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Comparative thromboembolic risk in secondary and primary atrial fibrillation in a nationwide cohort

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4 1 **Comparative thromboembolic risk in secondary and primary atrial fibrillation**
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7 2 **in a nationwide cohort**
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For peer review only

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4 1 **Abstract:** 263 words (max 300 words)
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6 2 Objectives: We studied long-term outcomes in patients with different subtypes of secondary AF and
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8 compared them with primary AF.
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11 4 Design and setting: Retrospective cohort study based on Danish nationwide registries.
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13 5 Participants: All Danish residents admitted with AF for the first time from 1996-2015. Patients with
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15 secondary AF (AF with a concurrent precipitant) and patients with primary AF (AF without a
16
17 precipitant) were matched 1:1 according to age, sex, calendar year, CHA₂DS₂-VASc score, and
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19 OAC therapy status at the index date (4 weeks after discharge) resulting in a cohort of 39,723
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21 patients with secondary AF and the same number of patients with primary AF. Secondary
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23 precipitants included alcohol intoxication, thyrotoxicosis, myocardial infarction, surgery, and
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25 infection in conjunction with AF.
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29 12 Primary and secondary outcomes: The primary outcome in this study was thromboembolic events.
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31 Secondary outcomes included AF re-hospitalization and death. Long-term risks of outcomes were
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33 examined by multivariable Cox regression analysis.
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36 15 Results: The most common precipitants were infection (55.0%), surgery (13.2%), and myocardial
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38 infarction (12.0%). Among those initiated on OAC therapy as well as those not initiated on OAC
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40 therapy, secondary AF was associated with the same or an even higher thromboembolic risk than
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42 primary AF. One exception was patients with AF secondary to thyrotoxicosis: those not initiated on
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44 OAC therapy carried a lower thromboembolic risk the 1st year of follow up than matched patients
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46 with primary AF and no OAC therapy.
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50 21 Conclusions: In general, secondary AF was associated with the same thromboembolic risk as
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52 primary AF. Consequently, this study highlights the need for more research regarding the long-term
53
54 management of patients with secondary AF.
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57 24 Key words: Secondary precipitant, reversible atrial fibrillation, recurrence
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4 1 **Article summary: strengths and limitations of this study**
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- 6
7 2 • The study was based on high-quality nationwide registries with many years of follow up.
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9 3 • Complete follow-up was possible
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11 4 • Only associations could be drawn because of the retrospective and non-randomized design.
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14 5 • Secondary and primary AF were defined from diagnosis codes at discharge
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16 6 • We had no data on electrocardiograms at discharge
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1 2 3 4 1 **Introduction**

5
6 2 Atrial fibrillation (AF) may occur as an isolated event (primary AF) or together with a precipitant
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8 3 (secondary AF). AF is associated with a fivefold increased risk of ischemic stroke, and detailed
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10 4 treatment strategies regarding stroke prophylaxis in patients with primary AF exist in both
11
12 5 European and American treatment guidelines.[1–4] In contrast, there is no consensus regarding
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14 6 stroke prophylaxis in patients with secondary AF. Previous guidelines stated that AF occurring
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16 7 secondary to another precipitant usually will terminate without recurrence.[1] In current guidelines,
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18 8 however, this statement has been omitted, and the need for data regarding secondary AF
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20 9 highlighted.[3,4] Studies investigating long-term outcomes in secondary AF are sparse and data
21
22 10 differentiating between subtypes of secondary AF and taking oral anticoagulation (OAC) therapy
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24 11 into account are missing.

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26 12 To address this lack in current knowledge, we aimed to compare long-term outcomes including
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28 13 thromboembolic events, AF re-hospitalization, and death in patients with AF and a secondary
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30 14 precipitant (incl. alcohol, intoxication, thyrotoxicosis, myocardial infarction, surgery, and infection)
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32 15 and patients with primary AF. Further, we were able to differentiate between patients receiving and
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34 16 not receiving stroke prophylaxis with OAC therapy.

35 17 36 37 18 **Materials and methods**

38 19 *Data sources*

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40 20 In Denmark, healthcare is tax-financed and with equal availability regardless of socioeconomic
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42 21 status. Date of birth, date and cause of death, emigration and immigration status, diagnosis and
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44 22 surgery codes etc. from all hospital contacts, fulfilled prescriptions of medicine, and several other
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46 23 parameters are registered in different nationwide registries. Since all Danish citizens are provided a
47
48 24 unique personal identifier code at birth (or immigration), data from the registries can be crosslinked

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4 1 on an individual level. We linked data from the following registries: The Danish Civil Registration
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6 2 System,[5] The Danish National Patient Registry (diagnoses were registered in terms of the
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8 3 International Classification of Diseases (ICD) system (ICD-8 until 1994 and in terms of ICD-10
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10 4 thereafter)),[6] The Danish Register of Causes of Death,[7] and the Danish National Registry of
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12 5 Medicinal Statistics (medicine were registered according to the Anatomical Therapeutic Chemical
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14 6 classification system (ATC)).[8]
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21 8 *Study population*

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23 9 The patient selection is depicted in Figure 1. We included all Danes diagnosed and admitted to a
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25 10 hospital with AF for the first time between 1996 and 2015. Patients <18 years or >100 years and
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27 11 those with valvular AF (defined as AF without: rheumatic valve disease of aortic valve or mitral
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29 12 valve or prosthetic heart valve (any valve)) were excluded. Since there was a possibility that some
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31 13 of the patients had been diagnosed with AF at their general practitioner before their hospital
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33 14 admission, we excluded those who previously had fulfilled a prescription of antiarrhythmic therapy
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35 15 or rate-controlling drugs (incl. amiodarone, flecainide, and digoxin) and those who had fulfilled a
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37 16 prescription of OAC therapy up to 100 days before their hospital admission. Further, patients who
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39 17 died or had a thromboembolic event during the hospital admission or a constructed blanking period
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41 18 of 4 weeks from hospital discharge to the index date were excluded.
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46 19 Patients were grouped in those with secondary and primary AF, respectively. Patients who had a
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48 20 diagnosis of one of the following precipitants from their AF hospital admission were defined as
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50 21 patients with secondary AF: alcohol intoxication, thyrotoxicosis, myocardial infarction, and
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52 22 infection. Also, patients who were diagnosed with AF after, but during the same hospital admission
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54 23 they received surgery were defined as having secondary AF. Primary AF was defined as AF
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56 24 without a concurrent precipitant. We restricted the primary AF population to patients with AF as the
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1 primary diagnosis from their hospital admission. Patients with secondary AF were matched 1:1 with
2 patients with primary AF by incidence density sampling according to age (allowing a difference of
3 up to two years), sex, calendar year (allowing a difference up to two years), CHA₂DS₂-VASc group
4 (0, 1-2, >2) and OAC therapy status at the index date. These patients comprised the study
5 population. We used a previously described function to perform the match.[9]

7 *Long-term outcomes*

8 The index date was defined 4 weeks from AF hospital discharge. Initiation of OAC therapy and
9 antiarrhythmic and rate controlling drugs was assessed during this blanking period from discharge
10 to index date. Patients were followed from the index date and until the first event of the following:
11 an outcome of interest, death, 5 years from the index date, emigration, or June 30, 2015. The
12 primary outcome of interest was thromboembolic events (a composite of ischemic stroke, transient
13 ischemic attack (TIA), and systemic thrombosis or embolism) while secondary outcomes included
14 AF re-hospitalization and all-cause death. AF-rehospitalization was defined as a hospitalization
15 with AF as the primary discharge diagnosis. The diagnoses of AF, ischemic stroke, and myocardial
16 infarction have been validated in the Danish registries with positive predictive values of 93%, 97%,
17 and 100%, respectively.[10,11]

19 *Statistics*

20 Kaplan Meier curves for death were drawn and cumulative incidences of thromboembolic events
21 (with incorporated competing risk of death) calculated using the Aalen Johansen estimator. The
22 Log-Rank test and the Gray's test were used to test for differences in the cumulative incidence of
23 long-term outcomes. Cox regression analyses were performed to calculate hazard ratios (HR) of
24 long-term outcomes in patients with secondary vs. primary AF according to OAC therapy at the

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4 1 index date. The multivariate models were adjusted for comorbidities at the index date (incl.
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6 2 peripheral artery disease, heart failure, hypertension, prior thromboembolic event, ischemic heart
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9 3 disease, chronic kidney disease, diabetes, prior bleeding event, cancer) and antiarrhythmic and rate-
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11 4 controlling therapy during the blanking period (amiodarone, digoxin, flecainide). The analyses took
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13 5 matching variables into account and each secondary AF group was compared with its respective
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15 6 matches from the matching procedure. The models were tested for the assumption of proportional
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17 7 hazards. For specification of diagnosis codes and ATC-codes please see Online Table 1. A P-value
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19 8 <0.05 was considered statistically significant. All statistical analyses were performed in SAS
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21 9 statistical software version 9.4 or R.[12]
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28 11 *Other analyses*

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30 12 Analyses of long-term outcomes were also performed on a non-matched population including all
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32 13 patients available before the matching (Figure 1).
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37 15 *Ethics*

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39 16 Approval from the Research Ethics Committee System is not required in retrospective registry-
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41 17 based studies in Denmark. The Danish Data Protection Agency approved use of data for this study
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43 18 (ret.no: 2007-58-0015 / GEH-2014-013 I-Suite no: 02731).
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48 20 **Results**

49 50 21 *Study population*

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52 22 As shown in Figure 1, the most common precipitant was infection (21,824 patients, 55.0%).
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54 23 Further, 335 (0.8%) patients had a concurrent alcohol intoxication, 2507 (6.3%) had thyrotoxicosis,
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56 24 4773 (12.0%) had acute myocardial infarction, 5229 (13.2%) had underwent surgery, and 5055
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(12.7%) had >1 precipitant. Of those with >1 precipitant, 4788 (94.7%) patients had two secondary precipitants, while 267 (5.3%) had three or four precipitants. Infection and surgery was the most common combination of precipitants. The patients with >1 precipitant were grouped in one group, and were not included in the other groups of patients with secondary AF. During the blanking period, 14% of the patients with secondary AF and 2% of the patients with primary AF died, while 5% and 2%, respectively, had a thromboembolic event. These patients were excluded before the matching.

Baseline characteristics

Baseline characteristics of the matched study population are shown in Table 1. In general, patients with secondary AF had more comorbidities than patients with primary AF. Baseline characteristics of the non-matched population according to OAC therapy at the index date are shown in online Table 2 and 3. Especially those with AF secondary to myocardial infarction, surgery, infection, and >1 precipitant were older, had more comorbidities, and higher risk scores for stroke and bleeding compared with patients with primary AF. Among the patients with secondary AF (non-matched study population), 9.9% with alcohol intoxication, 43.9% with thyrotoxicosis, 27.2% with myocardial infarction, 21.9% with surgery, 27.1% with infection, and 21.4% with >1 precipitant received OAC therapy at the index date, respectively. Among patients with primary AF, 38.5% received OAC therapy at the index date. In general for patients with secondary as well as patients with primary AF, those initiated on OAC therapy suffered from less cancer, chronic kidney disease, peripheral artery disease, and had fewer previous bleeding events than those not initiated on OAC. 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.

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4 1 *Long-term outcomes*

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6 2 During follow up, the cumulative incidence of thromboembolic events (taking death as an
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9 3 competing risk into account) was 8.3% (alcohol intoxication), 8.5% (thyrotoxicosis), 12.1%
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11 4 (myocardial infarction), 11.6% (surgery), 12.2% (infection), 10.1% (>1 precipitant), and 12.3%
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13 5 (primary AF). Figure 2 depicts cumulative incidences of thromboembolic events and death in
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15 6 patients with secondary vs. primary AF. Number of events, incidence rates, and crude and adjusted
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17 7 hazard ratios (HRs) of thromboembolic events and death in patients with secondary AF compared
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19 8 with patients with primary AF initiated and not initiated on OAC therapy at the index date are
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21 9 presented in Figure 3. With few exceptions, secondary AF was associated with the same
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23 10 thromboembolic risk as primary AF. Regardless of OAC therapy status at the index date, AF
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25 11 secondary to infection was associated with a significantly increased risk of thromboembolic events
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27 12 compared with primary AF. Among those not initiated on OAC therapy, AF secondary to
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29 13 thyrotoxicosis was associated with a significantly lower risk of thromboembolic events compared
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31 14 with primary AF. In those initiated on OAC therapy, no differences in thromboembolic risk was
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33 15 observed between patients with AF secondary to thyrotoxicosis and primary AF.
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41 17 OAC therapy initiation compared with no OAC therapy initiation was associated with a lower
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43 18 thromboembolic risk in patients with secondary as well as primary AF, although the results did not
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45 19 reach statistical significance in patients with AF secondary to alcohol intoxication, thyrotoxicosis,
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47 20 myocardial infarction, and surgery (Figure 4). From the index date to end of follow up, the
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49 21 cumulative incidences of AF re-hospitalization (taking death as a competing risk into account) were
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51 22 19.6% (alcohol intoxication), 30.8% (thyrotoxicosis), 27.2% (myocardial infarction), 14.8%
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53 23 (surgery), 20.9% (infection), 19.3% (>1 precipitant), and 34.4% (primary AF). In multivariable
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55 24 Cox regression models the risk of AF re-hospitalizations in patients with secondary vs. primary AF
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4 1 were: HR 0.40, 95% confidence interval 0.28-0.58 (alcohol intoxication), HR 0.66, 95% CI 0.59-
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6 2 0.73 (thyrotoxicosis), HR 0.73, 95% CI 0.65-0.82 (myocardial infarction), HR 0.52, 95% CI 0.48-
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8 3 0.57 (surgery), HR 0.61, 95% CI 0.59-0.64 (infection), and HR 0.46, 95% CI 0.42-0.51 (>1
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10 precipitant)).
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16 6 *Other analyses*

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18 7 The long-term risk of thromboembolic events for patients with secondary vs. primary AF in the
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20 8 non-matched population were comparable to the risks found in the main analysis, except that AF
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22 9 secondary to thyrotoxicosis reached statistical significance and hence was associated with a
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24 significantly lower risk of thromboembolic events (HR 0.75, 95% CI 0.60-0.95 for those initiated
25 10 on OAC therapy and HR 0.77, 95% CI 0.64-0.92 for those not initiated on OAC therapy). Further,
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27 11 among those initiated on OAC therapy, AF secondary to surgery AF was associated with an
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29 12 increased risk of thromboembolic events (HR 1.23, 95% CI 1.01-1.50)
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36 15 **Discussion**

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39 16 We examined long-term outcomes in patients with secondary and primary AF. The study had two
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41 17 main findings: first, different subtypes of secondary AF were in general associated with the same
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43 18 thromboembolic risk as primary AF. Secondly, OAC initiation-rates differed significantly across
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45 19 secondary AF subtypes. Further, OAC therapy vs. no OAC therapy were associated with a lower
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47 20 thromboembolic risk in those with AF secondary to infections and >1 precipitant while no
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49 21 significant risk-reduction was seen for patients with AF secondary to the other precipitants.
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55 23 *Thromboembolic risk*

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4 1 Despite of lower re-hospitalization rates with AF, secondary AF was in general associated with the
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6 2 same thromboembolic risk as primary AF. AF secondary to thyrotoxicosis was associated with a
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9 3 lower thromboembolic risk compared with primary. In contrast, AF secondary to infections were
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11 4 associated with an increased thromboembolic risk compared with primary AF. This is in accordance
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14 5 with previous findings.[13–15] In two previous studies, Lubitz et al. and Fauchier et al. examined
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16 6 long-term outcomes in patients with AF secondary to a reversible precipitant compared with
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18 7 primary AF in patients. In both studies, AF secondary to a reversible precipitant was associated
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20 8 with the same thromboembolic risk as presumed primary AF. However, both studies were smaller
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23 9 and with patients included before 2012 and 2010, respectively.[16,17] In summary, our results
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25 10 together with previous studies suggest that secondary AF in general, and maybe with the exception
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28 11 of AF secondary to thyrotoxicosis, may be considered at as similar to primary AF with respect to
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30 12 thromboembolic risk.

31 32 13 33 34 14 *OAC therapy*

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36 15 OAC therapy showed a tendency towards a lower thromboembolic risk in secondary AF patients,
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39 16 but did only reach statistical significance for patients with AF secondary to infection and >1
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41 17 precipitant. Recently, Quon et al. examined risk of thromboembolic events and bleeding in patients
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44 18 with AF secondary to acute coronary syndrome, acute pulmonary disease, and infection according
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46 19 to OAC therapy status after discharge. In that study, OAC therapy was not associated with lower
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48 20 risk of thromboembolic events in patients with AF secondary to the before mentioned precipitants.
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51 21 However, the analyses on long-term outcomes were based on logistic regression analysis, and did
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53 22 therefore not include survival time in the model. Since patients with secondary AF in our study
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55 23 seemed to die at a higher rate than patients with regular AF, the time perspective is crucial when
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58 24 studying long-term outcomes in this setting.[18] Studies with a clinical randomized design would
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4 1 be able to show whether patients with secondary AF benefit from OAC therapy on the same terms
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6 2 as patients with primary AF.
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11 4 *OAC treatment-rates*

13 5 The non-matched population allowed us to describe trends in OAC therapy initiation in patients
14 6 with secondary and primary AF. In patients with primary AF, 38.5% of the patients were initiated
15 7 on OAC therapy at the index date. This is in accordance with previous findings, taking into account
16 8 that our study period went back to 1996 when treatment rates were lower than today.[19,20] In
17 9 2017, Chean et al. assessed current practice of AF among critically ill patients with new-onset AF.
18 10 The study was based on questionnaires answered by members of the Intensive Care Society in UK.
19 11 The results revealed that 63.8% of the respondents would not regularly anti-coagulate critically ill
20 12 patients with new-onset AF. We found important differences in OAC therapy initiation rates in
21 13 patients with secondary AF according to precipitant. Patients with alcohol intoxication had the
22 14 lowest initiation rate of OAC therapy (9.9%). Almost 50% of this patient group had a CHA₂DS₂-
23 15 VASc score of 0 and hence no indication for OAC therapy. Further patients with alcohol abuse may
24 16 have poor compliance and increased bleeding risk.[21] Consequently, there may be caution among
25 17 physicians in prescribing OACs for this patient group. In 2011, Traube and colleagues reviewed the
26 18 literature with respect to thromboembolic risk in patients with AF secondary to thyrotoxicosis. They
27 19 concluded that OAC therapy should be initiated for those patients who did not have any
28 20 contraindications for treatment.[22] This could explain the high OAC treatment initiation rates in
29 21 this patient group (43.9%).
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55 23 *Limitations*

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4 1 First of all, this study was a retrospective registry-based study and hence no causative relationships
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6 2 can be drawn. Our definition of secondary AF was based on a hospital admission with AF and a
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8 3 reversible precipitant. Both diagnoses were registered at the discharge date, and therefore we may
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10 4 have included patients in the secondary AF group who developed AF before the precipitant (e.g.
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12 5 patients admitted with AF who developed infection during their hospital stay), and thereby should
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14 6 have been classified as patients with primary AF. Moreover, we had no access to patient files, and
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16 7 we did not know whether the patients were discharged in sinus rhythm or with AF. Also, no data
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18 8 were available with regard to the physicians' considerations when choosing between OAC therapy
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20 9 and no OAC therapy. However, this study was based on a nationwide cohort of patients with many
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22 10 years of follow-up and data from high-quality registries. It reveals unexpected results that should be
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24 11 considered in future treatment guidelines for patients with secondary AF.
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32 13 *Conclusion*

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34 14 In this study we found that patients with secondary AF carried a similar associated thromboembolic
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36 15 risk as those with primary AF. Current guidelines lack data on this subject and our results suggests
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38 16 that AF in relation to known triggers may be considered as other singular AF.
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44
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47 20 for-profit sectors.
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52 22 **Conflicts of interest**

53
54 23 AG: None. TK: Consultant fees from BMS, Astra Zeneca, Roche, Boehringer-Ingelheim, Bayer,
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56 24 MSD. JBO: Speaker for Bristol-Myers Squibb, Boehringer Ingelheim, Bayer, and AstraZeneca.
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16 6

7 **Author contributions**

8 The study idea was conceived by AG, TK, and ELF, study design was developed by AG, TK, JBO,
9 ANB, JHB, GHG, CTP, LK, and ELF, data analyses were made by AG. AG drafted the first version
10 of the paper and all authors participated in the critical discussions and interpretation of findings. All
11 authors have participated in the revisions of the draft and have approved the final version.
12

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14 None.

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4 **1 Figure legends**

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7 2 Figure 1: Patient selection

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9 3 Figure 2: Cumulative incidence of long-term outcomes by secondary precipitant and OAC therapy
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11 4 at the index date. A: Thromboembolic events, B: Death

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13 5 Figure 3: Number of events, incidence rates, and crude and adjusted Hazard ratios of long-term
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15 6 outcomes in patients with secondary vs. primary AF

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18 7 Figure 4: Adjusted hazard ratios of long-term outcomes in patients with AF initiated vs. not
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20 8 initiated on OAC therapy (stratified according to type of AF)
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Table 1: Baseline characteristics of the matched population

	Alcohol intoxication group		Thyrotoxicosis group		Myocardial infarction group		Surgery group		Infection group		>1 precipitant group	
	Sec. AF N=335	Prim. AF N=335	Sec. AF N=2507	Prim. AF N=2507	Sec. AF N=4773	Prim. AF N=4773	Sec. AF N=5229	Prim. AF N=5229	Sec. AF N=21,824	Prim. AF N=21,824	Sec. AF N=5055	Prim. AF N=5055
Demographics												
Age, median (IQR*)	59 (49-66)	59 (49-66)	73 (63-81)	73 (63-81)	77 (69-83)	77 (69-83)	75 (67-82)	75 (67-82)	79 (71-86)	79 (71-86)	76 (68-83)	76 (68-83)
Male, n (%)	276 (82.4)	276 (82.4)	521 (20.8)	521 (20.8)	2705 (56.7)	2705 (56.7)	2724 (52.1)	2724 (52.1)	10,370 (47.5)	10,370 (47.5)	2676 (52.9)	2676 (52.9)
Comorbidities, n (%)												
Cancer	16 (4.8)	29 (8.7)	288 (11.5)	296 (11.8)	586 (12.3)	688 (14.4)	1349 (25.8)	882 (16.9)	4341 (19.9)	3571 (16.4)	958 (19.0)	807 (16.0)
Chronic kidney disease	11 (3.3)	8 (2.4)	61 (2.4)	49 (2.0)	289 (6.1)	233 (4.7)	352 (6.7)	198 (3.8)	1564 (7.2)	748 (3.4)	431 (8.5)	212 (4.2)
COPD†	28 (8.4)	23 (6.9)	234 (9.3)	221 (8.8)	619 (13.0)	565 (11.8)	665 (12.7)	520 (9.9)	4696 (21.5)	2093 (9.6)	914 (18.1)	519 (10.3)
Diabetes	26 (7.8)	18 (5.4)	189 (7.5)	159 (6.3)	575 (12.0)	556 (11.6)	503 (9.6)	423 (8.1)	2167 (9.9)	1737 (8.0)	498 (9.9)	554 (11.0)
Heart failure	24 (7.2)	18 (5.4)	445 (17.8)	388 (15.5)	1660 (34.8)	1076 (22.5)	966 (18.5)	851 (16.3)	5109 (23.4)	3709 (17.0)	1574 (31.1)	925 (18.3)
Hypertension	64 (19.1)	78 (23.3)	1309 (52.2)	1249 (49.8)	3290 (68.9)	3204 (67.1)	2484 (47.5)	2695 (51.5)	10,445 (47.9)	11,475 (52.6)	2694 (53.3)	3007 (59.5)
IHD‡	43 (12.8)	53 (15.8)	333 (13.3)	455 (18.1)	4773 (100)	1604 (33.6)	1753 (33.5)	1332 (25.5)	4696 (21.5)	5069 (23.2)	3072 (60.8)	1423 (28.2)
PAD§	7 (2.1)	8 (2.4)	78 (3.1)	83 (3.3)	375 (7.9)	293 (6.1)	468 (9.0)	233 (4.5)	1392 (6.4)	932 (4.3)	448 (8.9)	269 (5.3)
Prior bleeding event	81 (24.2)	42 (12.5)	243 (9.7)	249 (9.9)	722 (15.1)	715 (15.0)	1267 (24.2)	833 (15.9)	4319 (19.8)	3463 (15.9)	1171 (23.2)	811 (16.0)
Prior thromboembolic event	24 (7.2)	24 (7.2)	138 (5.5)	183 (7.3)	483 (10.1)	698 (14.6)	571 (10.9)	570 (10.9)	2651 (12.1)	2278 (10.4)	603 (11.9)	635 (12.6)
Risk scores												
CHA ₂ DS ₂ -VASC												
Median (IQR*)	1 (0-2)	1 (0-2)	3 (2-4)	3 (2-4)	4 (3-5)	3 (3-4)	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)	4 (2-5)	3 (2.4)
0	158 (47.2)	158 (47.2)	405 (16.2)	405 (16.2)	0	0	391 (7.5)	391 (7.5)	1328 (6.1)	1328 (6.1)	269 (5.3)	269 (5.3)
1-2	118 (35.2)	118 (35.2)	530 (3.0)	530 (3.0)	670 (14.0)	670 (14.0)	1406 (26.9)	1406 (26.9)	5148 (23.6)	5148 (23.6)	1005 (19.9)	1005 (19.9)
≥3	59 (17.6)	59 (17.6)	1572 (62.7)	1572 (62.7)	4103 (86.0)	4103 (86.0)	3432 (65.6)	3432 (65.6)	15,348 (70.3)	15,348 (70.3)	3781 (74.8)	3781 (74.8)
HAS-BLED [#]												
Median (IQR*)	2 (1-3)	1 (0-2)	2 (1-3)	2 (1-3)	3 (2-3)	2 (2-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (2-3)	2 (2-3)
0	0	0	355 (14.2)	331 (13.2)	134 (2.8)	76 (1.6)	289 (5.5)	381 (7.3)	1003 (4.6)	1147 (5.2)	208 (4.1)	242 (4.8)
1-2	232 (69.3)	155 (46.3)	1460 (58.2)	1440 (57.4)	2552 (53.5)	2863 (54.8)	2863 (54.8)	2935 (56.1)	12,130 (55.6)	12,129 (55.6)	2422 (47.9)	2638 (52.2)
≥3	103 (30.8)	52 (15.5)	692 (27.6)	736 (29.4)	2145 (6.7)	2077 (6.5)	2077 (39.7)	1913 (36.6)	8691 (39.8)	8548 (39.2)	2425 (48.0)	2175 (43.0)
Pharmacotherapy, n (%)												
OAC ^{**} therapy, n (%)	33 (9.9)	33 (9.9)	1100 (43.9)	1100 (43.9)	1311 (27.5)	1311 (27.5)	1150 (22.0)	1150 (22.0)	5985 (27.4)	5985 (27.4)	1087 (21.5)	1087 (21.5)
Amiodarone	≤3	6 (1.8)	33 (1.3)	62 (2.5)	359 (7.5)	158 (3.3)	443 (8.5)	163 (3.1)	617 (2.8)	574 (2.6)	418 (8.3)	154 (3.0)

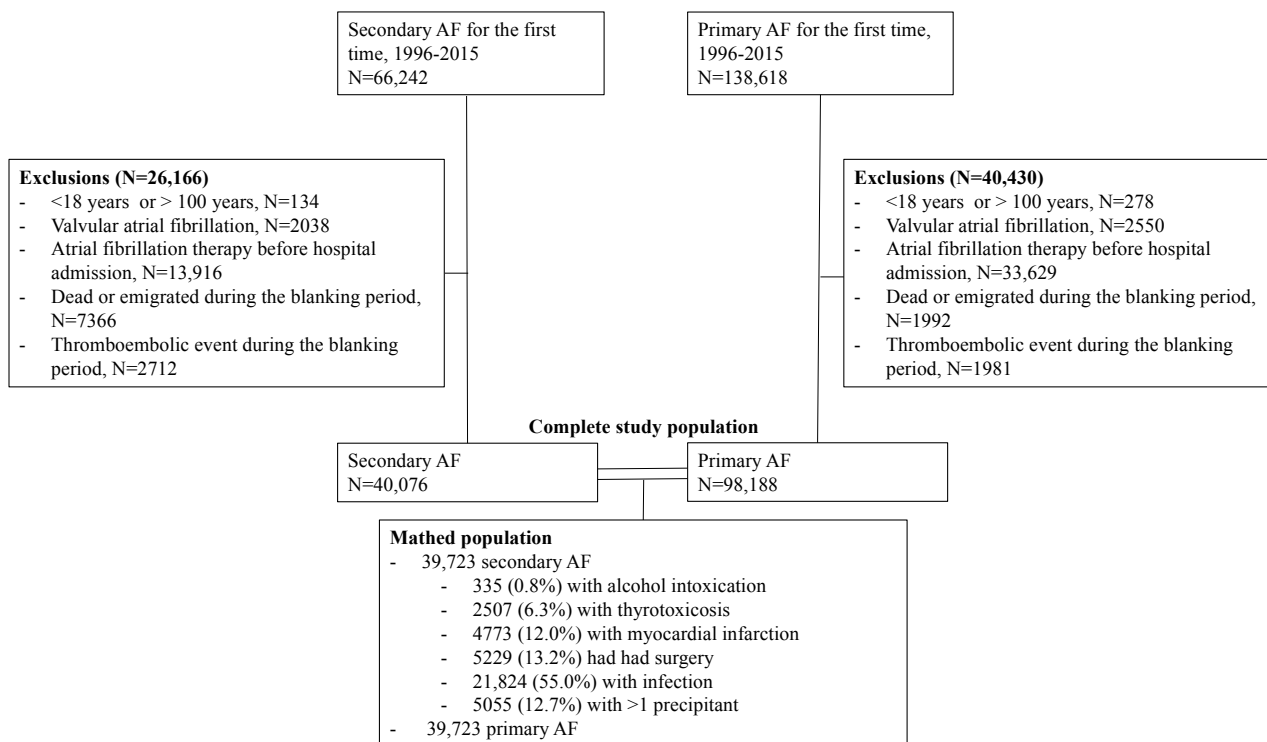
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Digoxin	49 (14.6)	29 (8.7)	1000 (39.9)	916 (36.5)	1207 (25.3)	1502 (31.5)	1089 (20.8)	1285 (24.6)	7973 (36.5)	6286 (28.8)	1184 (23.4)	1223 (24.2)
Flecainide	0 (0)	≤ 3	13 (0.5)	29 (1.2)	9 (0.2)	32 (0.7)	12 (0.2)	52 (1.0)	40 (0.2)	156 (0.7)	6 (0.1)	27 (0.5)

*IQR: interquartile range. †COPD: chronic obstructive pulmonary disease. ‡IHD: ischemic heart disease. §PAD: peripheral artery disease. ||CHA₂DS₂-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. **OAC: oral anticoagulation.

