9.6) | 508 (8.5) | 1250 (6.8) |
| Heart failure | 1452 (24.3) | 4502 (24.6) | 1202 (20.1) | 3093 (16.9) |
| Hypertension | 3819 (63.9) | 8295 (45.2) | 3975 (66.5) | 8829 (48.1) |
| Ischemic heart disease | 1348 (22.5) | 4852 (26.5) | 1342 (22.4) | 4511 (24.6) |
| Liver disease | 21 (0.4) | 120 (0.7) | 8 (0.1) | 38 (0.2) |
| Peripheral artery disease | 349 (5.8) | 1316 (7.2) | 240 (4.0) | 934 (5.1) |
| Prior bleeding event | 964 (16.1) | 4013 (21.9) | 825 (13.8) | 3112 (17.0) |
| Prior thromboembolic event | 666 (11.1) | 2306 (12.6) | 541 (9.1) | 1811 (9.9) |
| Thyroid disease | 369 (6.2) | 1068 (5.8) | 426 (7.1) | 1119 (6.1) |
| **Risk scores** | | | | |
| $CHA_2DS_2$-VASc[‡] mean ±std[¶] | 3.4 (1.6) | 3.4 (1.7) | 3.3 (1.6) | 3.2 (1.7) |
| $CHA_2DS_2$-VASc[‡], median (IQR[‖]) | 3 (2-4) | 3 (2-5) | 3 (2-4) | 3 (2-4) |
| $CHADS_2$[†], mean ±std[¶] | 1.8 (1.2) | 1.7 (1.2) | 1.7 (1.1) | 1.6 (1.2) |
| $CHADS_2$[†], median (IQR[‖]) | 2 (1-2) | 2 (1-2) | 2 (1-2) | 1 (1-2) |
| HAS-BLED[§], mean ±std[¶] | 2.3 (1.1) | 2.3 (1.2) | 2.2 (1.1) | 2.2 (1.1) |
| HAS-BLED[§], median (IQR[‖]) | 2 (1-3) | 2 (1-2) | 2 (1-3) | 2 (1-3) |
| **Pharmacotherapy initiated during the blanking period, no. (%)** | | | | |
| Amiodarone | 313 (5.2) | 489 (2.7) | 265 (4.4) | 484 (2.6) |
| Digoxin | 3001 (50.2) | 5773 (31.5) | 2725 (45.6) | 4902 (26.7) |
| Dronedarone | <5 | <5 | <5 | <5 |
| Flecainide | 10 (0.2) | 31 (0.2) | 22 (0.4) | 139 (0.8) |

*AF: atrial fibrillation. [†]$CHADS_2$: Risk score for stroke: congestive heart failure/LV function, hypertension, age>74 years, diabetes, stroke/TIA/systemic embolism (2 points). [‡]$CHA_2DS_2$-VASc: Risk score for stroke: congestive heart failure/LV function, hypertension, age 65-74 years, age>74 years (2 points), diabetes, stroke/TIA/ systemic embolism (2 points), vascular disease, sex category (female). [§]HAS-BLED: Risk score for bleeding: hypertension, abnormal renal/liver function, history of stroke, history of bleeding, INR (left out due to missing data), age>65 years, drug consumption with antiplatelet agents/non-steroidal inflammatory drugs, alcohol abuse. [‖]Interquartile range. [¶]Standard deviation. [#]Oral anticoagulation therapy status at the index date

## Figure legends

Figure 1: Patient selection. AF: atrial fibrillation.

Figure 2: Cumulative incidence of thromboembolic events in AF patients with and without a concurrent infection according to OAC therapy status at the index date. (A: thromboembolic events, 1st year since index date), B: thromboembolic events, one to five years since index date) and C: death, entire study period. AF: atrial fibrillation. OAC: oral anticoagulation.