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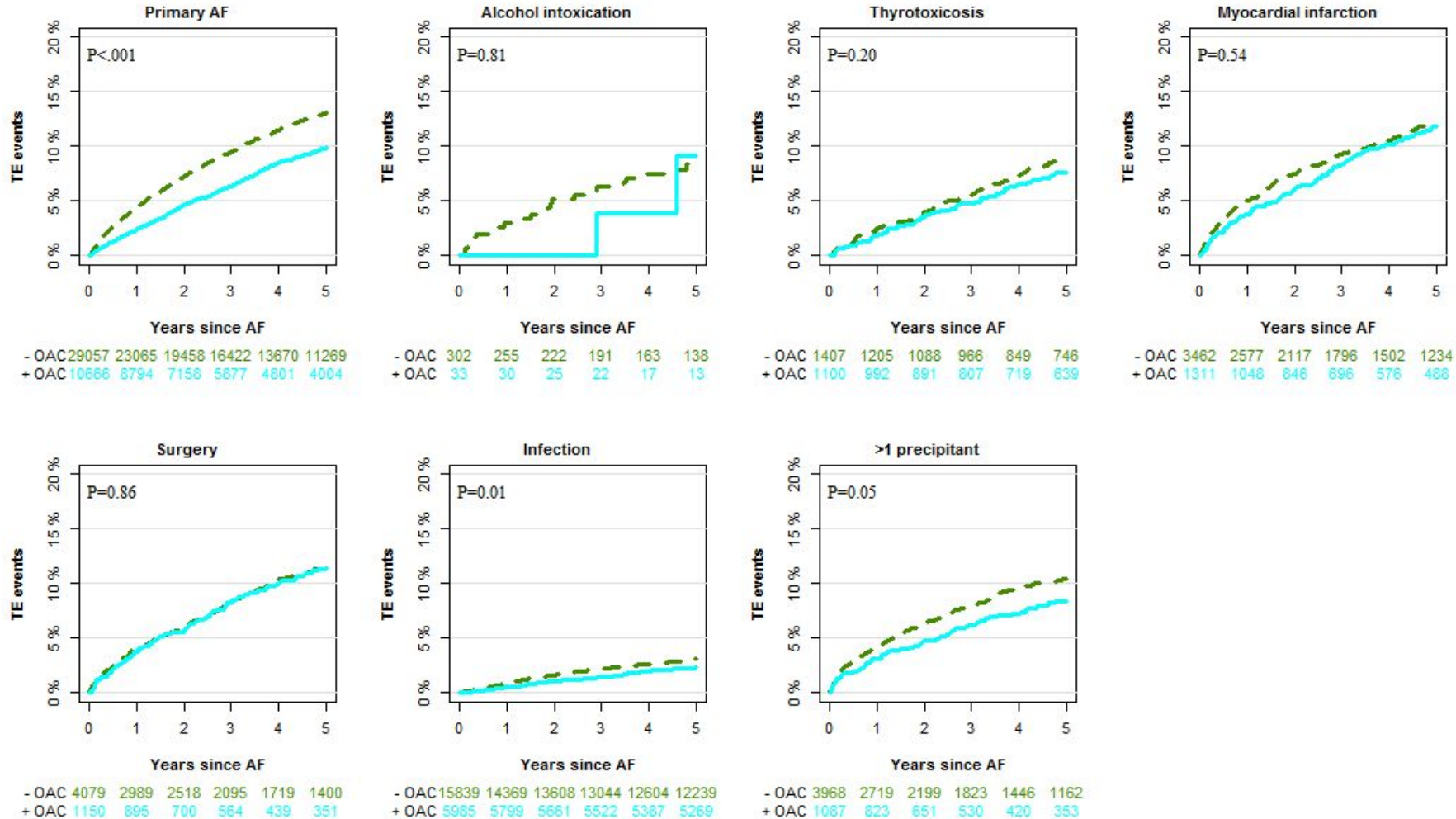
Figure 1: Patient selection



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Figure 2: Cumulative incidence of long-term outcomes by type of AF and OAC therapy at the index date

A: Thromboembolic events



B: Death

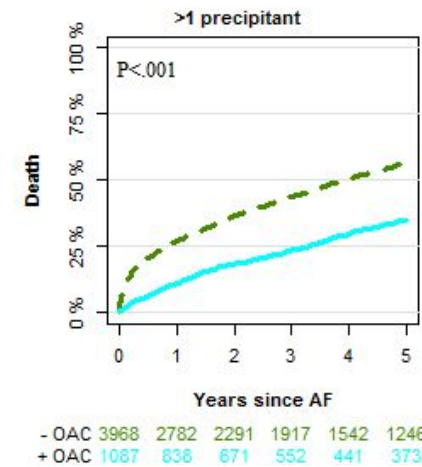
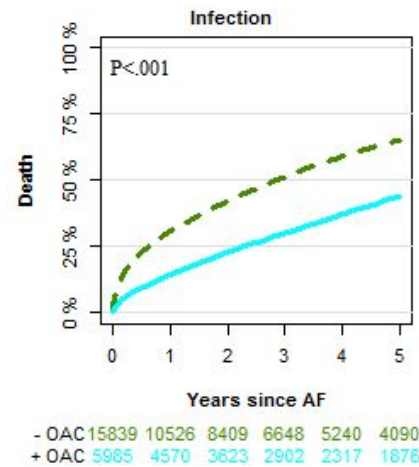
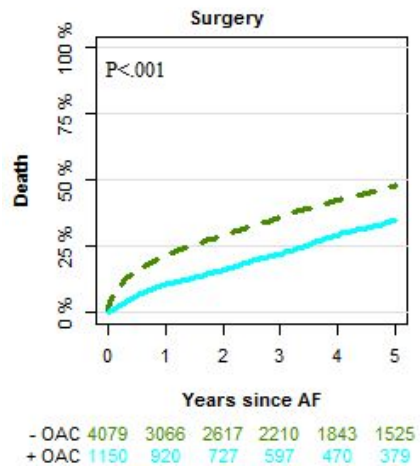
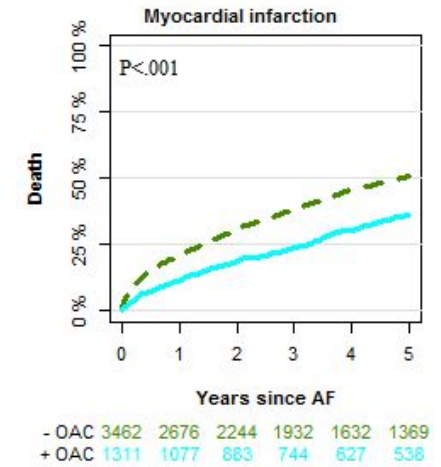
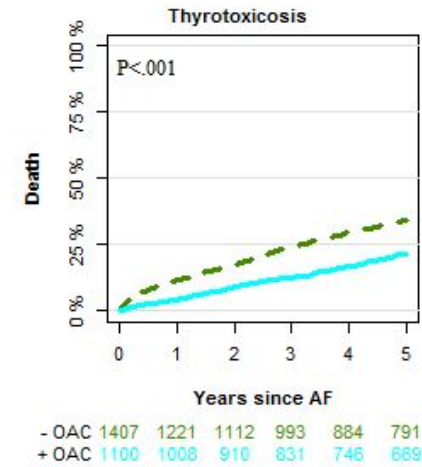
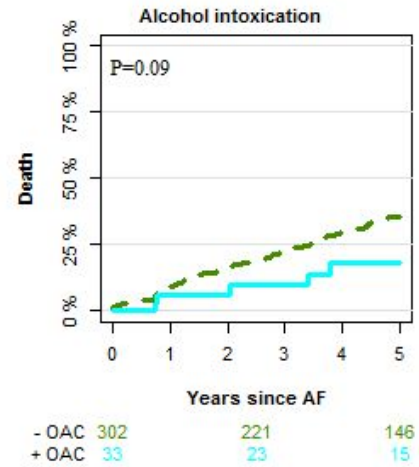
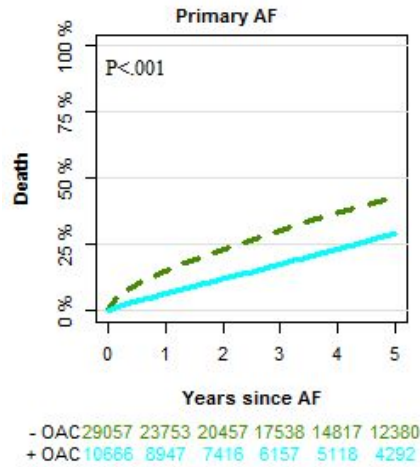
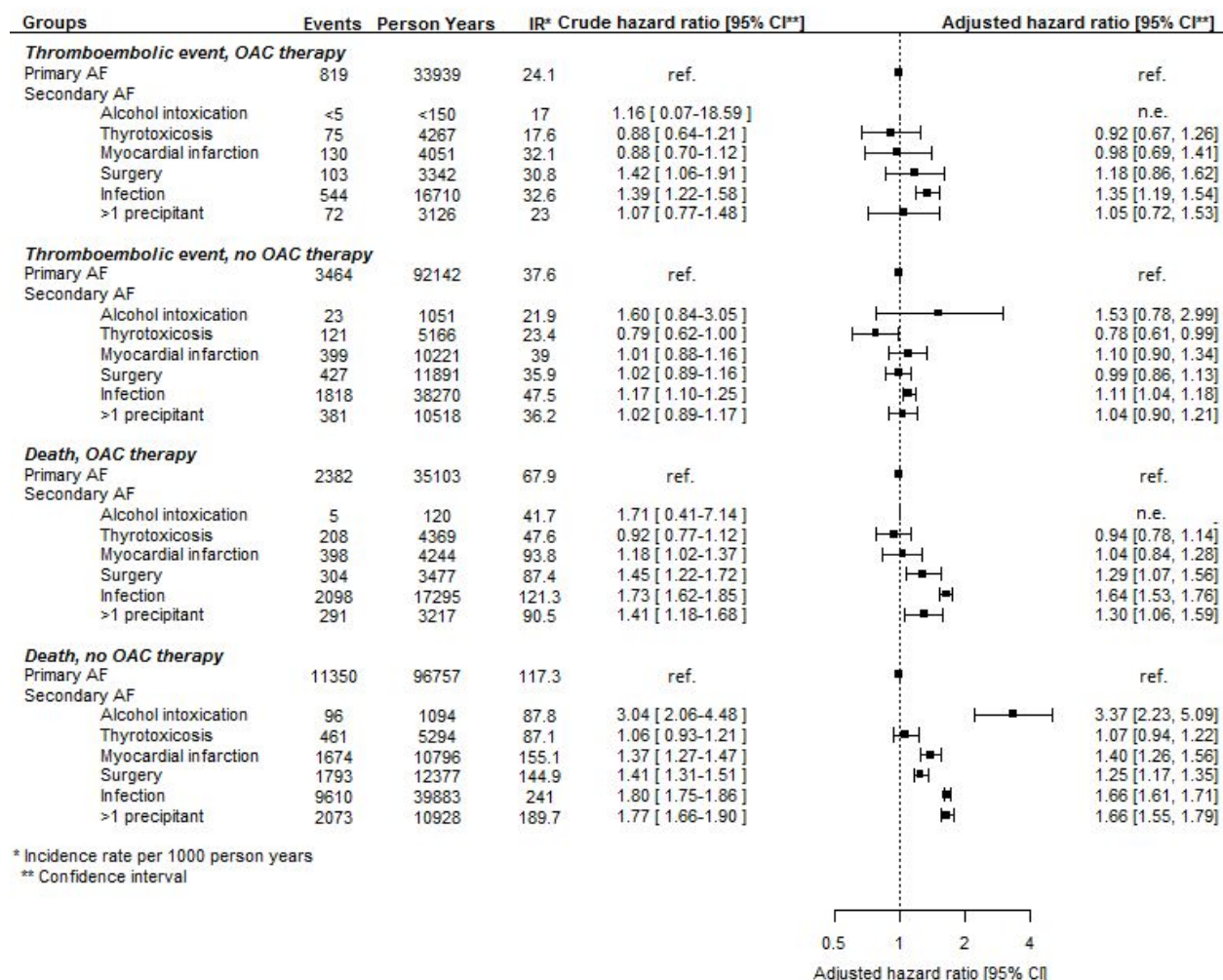
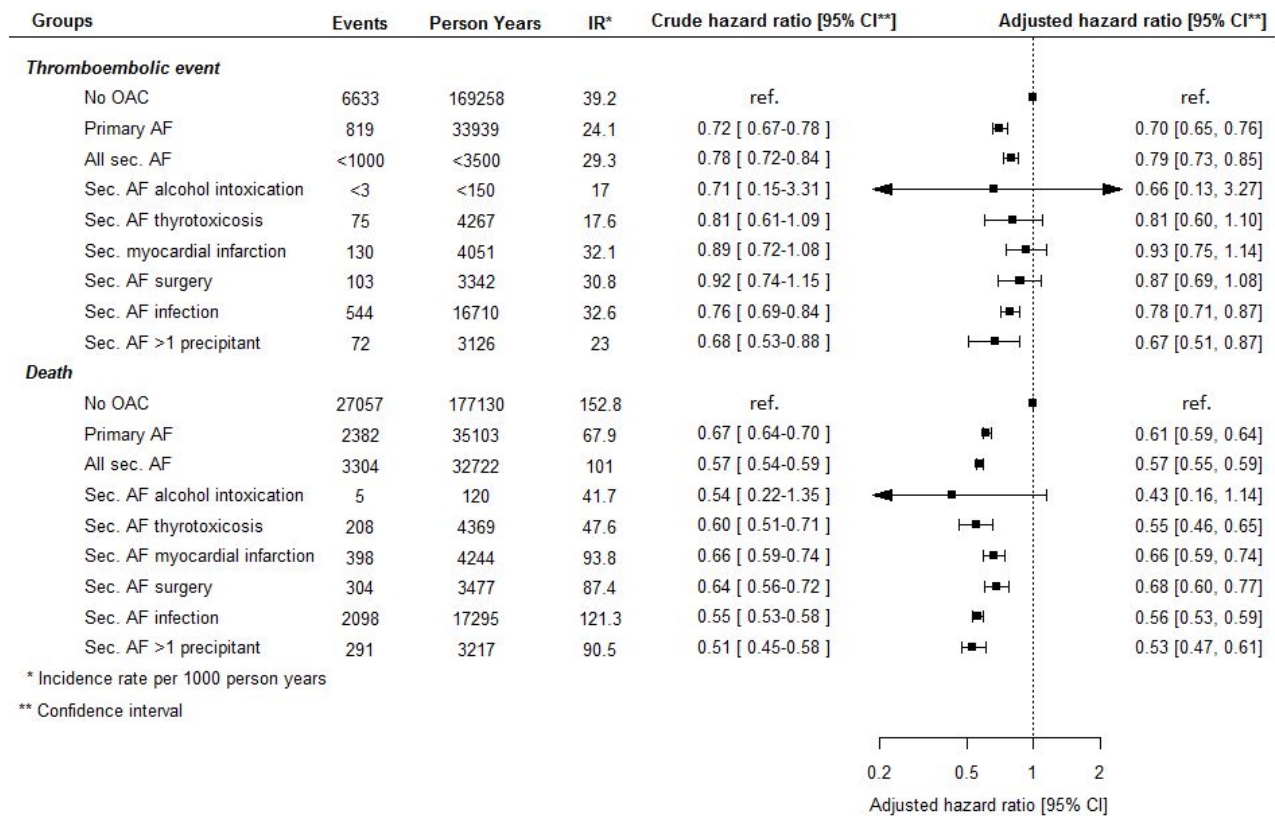


Figure 3: Number of events, incidence rates, and crude and adjusted hazard ratios of long-term outcomes in patients with secondary vs. primary AF according to secondary precipitant and OAC therapy at the index date



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.

Figure 4: 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, 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.

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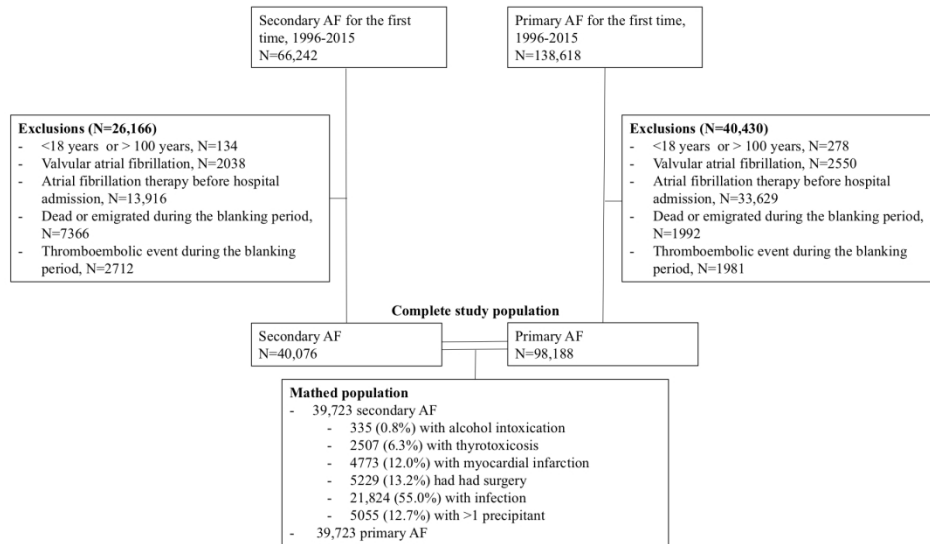


Figure 1

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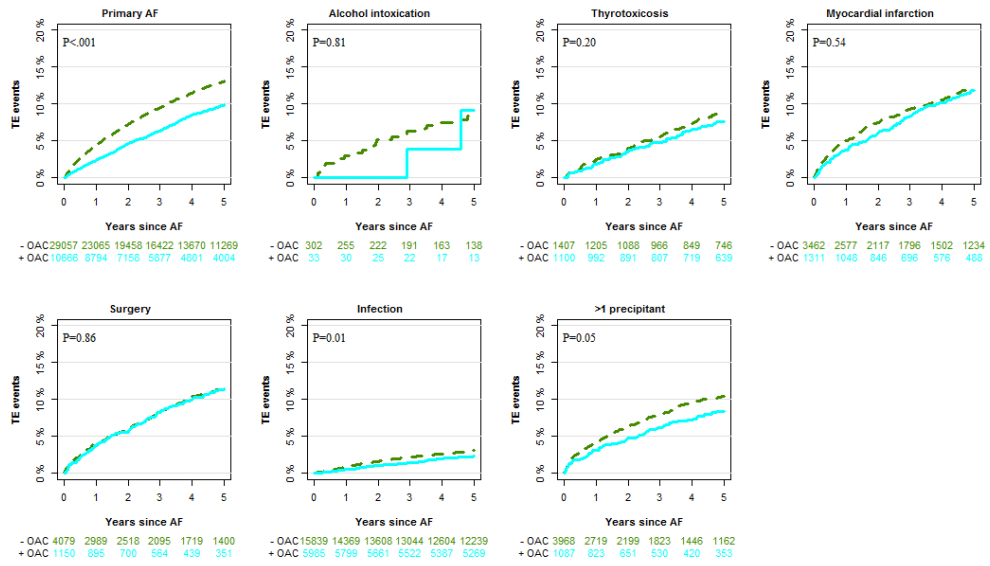


Figure 2A

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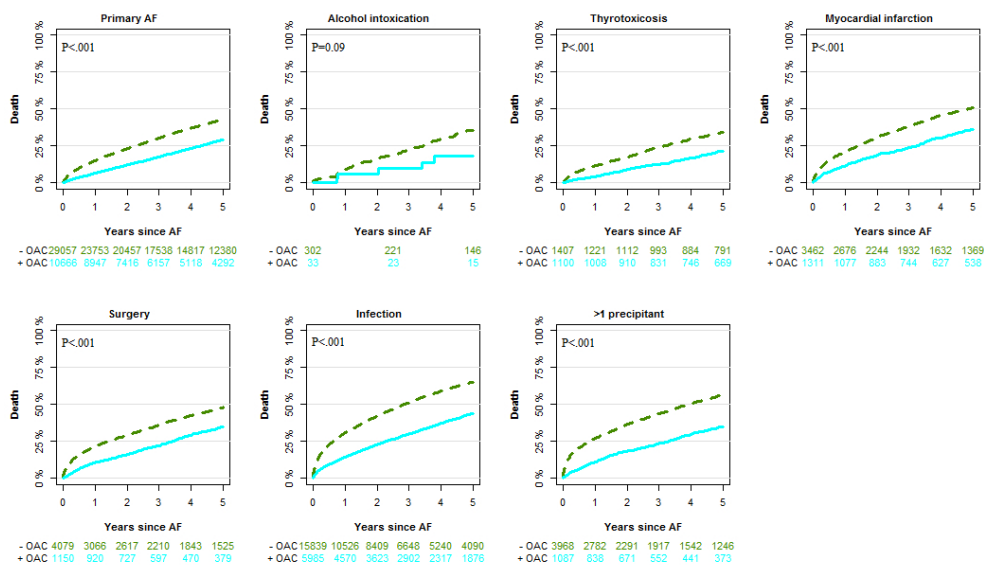


Figure 2B

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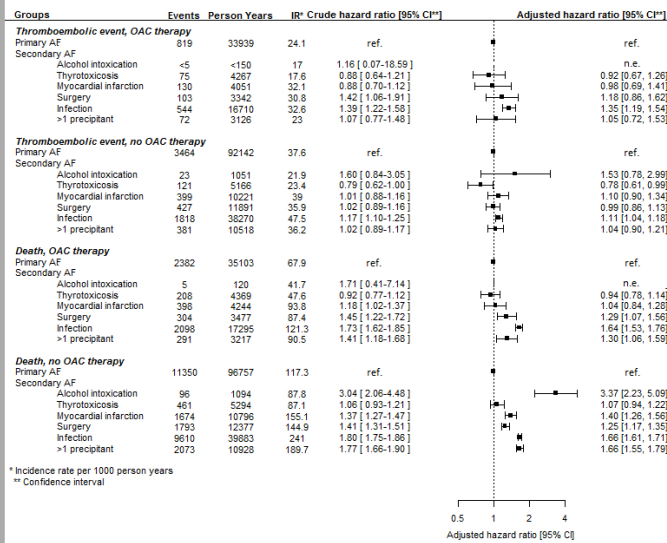


Figure 3

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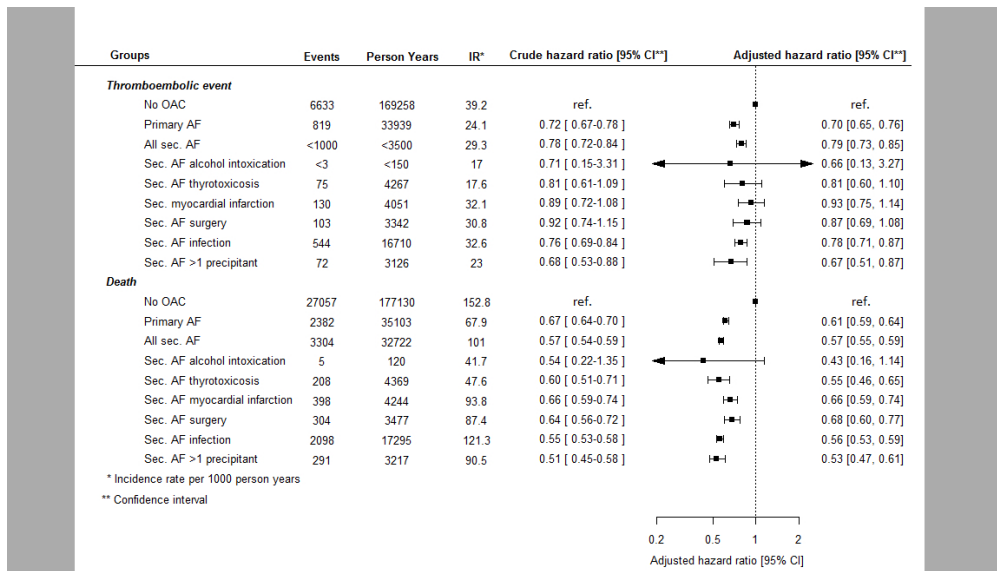


Figure 4

304x172mm (96 x 96 DPI)

Supplemental material

Comparative thromboembolic risk in secondary atrial fibrillation in a nationwide cohort

Anna Gundlund, MD, PhD; Thomas Kümler, MD, PhD; Anders N. Bonde, MD; Jawad H. Butt, MD; Gunnar H. Gislason, MD, PhD; Christian Torp-Pedersen, MD, DMSc; Lars Køber, MD, DMSc; Jonas B. Olesen, MD, PhD; Emil L. Fosbøl, MD, PhD

Online Table 1: Specification of diagnoses by international classification of diseases (ICD-8 and ICD-10) codes and pharmacotherapy by anatomical therapeutic chemical classification (ATC) codes.