Figure 3: Incidence rates and adjusted HRs of long-term outcomes in patients with infection-related AF and non-infection-related AF according to OAC therapy status at the index date. AF: atrial fibrillation. CI: confidence interval. HR: hazard ratio. OAC: oral anticoagulation.

Figure 4: Adjusted HRs of long-term outcomes in AF patients with and without a concurrent infection according to OAC therapy status at the index date. AF: atrial fibrillation. HR: hazard ratio. CI: confidence interval. OAC: oral anticoagulation.

**Figure 1: Patient selection.** AF: atrial fibrillation.

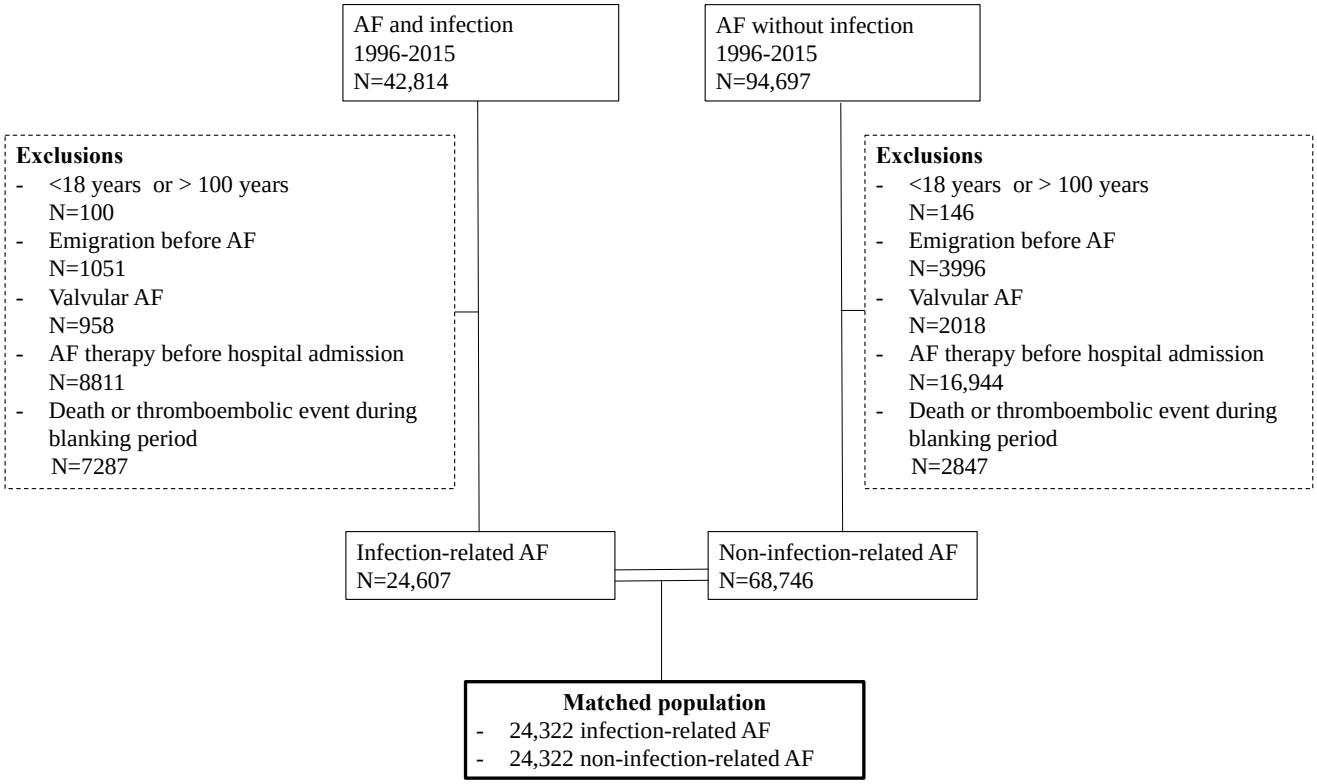
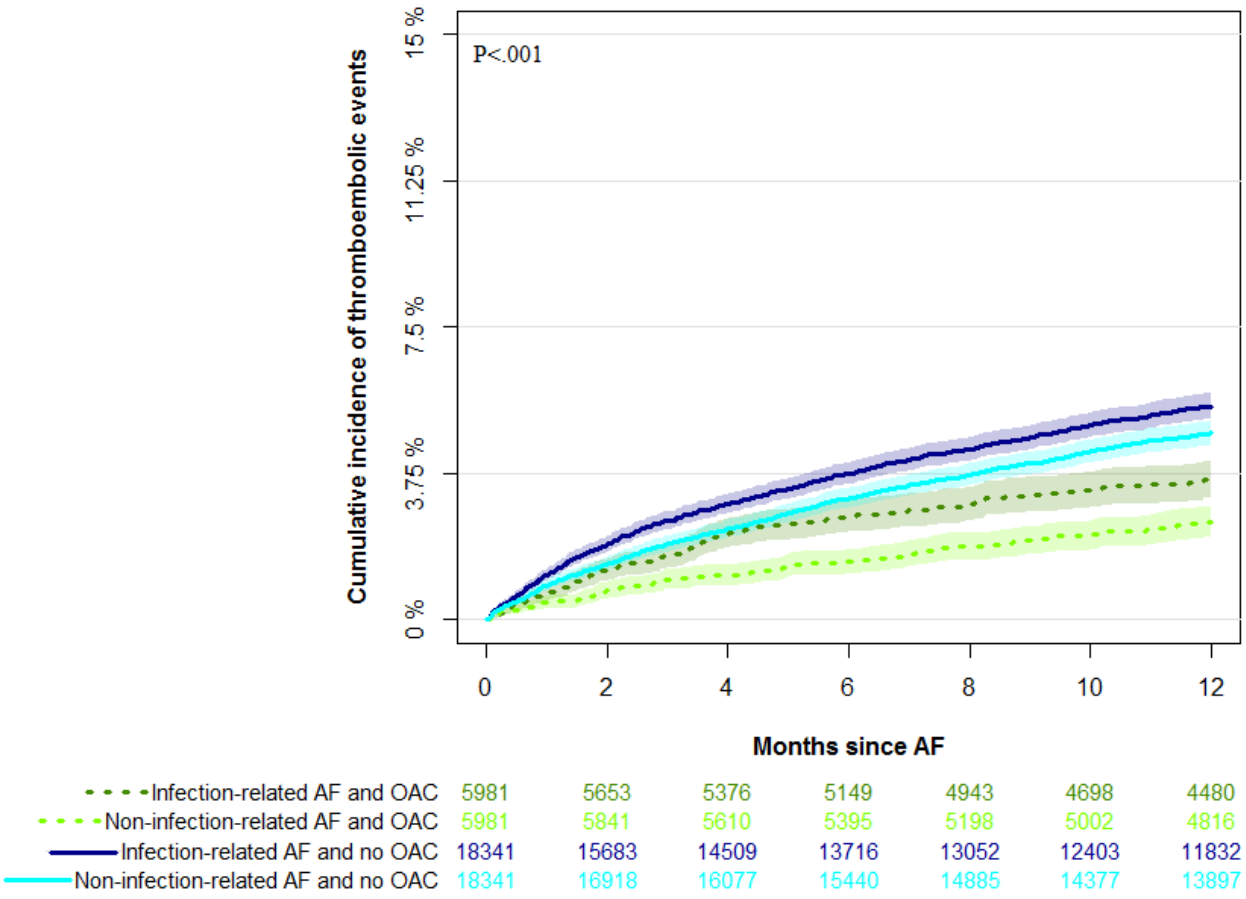


**Figure 2: Cumulative incidence of thromboembolic events in AF patients with and without a concurrent infection according to OAC therapy status at the index date. (A: thromboembolic events, 1st year since index date), B: thromboembolic events, one to five years since index date) and C: death, entire study period.** AF: atrial fibrillation. OAC: oral anticoagulation.

**A:**



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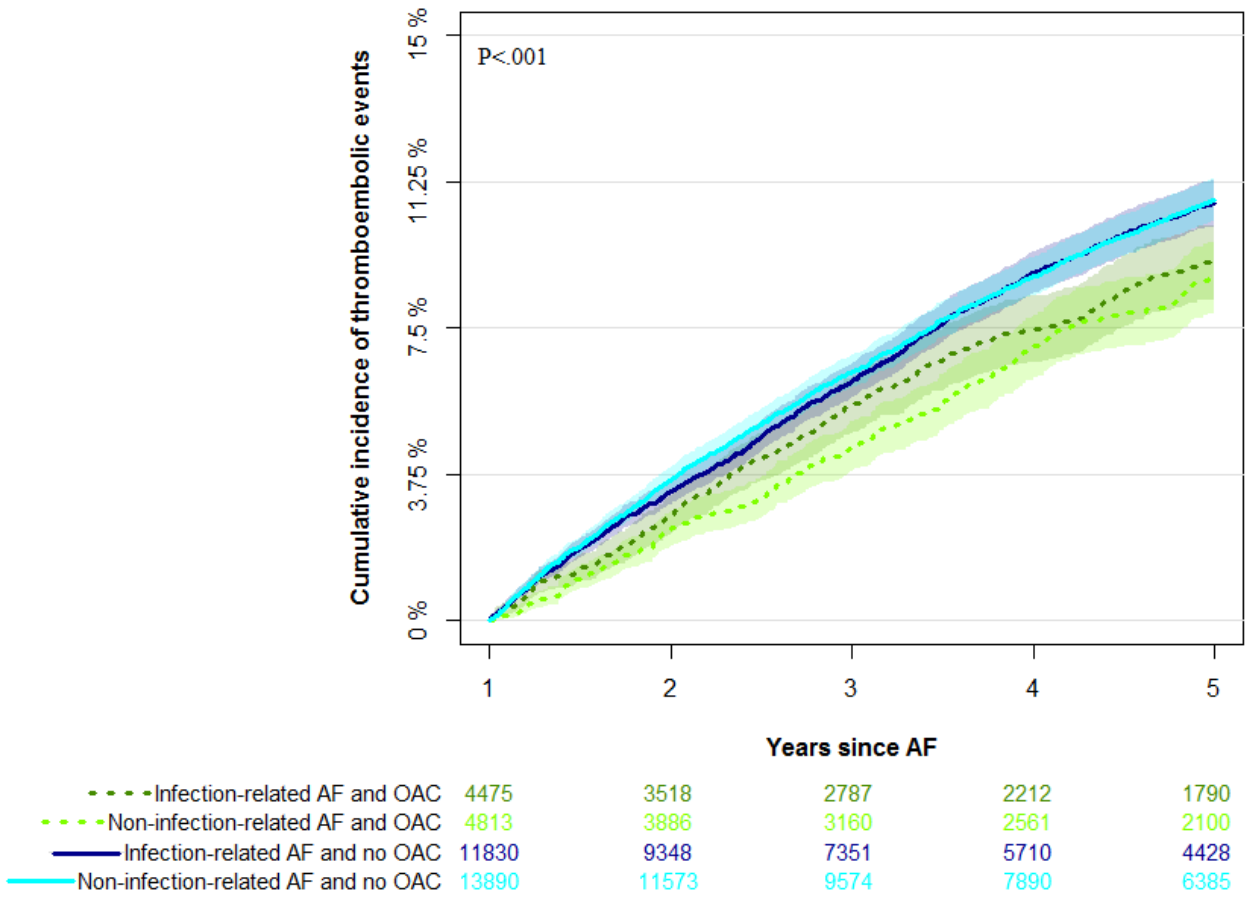