Online Table 2: Baseline characteristics of the non-matched population, patients initiated on OAC therapy

Online S3: Baseline characteristics of the non-matched population, patients not initiated on OAC therapy

Online Table 1: Specification of diagnoses by international classification of diseases (ICD-8 and ICD-10) codes and pharmacotherapy by anatomical therapeutic chemical classification (ATC) codes.

Precipitants	ICD-10 codes and NCSP, NOMESCO Classification of Surgical Procedures
Alcohol intoxication	ICD-10: F100, F103, F104, R780, T51, X65
Infections	ICD-10: Certain infectious and parasitic diseases: A00-B99. Infections in the eye and adnexa: H00, H01, H10, H20, H30, H44, H60, H65-H68, H70, H73.0, H73.1 Infections in the cardiovascular organs: I30, I32, I33, I38-I41 Infections in pulmonary system: J00-J22, J32, J36, J85, J86 Infections in the gastrointestinal system: K12, K20, K35-K37, K57, K65, K67, K81, K85 Infections in the skin, subcutaneous tissue, bones, muscles, and connective tissue: L00-L08, M00, M01, M60, M63.2, M65, M86, M90.0, M90.1, M90.2 Infections in the urogenital system: N00, N01, N05, N30, N70-N77.
Myocardial infarction	ICD-10: I21
Pulmonary embolism	ICD-10: I260, I269, O882D, O882E, T817D
Surgery	NCSP, NOMESCO Classification of Surgical Procedures: KF, KM, KN, KD, KPH, KPI, KJ, KH, KQ, KB, KC, KL, KE, KA, KG, KK.
Thyrotoxicosis	ICD-10: E05
Outcomes	
Atrial fibrillation re-hospitalization	Hospital admission with primary diagnosis of atrial fibrillation: I48
Thromboembolic event	Ischemic stroke: I63, I64 Death from stroke: I61-I64 Transient ischemic attack: G458, G459 Thrombosis or embolism in arteries: I74
Comorbidities	ICD-8 and ICD-10 codes

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4	Atrial fibrillation	ICD-10: I48
5		ICD-8: 42793, 42794
6		
7	Alcohol abuse	ICD-10: E24.4, E52, F10, G31.2, G62.1, G72.1,
8		I42.6, K29.2, K70, K86.0, L27.8A, O35.4, T51,
9		Z71.4, Z72.1.
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11		ATC: N07BB
12		
13	Cancer	ICD-10: C
14		
15	Chronic kidney disease	ICD-10: E10.2, E11.2, E13.2, E14.2, I12.0,
16		M32.1B, N02-N08, N11, N12, N14, N15.8,
17		N15.9, N16.0, N16.2-N16.4, N16.8, N18, N19,
18		N26, Q61
19	Chronic obstructive pulmonary disease	ICD-10: J42, J43, J44
20	Diabetes	ATC: A10 (3 months before index)
21	Heart failure	ICD-10: I11.0, I42, I50, J81
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23	Hypertension	Usage of a combination of at least two of the
24		seven different drug classes at the same time:
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26		1. Non-loop diuretics
27		2. Loop diuretics
28		3. Antiadrenergic agents
29		4. Beta-blockers
30		5. Vasodilators
31		6. Calcium channel blockers
32		7. Renin-angiotensin system inhibitors
33		
34		
35		
36	Ischemic heart disease	ICD-10: I20-I25
37	Peripheral artery disease	ICD-10: I70
38	Prior bleeding	ICD-10: D50.0, D62, G951A, H31.3, H05.2A,
39		H35.6, H43.1, H45.0, I31.2, I60-I62, I85.0,
40		I86.4A, J94.2, K22.8F, K25.0, K25.2, K25.4,
41		K25.6, K26.0, K26.2, K26.4, K26.6, K27.0
42		K27.2, K27.4, K27.6, K28.0, K28.2, K28.4,
43		K28.6, K29.8A, K62.5, K63.8B, K63.8C, K66.1,
44		K83.8F, K86.8G, K92.0-K92.2, N02, R04, R31,
45		S06.4-S06.6, S36.8D
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51	Thromboembolic event	ICD-10: G45.8, G45.9, I63, I64, I74
52		
53	Valvular atrial fibrillation	Atrial fibrillation without:
54		ICD-10: I05, I06, I080A, I081A, I082A, I083A,
55		Z952, Z954
56		ICD-8: 39500-39502, 39508, 39509, 39600-
57		39604, 39608, 39609
58		Procedures: FKD, FKH, FMD, FMH, FGE, FJE
59	Pharmacotherapy	ACT-codes
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ADP-receptor blockers	B01AC04, B01AC22, B01AC24
Amiodarone	C01BD01
Antiadrenergic agents	C02A, C02B, C02C
Oral anticoagulation therapy	Vitamin K antagonists: B01AA03, B01AA04 Non-vitamin K antagonist oral anticoagulants: B01AF01, B01AF02, B01AE07
Beta-blockers	C07A, C07B, C07C, C07D, C07F
Calcium channel blockers	C08, C09BB, C09DB
Digoxin	C01AA
Flecainide	C01BC
Loop diuretics	C03C, C03EB
Non-loop diuretics	C02DA, C03EA, C03EB, C02L, C03A, C03B, C03D, C03E, C03X, C07B, C07C, C07D, C08G, C09BA, C09DA, C09XA52
Renin-angiotensin system inhibitors	C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C09XA02, C09XA52
Vasodilators	C02DB, C02DD, C02DG

Online Table 2: Baseline characteristics of the non-matched population, patients initiated on OAC therapy

	Secondary AF N=10,673						Primary AF N=37,827
	Alcohol intoxication N=33	Thyro- toxicosis N=1103	Myocardial infarction N=1312	Surgery N=1151	Infection N=5987	>1 precipitant N=1087	
Demographics							
Age, median (IQR*)	64 (55-68)	72 (64-79)	75 (68-81)	74 (67-81)	77 (69-83)	75 (68-81)	72 (64-79)
Male, n (%)	28 (84.8)	259 (23.5)	842 (64.2)	667 (57.9)	3189 (53.3)	634 (58.3)	21,386 (56.5)
Comorbidities, n (%)							
Cancer	≤ 3	114 (10.3)	146 (11.1)	239 (20.8)	927 (15.5)	171 (15.1)	4617 (12.2)
Chronic kidney disease	4 (12.1)	23 (2.1)	62 (4.7)	65 (5.6)	372 (6.2)	59 (5.4)	1011 (2.7)
COPD†	≤ 3	106 (9.6)	133 (10.1)	128 (11.1)	1251 (20.9)	157 (14.4)	3426 (9.1)
Diabetes	≤ 3	84 (7.6)	159 (12.1)	111 (9.6)	712 (11.9)	112 (10.3)	3384 (8.9)
Heart failure	6 (18.2)	236 (21.4)	464 (35.4)	228 (19.8)	1440 (24.1)	359 (33.0)	6791 (18.0)
Hypertension	11 (33.3)	658 (59.7)	982 (74.8)	687 (59.7)	3652 (61.0)	723 (66.5)	23,057 (61.0)
IHD‡	5 (15.2)	129 (11.7)	1312 (100)	434 (37.7)	1202 (20.1)	744 (68.4)	7360 (19.5)
PAD§	≤ 3	29 (2.6)	83 (6.3)	101 (8.8)	353 (5.9)	77 (7.1)	1258 (3.3)
Prior bleeding event	7 (21.2)	86 (7.8)	150 (11.4)	213 (18.5)	966 (16.1)	182 (16.7)	4564 (12.1)
Prior thromboembolic event	≤ 3	60 (5.4)	142 (10.8)	153 (13.3)	672 (11.2)	133 (12.2)	3313 (8.8)
Risk scores							
CHA ₂ DS ₂ -VASC							
Median (IQR*)	1 (0-2)	3 (2-4)	4 (3-5)	3 (2-4)	3 (2-4)	4 (3-5)	3 (2-4)
0	11 (33.3)	134 (12.2)	0	74 (6.4)	269 (4.5)	28 (2.6)	3592 (9.5)
1-2	16 (48.5)	263 (23.8)	181 (13.8)	289 (25.1)	1493 (24.9)	181 (16.6)	12,341 (32.6)
≥3	6 (18.2)	706 (64.0)	1131 (86.2)	788 (68.5)	4225 (70.6)	878 (80.8)	21,894 (57.9)
HAS-BLED [#]							
Median (IQR*)	2 (1-3)	2 (1-2)	3 (2-3)	2 (1-3)	2 (1-3)	2 (2-3)	2 (1-3)
0	0	128 (11.6)	32 (2.4)	60 (5.2)	259 (4.3)	33 (3.0)	3361 (8.9)
1-2	21 (63.6)	706 (64.0)	571 (43.5)	611 (53.1)	3433 (57.3)	515 (47.4)	22,792 (60.3)
≥3	12 (36.4)	269 (24.4)	709 (54.0)	480 (41.7)	2295 (38.3)	539 (49.6)	11,674 (30.9)
Pharmacotherapy, n (%)							
Amiodarone	0	19 (1.7)	104 (7.9)	181 (15.7)	261 (4.4)	141 (13.0)	1493 (3.9)

Digoxin	11 (33.3)	605 (54.9)	437 (33.3)	312 (27.1)	2847 (47.6)	368 (33.9)	14,803 (39.1)
Flecainide	0	5 (0.5)	≤ 3	≤ 3	10 (0.2)	≤ 3	248 (0.7)

*IQR: interquartile range. †COPD: chronic obstructive pulmonary disease. ‡IHD: ischemic heart disease. §PAD: peripheral artery disease. ||CHA₂DS₂-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.

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Online Table 3: Baseline characteristics of the non-matched population, patients not initiated on OAC therapy

	Secondary AF N=29,403						Primary AF N=60,361
	Alcohol intoxication N=302	Thyro- toxicosis N=1408	Myocardial infarction N=3508	Surgery N=4101	Infection N=16,079	>1 precipitant N=4005	
Demographics							
Age, median (IQR*)	58 (48-66)	74 (62-82)	78 (69-84)	76 (67-82)	80 (72-87)	76 (68-83)	69 (58-80)
Male, n (%)	248 (82.1)	263 (18.7)	1907 (54.4)	2069 (50.5)	7352 (45.7)	2073 (51.8)	31,074 (51.5)
Comorbidities, n (%)							
Cancer	15 (5.0)	174 (12.4)	454 (12.9)	1115 (27.2)	3474 (21.6)	795 (19.9)	7915 (13.1)
Chronic kidney disease	7 (2.3)	38 (2.7)	236 (6.7)	289 (7.0)	1223 (7.6)	375 (9.4)	1733 (2.9)
COPD†	26 (8.6)	128 (9.1)	495 (14.1)	539 (13.1)	3493 (21.7)	765 (19.1)	4544 (7.5)
Diabetes	24 (7.9)	105 (7.5)	417 (11.9)	396 (9.7)	1473 (9.2)	387 (9.7)	3566 (5.9)
Heart failure	18 (6.0)	209 (14.8)	1218 (34.7)	744 (18.1)	3752 (23.3)	1231 (30.7)	6328 (10.5)
Hypertension	53 (17.5)	653 (46.4)	2348 (66.9)	1808 (44.1)	6942 (43.2)	1991 (49.7)	22,309 (37.0)
IHD‡	38 (12.6)	207 (14.7)	3508 (100)	1326 (32.3)	3558 (22.1)	2354 (58.8)	11,528 (19.1)
PAD§	6 (2.0)	49 (3.5)	298 (8.5)	371 (9.0)	1057 (6.6)	374 (9.3)	1913 (3.2)
Prior bleeding event	74 (24.5)	157 (11.2)	585 (16.7)	1062 (25.9)	3420 (21.3)	998 (24.9)	7616 (12.6)
Prior thromboembolic event	22 (7.3)	78 (5.5)	350 (10.0)	422 (10.3)	2029 (12.6)	478 (11.9)	4301 (7.1)
Risk scores							
CHA ₂ DS ₂ -VASc							
Median (IQR*)	1 (0-2)	3 (2-4)	4 (3-5)	3 (2-4)	3 (2-4)	4 (2-5)	2 (0-4)
0	147 (48.7)	271 (19.2)	0	317 (7.7)	1059 (6.6)	241 (6.0)	15,957 (26.4)
1-2	102 (33.8)	270 (19.2)	489 (13.9)	1119 (27.3)	3671 (22.8)	824 (20.6)	17,513 (29.0)
≥3	53 (17.5)	867 (61.6)	3019 (86.1)	2665 (65.0)	11,349 (70.6)	2940 (73.4)	26,891 (44.6)
HAS-BLED [#]							
Median (IQR*)	2 (1-3)	2 (1-3)	3 (2-3)	2 (1-3)	2 (1-3)	2 (2-3)	2 (1-3)
0	0	228 (16.2)	102 (2.9)	229 (5.6)	745 (4.6)	175 (4.4)	12,875 (21.3)
1-2	211 (69.9)	756 (53.7)	1424 (40.6)	2265 (55.2)	8795 (54.7)	1924 (48.0)	31,914 (52.9)
≥3	91 (30.1)	424 (30.1)	1982 (56.5)	1607 (39.2)	6539 (40.7)	1906 (47.6)	15,572 (25.8)
Pharmacotherapy, n (%)							

Amiodarone	≤ 3	14 (1.0)	259 (7.4)	262 (6.4)	361 (2.2)	278 (6.9)	1133 (1.9)
Digoxin	38 (12.6)	398 (28.3)	784 (22.3)	782 (19.1)	5210 (32.4)	828 (20.7)	10,336 (17.1)
Flecainide	0	8 (0.6)	8 (0.2)	10 (0.2)	30 (0.2)	5 (0.1)	786 (1.3)

*IQR: interquartile range. †COPD: chronic obstructive pulmonary disease. ‡IHD: ischemic heart disease. §PAD: peripheral artery disease. ||CHA₂DS₂-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.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract YES, p.1 and 3. (b) Provide in the abstract an informative and balanced summary of what was done and what was found YES, p. 3.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported YES, p. 5
Objectives	3	State specific objectives, including any prespecified hypotheses YES, p. 5
Methods		
Study design	4	Present key elements of study design early in the paper YES, p. 5-7.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection YES, p. 5-7.
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up YES, p. 6-7. <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed YES, p. 8. <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable YES, p. 7-8. Figure 3. Specification of diagnosis can be found in the Online Table 1.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group YES, p. 5-6 and eTable 1.
Bias	9	Describe any efforts to address potential sources of bias YES, p. 8.
Study size	10	Explain how the study size was arrived at YES, p. 6-7, figure 1.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why

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YES, p. 6-7.

Statistical methods

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(a) Describe all statistical methods, including those used to control for confounding

YES, p. 7-8.

(b) Describe any methods used to examine subgroups and interactions

YES, p. 7-8.

(c) Explain how missing data were addressed

No missing data

(d) *Cohort study*—If applicable, explain how loss to follow-up was addressed

No loss to follow-up.

Case-control study—If applicable, explain how matching of cases and controls was addressed

Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy

(e) Describe any sensitivity analyses

YES, p. 7.

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Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed YES, p. 8-9 and Figure 1.
		(b) Give reasons for non-participation at each stage YES, p. 8-9 and Figure 1.
		(c) Consider use of a flow diagram YES, Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders YES, p. 9, Table 1.
		(b) Indicate number of participants with missing data for each variable of interest No missing data
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) YES, Figure 2.
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time YES, p. 10 and Figure 2, 3.
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included YES, Figure 3.
		(b) Report category boundaries when continuous variables were categorized Continuous variables were not categorized.
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses YES, p. 11.
Discussion		
Key results	18	Summarise key results with reference to study objectives YES, p. 11.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias YES, p. 13-14.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence YES, p. 12-13.
Generalisability	21	Discuss the generalisability (external validity) of the study results YES, p. 14.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

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2 YES, p. 14.
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4 *Give information separately for cases and controls in case-control studies and, if applicable, for exposed and
5 unexposed groups in cohort and cross-sectional studies.
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8 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and
9 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely
10 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
11 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
12 available at www.strobe-statement.org.
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BMJ Open

Comparative thromboembolic risk in atrial fibrillation with and without a secondary precipitant– a Danish nationwide cohort study

Journal:	<i>BMJ Open</i>
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Secondary Subject Heading:	Epidemiology
Keywords:	Cardiac Epidemiology < CARDIOLOGY, Thromboembolism < CARDIOLOGY, Pacing & electrophysiology < CARDIOLOGY

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Manuscripts

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4 1 **Comparative thromboembolic risk in atrial fibrillation with and without a**
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7 2 **secondary precipitant– a Danish nationwide cohort study**
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4 1 **Abstract:** 292 words (max 300 words)
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6 2 Objectives: We compared long-term outcomes in patients with atrial fibrillation (AF) with and
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9 3 without a secondary precipitant.
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11 4 Design and setting: Retrospective cohort study based on Danish nationwide registries.
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13 5 Participants: Patients with AF with and without secondary precipitants (1996-2015) were matched
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16 6 1:1 according to age, sex, calendar year, CHA₂DS₂-VASc score, and oral anticoagulation therapy
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18 7 (OAC) therapy, resulting in a cohort of 39,723 patients with AF with a secondary precipitant and
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20 8 the same number of patients with AF without a secondary precipitant. Secondary precipitants
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23 9 included alcohol intoxication, thyrotoxicosis, myocardial infarction, surgery, and infection in
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25 10 conjunction with AF.
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27 11 Primary and secondary outcomes: The primary outcome in this study was thromboembolic events.
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29
30 12 Secondary outcomes included AF re-hospitalization and death. Long-term risks of outcomes were
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32 13 examined by multivariable Cox regression analysis.
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34 14 Results: The most common precipitants were infection (55.0%), surgery (13.2%), and myocardial
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36 15 infarction (12.0%). The 5-year absolute risk of thromboembolic events (taking death into account as
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39 16 a competing risk) in patients with AF grouped according to secondary precipitant were 8.3%
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41 17 (alcohol intoxication), 8.5% (thyrotoxicosis), 12.1% (myocardial infarction), 11.6% (surgery),
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43 18 12.2% (infection), 10.1% (>1 precipitant), and 12.3% (no secondary precipitant). In the
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46 19 multivariable analyses, AF with a secondary precipitant was associated with the same or an even
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48 20 higher thromboembolic risk than AF without a secondary precipitant. One exception was patients
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50 21 with AF and thyrotoxicosis: those not initiated on OAC therapy carried a lower thromboembolic
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52 22 risk the 1st year of follow up than matched patients with AF without a secondary precipitant and no
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55 23 OAC therapy.
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4 1 Conclusions: In general, AF with a secondary precipitant was associated with the same
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6 2 thromboembolic risk as AF without a secondary precipitant. Consequently, this study highlights the
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8 3 need for more research regarding the long-term management of patients with AF associated with a
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10 4 secondary precipitant.
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13 5 Key words: Secondary precipitant, reversible atrial fibrillation, recurrence
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For peer review only

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4 **1 Article summary: strengths and limitations of this study**
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7 2 • The study was based on high-quality nationwide registries with many years of follow up.
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9 3 • Complete follow-up was possible
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11 4 • Only associations could be drawn because of the retrospective and non-randomized design.
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14 5 • AF with and without a secondary precipitant were defined from diagnosis codes at discharge
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16 6 • We had no data on electrocardiograms at discharge
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1 **Introduction**

2 The aetiology of atrial fibrillation (AF) remains partly unknown. Studies have shown, that an
3 inflammatory reaction inside the atria always precipitate AF.(1) However, in clinical practice, AF
4 may occur as an isolated event or together with a secondary precipitant. AF is associated with a
5 fivefold increased risk of ischemic stroke, and detailed treatment strategies regarding stroke
6 prophylaxis in patients with AF occurring without secondary precipitants exist in both European
7 and American treatment guidelines.(2–5)] In contrast, there is no consensus regarding stroke
8 prophylaxis in patients with AF occurring with a secondary precipitant. Previous guidelines stated
9 that AF occurring secondary to another precipitant usually will terminate without recurrence.(2) In
10 current guidelines, however, this statement has been omitted, and the need for data regarding AF
11 associated with a secondary precipitant highlighted.(4,5) Studies investigating long-term outcomes
12 in AF associated with a secondary precipitant are sparse and data differentiating between different
13 secondary precipitants and taking oral anticoagulation (OAC) therapy into account are missing.
14 To address this lack in current knowledge, we aimed to compare long-term outcomes including
15 thromboembolic events, AF re-hospitalization, and death in patients with AF with a secondary
16 precipitant (incl. alcohol, intoxication, thyrotoxicosis, myocardial infarction, surgery, and infection)
17 and patients with AF without a secondary precipitant. Further, we were able to differentiate
18 between patients receiving and not receiving stroke prophylaxis with OAC therapy.

19 **Materials and methods**

20 *Data sources*

21 In Denmark, healthcare is tax-financed and with equal availability regardless of socioeconomic
22 status. Date of birth, date and cause of death, emigration and immigration status, diagnosis and
23 surgery codes etc. from all hospital contacts, fulfilled prescriptions of medicine, and several other
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parameters are registered in different nationwide registries. Since all Danish citizens are provided a unique personal identifier code at birth (or immigration), data from the registries can be crosslinked on an individual level. We linked data from the following registries: The Danish Civil Registration System,(6) The Danish National Patient Registry (diagnoses were registered in terms of the International Classification of Diseases (ICD) system (ICD-8 until 1994 and in terms of ICD-10 thereafter)),(7) The Danish Register of Causes of Death,(8) and the Danish National Registry of Medicinal Statistics (medicine were registered according to the Anatomical Therapeutic Chemical classification system (ATC)).(9)

Study population

The patient selection is depicted in Figure 1. We included all Danes diagnosed and admitted to a hospital with AF for the first time between 1996 and 2015. Patients <18 years or >100 years and those with valvular AF (defined as AF without: rheumatic valve disease of aortic valve or mitral valve or prosthetic heart valve (any valve)) were excluded. Since there was a possibility that some of the patients had been diagnosed with AF at their general practitioner before their hospital admission, we excluded those who previously had fulfilled a prescription of antiarrhythmic therapy or rate-controlling drugs (incl. amiodarone, flecainide, and digoxin) and those who had fulfilled a prescription of OAC therapy up to 100 days before their hospital admission. Further, patients who died or had a thromboembolic event during the hospital admission or a constructed blanking period of 4 weeks from hospital discharge to the index date were excluded.

Patients were grouped in those with and without a secondary precipitant. Patients who had a diagnosis of one of the following precipitants from their AF hospital admission were defined as patients with a secondary precipitant: alcohol intoxication, thyrotoxicosis, myocardial infarction, and infection. Also, patients who were diagnosed with AF after, but during the same hospital

1 admission they received surgery were defined as having AF with a secondary precipitant. We
2 restricted the population of patients with AF without a secondary precipitant to patients with AF
3 without a diagnosis of a secondary precipitant from their hospital admission. Patients with AF with
4 and without a secondary precipitant were matched 1:1 by incidence density sampling according to
5 age (allowing a difference of up to two years), sex, calendar year (allowing a difference up to two
6 years), CHA₂DS₂-VASc group (0, 1-2, >2) and OAC therapy status at the index date. Consequently,
7 each case was matched with a control diagnosed at the same time and in the same age with AF.
8 Further, the control had the same sex and was categorized in the same CHA₂DS₂-VASc group as
9 the case. These patients comprised the study population. We used a previously described function to
10 perform the match.(10)

11 12 *Long-term outcomes*

13 The index date was defined 4 weeks from AF hospital discharge. Initiation of OAC therapy and
14 antiarrhythmic and rate controlling drugs was assessed during this blanking period from discharge
15 to index date. Patients were followed from the index date and until the first event of the following:
16 an outcome of interest, death, 5 years from the index date, emigration, or June 30, 2015. The
17 primary outcome of interest was thromboembolic events (a composite of ischemic stroke, transient
18 ischemic attack (TIA), and systemic thrombosis or embolism) while secondary outcomes included
19 AF re-hospitalization and all-cause death. AF-rehospitalization was defined as a hospitalization
20 with AF as the primary discharge diagnosis. The diagnoses of AF, ischemic stroke, and myocardial
21 infarction have been validated in the Danish registries with positive predictive values of 93%, 97%,
22 and 100%, respectively.(11,12)

1 2 3 4 1 *Statistics*

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6 2 Kaplan Meier curves for death were drawn and cumulative incidences of thromboembolic events
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8 3 (with incorporated competing risk of death) calculated using the Aalen Johansen estimator. The
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10 4 Log-Rank test and the Gray's test were used to test for differences in the cumulative incidence of
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12 5 long-term outcomes. Cox regression analyses were performed to calculate hazard ratios (HR) of
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14 6 long-term outcomes in patients with AF with and without a secondary precipitant according to OAC
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16 7 therapy at the index date. All analyzes were performed on the matched population. The multivariate
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18 8 models were adjusted for other potential confounders than the matching criteria (incl. comorbidities
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20 9 at the index date (incl. peripheral artery disease, heart failure, hypertension, prior thromboembolic
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22 10 event, ischemic heart disease, chronic kidney disease, diabetes, prior bleeding event, cancer) and
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24 11 antiarrhythmic and rate-controlling therapy during the blanking period (amiodarone, digoxin,
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26 12 flecainide)). The analyses took matching variables into account and each group of patients with AF
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28 13 with a secondary precipitant was compared with its respective matches from the matching
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30 14 procedure. The models were tested for the assumption of proportional hazards. For specification of
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32 15 diagnosis codes and ATC-codes please see Online Table 1. A P-value <0.05 was considered
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34 16 statistically significant. All statistical analyses were performed in SAS statistical software version
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36 17 9.4 or R.(13)
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45 19 *Other analyses*

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47 20 Analyses of long-term outcomes were also performed on a non-matched population including all
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49 21 patients available before the matching (Figure 1). To account for changes in OAC therapy status
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51 22 over time, we did a sensitivity analysis not stratifying patients with regard to their OAC therapy
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53 23 status at the index date, but instead adjusting for OAC therapy status as a time-dependent variable.
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4 1 Consequently, new initiations and discontinuations were taking into account. The method used, has
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6 2 been used and described previously.(14–16)
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9 3 10 11 4 *Ethics*

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13 5 Approval from the Research Ethics Committee System is not required in retrospective registry-
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15 6 based studies in Denmark. The Danish Data Protection Agency approved use of data for this study
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17 7 (ret.no: 2007-58-0015 / GEH-2014-013 I-Suite no: 02731).
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21 22 23 9 **Patient and Public Involvement**

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25 10 This was a retrospective study based on administrative registries. Patients and the public were not
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27 11 involved in the development of the study.
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31 32 13 **Data availability statement**

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34 14 Data in this study are not available for the public.
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38 39 16 **Results**

40 41 17 *Study population*

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43 18 As shown in Figure 1, the most common secondary precipitant was infection (21,824 patients,
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45 19 55.0%). Further, 335 (0.8%) patients had a concurrent alcohol intoxication, 2507 (6.3%) had
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47 20 thyrotoxicosis, 4773 (12.0%) had acute myocardial infarction, 5229 (13.2%) had underwent
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49 21 surgery, and 5055 (12.7%) had >1 precipitant. Of those with >1 precipitant, 4788 (94.7%) patients
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51 22 had two secondary precipitants, while 267 (5.3%) had three or four secondary precipitants.
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53 23 Infection and surgery was the most common combination of secondary precipitants. The patients
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55 24 with >1 precipitant were grouped in one group, and were not included in the other groups of
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4 1 patients with AF with a secondary precipitant. During the blanking period, 14% of the patients with
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6 2 AF and a secondary precipitant and 2% of the patients with AF without a secondary precipitant
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8 3 died, while 5% and 2%, respectively, had a thromboembolic event. These patients were excluded
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10 4 before the matching.
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16 6 *Baseline characteristics*

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18 7 Baseline characteristics of the matched study population are shown in Table 1. In general, patients
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20 8 with AF with a secondary precipitant had more comorbidities than patients with AF without a
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22 9 secondary precipitant. Baseline characteristics of the non-matched population according to OAC
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24 10 therapy at the index date are shown in online Table 2 and 3. Especially those with AF and
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26 11 myocardial infarction, surgery, infection, and >1 precipitant were older, had more comorbidities,
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28 12 and higher risk scores for stroke and bleeding compared with patients with AF without a secondary
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30 13 precipitant. Among the patients with AF with a secondary precipitant (non-matched study
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32 14 population), 9.9% with alcohol intoxication, 43.9% with thyrotoxicosis, 27.2% with myocardial
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34 15 infarction, 21.9% with surgery, 27.1% with infection, and 21.4% with >1 precipitant received OAC
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36 16 therapy at the index date, respectively. Among patients with AF without a secondary precipitant,
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38 17 38.5% received OAC therapy at the index date. In general for patients with AF with and without a
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40 18 secondary precipitant, those initiated on OAC therapy suffered from less cancer, chronic kidney
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42 19 disease, peripheral artery disease, and had fewer previous bleeding events than those not initiated
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44 20 on OAC. On the other hand, they were more likely to suffer from stroke risk factors (incl. diabetes,
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46 21 heart failure, ischemic heart disease, and hypertension) than those not initiated on OAC therapy.
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55 23 *Long-term outcomes*

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4 1 Number of events, incidence rates, and crude and adjusted hazard ratios (HRs) of thromboembolic
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6 2 events and death in AF patients with a secondary precipitant compared with AF patients without a
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9 3 secondary precipitant initiated and not initiated on OAC therapy at the index date are presented in
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11 4 Figure 2. With few exceptions, AF with a secondary precipitant was associated with the same
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13 5 thromboembolic risk as AF without a secondary precipitant. Regardless of OAC therapy status at
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15 6 the index date, AF with infection was associated with a significantly increased risk of
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17 7 thromboembolic events compared with AF without a secondary precipitant. Among those not
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19 8 initiated on OAC therapy, AF with thyrotoxicosis was associated with a significantly lower risk of
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21 9 thromboembolic events compared with AF without a secondary precipitant. In those initiated on
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23 10 OAC therapy, no differences in thromboembolic risk was observed between patients with AF and
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25 11 thyrotoxicosis and patients with AF without a secondary precipitant. All subgroups of AF with a
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27 12 secondary precipitant were associated with a significantly lower risk of AF re-hospitalization
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29 13 compared with AF without a secondary precipitant (Figure 2).
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36 15 Figure 3 and 4 depicts cumulative incidences of thromboembolic events and death in patients with
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38 16 AF with and without a secondary precipitant. During follow up, the cumulative incidence of
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40 17 thromboembolic events (taking death as an competing risk into account) according to type of
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42 18 secondary precipitant was 8.3% (alcohol intoxication), 8.5% (thyrotoxicosis), 12.1% (myocardial
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44 19 infarction), 11.6% (surgery), 12.2% (infection), 10.1% (>1 precipitant), and 12.3% (no secondary
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46 20 precipitant). The cumulative incidence of AF re-hospitalization were 19.6% (alcohol intoxication),
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48 21 30.8% (thyrotoxicosis), 27.2% (myocardial infarction), 14.8% (surgery), 20.9% (infection), 19.3%
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50 22 (>1 precipitant), and 34.4% (no secondary precipitant) (not included in the figures).
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55 23 OAC therapy initiation compared with no OAC therapy initiation was associated with a lower
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57 24 thromboembolic risk in patients with AF with and without a secondary precipitant, although the
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1 results did not reach statistical significance in patients with AF with alcohol intoxication,
2 thyrotoxicosis, myocardial infarction, and surgery as secondary precipitants (Figure 5).

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4 *Other analyses*

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

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

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15 **Discussion**

16 We examined long-term outcomes in patients with AF with and without a secondary precipitant.

17 The study had two main findings: first, AF with different secondary precipitants was in general

18 associated with the same thromboembolic risk as AF without a secondary precipitant. Secondly,

19 OAC initiation-rates differed significantly according to type of secondary precipitant. Further, OAC

20 therapy vs. no OAC therapy were associated with a lower thromboembolic risk in those with AF

21 and infection and >1 precipitant while no significant risk-reduction was seen for patients with AF

22 with the other secondary precipitants.

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24 *Thromboembolic risk*

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4 1 Despite of lower re-hospitalization rates with AF, AF with a secondary precipitant was in general
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6 2 associated with the same thromboembolic risk as AF without a secondary precipitant. AF with
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8 3 thyrotoxicosis was associated with a lower thromboembolic risk compared with AF without a
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10 4 secondary precipitant In contrast, AF with infection was associated with an increased
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12 5 thromboembolic risk compared with AF without a secondary precipitant. This is in accordance with
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14 6 previous findings.(17–19) In two previous studies, Lubitz et al. and Fauchier et al. examined long-
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16 7 term outcomes in patients with AF secondary to a reversible precipitant compared with patients
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18 8 with AF without a secondary precipitant. In both studies, AF secondary to a reversible precipitant
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20 9 was associated with the same thromboembolic risk as AF without secondary precipitants. However,
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22 10 both studies were smaller and with patients included before 2012 and 2010, respectively.(20,21) In
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24 11 summary, our results together with previous studies suggest that AF with a secondary precipitant in
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26 12 general, and maybe with the exception of AF with thyrotoxicosis, may be considered as similar to
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28 13 AF without a secondary precipitant with respect to thromboembolic risk.
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36 15 *OAC therapy*

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38 16 OAC therapy showed a tendency towards a lower thromboembolic risk in AF with a secondary
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40 17 precipitant patients, but did only reach statistical significance for patients with AF and infection and
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42 18 >1 precipitant. Recently, Quon et al. examined risk of thromboembolic events and bleeding in
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44 19 patients with AF and acute coronary syndrome, acute pulmonary disease, and infection according to
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46 20 OAC therapy status after discharge. In that study, OAC therapy was not associated with lower risk
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48 21 of thromboembolic events in patients with AF and the before mentioned precipitants. However, the
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50 22 analyses on long-term outcomes were based on logistic regression analysis, and did therefore not
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52 23 include survival time in the model. Since patients with AF with a secondary precipitant in our study
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54 24 seemed to die at a higher rate than patients with AF without a secondary precipitant, the time
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4 1 perspective is crucial when studying long-term outcomes in this setting.(22) Studies with a clinical
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6 2 randomized design would be able to show whether patients with AF with a secondary precipitant
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9 3 benefit from OAC therapy on the same terms as patients with AF without a secondary precipitant.
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13 5 *OAC treatment-rates*

15 6 The non-matched population allowed us to describe trends in OAC therapy initiation in patients
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18 7 with AF with and without a secondary precipitant. In patients with AF without a secondary
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20 8 precipitant, 38.5% of the patients were initiated on OAC therapy at the index date. This is in
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22 9 accordance with previous findings, taking into account that our study period went back to 1996
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24 10 when treatment rates were lower than today.(23,24) In 2017, Chean et al. assessed current practice
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26 11 of AF among critically ill patients with new-onset AF. The study was based on questionnaires
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28 12 answered by members of the Intensive Care Society in UK. The results revealed that 63.8% of the
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30 13 respondents would not regularly anti-coagulate critically ill patients with new-onset AF. We found
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32 14 important differences in OAC therapy initiation rates in patients with AF with a secondary
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34 15 precipitant according to type of precipitant. Patients with alcohol intoxication had the lowest
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36 16 initiation rate of OAC therapy (9.9%). Almost 50% of this patient group had a CHA₂DS₂-VASc
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38 17 score of 0 and hence no indication for OAC therapy. Further patients with alcohol abuse may have
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40 18 poor compliance and increased bleeding risk.(25) Consequently, there may be caution among
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42 19 physicians in prescribing OACs for this patient group. In 2011, Traube and colleagues reviewed the
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44 20 literature with respect to thromboembolic risk in patients with AF and thyrotoxicosis. They
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46 21 concluded that OAC therapy should be initiated for those patients who did not have any
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48 22 contraindications for treatment.(26) This could explain the high OAC treatment initiation rates in
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50 23 this patient group (43.9%).
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4 1 *Limitations*

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6 2 First of all, this study was a retrospective registry-based study and hence no causative relationships
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8 3 can be drawn. Our definition of AF with a secondary precipitant was based on diagnosis codes from
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10 4 hospital admissions with AF and a reversible precipitant. Both diagnoses were registered at the
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12 5 discharge date, and therefore we may have included patients in the the group of AF with a
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14 6 secondary precipitant who developed AF before the secondary precipitant (e.g. patients admitted
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16 7 with AF who developed infection during their hospital stay), and thereby should have been
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18 8 classified as patients with AF without a secondary precipitant. Moreover, we had no access to
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20 9 patient files, and we did not know whether the patients were discharged in sinus rhythm or with AF.
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22 10 Also, no data were available with regard to the physicians' considerations when choosing between
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24 11 OAC therapy and no OAC therapy, patients compliance, and measurements of international
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26 12 normalized ratio (INR) and time in therapeutic range for warfarin users. Previous studies have
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28 13 shown an association between an impaired platelet nitric oxide response and recent onset AF and
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30 14 that disturbances in nitric oxide function are associated with outcomes (including thromboembolic
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32 15 events, bleeding events, and death) in AF. Unfortunately, we did not have any information on nitric
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34 16 oxide levels in our study cohort.(27,28)

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41 17 However, this study was based on a nationwide cohort of patients with many years of follow-up and
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43 18 data from high-quality registries. It reveals unexpected results that should be considered in future
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45 19 treatment guidelines for patients with AF and a secondary precipitant.
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50 21 Recent onset of AF is associated with marked impairment of platelet NO response. These findings
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52 22 may contribute to thromboembolic risk in such patients.
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4 1 nitric oxide signaling, and that the standard scoring systems for thrombo-embolic risk in patients

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6 2 with AF partially parallel plasma concentrations of the NO synthase inhibitor ADMA

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13 5 *Conclusion*

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15 6 In this study we found that patients with AF and a secondary precipitant carried a similar associated

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17 7 thromboembolic risk as those with AF without a secondary precipitant. Current guidelines lack data

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19 8 on this subject and our results suggests that AF in relation to known triggers may be considered as

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21 9 AF in general.

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4 **Conflicts of interest**

5 AG: None. TK: Consultant fees from BMS, Astra Zeneca, Roche, Boehringer-Ingelheim, Bayer,
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12
13

14 **Author contributions**

15 The study idea was conceived by AG, TK, and ELF, study design was developed by AG, TK, JBO,
16 ANB, JHB, GHG, CTP, LK, and ELF, data analyses were made by AG. AG drafted the first version
17 of the paper and all authors participated in the critical discussions and interpretation of findings. All
18 authors have participated in the revisions of the draft and have approved the final version.
19

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21 None.
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4 **1 Figure legends**

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6 **2 Figure 1: Patient selection**

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9 **3 Figure 2: Number of events, incidence rates, and crude and adjusted Hazard ratios of long-term**
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11 **4 outcomes in patients with AF with and without a secondary precipitant .**

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13 **5 Figure 3: Cumulative incidence of thromboembolic events outcomes by secondary precipitant and**
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15 **6 OAC therapy at the index date.**

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18 **7 Figure 4: Cumulative incidence of death events outcomes by secondary precipitant and OAC**
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20 **8 therapy at the index date**

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23 **9 Figure 5: Adjusted hazard ratios of long-term outcomes in patients with AF initiated vs. not**
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25 **10 initiated on OAC therapy (stratified according to type of AF)**

Table 1: Baseline characteristics of the matched population

	Alcohol intoxication group		Thyrotoxicosis group		Myocardial infarction group		Surgery group		Infection group		>1 precipitant group	
+/- secondary precipitant:	+	-	+	-	+	-	+	-	+	-	+	-
	N=335	N=335	N=2507	N=2507	N=4773	N=4773	N=5229	N=5229	N=21,824	N=21,824	N=5055	N=5055
Demographics												
Age, median (IQR*)	59 (49-66)	59 (49-66)	73 (63-81)	73 (63-81)	77 (69-83)	77 (69-83)	75 (67-82)	75 (67-82)	79 (71-86)	79 (71-86)	76 (68-83)	76 (68-83)
Male, n (%)	276 (82.4)	276 (82.4)	521 (20.8)	521 (20.8)	2705 (56.7)	2705 (56.7)	2724 (52.1)	2724 (52.1)	10,370 (47.5)	10,370 (47.5)	2676 (52.9)	2676 (52.9)
Comorbidities, n (%)												
Cancer	16 (4.8)	29 (8.7)	288 (11.5)	296 (11.8)	586 (12.3)	688 (14.4)	1349 (25.8)	882 (16.9)	4341 (19.9)	3571 (16.4)	958 (19.0)	807 (16.0)
Chronic kidney disease	11 (3.3)	8 (2.4)	61 (2.4)	49 (2.0)	289 (6.1)	233 (4.7)	352 (6.7)	198 (3.8)	1564 (7.2)	748 (3.4)	431 (8.5)	212 (4.2)
COPD†	28 (8.4)	23 (6.9)	234 (9.3)	221 (8.8)	619 (13.0)	565 (11.8)	665 (12.7)	520 (9.9)	4696 (21.5)	2093 (9.6)	914 (18.1)	519 (10.3)
Diabetes	26 (7.8)	18 (5.4)	189 (7.5)	159 (6.3)	575 (12.0)	556 (11.6)	503 (9.6)	423 (8.1)	2167 (9.9)	1737 (8.0)	498 (9.9)	554 (11.0)
Heart failure	24 (7.2)	18 (5.4)	445 (17.8)	388 (15.5)	1660 (34.8)	1076 (22.5)	966 (18.5)	851 (16.3)	5109 (23.4)	3709 (17.0)	1574 (31.1)	925 (18.3)
Hypertension	64 (19.1)	78 (23.3)	1309 (52.2)	1249 (49.8)	3290 (68.9)	3204 (67.1)	2484 (47.5)	2695 (51.5)	10,445 (47.9)	11,475 (52.6)	2694 (53.3)	3007 (59.5)
IHD‡	43 (12.8)	53 (15.8)	333 (13.3)	455 (18.1)	4773 (100)	1604 (33.6)	1753 (33.5)	1332 (25.5)	4696 (21.5)	5069 (23.2)	3072 (60.8)	1423 (28.2)
PAD§	7 (2.1)	8 (2.4)	78 (3.1)	83 (3.3)	375 (7.9)	293 (6.1)	468 (9.0)	233 (4.5)	1392 (6.4)	932 (4.3)	448 (8.9)	269 (5.3)
Prior bleeding event	81 (24.2)	42 (12.5)	243 (9.7)	249 (9.9)	722 (15.1)	715 (15.0)	1267 (24.2)	833 (15.9)	4319 (19.8)	3463 (15.9)	1171 (23.2)	811 (16.0)
Prior thromboembolic event	24 (7.2)	24 (7.2)	138 (5.5)	183 (7.3)	483 (10.1)	698 (14.6)	571 (10.9)	570 (10.9)	2651 (12.1)	2278 (10.4)	603 (11.9)	635 (12.6)
Risk scores												
CHA ₂ DS ₂ -VASC												
Median (IQR*)	1 (0-2)	1 (0-2)	3 (2-4)	3 (2-4)	4 (3-5)	3 (3-4)	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)	4 (2-5)	3 (2.4)
0	158 (47.2)	158 (47.2)	405 (16.2)	405 (16.2)	0	0	391 (7.5)	391 (7.5)	1328 (6.1)	1328 (6.1)	269 (5.3)	269 (5.3)
1-2	118 (35.2)	118 (35.2)	530 (3.0)	530 (3.0)	670 (14.0)	670 (14.0)	1406 (26.9)	1406 (26.9)	5148 (23.6)	5148 (23.6)	1005 (19.9)	1005 (19.9)
≥3	59 (17.6)	59 (17.6)	1572 (62.7)	1572 (62.7)	4103 (86.0)	4103 (86.0)	3432 (65.6)	3432 (65.6)	15,348 (70.3)	15,348 (70.3)	3781 (74.8)	3781 (74.8)
HAS-BLED [#]												
Median (IQR*)	2 (1-3)	1 (0-2)	2 (1-3)	2 (1-3)	3 (2-3)	2 (2-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (2-3)	2 (2-3)
0	0	0	355 (14.2)	331 (13.2)	134 (2.8)	76 (1.6)	289 (5.5)	381 (7.3)	1003 (4.6)	1147 (5.2)	208 (4.1)	242 (4.8)
1-2	232 (69.3)	155 (46.3)	1460 (58.2)	1440 (57.4)	2552 (53.5)	2863 (54.8)	2863 (54.8)	2935 (56.1)	12,130 (55.6)	12,129 (55.6)	2422 (47.9)	2638 (52.2)
≥3	103 (30.8)	52 (15.5)	692 (27.6)	736 (29.4)	2145 (6.7)	2077 (6.5)	2077 (39.7)	1913 (36.6)	8691 (39.8)	8548 (39.2)	2425 (48.0)	2175 (43.0)
Pharmacotherapy, n (%)												
OAC ^{**} therapy, n (%)	33 (9.9)	33 (9.9)	1100 (43.9)	1100 (43.9)	1311 (27.5)	1311 (27.5)	1150 (22.0)	1150 (22.0)	5985 (27.4)	5985 (27.4)	1087 (21.5)	1087 (21.5)
Amiodarone	≤3	6 (1.8)	33 (1.3)	62 (2.5)	359 (7.5)	158 (3.3)	443 (8.5)	163 (3.1)	617 (2.8)	574 (2.6)	418 (8.3)	154 (3.0)

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2	Digoxin	49 (14.6)	29 (8.7)	1000 (39.9)	916 (36.5)	1207 (25.3)	1502 (31.5)	1089 (20.8)	1285 (24.6)	7973 (36.5)	6286 (28.8)	1184 (23.4)	1223 (24.2)
3	Flecainide	0 (0)	≤ 3	13 (0.5)	29 (1.2)	9 (0.2)	32 (0.7)	12 (0.2)	52 (1.0)	40 (0.2)	156 (0.7)	6 (0.1)	27 (0.5)
4	*IQR: interquartile range. †COPD: chronic obstructive pulmonary disease. ‡IHD: ischemic heart disease. §PAD: peripheral artery disease. CHA ₂ DS ₂ -VASc: Risk score for stroke: congestive												
5	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												
6	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												
7	agents/non-steroidal inflammatory drugs, alcohol abuse. **OAC: oral anticoagulation.												
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AF for the first time with a secondary precipitant, 1996-2015
N=66,242

AF for the first time without a secondary precipitant, 1996-2015
N=138,618

Exclusions (N=26,166)

- <18 years or > 100 years, N=134
- Valvular atrial fibrillation, N=2038
- Atrial fibrillation therapy before hospital admission, N=13,916
- Dead or emigrated during the blanking period, N=7366
- Thromboembolic event during the blanking period, N=2712

Exclusions (N=40,430)

- <18 years or > 100 years, N=278
- Valvular atrial fibrillation, N=2550
- Atrial fibrillation therapy before hospital admission, N=33,629
- Dead or emigrated during the blanking period, N=1992
- Thromboembolic event during the blanking period, N=1981

Complete study population

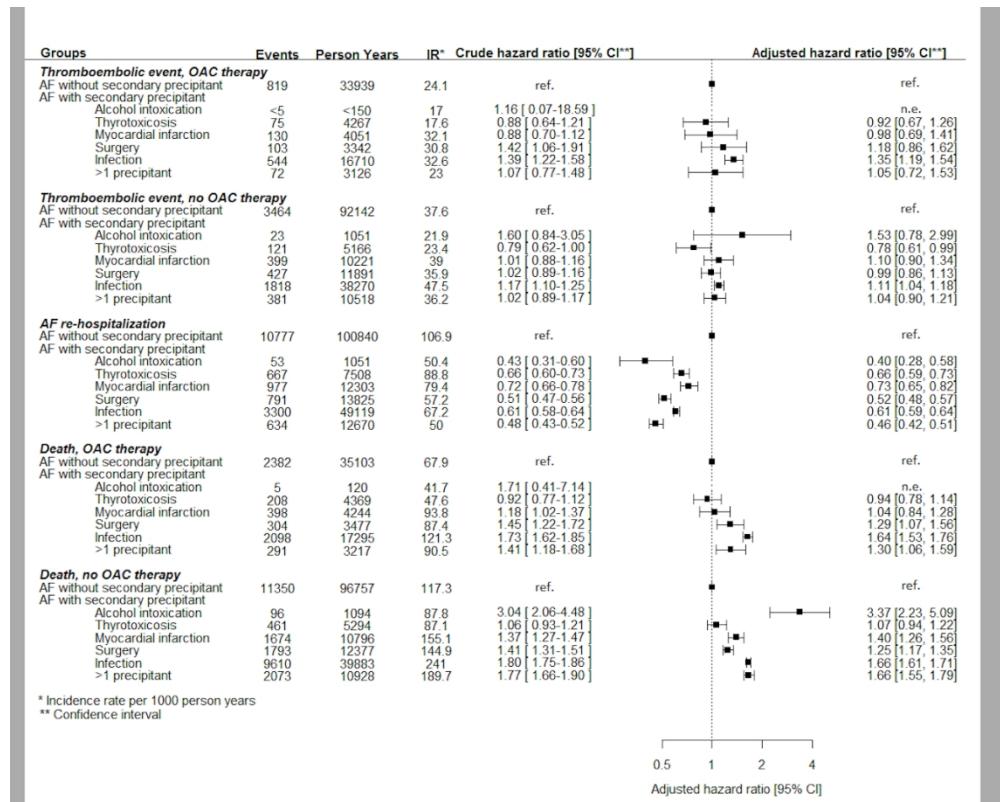
AF with secondary precipitant
N=40,076

AF without secondary precipitant
N=98,188

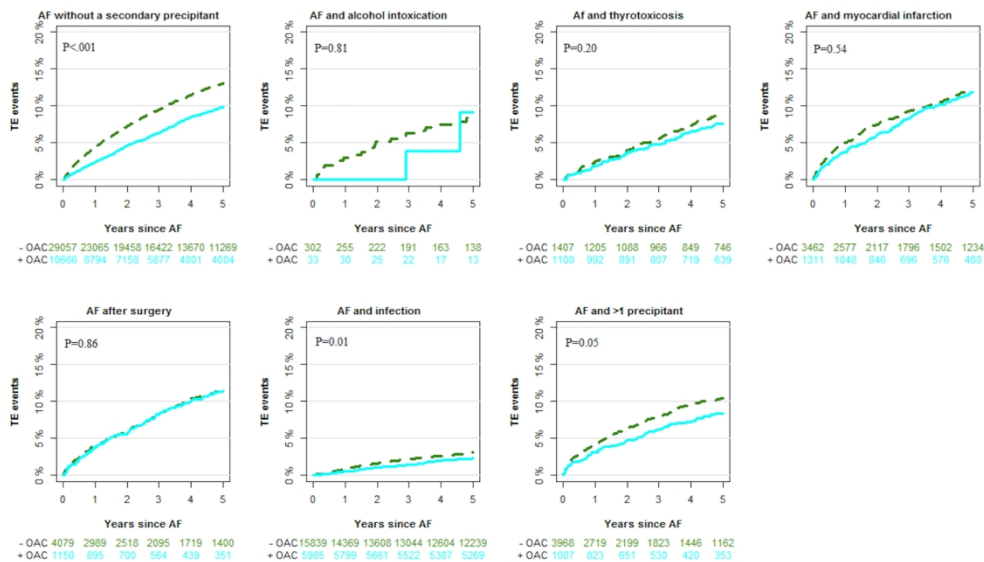
Matched population

- 39,723 patients with AF with secondary precipitant
 - 335 (0.8%) with alcohol intoxication
 - 2507 (6.3%) with thyrotoxicosis
 - 4773 (12.0%) with myocardial infarction
 - 5229 (13.2%) had had surgery
 - 21,824 (55.0%) with infection
 - 5055 (12.7%) with >1 precipitant
- 39,723 patients with AF without a secondary precipitant

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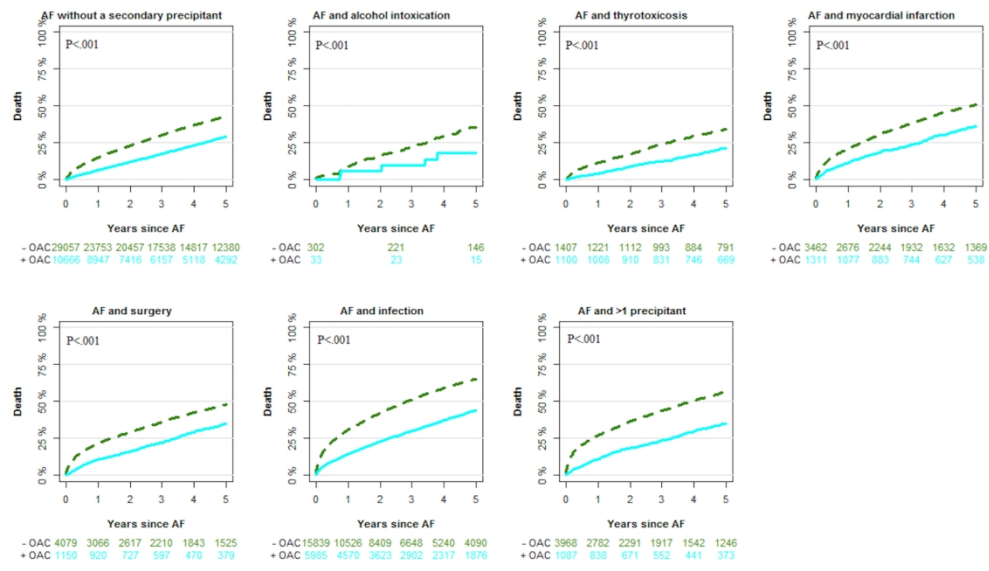


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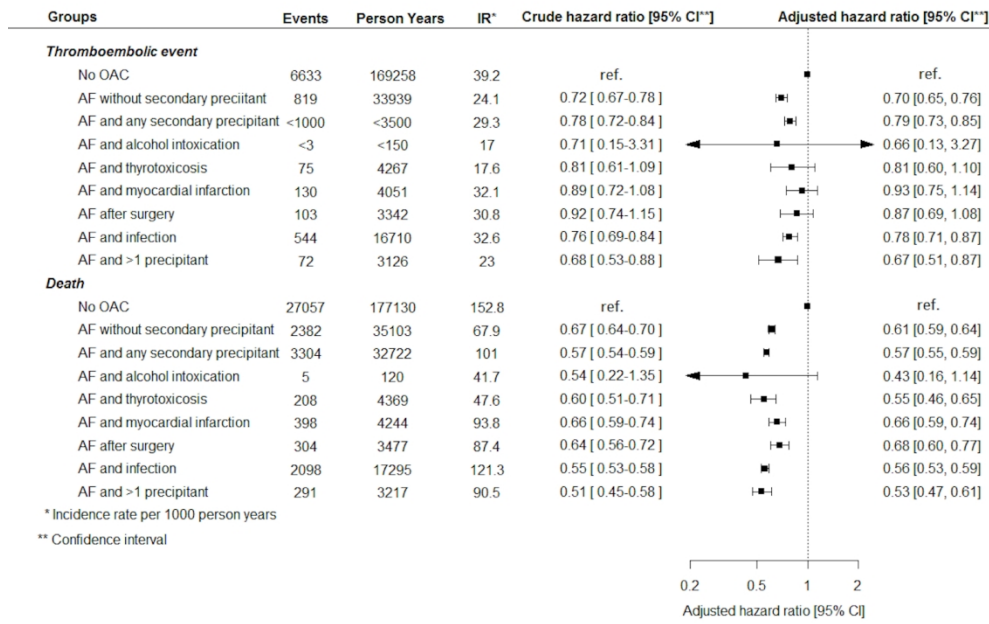
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Supplemental material

Comparative thromboembolic risk in atrial fibrillation with and without a secondary precipitant – a Danish nationwide cohort study

Anna Gundlund, MD, PhD; Thomas Kümler, MD, PhD; Anders N. Bonde, MD; Jawad H. Butt, MD; Gunnar H. Gislason, MD, PhD; Christian Torp-Pedersen, MD, DMSc; Lars Køber, MD, DMSc; Jonas B. Olesen, MD, PhD; Emil L. Fosbøl, MD, PhD

Online Table 1: Specification of diagnoses by international classification of diseases (ICD-8 and ICD-10) codes and pharmacotherapy by anatomical therapeutic chemical classification (ATC) codes.