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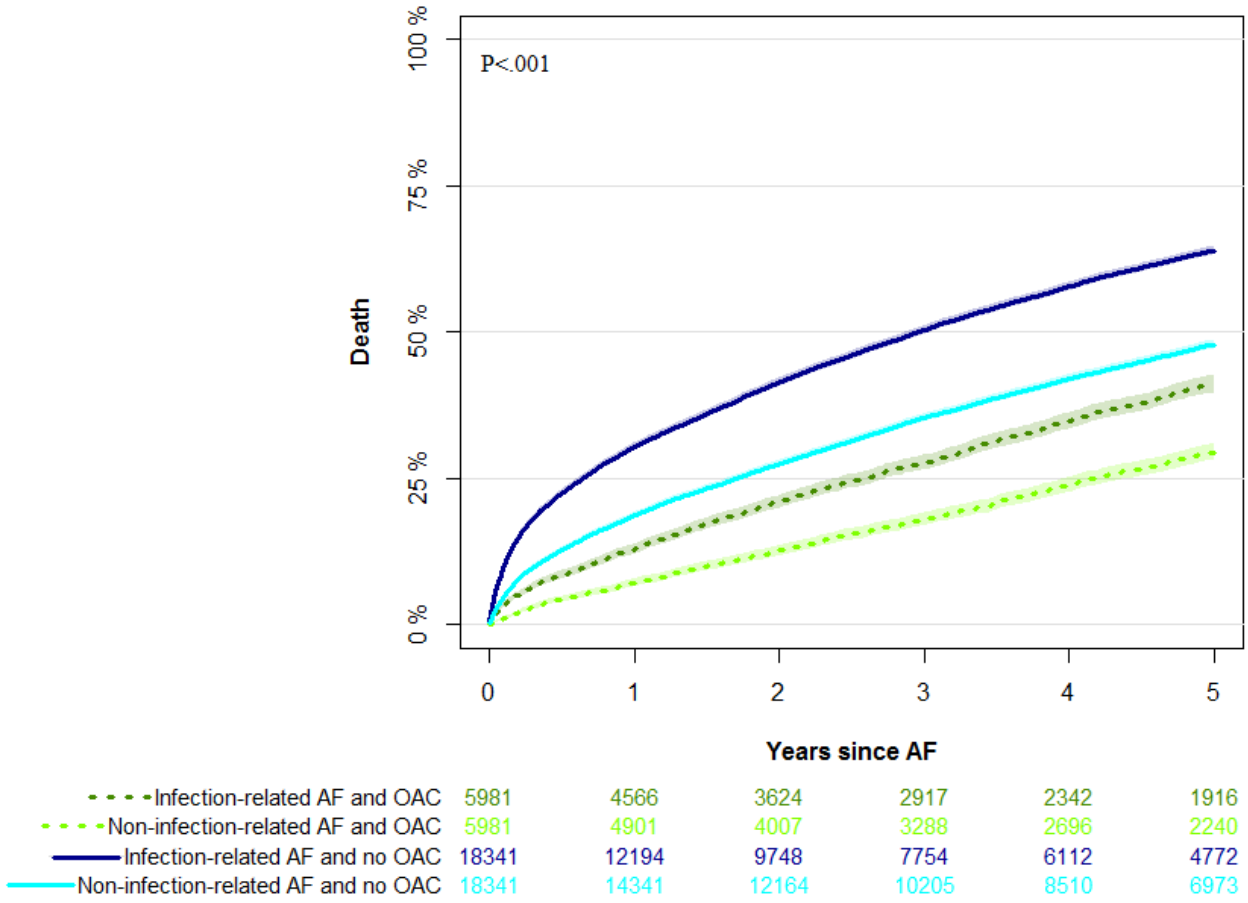