Online Table 2: Baseline characteristics of the non-matched population, patients initiated on OAC therapy

Online Table 3: Baseline characteristics of the non-matched population, patients not initiated on OAC therapy

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.

Online Table 1: Specification of diagnoses by international classification of diseases (ICD-8 and ICD-10) codes and pharmacotherapy by anatomical therapeutic chemical classification (ATC) codes.

Precipitants	ICD-10 codes and NCSP, NOMESCO Classification of Surgical Procedures
Alcohol intoxication	ICD-10: F100, F103, F104, R780, T51, X65
Infections	ICD-10: Certain infectious and parasitic diseases: A00-B99. Infections in the eye and adnexa: H00, H01, H10, H20, H30, H44, H60, H65-H68, H70, H73.0, H73.1 Infections in the cardiovascular organs: I30, I32, I33, I38-I41 Infections in pulmonary system: J00-J22, J32, J36, J85, J86 Infections in the gastrointestinal system: K12, K20, K35-K37, K57, K65, K67, K81, K85 Infections in the skin, subcutaneous tissue, bones, muscles, and connective tissue: L00-L08, M00, M01, M60, M63.2. M65, M86, M90.0, M90.1, M90.2 Infections in the urogenital system: N00, N01, N05, N30, N70-N77.
Myocardial infarction	ICD-10: I21
Pulmonary embolism	ICD-10: I260, I269, O882D, O882E, T817D
Surgery	NCSP, NOMESCO Classification of Surgical Procedures: KF, KM, KN, KD, KPH, KPJ, KJ, KH, KQ, KB, KC, KL, KE, KA, KG, KK.
Thyrotoxicosis	ICD-10: E05
Outcomes	
Atrial fibrillation re-hospitalization	Hospital admission with primary diagnosis of atrial fibrillation: I48
Thromboembolic event	Ischemic stroke: I63, I64 Death from stroke: I61-I64 Transient ischemic attack: G458, G459 Thrombosis or embolism in arteries: I74
Comorbidities	ICD-8 and ICD-10 codes

Atrial fibrillation	ICD-10: I48 ICD-8: 42793, 42794
Alcohol abuse	ICD-10: E24.4, E52, F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, L27.8A, O35.4, T51, Z71.4, Z72.1. ATC: N07BB
Cancer	ICD-10: C
Chronic kidney disease	ICD-10: E10.2, E11.2, E13.2, E14.2, I12.0, M32.1B, N02-N08, N11, N12, N14, N15.8, N15.9, N16.0, N16.2-N16.4, N16.8, N18, N19, N26, Q61
Chronic obstructive pulmonary disease	ICD-10: J42, J43, J44
Diabetes	ATC: A10 (3 months before index)
Heart failure	ICD-10: I11.0, I42, I50, J81
Hypertension	Usage of a combination of at least two of the seven different drug classes at the same time: <ol style="list-style-type: none"> 1. Non-loop diuretics 2. Loop diuretics 3. Antiadrenergic agents 4. Beta-blockers 5. Vasodilators 6. Calcium channel blockers 7. Renin-angiotensin system inhibitors
Ischemic heart disease	ICD-10: I20-I25
Peripheral artery disease	ICD-10: I70
Prior bleeding	ICD-10: D50.0, D62, G951A, H31.3, H05.2A, H35.6, H43.1, H45.0, I31.2, I60-I62, I85.0, I86.4A, J94.2, K22.8F, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.8A, K62.5, K63.8B, K63.8C, K66.1, K83.8F, K86.8G, K92.0-K92.2, N02, R04, R31, S06.4-S06.6, S36.8D
Thromboembolic event	ICD-10: G45.8, G45.9, I63, I64, I74
Valvular atrial fibrillation	Atrial fibrillation without: ICD-10: I05, I06, I080A, I081A, I082A, I083A, Z952, Z954 ICD-8: 39500-39502, 39508, 39509, 39600-39604, 39608, 39609 Procedures: FKD, FKH, FMD, FMH, FGE, FJE
Pharmacotherapy	ACT-codes

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ADP-receptor blockers	B01AC04, B01AC22, B01AC24
Amiodarone	C01BD01
Antiadrenergic agents	C02A, C02B, C02C
Oral anticoagulation therapy	Vitamin K antagonists: B01AA03, B01AA04 Non-vitamin K antagonist oral anticoagulants: B01AF01, B01AF02, B01AE07
Beta-blockers	C07A, C07B, C07C, C07D, C07F
Calcium channel blockers	C08, C09BB, C09DB
Digoxin	C01AA
Flecainide	C01BC
Loop diuretics	C03C, C03EB
Non-loop diuretics	C02DA, C03EA, C03EB, C02L, C03A, C03B, C03D, C03E, C03X, C07B, C07C, C07D, C08G, C09BA, C09DA, C09XA52
Renin-angiotensin system inhibitors	C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C09XA02, C09XA52
Vasodilators	C02DB, C02DD, C02DG

Online Table 2: Baseline characteristics of the non-matched population, patients initiated on OAC therapy

	AF with a secondary precipitant N=10,673						AF without a secondary precipitant N=37,827
	Alcohol intoxication N=33	Thyro- toxicosis N=1103	Myocardial infarction N=1312	Surgery N=1151	Infection N=5987	>1 precipitant N=1087	
Demographics							
Age, median (IQR*)	64 (55-68)	72 (64-79)	75 (68-81)	74 (67-81)	77 (69-83)	75 (68-81)	72 (64-79)
Male, n (%)	28 (84.8)	259 (23.5)	842 (64.2)	667 (57.9)	3189 (53.3)	634 (58.3)	21,386 (56.5)
Comorbidities, n (%)							
Cancer	≤3	114 (10.3)	146 (11.1)	239 (20.8)	927 (15.5)	171 (15.1)	4617 (12.2)
Chronic kidney disease	4 (12.1)	23 (2.1)	62 (4.7)	65 (5.6)	372 (6.2)	59 (5.4)	1011 (2.7)
COPD†	≤3	106 (9.6)	133 (10.1)	128 (11.1)	1251 (20.9)	157 (14.4)	3426 (9.1)
Diabetes	≤3	84 (7.6)	159 (12.1)	111 (9.6)	712 (11.9)	112 (10.3)	3384 (8.9)
Heart failure	6 (18.2)	236 (21.4)	464 (35.4)	228 (19.8)	1440 (24.1)	359 (33.0)	6791 (18.0)
Hypertension	11 (33.3)	658 (59.7)	982 (74.8)	687 (59.7)	3652 (61.0)	723 (66.5)	23,057 (61.0)
IHD‡	5 (15.2)	129 (11.7)	1312 (100)	434 (37.7)	1202 (20.1)	744 (68.4)	7360 (19.5)
PAD§	≤3	29 (2.6)	83 (6.3)	101 (8.8)	353 (5.9)	77 (7.1)	1258 (3.3)
Prior bleeding event	7 (21.2)	86 (7.8)	150 (11.4)	213 (18.5)	966 (16.1)	182 (16.7)	4564 (12.1)
Prior thromboembolic event	≤3	60 (5.4)	142 (10.8)	153 (13.3)	672 (11.2)	133 (12.2)	3313 (8.8)
Risk scores							
CHA ₂ DS ₂ -VASc							
Median (IQR*)	1 (0-2)	3 (2-4)	4 (3-5)	3 (2-4)	3 (2-4)	4 (3-5)	3 (2-4)
0	11 (33.3)	134 (12.2)	0	74 (6.4)	269 (4.5)	28 (2.6)	3592 (9.5)
1-2	16 (48.5)	263 (23.8)	181 (13.8)	289 (25.1)	1493 (24.9)	181 (16.6)	12,341 (32.6)
≥3	6 (18.2)	706 (64.0)	1131 (86.2)	788 (68.5)	4225 (70.6)	878 (80.8)	21,894 (57.9)
HAS-BLED [#]							
Median (IQR*)	2 (1-3)	2 (1-2)	3 (2-3)	2 (1-3)	2 (1-3)	2 (2-3)	2 (1-3)
0	0	128 (11.6)	32 (2.4)	60 (5.2)	259 (4.3)	33 (3.0)	3361 (8.9)
1-2	21 (63.6)	706 (64.0)	571 (43.5)	611 (53.1)	3433 (57.3)	515 (47.4)	22,792 (60.3)
≥3	12 (36.4)	269 (24.4)	709 (54.0)	480 (41.7)	2295 (38.3)	539 (49.6)	11,674 (30.9)
Pharmacotherapy, n (%)							

Amiodarone	0	19 (1.7)	104 (7.9)	181 (15.7)	261 (4.4)	141 (13.0)	1493 (3.9)
Digoxin	11 (33.3)	605 (54.9)	437 (33.3)	312 (27.1)	2847 (47.6)	368 (33.9)	14,803 (39.1)
Flecainide	0	5 (0.5)	≤3	≤3	10 (0.2)	≤3	248 (0.7)

*IQR: interquartile range. †COPD: chronic obstructive pulmonary disease. ‡IHD: ischemic heart disease. §PAD: peripheral artery disease. ¶CHA₂DS₂-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.

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Online Table 3: Baseline characteristics of the non-matched population, patients not initiated on OAC therapy

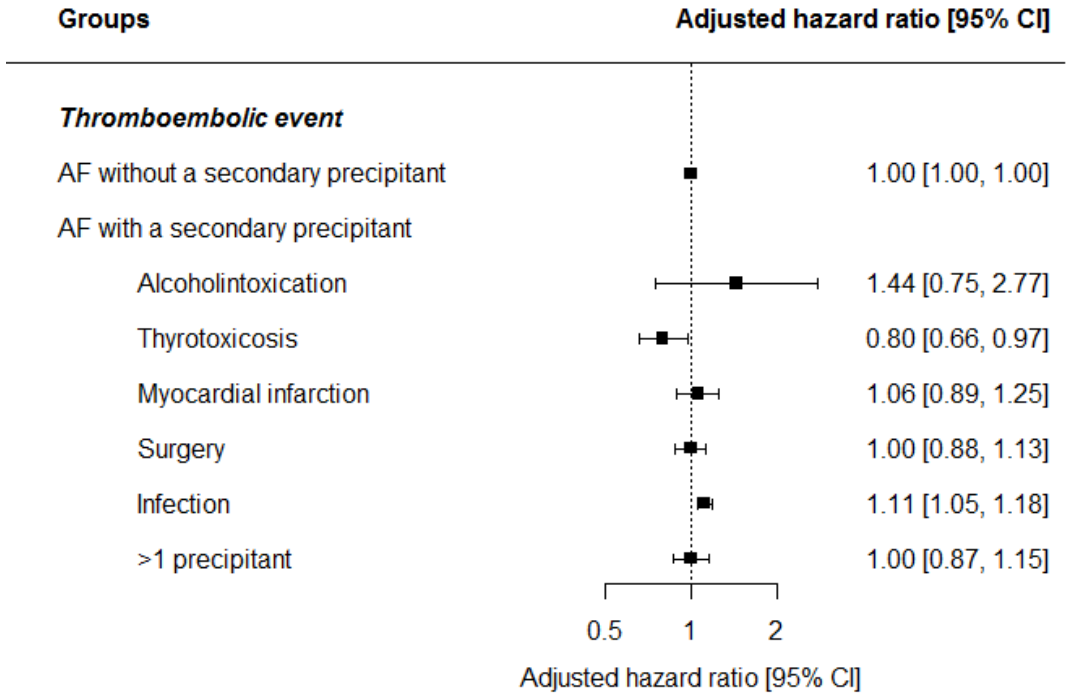
	AF with a secondary precipitant N=29,403						AF without a secondary precipitant N=60,361
	Alcohol intoxication N=302	Thyro- toxicosis N=1408	Myocardial infarction N=3508	Surgery N=4101	Infection N=16,079	>1 precipitant N=4005	
Demographics							
Age, median (IQR*)	58 (48-66)	74 (62-82)	78 (69-84)	76 (67-82)	80 (72-87)	76 (68-83)	69 (58-80)
Male, n (%)	248 (82.1)	263 (18.7)	1907 (54.4)	2069 (50.5)	7352 (45.7)	2073 (51.8)	31,074 (51.5)
Comorbidities, n (%)							
Cancer	15 (5.0)	174 (12.4)	454 (12.9)	1115 (27.2)	3474 (21.6)	795 (19.9)	7915 (13.1)
Chronic kidney disease	7 (2.3)	38 (2.7)	236 (6.7)	289 (7.0)	1223 (7.6)	375 (9.4)	1733 (2.9)
COPD†	26 (8.6)	128 (9.1)	495 (14.1)	539 (13.1)	3493 (21.7)	765 (19.1)	4544 (7.5)
Diabetes	24 (7.9)	105 (7.5)	417 (11.9)	396 (9.7)	1473 (9.2)	387 (9.7)	3566 (5.9)
Heart failure	18 (6.0)	209 (14.8)	1218 (34.7)	744 (18.1)	3752 (23.3)	1231 (30.7)	6328 (10.5)
Hypertension	53 (17.5)	653 (46.4)	2348 (66.9)	1808 (44.1)	6942 (43.2)	1991 (49.7)	22,309 (37.0)
IHD‡	38 (12.6)	207 (14.7)	3508 (100)	1326 (32.3)	3558 (22.1)	2354 (58.8)	11,528 (19.1)
PAD§	6 (2.0)	49 (3.5)	298 (8.5)	371 (9.0)	1057 (6.6)	374 (9.3)	1913 (3.2)
Prior bleeding event	74 (24.5)	157 (11.2)	585 (16.7)	1062 (25.9)	3420 (21.3)	998 (24.9)	7616 (12.6)
Prior thromboembolic event	22 (7.3)	78 (5.5)	350 (10.0)	422 (10.3)	2029 (12.6)	478 (11.9)	4301 (7.1)
Risk scores							
CHA ₂ DS ₂ -VASC							
Median (IQR*)	1 (0-2)	3 (2-4)	4 (3-5)	3 (2-4)	3 (2-4)	4 (2-5)	2 (0-4)
0	147 (48.7)	271 (19.2)	0	317 (7.7)	1059 (6.6)	241 (6.0)	15,957 (26.4)
1-2	102 (33.8)	270 (19.2)	489 (13.9)	1119 (27.3)	3671 (22.8)	824 (20.6)	17,513 (29.0)
≥3	53 (17.5)	867 (61.6)	3019 (86.1)	2665 (65.0)	11,349 (70.6)	2940 (73.4)	26,891 (44.6)
HAS-BLED [#]							
Median (IQR*)	2 (1-3)	2 (1-3)	3 (2-3)	2 (1-3)	2 (1-3)	2 (2-3)	2 (1-3)
0	0	228 (16.2)	102 (2.9)	229 (5.6)	745 (4.6)	175 (4.4)	12,875 (21.3)
1-2	211 (69.9)	756 (53.7)	1424 (40.6)	2265 (55.2)	8795 (54.7)	1924 (48.0)	31,914 (52.9)
≥3	91 (30.1)	424 (30.1)	1982 (56.5)	1607 (39.2)	6539 (40.7)	1906 (47.6)	15,572 (25.8)

Pharmacotherapy, n (%)							
Amiodarone	≤3	14 (1.0)	259 (7.4)	262 (6.4)	361 (2.2)	278 (6.9)	1133 (1.9)
Digoxin	38 (12.6)	398 (28.3)	784 (22.3)	782 (19.1)	5210 (32.4)	828 (20.7)	10,336 (17.1)
Flecainide	0	8 (0.6)	8 (0.2)	10 (0.2)	30 (0.2)	5 (0.1)	786 (1.3)

*IQR: interquartile range. †COPD: chronic obstructive pulmonary disease. ‡IHD: ischemic heart disease. §PAD: peripheral artery disease. ||CHA₂DS₂-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.

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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.



view only

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract YES, p.1 and 3. (b) Provide in the abstract an informative and balanced summary of what was done and what was found YES, p. 3.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported YES, p. 5
Objectives	3	State specific objectives, including any prespecified hypotheses YES, p. 5
Methods		
Study design	4	Present key elements of study design early in the paper YES, p. 5-7.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection YES, p. 5-7.
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up YES, p. 6-7. <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed YES, p. 8. <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable YES, p. 7-8. Figure 3. Specification of diagnosis can be found in the Online Table 1.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group YES, p. 5-6 and eTable 1.
Bias	9	Describe any efforts to address potential sources of bias YES, p. 8.
Study size	10	Explain how the study size was arrived at YES, p. 6-7, figure 1.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why

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YES, p. 6-7.

Statistical methods

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(a) Describe all statistical methods, including those used to control for confounding

YES, p. 7-8.

(b) Describe any methods used to examine subgroups and interactions

YES, p. 7-8.

(c) Explain how missing data were addressed

No missing data

(d) *Cohort study*—If applicable, explain how loss to follow-up was addressed

No loss to follow-up.

Case-control study—If applicable, explain how matching of cases and controls was addressed

Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy

(e) Describe any sensitivity analyses

YES, p. 7.

Continued on next page

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Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed YES, p. 8-9 and Figure 1.
		(b) Give reasons for non-participation at each stage YES, p. 8-9 and Figure 1.
		(c) Consider use of a flow diagram YES, Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders YES, p. 9, Table 1.
		(b) Indicate number of participants with missing data for each variable of interest No missing data
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) YES, Figure 2.
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time YES, p. 10 and Figure 2, 3.
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included YES, Figure 3.
		(b) Report category boundaries when continuous variables were categorized Continuous variables were not categorized.
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses YES, p. 11.
Discussion		
Key results	18	Summarise key results with reference to study objectives YES, p. 11.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias YES, p. 13-14.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence YES, p. 12-13.
Generalisability	21	Discuss the generalisability (external validity) of the study results YES, p. 14.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

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2 YES, p. 14.
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4 *Give information separately for cases and controls in case-control studies and, if applicable, for exposed and
5 unexposed groups in cohort and cross-sectional studies.
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8 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and
9 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely
10 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
11 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
12 available at www.strobe-statement.org.
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BMJ Open

Comparative thromboembolic risk in atrial fibrillation with and without a secondary precipitant– a Danish nationwide cohort study

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Epidemiology
Keywords:	Cardiac Epidemiology < CARDIOLOGY, Thromboembolism < CARDIOLOGY, Pacing & electrophysiology < CARDIOLOGY

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Manuscripts

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4 1 **Comparative thromboembolic risk in atrial fibrillation with and without a**
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7 2 **secondary precipitant– a Danish nationwide cohort study**
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4 1 **Abstract:** 292 words (max 300 words)
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6 2 Objectives: We compared long-term outcomes in patients with atrial fibrillation (AF) with and
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8
9 3 without a secondary precipitant.
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11 4 Design and setting: Retrospective cohort study based on Danish nationwide registries.
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13 5 Participants: Patients with AF with and without secondary precipitants (1996-2015) were matched
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16 6 1:1 according to age, sex, calendar year, CHA₂DS₂-VASc score, and oral anticoagulation therapy
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18 7 (OAC) therapy, resulting in a cohort of 39,723 patients with AF with a secondary precipitant and
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20 8 the same number of patients with AF without a secondary precipitant. Secondary precipitants
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23 9 included alcohol intoxication, thyrotoxicosis, myocardial infarction, surgery, and infection in
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25 10 conjunction with AF.
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27 11 Primary and secondary outcomes: The primary outcome in this study was thromboembolic events.
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30 12 Secondary outcomes included AF re-hospitalization and death. Long-term risks of outcomes were
31
32 13 examined by multivariable Cox regression analysis.
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34 14 Results: The most common precipitants were infection (55.0%), surgery (13.2%), and myocardial
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36 15 infarction (12.0%). The 5-year absolute risk of thromboembolic events (taking death into account as
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39 16 a competing risk) in patients with AF grouped according to secondary precipitants were 8.3%
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41 17 (alcohol intoxication), 8.5% (thyrotoxicosis), 12.1% (myocardial infarction), 11.6% (surgery),
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43 18 12.2% (infection), 10.1% (>1 precipitant), and 12.3% (no secondary precipitant). In the
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46 19 multivariable analyses, AF with a secondary precipitant was associated with the same or an even
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48 20 higher thromboembolic risk than AF without a secondary precipitant. One exception was patients
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50 21 with AF and thyrotoxicosis: those not initiated on OAC therapy carried a lower thromboembolic
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52 22 risk the 1st year of follow up than matched patients with AF without a secondary precipitant and no
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55 23 OAC therapy.
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4 1 Conclusions: In general, AF with a secondary precipitant was associated with the same
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6 2 thromboembolic risk as AF without a secondary precipitant. Consequently, this study highlights the
7
8 3 need for more research regarding the long-term management of patients with AF associated with a
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10 4 secondary precipitant.
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13 5 Key words: Secondary precipitant, reversible atrial fibrillation, recurrence
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4 **1 Article summary: strengths and limitations of this study**
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- 6
7 2 • The study was based on high-quality nationwide registries with many years of follow up.
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9 3 • Complete follow-up was possible
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11 4 • Only associations could be drawn because of the retrospective and non-randomized design.
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14 5 • AF with and without a secondary precipitant were defined from diagnosis codes at discharge
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16 6 • We had no data on electrocardiograms at discharge
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1 **Introduction**

2 The etiology of atrial fibrillation (AF) remains partly unknown. Studies have shown, that an
3 inflammatory reaction inside the atria always precipitate AF.(1) However, in clinical practice, AF
4 may occur as an isolated event or together with a secondary precipitant. AF is associated with a
5 fivefold increased risk of ischemic stroke, and detailed treatment strategies regarding stroke
6 prophylaxis in patients with AF occurring without secondary precipitants exist in both European
7 and American treatment guidelines.(2–5)] In contrast, there is no consensus regarding stroke
8 prophylaxis in patients with AF occurring with a secondary precipitant. Previous guidelines stated
9 that AF occurring secondary to another precipitant usually will terminate without recurrence.(2) In
10 current guidelines, however, this statement has been omitted, and the need for data regarding AF
11 associated with a secondary precipitant highlighted.(4,5) Studies investigating long-term outcomes
12 in AF associated with a secondary precipitant are sparse and data differentiating between different
13 secondary precipitants and taking oral anticoagulation (OAC) therapy into account are missing.
14 To address this lack in current knowledge, we aimed to compare long-term outcomes including
15 thromboembolic events, AF re-hospitalization, and death in patients with AF with a secondary
16 precipitant (incl. alcohol, intoxication, thyrotoxicosis, myocardial infarction, surgery, and infection)
17 and patients with AF without a secondary precipitant. Further, we were able to differentiate
18 between patients receiving and not receiving stroke prophylaxis with OAC therapy.

19 **Materials and methods**

20 *Data sources*

21 In Denmark, healthcare is tax-financed and with equal availability regardless of socioeconomic
22 status. Date of birth, date and cause of death, emigration and immigration status, diagnosis and
23 surgery codes etc. from all hospital contacts, fulfilled prescriptions of medicine, and several other
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parameters are registered in different nationwide registries. Since all Danish citizens are provided a unique personal identifier code at birth (or immigration), data from the registries can be crosslinked on an individual level. We linked data from the following registries: The Danish Civil Registration System,(6) The Danish National Patient Registry (diagnoses were registered in terms of the International Classification of Diseases (ICD) system (ICD-8 until 1994 and in terms of ICD-10 thereafter)),(7) The Danish Register of Causes of Death,(8) and the Danish National Registry of Medicinal Statistics (medicine were registered according to the Anatomical Therapeutic Chemical classification system (ATC)).(9)

Study population

The patient selection is depicted in Figure 1. We included all Danes diagnosed and admitted to a Danish hospital with AF for the first time between 1996 and 2015. Patients <18 years or >100 years and those with valvular AF (defined as AF without: rheumatic valve disease of aortic valve or mitral valve or prosthetic heart valve (any valve)) were excluded. Since there was a possibility that some of the patients had been diagnosed with AF at their general practitioner before their hospital admission, we excluded those who previously had fulfilled a prescription of antiarrhythmic therapy or rate-controlling drugs (incl. amiodarone, flecainide, and digoxin) and those who had fulfilled a prescription of OAC therapy up to 100 days before their hospital admission. Further, patients who died or had a thromboembolic event during the hospital admission or a constructed blanking period of 4 weeks from hospital discharge to the index date were excluded.