**Figure 3: Incidence rates and adjusted HRs of long-term outcomes in patients with infection-related AF and non-infection-related AF according to OAC therapy status at the index date.** AF: atrial fibrillation. CI: confidence interval. HR: hazard ratio. OAC: oral anticoagulation.

| Groups | Events | Person Years | IR* | Crude HR [95% CI] | Adjusted HR [95% CI] |
|---|---|---|---|---|---|
| ***Thromboembolic event*** | | | | | |
| ***0-1 year*** | | | | | |
| ***OAC therapy*** | | | | | |
| Non-infection-related AF | 144 | 5404 | 26.6 | 1.00 [ 1.00-1.00 ] | 1.00 [1.00, 1.00] |
| Infection-related AF | 208 | 5171 | 40.2 | 1.51 [ 1.22-1.86 ] | 1.44 [1.16, 1.78] |
| ***No OAC therapy*** | | | | | |
| Non-infection-related AF | 865 | 15606 | 55.4 | 1.00 [ 1.00-1.00 ] | 1.00 [1.00, 1.00] |
| Infection-related AF | 988 | 14006 | 70.5 | 1.26 [ 1.15-1.38 ] | 1.17 [1.06, 1.28] |
| ***>1 year*** | | | | | |
| ***OAC therapy*** | | | | | |
| Non-infection-related AF | 328 | 17788 | 18.4 | 1.00 [ 1.00-1.00 ] | 1.00 [1.00, 1.00] |
| Infection-related AF | 332 | 16044 | 20.7 | 1.15 [ 0.98-1.34 ] | 1.08 [0.93, 1.26] |
| ***No OAC therapy*** | | | | | |
| Non-infection-related AF | 1358 | 52870 | 25.7 | 1.00 [ 1.00-1.00 ] | 1.00 [1.00, 1.00] |
| Infection-related AF | 1143 | 42148 | 27.1 | 1.08 [ 1.00-1.17 ] | 1.02 [0.94, 1.11] |
| ***Bleeding*** | | | | | |
| ***OAC therapy*** | | | | | |
| Non-infection-related AF | 690 | 17686 | 39 | 1.00 [ 1.00-1.00 ] | 1.00 [1.00, 1.00] |
| Infection-related AF | 707 | 16133 | 40.7 | 1.11 [ 1.00-1.24 ] | 1.06 [0.95, 1.18] |
| ***No OAC therapy*** | | | | | |
| Non-infection-related AF | 1832 | 54460 | 33.6 | 1.00 [ 1.00-1.00 ] | 1.00 [1.00, 1.00] |
| Infection-related AF | 1929 | 43504 | 44.3 | 1.29 [ 1.21-1.38 ] | 1.19 [1.11, 1.27] |
| ***Death*** | | | | | |
| ***OAC therapy*** | | | | | |
| Non-infection-related AF | 1318 | 18971 | 69.5 | 1.00 [ 1.00-1.00 ] | 1.00 [1.00, 1.00] |
| Infection-related AF | 1920 | 17337 | 110.7 | 1.61 [ 1.50-1.73 ] | 1.44 [1.34, 1.55] |
| ***No OAC therapy*** | | | | | |
| Non-infection-related AF | 8014 | 57362 | 139.7 | 1.00 [ 1.00-1.00 ] | 1.00 [1.00, 1.00] |
| Infection-related AF | 10817 | 46289 | 233.7 | 1.62 [ 1.58-1.67 ] | 1.44 [1.40, 1.49] |

* Incidence rate per 1000 person years

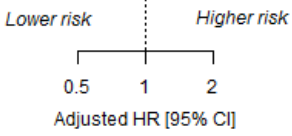

**Figure 4: Adjusted HRs of long-term outcomes in AF patients with and without a concurrent infection according to OAC therapy status at the index date.** AF: atrial fibrillation. HR: hazard ratio. CI: confidence interval. OAC: oral anticoagulation.