Patients were grouped in those with and without a secondary precipitant. Patients who had a diagnosis of one of the following precipitants from their AF hospital admission were defined as patients with a secondary precipitant: alcohol intoxication, thyrotoxicosis, myocardial infarction, and infection. Also, patients who were diagnosed with AF after, but during the same hospital

1 admission they received surgery were defined as having AF with a secondary precipitant. We
2 restricted the population of patients with AF without a secondary precipitant to patients with AF
3 without a diagnosis of a secondary precipitant from their hospital admission. Patients with AF with
4 and without a secondary precipitant were matched 1:1 by incidence density sampling according to
5 age (allowing a difference of up to two years), sex, calendar year (allowing a difference up to two
6 years), CHA₂DS₂-VASc group (0, 1-2, >2) and OAC therapy status at the index date. Consequently,
7 each case was matched with a control diagnosed at the same time and in the same age with AF.
8 Further, the control had the same sex and was categorized in the same CHA₂DS₂-VASc group as
9 the case. These patients comprised the study population. We used a previously described function to
10 perform the match.(10)

11 12 *Long-term outcomes*

13 The index date was defined 4 weeks from AF hospital discharge. Initiation of OAC therapy and
14 antiarrhythmic and rate controlling drugs was assessed during this blanking period from discharge
15 to index date. Patients were followed from the index date and until the first event of the following:
16 an outcome of interest, death, 5 years from the index date, emigration, or June 30, 2015. The
17 primary outcome of interest was thromboembolic events (a composite of ischemic stroke, transient
18 ischemic attack (TIA), and systemic thrombosis or embolism) while secondary outcomes included
19 AF rehospitalization and all-cause death. AF rehospitalization was defined as a hospitalization with
20 AF as the primary discharge diagnosis. The diagnoses of AF, ischemic stroke, and myocardial
21 infarction have been validated in the Danish registries with positive predictive values of 93%, 97%,
22 and 100%, respectively.(11,12)

1 2 3 4 1 *Statistics*

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6 2 Kaplan Meier curves for death were drawn and cumulative incidences of thromboembolic events
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9 3 (with incorporated competing risk of death) calculated using the Aalen Johansen estimator. The
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11 4 Log-Rank test and the Gray's test were used to test for differences in the cumulative incidence of
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13 5 long-term outcomes. Cox regression analyses were performed to calculate hazard ratios (HR) of
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15 6 long-term outcomes in patients with AF with and without a secondary precipitant according to OAC
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17 7 therapy at the index date. All analyzes were performed on the matched population. The multivariate
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19 8 models were adjusted for other potential confounders than the matching criteria (incl. comorbidities
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21 9 at the index date (incl. peripheral artery disease, heart failure, hypertension, prior thromboembolic
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23 10 event, ischemic heart disease, chronic kidney disease, diabetes, prior bleeding event, cancer) and
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25 11 antiarrhythmic and rate-controlling therapy during the blanking period (amiodarone, digoxin,
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27 12 flecainide)). The analyses took matching variables into account and each group of patients with AF
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29 13 with a secondary precipitant was compared with its respective matches from the matching
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31 14 procedure. The models were tested for the assumption of proportional hazards. For specification of
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33 15 diagnosis codes and ATC-codes please see Online Table 1. A P-value <0.05 was considered
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35 16 statistically significant. All statistical analyses were performed in SAS statistical software version
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37 17 9.4 or R.(13)
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45 19 *Other analyses*

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48 20 Analyses of long-term outcomes were also performed on a non-matched population including all
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50 21 patients available before the matching (Figure 1). To account for changes in OAC therapy status
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52 22 over time, we did a sensitivity analysis not stratifying patients with regard to their OAC therapy
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54 23 status at the index date, but instead adjusting for OAC therapy status as a time-dependent variable.
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4 1 Consequently, new initiations and discontinuations were taking into account. The method used, has
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6 2 been used and described previously.(14–16)
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9 3 10 11 4 *Ethics*

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13 5 Approval from the Research Ethics Committee System is not required in retrospective registry-
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15 6 based studies in Denmark. The Danish Data Protection Agency approved use of data for this study
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17 7 (ret.no: 2007-58-0015 / GEH-2014-013 I-Suite no: 02731).
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21 22 23 9 *Patient and Public Involvement*

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25 10 This was a retrospective study based on administrative registries. Patients and the public were not
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27 11 involved in the development of the study.
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31 32 13 *Data availability statement*

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34 14 This study was based on deidentified data about the entire Danish population. Data are not
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36 15 available.
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40 41 17 *Contributorship statement*

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43 18 The study idea was conceived by AG, TK, and ELF., study design was developed by AG, TK, JBO,
44
45 19 ANB, JHB, GHG, CTP, LK, and ELF, data analyses were made by AG. AG drafted the first version
46
47 20 of the paper and all authors participated in the critical discussions and interpretation of findings. All
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49 21 authors have participated in the revisions of the draft and have approved the final version.
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53 54 23 **Results**

55 56 24 *Study population* 57 58 59 60

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4 1 As shown in Figure 1, the most common secondary precipitant was infection (21,824 patients,
5 55.0%). Further, 335 (0.8%) patients had a concurrent alcohol intoxication, 2507 (6.3%) had
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7 3 thyrotoxicosis, 4773 (12.0%) had acute myocardial infarction, 5229 (13.2%) had underwent
8 4
9 5 surgery, and 5055 (12.7%) had >1 precipitant. Of those with >1 precipitant, 4788 (94.7%) patients
10 6
11 7 had two secondary precipitants, while 267 (5.3%) had three or four secondary precipitants.
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13 9 Infection and surgery was the most common combination of secondary precipitants. The patients
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15 11 with >1 precipitant were grouped in one group, and were not included in the other groups of
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17 13 patients with AF with a secondary precipitant. During the blanking period, 14% of the patients with
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19 15 AF and a secondary precipitant and 2% of the patients with AF without a secondary precipitant
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21 17 died, while 5% and 2%, respectively, had a thromboembolic event. These patients were excluded
22 18
23 19 before the matching.
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Baseline characteristics

34 14 Baseline characteristics of the matched study population are shown in Table 1. In general, patients
35 15
36 16 with AF with a secondary precipitant had more comorbidities than patients with AF without a
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38 18 secondary precipitant. Baseline characteristics of the non-matched population according to OAC
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40 20 therapy at the index date are shown in online Table 2 and 3. Especially those with AF and
41 21
42 22 myocardial infarction, surgery, infection, and >1 precipitant were older, had more comorbidities,
43 23
44 24 and higher risk scores for stroke and bleeding compared with patients with AF without a secondary
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46 26 precipitant. Among the patients with AF with a secondary precipitant (non-matched study
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48 28 population), 9.9% with alcohol intoxication, 43.9% with thyrotoxicosis, 27.2% with myocardial
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50 30 infarction, 21.9% with surgery, 27.1% with infection, and 21.4% with >1 precipitant received OAC
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52 32 therapy at the index date, respectively. Among patients with AF without a secondary precipitant,
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54 34 38.5% received OAC therapy at the index date. In general for patients with AF with and without a
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4 1 secondary precipitant, those initiated on OAC therapy suffered from less cancer, chronic kidney
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6 2 disease, peripheral artery disease, and had fewer previous bleeding events than those not initiated
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9 3 on OAC therapy. On the other hand, they were more likely to suffer from stroke risk factors (incl.
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11 4 diabetes, heart failure, ischemic heart disease, and hypertension) than those not initiated on OAC
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13 5 therapy. During the first year after the index date, 9.9% and 17.3% of patients with AF with and
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15 6 without a secondary precipitant, respectively, had a new hospital admission with AF. One year after
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17 7 the index date, 19.8% and 32.7% of the patients with AF with and without a secondary precipitant,
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19 8 respectively, were in OAC therapy and 22.3% and 21.8% of the patients with AF with and without
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21 9 a secondary precipitant, respectively, were in antiarrhythmic therapy.
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27 11 *Long-term outcomes*

29 12 Number of events, incidence rates, and crude and adjusted hazard ratios (HRs) of thromboembolic
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31 13 events and death in AF patients with a secondary precipitant compared with AF patients without a
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33 14 secondary precipitant initiated and not initiated on OAC therapy at the index date are presented in
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35 15 Figure 2. With few exceptions, AF with a secondary precipitant was associated with the same
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37 16 thromboembolic risk as AF without a secondary precipitant. Regardless of OAC therapy status at
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39 17 the index date, AF with infection was associated with a significantly increased risk of
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41 18 thromboembolic events compared with AF without a secondary precipitant. Among those not
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43 19 initiated on OAC therapy, AF with thyrotoxicosis was associated with a significantly lower risk of
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45 20 thromboembolic events compared with AF without a secondary precipitant. In those initiated on
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47 21 OAC therapy, no differences in thromboembolic risk was observed between patients with AF and
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49 22 thyrotoxicosis and patients with AF without a secondary precipitant. All subgroups of AF with a
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51 23 secondary precipitant were associated with a significantly lower risk of AF re-hospitalization
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53 24 compared with AF without a secondary precipitant (Figure 2).
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2 Figure 3 and 4 depicts cumulative incidences of thromboembolic events and death in patients with
3 AF with and without a secondary precipitant. During follow up, the cumulative incidence of
4 thromboembolic events (taking death as an competing risk into account) according to type of
5 secondary precipitant was 8.3% (alcohol intoxication), 8.5% (thyrotoxicosis), 12.1% (myocardial
6 infarction), 11.6% (surgery), 12.2% (infection), 10.1% (>1 precipitant), and 12.3% (no secondary
7 precipitant). The cumulative incidence of AF re-hospitalization were 19.6% (alcohol intoxication),
8 30.8% (thyrotoxicosis), 27.2% (myocardial infarction), 14.8% (surgery), 20.9% (infection), 19.3%
9 (>1 precipitant), and 34.4% (no secondary precipitant) (not included in the figures).

10 OAC therapy initiation compared with no OAC therapy initiation was associated with a lower
11 thromboembolic risk in patients with AF with and without a secondary precipitant, although the
12 results did not reach statistical significance in patients with AF with alcohol intoxication,
13 thyrotoxicosis, myocardial infarction, and surgery as secondary precipitants (Figure 5).

15 *Other analyses*

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

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

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6 2 **Discussion**7
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9 3 We examined long-term outcomes in patients with AF with and without a secondary precipitant.10
11 4 The study had two main findings: first, AF with different secondary precipitants was in general12
13 5 associated with the same thromboembolic risk as AF without a secondary precipitant. Secondly,14
15 6 OAC initiation-rates differed significantly according to type of secondary precipitant. Further, OAC16
17 7 therapy vs. no OAC therapy were associated with a lower thromboembolic risk in those with AF18
19 8 and infection and >1 precipitant while no significant risk-reduction was seen for patients with AF20
21 9 with the other secondary precipitants.
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27 11 *Thromboembolic risk*28
29 12 Despite of lower re-hospitalization rates with AF, AF with a secondary precipitant was in general30
31 13 associated with the same thromboembolic risk as AF without a secondary precipitant. AF with32
33 14 thyrotoxicosis was associated with a lower thromboembolic risk compared with AF without a34
35 15 secondary precipitant. In contrast, AF with infection was associated with an increased36
37 16 thromboembolic risk compared with AF without a secondary precipitant. This is in accordance with38
39 17 previous findings.(17–19) In two previous studies, Lubitz et al. and Fauchier et al. examined long-40
41 18 term outcomes in patients with AF secondary to a reversible precipitant compared with patients42
43 19 with AF without a secondary precipitant. In both studies, AF secondary to a reversible precipitant44
45 20 was associated with the same thromboembolic risk as AF without secondary precipitants. However,46
47 21 both studies were smaller and with patients included before 2012 and 2010, respectively.(20,21) In48
49 22 summary, our results together with previous studies suggest that AF with a secondary precipitant in50
51 23 general, and maybe with the exception of AF with thyrotoxicosis, may be considered as similar to52
53 24 AF without a secondary precipitant with respect to thromboembolic risk.
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6 2 *OAC therapy*

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9 3 OAC therapy showed a tendency towards a lower thromboembolic risk in patients with AF and a
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11 4 secondary precipitant, but did only reach statistical significance for patients with AF and infection
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13 5 and >1 precipitant. Recently, Quon et al. examined risk of thromboembolic events and bleeding in
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15 6 patients with AF and acute coronary syndrome, acute pulmonary disease, and infection according to
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17 7 OAC therapy status after discharge. In that study, OAC therapy was not associated with lower risk
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19 8 of thromboembolic events in patients with AF and the before mentioned precipitants. However, the
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21 9 analyses on long-term outcomes were based on logistic regression analysis, and did therefore not
22
23 10 include survival time in the model. Since patients with AF with a secondary precipitant in our study
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25 11 seemed to die at a higher rate than patients with AF without a secondary precipitant, the time
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27 12 perspective is crucial when studying long-term outcomes in this setting.(22) Studies with a clinical
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29 13 randomized design would be able to show whether patients with AF with a secondary precipitant
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31 14 benefit from OAC therapy on the same terms as patients with AF without a secondary precipitant.
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39 16 *OAC treatment-rates*

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41 17 The non-matched population allowed us to describe trends in OAC therapy initiation in patients
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43 18 with AF with and without a secondary precipitant. In patients with AF without a secondary
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45 19 precipitant, 38.5% of the patients were initiated on OAC therapy at the index date. This is in
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47 20 accordance with previous findings, taking into account that our study period went back to 1996
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49 21 when treatment rates were lower than today.(23,24) In 2017, Chean et al. assessed current practice
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51 22 of AF among critically ill patients with new-onset AF. The study was based on questionnaires
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53 23 answered by members of the Intensive Care Society in UK. The results revealed that 63.8% of the
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55 24 respondents would not regularly anti-coagulate critically ill patients with new-onset AF. We found
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4 1 important differences in OAC therapy initiation rates in patients with AF with a secondary
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6 2 precipitant according to type of precipitant. Patients with alcohol intoxication had the lowest
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8 3 initiation rate of OAC therapy (9.9%). Almost 50% of this patient group had a CHA₂DS₂-VASc
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10 4 score of 0 and hence no indication for OAC therapy. Further patients with alcohol abuse may have
11
12 5 poor compliance and increased bleeding risk.(25) Consequently, there may be caution among
13
14 6 physicians in prescribing OACs for this patient group. In 2011, Traube and colleagues reviewed the
15
16 7 literature with respect to thromboembolic risk in patients with AF and thyrotoxicosis. They
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18 8 concluded that OAC therapy should be initiated for those patients who did not have any
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20 9 contraindications for treatment.(26) This could explain the high OAC treatment initiation rates in
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22 10 this patient group (43.9%).
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30 12 *Limitations*

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32 13 First of all, this study was a retrospective registry-based study and hence no causative relationships
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34 14 can be drawn. Our definition of AF with a secondary precipitant was based on diagnosis codes from
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36 15 hospital admissions with AF and a reversible precipitant. Both diagnoses were registered at the
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38 16 discharge date, and therefore we may have included patients in the group of AF with a secondary
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40 17 precipitant who developed AF before the secondary precipitant (e.g. patients admitted with AF who
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42 18 developed infection during their hospital stay), and thereby should have been classified as patients
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44 19 with AF without a secondary precipitant. Moreover, we had no access to patient files, and we did
45
46 20 not know the duration of AF or whether the patients were discharged in sinus rhythm or with AF.
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48 21 Also, no data were available with regard to the physicians' considerations when choosing between
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50 22 OAC therapy and no OAC therapy, patients compliance, and measurements of international
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52 23 normalized ratio (INR) and time in therapeutic range for warfarin users. Previous studies have
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54 24 shown an association between an impaired platelet nitric oxide response and recent onset AF and
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1 that disturbances in nitric oxide function are associated with outcomes (including thromboembolic
2 events, bleeding events, and death) in AF. Unfortunately, we did not have any information on nitric
3 oxide levels in our study cohort.(27,28)

4 However, this study was based on a nationwide cohort of patients with many years of follow-up and
5 data from high-quality registries. It reveals unexpected results that should be considered in future
6 treatment guidelines for patients with AF and a secondary precipitant.

8 Recent onset of AF is associated with marked impairment of platelet NO response. These findings
9 may contribute to thromboembolic risk in such patients.

11 nitric oxide signaling, and that the standard scoring systems for thrombo-embolic risk in patients
12 with AF partially parallel plasma concentrations of the NO synthase inhibitor ADMA

15 *Conclusion*

16 In this study we found that patients with AF and a secondary precipitant carried a similar associated
17 thromboembolic risk as those with AF without a secondary precipitant. Current guidelines lack data
18 on this subject and our results suggests that AF in relation to known triggers may be considered as
19 AF in general.

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3 for-profit sectors.

4 **Conflicts of interest**

5 AG: None. TK: Consultant fees from BMS, Astra Zeneca, Roche, Boehringer-Ingelheim, Bayer,
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12

13 **Author contributions**

14 The study idea was conceived by AG, TK, and ELF, study design was developed by AG, TK, JBO,
15 ANB, JHB, GHG, CTP, LK, and ELF, data analyses were made by AG. AG drafted the first version
16 of the paper and all authors participated in the critical discussions and interpretation of findings. All
17 authors have participated in the revisions of the draft and have approved the final version.
18

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20 None.

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For peer review only

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4 **1 Figure legends**

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6 **2 Figure 1: Patient selection**

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9 **3 Figure 2: Number of events, incidence rates, and crude and adjusted Hazard ratios of long-term**
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11 **4 outcomes in patients with AF with and without a secondary precipitant.**

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13 **5 Figure 3: Cumulative incidence of thromboembolic events outcomes by secondary precipitant and**
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15 **6 OAC therapy at the index date.**

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18 **7 Figure 4: Cumulative incidence of death events outcomes by secondary precipitant and OAC**
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20 **8 therapy at the index date.**

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23 **9 Figure 5: Adjusted hazard ratios of long-term outcomes in patients with AF initiated vs. not**
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25 **10 initiated on OAC therapy (stratified according to type of AF).**

Table 1: Baseline characteristics of the matched population

	Alcohol intoxication group		Thyrotoxicosis group		Myocardial infarction group		Surgery group		Infection group		>1 precipitant group	
+/- secondary precipitant:	+	-	+	-	+	-	+	-	+	-	+	-
	N=335	N=335	N=2507	N=2507	N=4773	N=4773	N=5229	N=5229	N=21,824	N=21,824	N=5055	N=5055
Demographics												
Age, median (IQR*)	59 (49-66)	59 (49-66)	73 (63-81)	73 (63-81)	77 (69-83)	77 (69-83)	75 (67-82)	75 (67-82)	79 (71-86)	79 (71-86)	76 (68-83)	76 (68-83)
Male, n (%)	276 (82.4)	276 (82.4)	521 (20.8)	521 (20.8)	2705 (56.7)	2705 (56.7)	2724 (52.1)	2724 (52.1)	10,370 (47.5)	10,370 (47.5)	2676 (52.9)	2676 (52.9)
Comorbidities, n (%)												
Cancer	16 (4.8)	29 (8.7)	288 (11.5)	296 (11.8)	586 (12.3)	688 (14.4)	1349 (25.8)	882 (16.9)	4341 (19.9)	3571 (16.4)	958 (19.0)	807 (16.0)
Chronic kidney disease	11 (3.3)	8 (2.4)	61 (2.4)	49 (2.0)	289 (6.1)	233 (4.7)	352 (6.7)	198 (3.8)	1564 (7.2)	748 (3.4)	431 (8.5)	212 (4.2)
COPD†	28 (8.4)	23 (6.9)	234 (9.3)	221 (8.8)	619 (13.0)	565 (11.8)	665 (12.7)	520 (9.9)	4696 (21.5)	2093 (9.6)	914 (18.1)	519 (10.3)
Diabetes	26 (7.8)	18 (5.4)	189 (7.5)	159 (6.3)	575 (12.0)	556 (11.6)	503 (9.6)	423 (8.1)	2167 (9.9)	1737 (8.0)	498 (9.9)	554 (11.0)
Heart failure	24 (7.2)	18 (5.4)	445 (17.8)	388 (15.5)	1660 (34.8)	1076 (22.5)	966 (18.5)	851 (16.3)	5109 (23.4)	3709 (17.0)	1574 (31.1)	925 (18.3)
Hypertension	64 (19.1)	78 (23.3)	1309 (52.2)	1249 (49.8)	3290 (68.9)	3204 (67.1)	2484 (47.5)	2695 (51.5)	10,445 (47.9)	11,475 (52.6)	2694 (53.3)	3007 (59.5)
IHD‡	43 (12.8)	53 (15.8)	333 (13.3)	455 (18.1)	4773 (100)	1604 (33.6)	1753 (33.5)	1332 (25.5)	4696 (21.5)	5069 (23.2)	3072 (60.8)	1423 (28.2)
PAD§	7 (2.1)	8 (2.4)	78 (3.1)	83 (3.3)	375 (7.9)	293 (6.1)	468 (9.0)	233 (4.5)	1392 (6.4)	932 (4.3)	448 (8.9)	269 (5.3)
Prior bleeding event	81 (24.2)	42 (12.5)	243 (9.7)	249 (9.9)	722 (15.1)	715 (15.0)	1267 (24.2)	833 (15.9)	4319 (19.8)	3463 (15.9)	1171 (23.2)	811 (16.0)
Prior thromboembolic event	24 (7.2)	24 (7.2)	138 (5.5)	183 (7.3)	483 (10.1)	698 (14.6)	571 (10.9)	570 (10.9)	2651 (12.1)	2278 (10.4)	603 (11.9)	635 (12.6)
Risk scores												
CHA ₂ DS ₂ -VASC												
Median (IQR*)	1 (0-2)	1 (0-2)	3 (2-4)	3 (2-4)	4 (3-5)	3 (3-4)	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)	4 (2-5)	3 (2.4)
0	158 (47.2)	158 (47.2)	405 (16.2)	405 (16.2)	0	0	391 (7.5)	391 (7.5)	1328 (6.1)	1328 (6.1)	269 (5.3)	269 (5.3)
1-2	118 (35.2)	118 (35.2)	530 (3.0)	530 (3.0)	670 (14.0)	670 (14.0)	1406 (26.9)	1406 (26.9)	5148 (23.6)	5148 (23.6)	1005 (19.9)	1005 (19.9)
≥3	59 (17.6)	59 (17.6)	1572 (62.7)	1572 (62.7)	4103 (86.0)	4103 (86.0)	3432 (65.6)	3432 (65.6)	15,348 (70.3)	15,348 (70.3)	3781 (74.8)	3781 (74.8)
HAS-BLED [#]												
Median (IQR*)	2 (1-3)	1 (0-2)	2 (1-3)	2 (1-3)	3 (2-3)	2 (2-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (2-3)	2 (2-3)
0	0	0	355 (14.2)	331 (13.2)	134 (2.8)	76 (1.6)	289 (5.5)	381 (7.3)	1003 (4.6)	1147 (5.2)	208 (4.1)	242 (4.8)
1-2	232 (69.3)	155 (46.3)	1460 (58.2)	1440 (57.4)	2552 (53.5)	2863 (54.8)	2863 (54.8)	2935 (56.1)	12,130 (55.6)	12,129 (55.6)	2422 (47.9)	2638 (52.2)
≥3	103 (30.8)	52 (15.5)	692 (27.6)	736 (29.4)	2145 (6.7)	2077 (6.5)	2077 (39.7)	1913 (36.6)	8691 (39.8)	8548 (39.2)	2425 (48.0)	2175 (43.0)
Pharmacotherapy, n (%)												
OAC ^{**} therapy, n (%)	33 (9.9)	33 (9.9)	1100 (43.9)	1100 (43.9)	1311 (27.5)	1311 (27.5)	1150 (22.0)	1150 (22.0)	5985 (27.4)	5985 (27.4)	1087 (21.5)	1087 (21.5)
Amiodarone	≤3	6 (1.8)	33 (1.3)	62 (2.5)	359 (7.5)	158 (3.3)	443 (8.5)	163 (3.1)	617 (2.8)	574 (2.6)	418 (8.3)	154 (3.0)

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2	Digoxin	49 (14.6)	29 (8.7)	1000 (39.9)	916 (36.5)	1207 (25.3)	1502 (31.5)	1089 (20.8)	1285 (24.6)	7973 (36.5)	6286 (28.8)	1184 (23.4)	1223 (24.2)
3	Flecainide	0 (0)	≤ 3	13 (0.5)	29 (1.2)	9 (0.2)	32 (0.7)	12 (0.2)	52 (1.0)	40 (0.2)	156 (0.7)	6 (0.1)	27 (0.5)
4	*IQR: interquartile range. †COPD: chronic obstructive pulmonary disease. ‡IHD: ischemic heart disease. §PAD: peripheral artery disease. CHA ₂ DS ₂ -VASc: Risk score for stroke: congestive												
5	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												
6	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												
7	agents/non-steroidal inflammatory drugs, alcohol abuse. **OAC: oral anticoagulation.												
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AF for the first time with a secondary precipitant, 1996-2015
N=66,242

AF for the first time without a secondary precipitant, 1996-2015
N=138,618

Exclusions (N=26,166)

- <18 years or > 100 years, N=134
- Valvular atrial fibrillation, N=2038
- Atrial fibrillation therapy before hospital admission, N=13,916
- Dead or emigrated during the blanking period, N=7366
- Thromboembolic event during the blanking period, N=2712

Exclusions (N=40,430)

- <18 years or > 100 years, N=278
- Valvular atrial fibrillation, N=2550
- Atrial fibrillation therapy before hospital admission, N=33,629
- Dead or emigrated during the blanking period, N=1992
- Thromboembolic event during the blanking period, N=1981

Complete study population

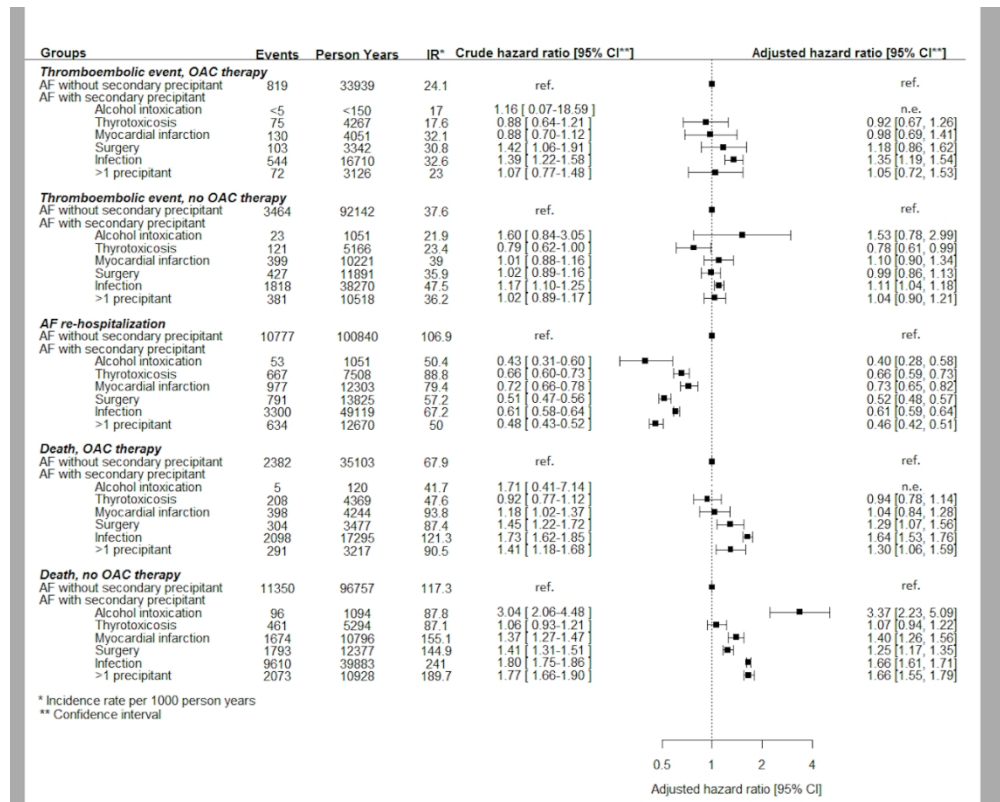
AF with secondary precipitant
N=40,076

AF without secondary precipitant
N=98,188

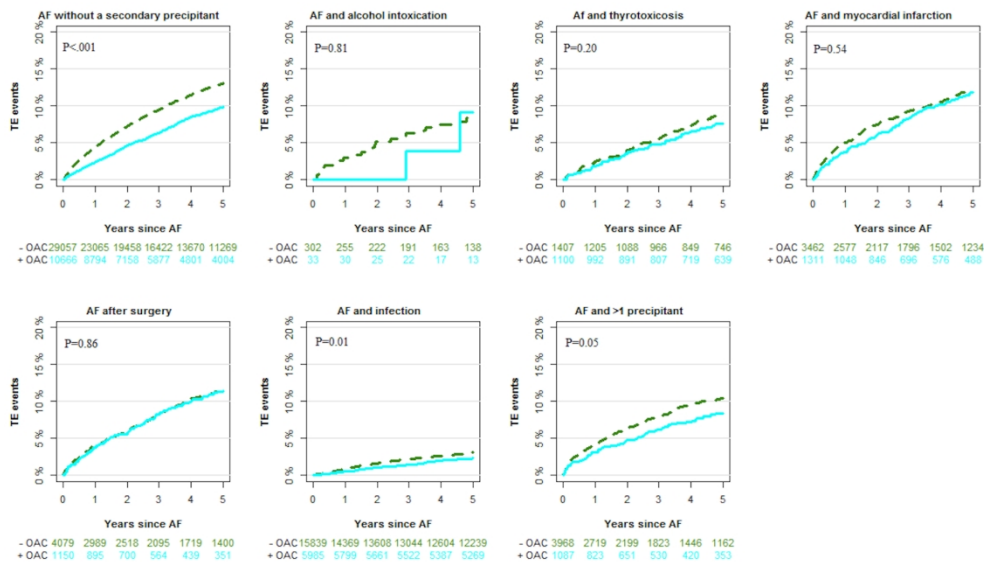
Matched population

- 39,723 patients with AF with secondary precipitant
 - 335 (0.8%) with alcohol intoxication
 - 2507 (6.3%) with thyrotoxicosis
 - 4773 (12.0%) with myocardial infarction
 - 5229 (13.2%) had had surgery
 - 21,824 (55.0%) with infection
 - 5055 (12.7%) with >1 precipitant
- 39,723 patients with AF without a secondary precipitant

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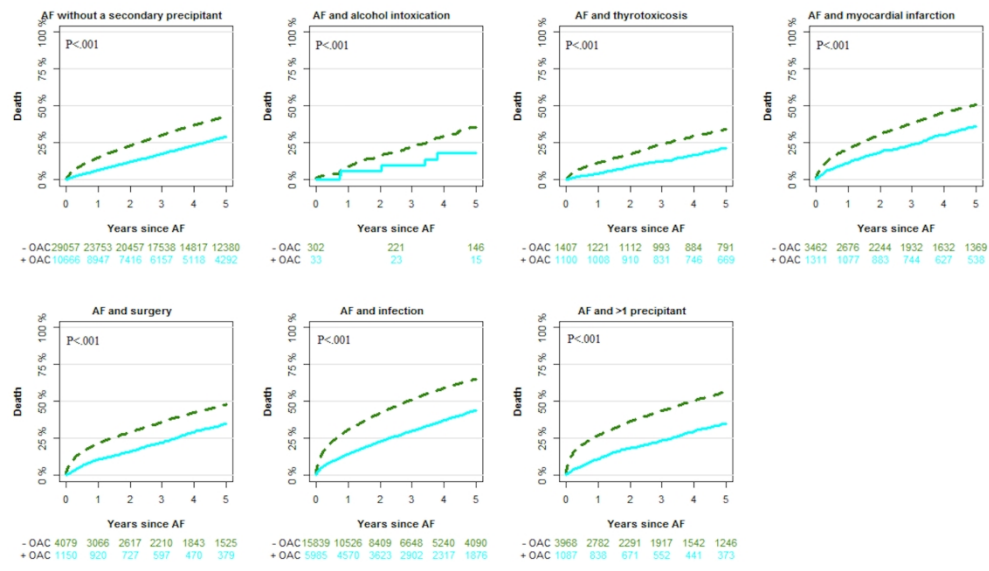


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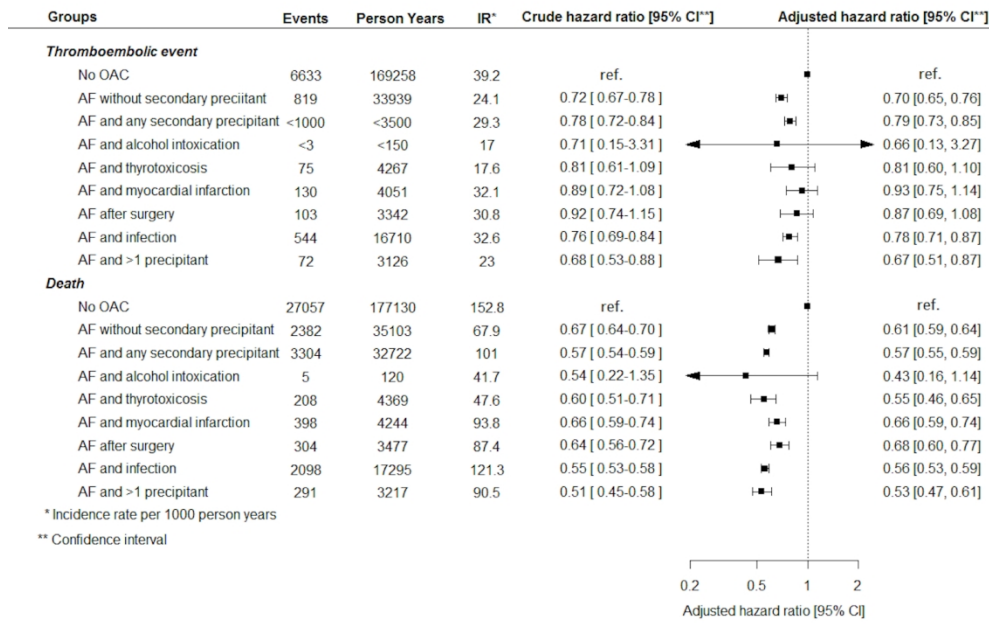
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Supplemental material

Comparative thromboembolic risk in atrial fibrillation with and without a secondary precipitant – a Danish nationwide cohort study

Anna Gundlund, MD, PhD; Thomas Kümler, MD, PhD; Anders N. Bonde, MD; Jawad H. Butt, MD; Gunnar H. Gislason, MD, PhD; Christian Torp-Pedersen, MD, DMSc; Lars Køber, MD, DMSc; Jonas B. Olesen, MD, PhD; Emil L. Fosbøl, MD, PhD

Online Table 1: Specification of diagnoses by international classification of diseases (ICD-8 and ICD-10) codes and pharmacotherapy by anatomical therapeutic chemical classification (ATC) codes.

Online Table 2: Baseline characteristics of the non-matched population, patients initiated on OAC therapy

Online Table 3: Baseline characteristics of the non-matched population, patients not initiated on OAC therapy

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.

Online Table 1: Specification of diagnoses by international classification of diseases (ICD-8 and ICD-10) codes and pharmacotherapy by anatomical therapeutic chemical classification (ATC) codes.

Precipitants	ICD-10 codes and NCSP, NOMESCO Classification of Surgical Procedures
Alcohol intoxication	ICD-10: F100, F103, F104, R780, T51, X65
Infections	ICD-10: Certain infectious and parasitic diseases: A00-B99. Infections in the eye and adnexa: H00, H01, H10, H20, H30, H44, H60, H65-H68, H70, H73.0, H73.1 Infections in the cardiovascular organs: I30, I32, I33, I38-I41 Infections in pulmonary system: J00-J22, J32, J36, J85, J86 Infections in the gastrointestinal system: K12, K20, K35-K37, K57, K65, K67, K81, K85 Infections in the skin, subcutaneous tissue, bones, muscles, and connective tissue: L00-L08, M00, M01, M60, M63.2, M65, M86, M90.0, M90.1, M90.2 Infections in the urogenital system: N00, N01, N05, N30, N70-N77.
Myocardial infarction	ICD-10: I21
Pulmonary embolism	ICD-10: I260, I269, O882D, O882E, T817D
Surgery	NCSP, NOMESCO Classification of Surgical Procedures: KF, KM, KN, KD, KPH, KPJ, KJ, KH, KQ, KB, KC, KL, KE, KA, KG, KK.
Thyrotoxicosis	ICD-10: E05
Outcomes	
Atrial fibrillation re-hospitalization	Hospital admission with primary diagnosis of atrial fibrillation: I48
Thromboembolic event	Ischemic stroke: I63, I64 Death from stroke: I61-I64 Transient ischemic attack: G458, G459 Thrombosis or embolism in arteries: I74
Comorbidities	ICD-8 and ICD-10 codes

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4	Atrial fibrillation	ICD-10: I48
5		ICD-8: 42793, 42794
6		
7	Alcohol abuse	ICD-10: E24.4, E52, F10, G31.2, G62.1, G72.1,
8		I42.6, K29.2, K70, K86.0, L27.8A, O35.4, T51,
9		Z71.4, Z72.1.
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11		ATC: N07BB
12		
13	Cancer	ICD-10: C
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15	Chronic kidney disease	ICD-10: E10.2, E11.2, E13.2, E14.2, I12.0,
16		M32.1B, N02-N08, N11, N12, N14, N15.8,
17		N15.9, N16.0, N16.2-N16.4, N16.8, N18, N19,
18		N26, Q61
19	Chronic obstructive pulmonary disease	ICD-10: J42, J43, J44
20	Diabetes	ATC: A10 (3 months before index)
21	Heart failure	ICD-10: I11.0, I42, I50, J81
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24	Hypertension	Usage of a combination of at least two of the
25		seven different drug classes at the same time:
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27		1. Non-loop diuretics
28		2. Loop diuretics
29		3. Antiadrenergic agents
30		4. Beta-blockers
31		5. Vasodilators
32		6. Calcium channel blockers
33		7. Renin-angiotensin system inhibitors
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36	Ischemic heart disease	ICD-10: I20-I25
37	Peripheral artery disease	ICD-10: I70
38	Prior bleeding	ICD-10: D50.0, D62, G951A, H31.3, H05.2A,
39		H35.6, H43.1, H45.0, I31.2, I60-I62, I85.0,
40		I86.4A, J94.2, K22.8F, K25.0, K25.2, K25.4,
41		K25.6, K26.0, K26.2, K26.4, K26.6, K27.0
42		K27.2, K27.4, K27.6, K28.0, K28.2, K28.4,
43		K28.6, K29.8A, K62.5, K63.8B, K63.8C, K66.1,
44		K83.8F, K86.8G, K92.0-K92.2, N02, R04, R31,
45		S06.4-S06.6, S36.8D
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51	Thromboembolic event	ICD-10: G45.8, G45.9, I63, I64, I74
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53	Valvular atrial fibrillation	Atrial fibrillation without:
54		ICD-10: I05, I06, I080A, I081A, I082A, I083A,
55		Z952, Z954
56		ICD-8: 39500-39502, 39508, 39509, 39600-
57		39604, 39608, 39609
58		Procedures: FKD, FKH, FMD, FMH, FGE, FJE
59	Pharmacotherapy	ACT-codes
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ADP-receptor blockers	B01AC04, B01AC22, B01AC24
Amiodarone	C01BD01
Antiadrenergic agents	C02A, C02B, C02C
Oral anticoagulation therapy	Vitamin K antagonists: B01AA03, B01AA04 Non-vitamin K antagonist oral anticoagulants: B01AF01, B01AF02, B01AE07
Beta-blockers	C07A, C07B, C07C, C07D, C07F
Calcium channel blockers	C08, C09BB, C09DB
Digoxin	C01AA
Flecainide	C01BC
Loop diuretics	C03C, C03EB
Non-loop diuretics	C02DA, C03EA, C03EB, C02L, C03A, C03B, C03D, C03E, C03X, C07B, C07C, C07D, C08G, C09BA, C09DA, C09XA52
Renin-angiotensin system inhibitors	C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C09XA02, C09XA52
Vasodilators	C02DB, C02DD, C02DG

Online Table 2: Baseline characteristics of the non-matched population, patients initiated on OAC therapy

	AF with a secondary precipitant N=10,673						AF without a secondary precipitant N=37,827
	Alcohol intoxication N=33	Thyro- toxicosis N=1103	Myocardial infarction N=1312	Surgery N=1151	Infection N=5987	>1 precipitant N=1087	
Demographics							
Age, median (IQR*)	64 (55-68)	72 (64-79)	75 (68-81)	74 (67-81)	77 (69-83)	75 (68-81)	72 (64-79)
Male, n (%)	28 (84.8)	259 (23.5)	842 (64.2)	667 (57.9)	3189 (53.3)	634 (58.3)	21,386 (56.5)
Comorbidities, n (%)							
Cancer	≤3	114 (10.3)	146 (11.1)	239 (20.8)	927 (15.5)	171 (15.1)	4617 (12.2)
Chronic kidney disease	4 (12.1)	23 (2.1)	62 (4.7)	65 (5.6)	372 (6.2)	59 (5.4)	1011 (2.7)
COPD†	≤3	106 (9.6)	133 (10.1)	128 (11.1)	1251 (20.9)	157 (14.4)	3426 (9.1)
Diabetes	≤3	84 (7.6)	159 (12.1)	111 (9.6)	712 (11.9)	112 (10.3)	3384 (8.9)
Heart failure	6 (18.2)	236 (21.4)	464 (35.4)	228 (19.8)	1440 (24.1)	359 (33.0)	6791 (18.0)
Hypertension	11 (33.3)	658 (59.7)	982 (74.8)	687 (59.7)	3652 (61.0)	723 (66.5)	23,057 (61.0)
IHD‡	5 (15.2)	129 (11.7)	1312 (100)	434 (37.7)	1202 (20.1)	744 (68.4)	7360 (19.5)
PAD§	≤3	29 (2.6)	83 (6.3)	101 (8.8)	353 (5.9)	77 (7.1)	1258 (3.3)
Prior bleeding event	7 (21.2)	86 (7.8)	150 (11.4)	213 (18.5)	966 (16.1)	182 (16.7)	4564 (12.1)
Prior thromboembolic event	≤3	60 (5.4)	142 (10.8)	153 (13.3)	672 (11.2)	133 (12.2)	3313 (8.8)
Risk scores							
CHA ₂ DS ₂ -VASC							
Median (IQR*)	1 (0-2)	3 (2-4)	4 (3-5)	3 (2-4)	3 (2-4)	4 (3-5)	3 (2-4)
0	11 (33.3)	134 (12.2)	0	74 (6.4)	269 (4.5)	28 (2.6)	3592 (9.5)
1-2	16 (48.5)	263 (23.8)	181 (13.8)	289 (25.1)	1493 (24.9)	181 (16.6)	12,341 (32.6)
≥3	6 (18.2)	706 (64.0)	1131 (86.2)	788 (68.5)	4225 (70.6)	878 (80.8)	21,894 (57.9)
HAS-BLED [#]							
Median (IQR*)	2 (1-3)	2 (1-2)	3 (2-3)	2 (1-3)	2 (1-3)	2 (2-3)	2 (1-3)
0	0	128 (11.6)	32 (2.4)	60 (5.2)	259 (4.3)	33 (3.0)	3361 (8.9)
1-2	21 (63.6)	706 (64.0)	571 (43.5)	611 (53.1)	3433 (57.3)	515 (47.4)	22,792 (60.3)
≥3	12 (36.4)	269 (24.4)	709 (54.0)	480 (41.7)	2295 (38.3)	539 (49.6)	11,674 (30.9)
Pharmacotherapy, n (%)							

Amiodarone	0	19 (1.7)	104 (7.9)	181 (15.7)	261 (4.4)	141 (13.0)	1493 (3.9)
Digoxin	11 (33.3)	605 (54.9)	437 (33.3)	312 (27.1)	2847 (47.6)	368 (33.9)	14,803 (39.1)
Flecainide	0	5 (0.5)	≤3	≤3	10 (0.2)	≤3	248 (0.7)

*IQR: interquartile range. †COPD: chronic obstructive pulmonary disease. ‡IHD: ischemic heart disease. §PAD: peripheral artery disease. ||CHA₂DS₂-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.

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Online Table 3: Baseline characteristics of the non-matched population, patients not initiated on OAC therapy

	AF with a secondary precipitant N=29,403						AF without a secondary precipitant N=60,361
	Alcohol intoxication N=302	Thyro- toxicosis N=1408	Myocardial infarction N=3508	Surgery N=4101	Infection N=16,079	>1 precipitant N=4005	
Demographics							
Age, median (IQR*)	58 (48-66)	74 (62-82)	78 (69-84)	76 (67-82)	80 (72-87)	76 (68-83)	69 (58-80)
Male, n (%)	248 (82.1)	263 (18.7)	1907 (54.4)	2069 (50.5)	7352 (45.7)	2073 (51.8)	31,074 (51.5)
Comorbidities, n (%)							
Cancer	15 (5.0)	174 (12.4)	454 (12.9)	1115 (27.2)	3474 (21.6)	795 (19.9)	7915 (13.1)
Chronic kidney disease	7 (2.3)	38 (2.7)	236 (6.7)	289 (7.0)	1223 (7.6)	375 (9.4)	1733 (2.9)
COPD [†]	26 (8.6)	128 (9.1)	495 (14.1)	539 (13.1)	3493 (21.7)	765 (19.1)	4544 (7.5)
Diabetes	24 (7.9)	105 (7.5)	417 (11.9)	396 (9.7)	1473 (9.2)	387 (9.7)	3566 (5.9)
Heart failure	18 (6.0)	209 (14.8)	1218 (34.7)	744 (18.1)	3752 (23.3)	1231 (30.7)	6328 (10.5)
Hypertension	53 (17.5)	653 (46.4)	2348 (66.9)	1808 (44.1)	6942 (43.2)	1991 (49.7)	22,309 (37.0)
IHD [‡]	38 (12.6)	207 (14.7)	3508 (100)	1326 (32.3)	3558 (22.1)	2354 (58.8)	11,528 (19.1)
PAD [§]	6 (2.0)	49 (3.5)	298 (8.5)	371 (9.0)	1057 (6.6)	374 (9.3)	1913 (3.2)
Prior bleeding event	74 (24.5)	157 (11.2)	585 (16.7)	1062 (25.9)	3420 (21.3)	998 (24.9)	7616 (12.6)
Prior thromboembolic event	22 (7.3)	78 (5.5)	350 (10.0)	422 (10.3)	2029 (12.6)	478 (11.9)	4301 (7.1)
Risk scores							
CHA ₂ DS ₂ -VASc							
Median (IQR*)	1 (0-2)	3 (2-4)	4 (3-5)	3 (2-4)	3 (2-4)	4 (2-5)	2 (0-4)
0	147 (48.7)	271 (19.2)	0	317 (7.7)	1059 (6.6)	241 (6.0)	15,957 (26.4)
1-2	102 (33.8)	270 (19.2)	489 (13.9)	1119 (27.3)	3671 (22.8)	824 (20.6)	17,513 (29.0)
≥3	53 (17.5)	867 (61.6)	3019 (86.1)	2665 (65.0)	11,349 (70.6)	2940 (73.4)	26,891 (44.6)
HAS-BLED [#]							
Median (IQR*)	2 (1-3)	2 (1-3)	3 (2-3)	2 (1-3)	2 (1-3)	2 (2-3)	2 (1-3)
0	0	228 (16.2)	102 (2.9)	229 (5.6)	745 (4.6)	175 (4.4)	12,875 (21.3)
1-2	211 (69.9)	756 (53.7)	1424 (40.6)	2265 (55.2)	8795 (54.7)	1924 (48.0)	31,914 (52.9)
≥3	91 (30.1)	424 (30.1)	1982 (56.5)	1607 (39.2)	6539 (40.7)	1906 (47.6)	15,572 (25.8)

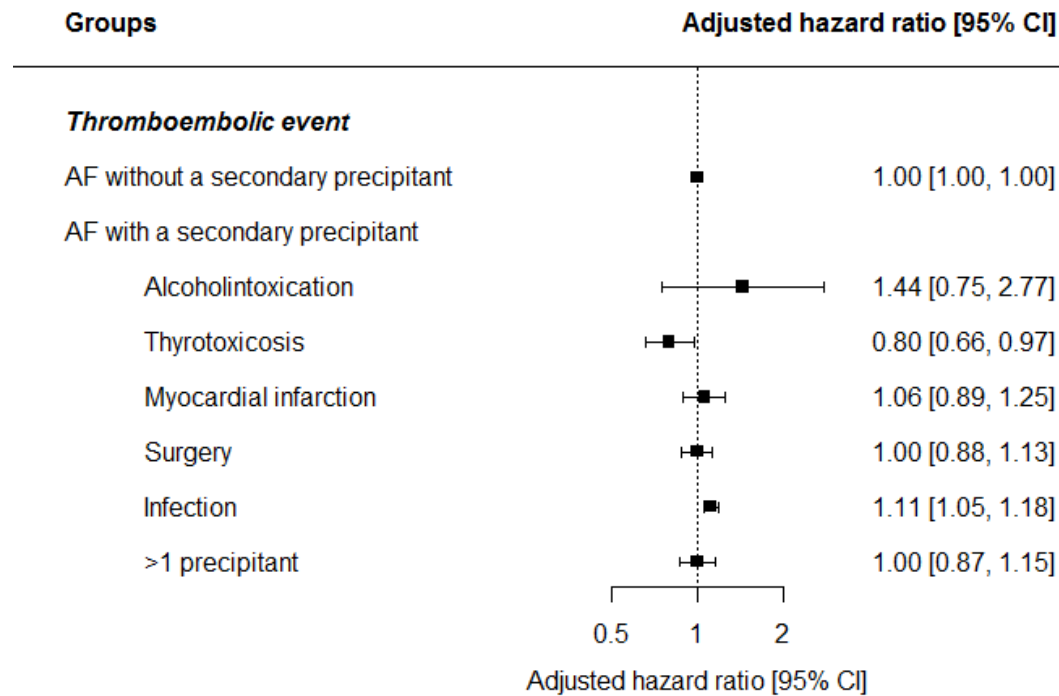
Pharmacotherapy, n (%)							
Amiodarone	≤3	14 (1.0)	259 (7.4)	262 (6.4)	361 (2.2)	278 (6.9)	1133 (1.9)
Digoxin	38 (12.6)	398 (28.3)	784 (22.3)	782 (19.1)	5210 (32.4)	828 (20.7)	10,336 (17.1)
Flecainide	0	8 (0.6)	8 (0.2)	10 (0.2)	30 (0.2)	5 (0.1)	786 (1.3)

*IQR: interquartile range. †COPD: chronic obstructive pulmonary disease. ‡IHD: ischemic heart disease. §PAD: peripheral artery disease. ||CHA₂DS₂-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.

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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.



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract YES, p.1 and 3. (b) Provide in the abstract an informative and balanced summary of what was done and what was found YES, p. 3.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported YES, p. 5
Objectives	3	State specific objectives, including any prespecified hypotheses YES, p. 5
Methods		
Study design	4	Present key elements of study design early in the paper YES, p. 5-7.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection YES, p. 5-7.
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up YES, p. 6-7. <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed YES, p. 8. <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable YES, p. 7-8. Figure 3. Specification of diagnosis can be found in the Online Table 1.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group YES, p. 5-6 and eTable 1.
Bias	9	Describe any efforts to address potential sources of bias YES, p. 8.
Study size	10	Explain how the study size was arrived at YES, p. 6-7, figure 1.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why

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YES, p. 6-7.

Statistical methods

12

(a) Describe all statistical methods, including those used to control for confounding

YES, p. 7-8.

(b) Describe any methods used to examine subgroups and interactions

YES, p. 7-8.

(c) Explain how missing data were addressed

No missing data

(d) *Cohort study*—If applicable, explain how loss to follow-up was addressed

No loss to follow-up.

Case-control study—If applicable, explain how matching of cases and controls was addressed

Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy

(e) Describe any sensitivity analyses

YES, p. 7.

Continued on next page

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Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed YES, p. 8-9 and Figure 1.
		(b) Give reasons for non-participation at each stage YES, p. 8-9 and Figure 1.
		(c) Consider use of a flow diagram YES, Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders YES, p. 9, Table 1.
		(b) Indicate number of participants with missing data for each variable of interest No missing data
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) YES, Figure 2.
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time YES, p. 10 and Figure 2, 3.
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included YES, Figure 3.
		(b) Report category boundaries when continuous variables were categorized Continuous variables were not categorized.
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses YES, p. 11.
Discussion		
Key results	18	Summarise key results with reference to study objectives YES, p. 11.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias YES, p. 13-14.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence YES, p. 12-13.
Generalisability	21	Discuss the generalisability (external validity) of the study results YES, p. 14.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

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2 YES, p. 14.
3

4 *Give information separately for cases and controls in case-control studies and, if applicable, for exposed and
5 unexposed groups in cohort and cross-sectional studies.
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8 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and
9 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely
10 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
11 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
12 available at www.strobe-statement.org.
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Comparative thromboembolic risk in atrial fibrillation with and without a secondary precipitant– a Danish nationwide cohort study

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Epidemiology
Keywords:	Cardiac Epidemiology < CARDIOLOGY, Thromboembolism < CARDIOLOGY, Pacing & electrophysiology < CARDIOLOGY

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Manuscripts

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4 1 **Comparative thromboembolic risk in atrial fibrillation with and without a**
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7 2 **secondary precipitant– a Danish nationwide cohort study**
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4 1 **Abstract:** 292 words (max 300 words)
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6 2 Objectives: We compared long-term outcomes in patients with atrial fibrillation (AF) with and
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8
9 3 without a secondary precipitant.
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11 4 Design and setting: Retrospective cohort study based on Danish nationwide registries.
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13 5 Participants: Patients with AF with and without secondary precipitants (1996-2015) were matched
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15
16 6 1:1 according to age, sex, calendar year, CHA₂DS₂-VASc score, and oral anticoagulation therapy
17
18 7 (OAC) therapy, resulting in a cohort of 39,723 patients with AF with a secondary precipitant and
19
20 8 the same number of patients with AF without a secondary precipitant. Secondary precipitants
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22
23 9 included alcohol intoxication, thyrotoxicosis, myocardial infarction, surgery, and infection in
24
25 10 conjunction with AF.
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27 11 Primary and secondary outcomes: The primary outcome in this study was thromboembolic events.
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29
30 12 Secondary outcomes included AF re-hospitalization and death. Long-term risks of outcomes were
31
32 13 examined by multivariable Cox regression analysis.
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34 14 Results: The most common precipitants were infection (55.0%), surgery (13.2%), and myocardial
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36 15 infarction (12.0%). The 5-year absolute risk of thromboembolic events (taking death into account as
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39 16 a competing risk) in patients with AF grouped according to secondary precipitants were 8.3%
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41 17 (alcohol intoxication), 8.5% (thyrotoxicosis), 12.1% (myocardial infarction), 11.6% (surgery),
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43 18 12.2% (infection), 10.1% (>1 precipitant), and 12.3% (no secondary precipitant). In the
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46 19 multivariable analyses, AF with a secondary precipitant was associated with the same or an even
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48 20 higher thromboembolic risk than AF without a secondary precipitant. One exception was patients
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50 21 with AF and thyrotoxicosis: those not initiated on OAC therapy carried a lower thromboembolic
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52 22 risk the 1st year of follow up than matched patients with AF without a secondary precipitant and no
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55 23 OAC therapy.
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4 1 Conclusions: In general, AF with a secondary precipitant was associated with the same
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6 2 thromboembolic risk as AF without a secondary precipitant. Consequently, this study highlights the
7
8 3 need for more research regarding the long-term management of patients with AF associated with a
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10 4 secondary precipitant.
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13 5 Key words: Secondary precipitant, reversible atrial fibrillation, recurrence
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4 **1 Article summary: strengths and limitations of this study**
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7 2 • The study was based on high-quality nationwide registries with many years of follow up.
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9 3 • Complete follow-up was possible
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11 4 • Only associations could be drawn because of the retrospective and non-randomized design.
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14 5 • AF with and without a secondary precipitant were defined from diagnosis codes at discharge
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16 6 • We had no data on electrocardiograms at discharge
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1 **Introduction**

2 The etiology of atrial fibrillation (AF) remains partly unknown. Studies have shown, that an
3 inflammatory reaction inside the atria always precipitate AF.(1) However, in clinical practice, AF
4 may occur as an isolated event or together with a secondary precipitant. AF is associated with a
5 fivefold increased risk of ischemic stroke, and detailed treatment strategies regarding stroke
6 prophylaxis in patients with AF occurring without secondary precipitants exist in both European
7 and American treatment guidelines.(2–5)] In contrast, there is no consensus regarding stroke
8 prophylaxis in patients with AF occurring with a secondary precipitant. Previous guidelines stated
9 that AF occurring secondary to another precipitant usually will terminate without recurrence.(2) In
10 current guidelines, however, this statement has been omitted, and the need for data regarding AF
11 associated with a secondary precipitant highlighted.(4,5) Studies investigating long-term outcomes
12 in AF associated with a secondary precipitant are sparse and data differentiating between different
13 secondary precipitants and taking oral anticoagulation (OAC) therapy into account are missing.
14 To address this lack in current knowledge, we aimed to compare long-term outcomes including
15 thromboembolic events, AF re-hospitalization, and death in patients with AF with a secondary
16 precipitant (incl. alcohol, intoxication, thyrotoxicosis, myocardial infarction, surgery, and infection)
17 and patients with AF without a secondary precipitant. Further, we were able to differentiate
18 between patients receiving and not receiving stroke prophylaxis with OAC therapy.

19 **Materials and methods**

20 *Data sources*

21 In Denmark, healthcare is tax-financed and with equal availability regardless of socioeconomic
22 status. Date of birth, date and cause of death, emigration and immigration status, diagnosis and
23 surgery codes etc. from all hospital contacts, fulfilled prescriptions of medicine, and several other
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parameters are registered in different nationwide registries. Since all Danish citizens are provided a unique personal identifier code at birth (or immigration), data from the registries can be crosslinked on an individual level. We linked data from the following registries: The Danish Civil Registration System,(6) The Danish National Patient Registry (diagnoses were registered in terms of the International Classification of Diseases (ICD) system (ICD-8 until 1994 and in terms of ICD-10 thereafter)),(7) The Danish Register of Causes of Death,(8) and the Danish National Registry of Medicinal Statistics (medicine were registered according to the Anatomical Therapeutic Chemical classification system (ATC)).(9)

Study population

The patient selection is depicted in Figure 1. We included all Danes diagnosed and admitted to a Danish hospital with AF for the first time between 1996 and 2015. Patients <18 years or >100 years and those with valvular AF (defined as AF without: rheumatic valve disease of aortic valve or mitral valve or prosthetic heart valve (any valve)) were excluded. Since there was a possibility that some of the patients had been diagnosed with AF at their general practitioner before their hospital admission, we excluded those who previously had fulfilled a prescription of antiarrhythmic therapy or rate-controlling drugs (incl. amiodarone, flecainide, and digoxin) and those who had fulfilled a prescription of OAC therapy up to 100 days before their hospital admission. Further, patients who died or had a thromboembolic event during the hospital admission or a constructed blanking period of 4 weeks from hospital discharge to the index date were excluded.

Patients were grouped in those with and without a secondary precipitant. Patients who had a diagnosis of one of the following precipitants from their AF hospital admission were defined as patients with a secondary precipitant: alcohol intoxication, thyrotoxicosis, myocardial infarction, and infection. Also, patients who were diagnosed with AF after, but during the same hospital

1 admission they received surgery were defined as having AF with a secondary precipitant. We
2 restricted the population of patients with AF without a secondary precipitant to patients with AF
3 without a diagnosis of a secondary precipitant from their hospital admission. Patients with AF with
4 and without a secondary precipitant were matched 1:1 by incidence density sampling according to
5 age (allowing a difference of up to two years), sex, calendar year (allowing a difference up to two
6 years), CHA₂DS₂-VASc group (0, 1-2, >2) and OAC therapy status at the index date. Consequently,
7 each case was matched with a control diagnosed at the same time and in the same age with AF.
8 Further, the control had the same sex and was categorized in the same CHA₂DS₂-VASc group as
9 the case. These patients comprised the study population. We used a previously described function to
10 perform the match.(10)

11 12 *Long-term outcomes*

13 The index date was defined 4 weeks from AF hospital discharge. Initiation of OAC therapy and
14 antiarrhythmic and rate controlling drugs was assessed during this blanking period from discharge
15 to index date. Patients were followed from the index date and until the first event of the following:
16 an outcome of interest, death, 5 years from the index date, emigration, or June 30, 2015. The
17 primary outcome of interest was thromboembolic events (a composite of ischemic stroke, transient
18 ischemic attack (TIA), and systemic thrombosis or embolism) while secondary outcomes included
19 AF rehospitalization and all-cause death. AF rehospitalization was defined as a hospitalization with
20 AF as the primary discharge diagnosis. The diagnoses of AF, ischemic stroke, and myocardial
21 infarction have been validated in the Danish registries with positive predictive values of 93%, 97%,
22 and 100%, respectively.(11,12)

1 2 3 4 1 *Statistics*

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6 2 Kaplan Meier curves for death were drawn and cumulative incidences of thromboembolic events
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9 3 (with incorporated competing risk of death) calculated using the Aalen Johansen estimator. The
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11 4 Log-Rank test and the Gray's test were used to test for differences in the cumulative incidence of
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13 5 long-term outcomes. Cox regression analyses were performed to calculate hazard ratios (HR) of
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15 6 long-term outcomes in patients with AF with and without a secondary precipitant according to OAC
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17 7 therapy at the index date. All analyzes were performed on the matched population. The multivariate
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19 8 models were adjusted for other potential confounders than the matching criteria (incl. comorbidities
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21 9 at the index date (incl. peripheral artery disease, heart failure, hypertension, prior thromboembolic
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23 10 event, ischemic heart disease, chronic kidney disease, diabetes, prior bleeding event, cancer) and
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25 11 antiarrhythmic and rate-controlling therapy during the blanking period (amiodarone, digoxin,
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27 12 flecainide)). The analyses took matching variables into account and each group of patients with AF
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29 13 with a secondary precipitant was compared with its respective matches from the matching
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31 14 procedure. The models were tested for the assumption of proportional hazards. For specification of
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33 15 diagnosis codes and ATC-codes please see Online Table 1. A P-value <0.05 was considered
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35 16 statistically significant. All statistical analyses were performed in SAS statistical software version
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37 17 9.4 or R.(13)
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45 19 *Other analyses*

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48 20 Analyses of long-term outcomes were also performed on a non-matched population including all
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50 21 patients available before the matching (Figure 1). To account for changes in OAC therapy status
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52 22 over time, we did a sensitivity analysis not stratifying patients with regard to their OAC therapy
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54 23 status at the index date, but instead adjusting for OAC therapy status as a time-dependent variable.
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4 1 Consequently, new initiations and discontinuations were taking into account. The method used, has
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6 2 been used and described previously.(14–16)
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11 4 *Ethics*
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13 5 Approval from the Research Ethics Committee System is not required in retrospective registry-
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15 6 based studies in Denmark. The Danish Data Protection Agency approved use of data for this study
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17 7 (ret.no: 2007-58-0015 / GEH-2014-013 I-Suite no: 02731).
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22 9 *Patient and Public Involvement*
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25 10 This was a retrospective study based on administrative registries. Patients and the public were not
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27 11 involved in the development of the study.
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32 13 *Data availability statement*
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34 14 This study was based on deidentified data about the entire Danish population. Data are not
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36 15 available.
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41 17 *Contributorship statement*
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43 18 The study idea was conceived by AG, TK, and ELF., study design was developed by AG, TK, JBO,
44
45 19 ANB, JHB, GHG, CTP, LK, and ELF, data analyses were made by AG. AG drafted the first version
46
47 20 of the paper and all authors participated in the critical discussions and interpretation of findings. All
48
49 21 authors have participated in the revisions of the draft and have approved the final version.
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54 23 **Results**
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57 24 *Study population*
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4 1 As shown in Figure 1, the most common secondary precipitant was infection (21,824 patients,
5 55.0%). Further, 335 (0.8%) patients had a concurrent alcohol intoxication, 2507 (6.3%) had
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7 3 thyrotoxicosis, 4773 (12.0%) had acute myocardial infarction, 5229 (13.2%) had underwent
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9 5 surgery, and 5055 (12.7%) had >1 precipitant. Of those with >1 precipitant, 4788 (94.7%) patients
10 6
11 7 had two secondary precipitants, while 267 (5.3%) had three or four secondary precipitants.
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13 9 Infection and surgery was the most common combination of secondary precipitants. The patients
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15 11 with >1 precipitant were grouped in one group, and were not included in the other groups of
16 12
17 13 patients with AF with a secondary precipitant. During the blanking period, 14% of the patients with
18 14
19 15 AF and a secondary precipitant and 2% of the patients with AF without a secondary precipitant
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21 17 died, while 5% and 2%, respectively, had a thromboembolic event. These patients were excluded
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23 19 before the matching.
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Baseline characteristics

Baseline characteristics of the matched study population are shown in Table 1. In general, patients with AF with a secondary precipitant had more comorbidities than patients with AF without a secondary precipitant. Baseline characteristics of the non-matched population according to OAC therapy at the index date are shown in online Table 2 and 3. Especially those with AF and myocardial infarction, surgery, infection, and >1 precipitant were older, had more comorbidities, and higher risk scores for stroke and bleeding compared with patients with AF without a secondary precipitant. Among the patients with AF with a secondary precipitant (non-matched study population), 9.9% with alcohol intoxication, 43.9% with thyrotoxicosis, 27.2% with myocardial infarction, 21.9% with surgery, 27.1% with infection, and 21.4% with >1 precipitant received OAC therapy at the index date, respectively. Among patients with AF without a secondary precipitant, 38.5% received OAC therapy at the index date. In general for patients with AF with and without a

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4 1 secondary precipitant, those initiated on OAC therapy suffered from less cancer, chronic kidney
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6 2 disease, peripheral artery disease, and had fewer previous bleeding events than those not initiated
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9 3 on OAC therapy. On the other hand, they were more likely to suffer from stroke risk factors (incl.
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11 4 diabetes, heart failure, ischemic heart disease, and hypertension) than those not initiated on OAC
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13 5 therapy. During the first year after the index date, 9.9% and 17.3% of patients with AF with and
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15 6 without a secondary precipitant, respectively, had a new hospital admission with AF. One year after
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17 7 the index date, 19.8% and 32.7% of the patients with AF with and without a secondary precipitant,
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19 8 respectively, were in OAC therapy and 22.3% and 21.8% of the patients with AF with and without
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21 9 a secondary precipitant, respectively, were in antiarrhythmic therapy.
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27 11 *Long-term outcomes*

29 12 Number of events, incidence rates, and crude and adjusted hazard ratios (HRs) of thromboembolic
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31 13 events and death in AF patients with a secondary precipitant compared with AF patients without a
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33 14 secondary precipitant initiated and not initiated on OAC therapy at the index date are presented in
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35 15 Figure 2. With few exceptions, AF with a secondary precipitant was associated with the same
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37 16 thromboembolic risk as AF without a secondary precipitant. Regardless of OAC therapy status at
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39 17 the index date, AF with infection was associated with a significantly increased risk of
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41 18 thromboembolic events compared with AF without a secondary precipitant. Among those not
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43 19 initiated on OAC therapy, AF with thyrotoxicosis was associated with a significantly lower risk of
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45 20 thromboembolic events compared with AF without a secondary precipitant. In those initiated on
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47 21 OAC therapy, no differences in thromboembolic risk was observed between patients with AF and
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49 22 thyrotoxicosis and patients with AF without a secondary precipitant. All subgroups of AF with a
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51 23 secondary precipitant were associated with a significantly lower risk of AF re-hospitalization
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53 24 compared with AF without a secondary precipitant (Figure 2).
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2 Figure 3 and 4 depicts cumulative incidences of thromboembolic events and death in patients with
3 AF with and without a secondary precipitant. During follow up, the cumulative incidence of
4 thromboembolic events (taking death as an competing risk into account) according to type of
5 secondary precipitant was 8.3% (alcohol intoxication), 8.5% (thyrotoxicosis), 12.1% (myocardial
6 infarction), 11.6% (surgery), 12.2% (infection), 10.1% (>1 precipitant), and 12.3% (no secondary
7 precipitant). The cumulative incidence of AF re-hospitalization were 19.6% (alcohol intoxication),
8 30.8% (thyrotoxicosis), 27.2% (myocardial infarction), 14.8% (surgery), 20.9% (infection), 19.3%
9 (>1 precipitant), and 34.4% (no secondary precipitant) (not included in the figures).

10 OAC therapy initiation compared with no OAC therapy initiation was associated with a lower
11 thromboembolic risk in patients with AF with and without a secondary precipitant, although the
12 results did not reach statistical significance in patients with AF with alcohol intoxication,
13 thyrotoxicosis, myocardial infarction, and surgery as secondary precipitants (Figure 5).

15 *Other analyses*

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

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

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6 2 **Discussion**7
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9 3 We examined long-term outcomes in patients with AF with and without a secondary precipitant.10
11 4 The study had two main findings: first, AF with different secondary precipitants was in general12
13 5 associated with the same thromboembolic risk as AF without a secondary precipitant. Secondly,14
15 6 OAC initiation-rates differed significantly according to type of secondary precipitant. Further, OAC16
17 7 therapy vs. no OAC therapy were associated with a lower thromboembolic risk in those with AF18
19 8 and infection and >1 precipitant while no significant risk-reduction was seen for patients with AF20
21 9 with the other secondary precipitants.
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27 11 *Thromboembolic risk*28
29 12 Despite of lower re-hospitalization rates with AF, AF with a secondary precipitant was in general30
31 13 associated with the same thromboembolic risk as AF without a secondary precipitant. AF with32
33 14 thyrotoxicosis was associated with a lower thromboembolic risk compared with AF without a34
35 15 secondary precipitant. In contrast, AF with infection was associated with an increased36
37 16 thromboembolic risk compared with AF without a secondary precipitant. This is in accordance with38
39 17 previous findings.(17–19) In two previous studies, Lubitz et al. and Fauchier et al. examined long-40
41 18 term outcomes in patients with AF secondary to a reversible precipitant compared with patients42
43 19 with AF without a secondary precipitant. In both studies, AF secondary to a reversible precipitant44
45 20 was associated with the same thromboembolic risk as AF without secondary precipitants. However,46
47 21 both studies were smaller and with patients included before 2012 and 2010, respectively.(20,21) In48
49 22 summary, our results together with previous studies suggest that AF with a secondary precipitant in50
51 23 general, and maybe with the exception of AF with thyrotoxicosis, may be considered as similar to52
53 24 AF without a secondary precipitant with respect to thromboembolic risk.
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6 2 *OAC therapy*

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9 3 OAC therapy showed a tendency towards a lower thromboembolic risk in patients with AF and a
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11 4 secondary precipitant, but did only reach statistical significance for patients with AF and infection
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13 5 and >1 precipitant. Recently, Quon et al. examined risk of thromboembolic events and bleeding in
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15 6 patients with AF and acute coronary syndrome, acute pulmonary disease, and infection according to
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17 7 OAC therapy status after discharge. In that study, OAC therapy was not associated with lower risk
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19 8 of thromboembolic events in patients with AF and the before mentioned precipitants. However, the
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21 9 analyses on long-term outcomes were based on logistic regression analysis, and did therefore not
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23 10 include survival time in the model. Since patients with AF with a secondary precipitant in our study
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25 11 seemed to die at a higher rate than patients with AF without a secondary precipitant, the time
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27 12 perspective is crucial when studying long-term outcomes in this setting.(22) Studies with a clinical
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29 13 randomized design would be able to show whether patients with AF with a secondary precipitant
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31 14 benefit from OAC therapy on the same terms as patients with AF without a secondary precipitant.
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39 16 *OAC treatment-rates*

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41 17 The non-matched population allowed us to describe trends in OAC therapy initiation in patients
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43 18 with AF with and without a secondary precipitant. In patients with AF without a secondary
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45 19 precipitant, 38.5% of the patients were initiated on OAC therapy at the index date. This is in
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47 20 accordance with previous findings, taking into account that our study period went back to 1996
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49 21 when treatment rates were lower than today.(23,24) In 2017, Chean et al. assessed current practice
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51 22 of AF among critically ill patients with new-onset AF. The study was based on questionnaires
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53 23 answered by members of the Intensive Care Society in UK. The results revealed that 63.8% of the
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55 24 respondents would not regularly anti-coagulate critically ill patients with new-onset AF. We found
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4 1 important differences in OAC therapy initiation rates in patients with AF with a secondary
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6 2 precipitant according to type of precipitant. Patients with alcohol intoxication had the lowest
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8 3 initiation rate of OAC therapy (9.9%). Almost 50% of this patient group had a CHA₂DS₂-VASc
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10 4 score of 0 and hence no indication for OAC therapy. Further patients with alcohol abuse may have
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12 5 poor compliance and increased bleeding risk.⁽²⁵⁾ Consequently, there may be caution among
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14 6 physicians in prescribing OACs for this patient group. In 2011, Traube and colleagues reviewed the
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16 7 literature with respect to thromboembolic risk in patients with AF and thyrotoxicosis. They
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18 8 concluded that OAC therapy should be initiated for those patients who did not have any
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20 9 contraindications for treatment.⁽²⁶⁾ This could explain the high OAC treatment initiation rates in
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22 10 this patient group (43.9%).
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30 12 *Limitations*

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32 13 First of all, this study was a retrospective registry-based study and hence no causative relationships
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34 14 can be drawn. Our definition of AF with a secondary precipitant was based on diagnosis codes from
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36 15 hospital admissions with AF and a reversible precipitant. Both diagnoses were registered at the
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38 16 discharge date, and therefore we may have included patients in the group of AF with a secondary
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40 17 precipitant who developed AF before the secondary precipitant (e.g. patients admitted with AF who
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42 18 developed infection during their hospital stay), and thereby should have been classified as patients
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44 19 with AF without a secondary precipitant. Moreover, we had no access to patient files, and we did
45
46 20 not know the duration of AF or whether the patients were discharged in sinus rhythm or with AF.
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48 21 Also, no data were available with regard to the physicians' considerations when choosing between
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50 22 OAC therapy and no OAC therapy, patients compliance, and measurements of international
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52 23 normalized ratio (INR) and time in therapeutic range for warfarin users.
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1 The retrospective, registry-based nature of this study also precluded consideration of the specific
2 impact of the molecular causes of both acute and chronic AF, including inflammatory activation
3 and impaired nitric oxide (NO) availability and signaling. For example, specific patterns and extent
4 of inflammatory activation associated with intercurrent infection could not be determined, and
5 while impaired NO anti-aggregatory effect occurs in acute AF (27) and increased plasma
6 concentrations of asymmetric dimethylarginine, which inhibits enzymatic generation of NO, predict
7 thromboembolic risk in AF (28), neither of these parameters were measured in the current
8 study. However, this study was based on a nationwide cohort of patients with many years of follow-
9 up and data from high-quality registries. It reveals unexpected results that should be considered in
10 future treatment guidelines for patients with AF and a secondary precipitant.

12 *Conclusion*

13 In this study we found that patients with AF and a secondary precipitant carried a similar associated
14 thromboembolic risk as those with AF without a secondary precipitant. Current guidelines lack data
15 on this subject and our results suggests that AF in relation to known triggers may be considered as
16 AF in general.

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3 for-profit sectors.

4 **Conflicts of interest**

5 AG: None. TK: Consultant fees from BMS, Astra Zeneca, Roche, Boehringer-Ingelheim, Bayer,
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12

13 **Author contributions**

14 The study idea was conceived by AG, TK, and ELF, study design was developed by AG, TK, JBO,
15 ANB, JHB, GHG, CTP, LK, and ELF, data analyses were made by AG. AG drafted the first version
16 of the paper and all authors participated in the critical discussions and interpretation of findings. All
17 authors have participated in the revisions of the draft and have approved the final version.
18

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20 None.

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For peer review only

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4 **1 Figure legends**
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6 **2 Figure 1: Patient selection**
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9 **3 Figure 2: Number of events, incidence rates, and crude and adjusted Hazard ratios of long-term**
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11 **4 outcomes in patients with AF with and without a secondary precipitant.**
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13 **5 Figure 3: Cumulative incidence of thromboembolic events outcomes by secondary precipitant and**
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15 **6 OAC therapy at the index date.**
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18 **7 Figure 4: Cumulative incidence of death events outcomes by secondary precipitant and OAC**
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20 **8 therapy at the index date.**
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23 **9 Figure 5: Adjusted hazard ratios of long-term outcomes in patients with AF initiated vs. not**
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25 **10 initiated on OAC therapy (stratified according to type of AF).**
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Table 1: Baseline characteristics of the matched population

	Alcohol intoxication group		Thyrotoxicosis group		Myocardial infarction group		Surgery group		Infection group		>1 precipitant group	
+/- secondary precipitant:	+	-	+	-	+	-	+	-	+	-	+	-
	N=335	N=335	N=2507	N=2507	N=4773	N=4773	N=5229	N=5229	N=21,824	N=21,824	N=5055	N=5055
Demographics												
Age, median (IQR*)	59 (49-66)	59 (49-66)	73 (63-81)	73 (63-81)	77 (69-83)	77 (69-83)	75 (67-82)	75 (67-82)	79 (71-86)	79 (71-86)	76 (68-83)	76 (68-83)
Male, n (%)	276 (82.4)	276 (82.4)	521 (20.8)	521 (20.8)	2705 (56.7)	2705 (56.7)	2724 (52.1)	2724 (52.1)	10,370 (47.5)	10,370 (47.5)	2676 (52.9)	2676 (52.9)
Comorbidities, n (%)												
Cancer	16 (4.8)	29 (8.7)	288 (11.5)	296 (11.8)	586 (12.3)	688 (14.4)	1349 (25.8)	882 (16.9)	4341 (19.9)	3571 (16.4)	958 (19.0)	807 (16.0)
Chronic kidney disease	11 (3.3)	8 (2.4)	61 (2.4)	49 (2.0)	289 (6.1)	233 (4.7)	352 (6.7)	198 (3.8)	1564 (7.2)	748 (3.4)	431 (8.5)	212 (4.2)
COPD†	28 (8.4)	23 (6.9)	234 (9.3)	221 (8.8)	619 (13.0)	565 (11.8)	665 (12.7)	520 (9.9)	4696 (21.5)	2093 (9.6)	914 (18.1)	519 (10.3)
Diabetes	26 (7.8)	18 (5.4)	189 (7.5)	159 (6.3)	575 (12.0)	556 (11.6)	503 (9.6)	423 (8.1)	2167 (9.9)	1737 (8.0)	498 (9.9)	554 (11.0)
Heart failure	24 (7.2)	18 (5.4)	445 (17.8)	388 (15.5)	1660 (34.8)	1076 (22.5)	966 (18.5)	851 (16.3)	5109 (23.4)	3709 (17.0)	1574 (31.1)	925 (18.3)
Hypertension	64 (19.1)	78 (23.3)	1309 (52.2)	1249 (49.8)	3290 (68.9)	3204 (67.1)	2484 (47.5)	2695 (51.5)	10,445 (47.9)	11,475 (52.6)	2694 (53.3)	3007 (59.5)
IHD‡	43 (12.8)	53 (15.8)	333 (13.3)	455 (18.1)	4773 (100)	1604 (33.6)	1753 (33.5)	1332 (25.5)	4696 (21.5)	5069 (23.2)	3072 (60.8)	1423 (28.2)
PAD§	7 (2.1)	8 (2.4)	78 (3.1)	83 (3.3)	375 (7.9)	293 (6.1)	468 (9.0)	233 (4.5)	1392 (6.4)	932 (4.3)	448 (8.9)	269 (5.3)
Prior bleeding event	81 (24.2)	42 (12.5)	243 (9.7)	249 (9.9)	722 (15.1)	715 (15.0)	1267 (24.2)	833 (15.9)	4319 (19.8)	3463 (15.9)	1171 (23.2)	811 (16.0)
Prior thromboembolic event	24 (7.2)	24 (7.2)	138 (5.5)	183 (7.3)	483 (10.1)	698 (14.6)	571 (10.9)	570 (10.9)	2651 (12.1)	2278 (10.4)	603 (11.9)	635 (12.6)
Risk scores												
CHA ₂ DS ₂ -VASc												
Median (IQR*)	1 (0-2)	1 (0-2)	3 (2-4)	3 (2-4)	4 (3-5)	3 (3-4)	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)	4 (2-5)	3 (2.4)
0	158 (47.2)	158 (47.2)	405 (16.2)	405 (16.2)	0	0	391 (7.5)	391 (7.5)	1328 (6.1)	1328 (6.1)	269 (5.3)	269 (5.3)
1-2	118 (35.2)	118 (35.2)	530 (3.0)	530 (3.0)	670 (14.0)	670 (14.0)	1406 (26.9)	1406 (26.9)	5148 (23.6)	5148 (23.6)	1005 (19.9)	1005 (19.9)
≥3	59 (17.6)	59 (17.6)	1572 (62.7)	1572 (62.7)	4103 (86.0)	4103 (86.0)	3432 (65.6)	3432 (65.6)	15,348 (70.3)	15,348 (70.3)	3781 (74.8)	3781 (74.8)
HAS-BLED [#]												
Median (IQR*)	2 (1-3)	1 (0-2)	2 (1-3)	2 (1-3)	3 (2-3)	2 (2-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (2-3)	2 (2-3)
0	0	0	355 (14.2)	331 (13.2)	134 (2.8)	76 (1.6)	289 (5.5)	381 (7.3)	1003 (4.6)	1147 (5.2)	208 (4.1)	242 (4.8)
1-2	232 (69.3)	155 (46.3)	1460 (58.2)	1440 (57.4)	2552 (53.5)	2863 (54.8)	2863 (54.8)	2935 (56.1)	12,130 (55.6)	12,129 (55.6)	2422 (47.9)	2638 (52.2)
≥3	103 (30.8)	52 (15.5)	692 (27.6)	736 (29.4)	2145 (6.7)	2077 (6.5)	2077 (39.7)	1913 (36.6)	8691 (39.8)	8548 (39.2)	2425 (48.0)	2175 (43.0)
Pharmacotherapy, n (%)												
OAC** therapy, n (%)	33 (9.9)	33 (9.9)	1100 (43.9)	1100 (43.9)	1311 (27.5)	1311 (27.5)	1150 (22.0)	1150 (22.0)	5985 (27.4)	5985 (27.4)	1087 (21.5)	1087 (21.5)
Amiodarone	≤3	6 (1.8)	33 (1.3)	62 (2.5)	359 (7.5)	158 (3.3)	443 (8.5)	163 (3.1)	617 (2.8)	574 (2.6)	418 (8.3)	154 (3.0)

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2	Digoxin	49 (14.6)	29 (8.7)	1000 (39.9)	916 (36.5)	1207 (25.3)	1502 (31.5)	1089 (20.8)	1285 (24.6)	7973 (36.5)	6286 (28.8)	1184 (23.4)	1223 (24.2)
3	Flecainide	0 (0)	≤ 3	13 (0.5)	29 (1.2)	9 (0.2)	32 (0.7)	12 (0.2)	52 (1.0)	40 (0.2)	156 (0.7)	6 (0.1)	27 (0.5)
4	*IQR: interquartile range. †COPD: chronic obstructive pulmonary disease. ‡IHD: ischemic heart disease. §PAD: peripheral artery disease. CHA ₂ DS ₂ -VASc: Risk score for stroke: congestive												
5	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												
6	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												
7	agents/non-steroidal inflammatory drugs, alcohol abuse. **OAC: oral anticoagulation.												
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AF for the first time with a
secondary precipitant, 1996-2015
N=66,242

AF for the first time without a
secondary precipitant, 1996-2015
N=138,618

Exclusions (N=26,166)

- <18 years or > 100 years, N=134
- Valvular atrial fibrillation, N=2038
- Atrial fibrillation therapy before hospital admission, N=13,916
- Dead or emigrated during the blanking period, N=7366
- Thromboembolic event during the blanking period, N=2712

Exclusions (N=40,430)

- <18 years or > 100 years, N=278
- Valvular atrial fibrillation, N=2550
- Atrial fibrillation therapy before hospital admission, N=33,629
- Dead or emigrated during the blanking period, N=1992
- Thromboembolic event during the blanking period, N=1981

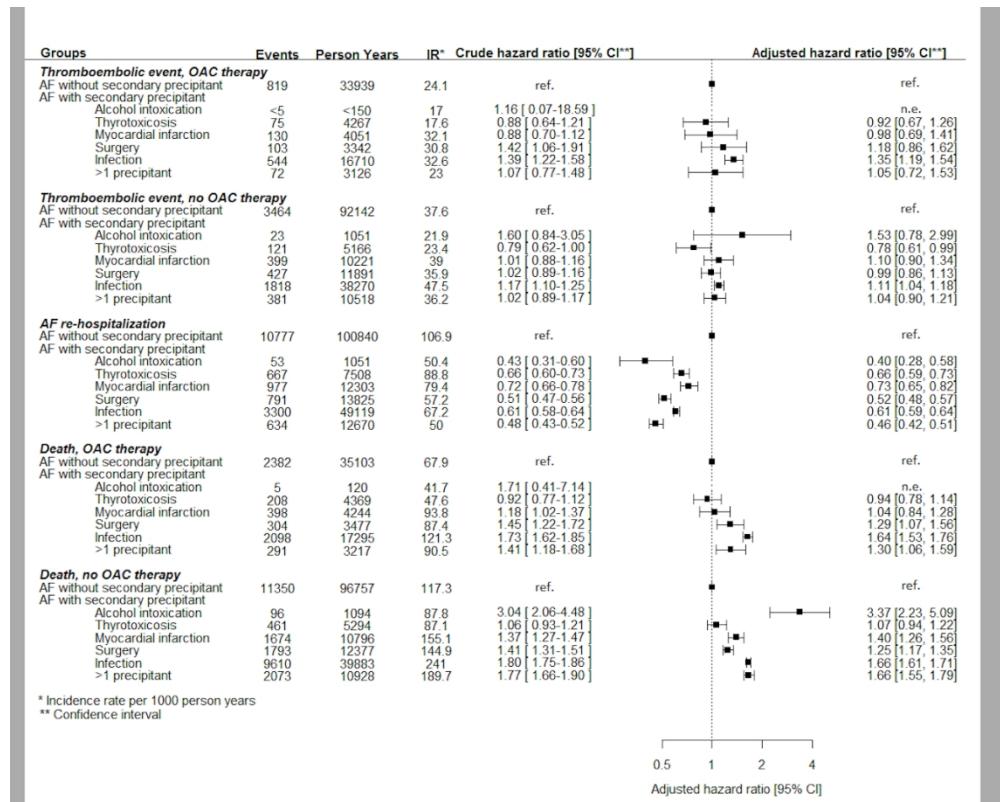
Complete study population

AF with secondary precipitant
N=40,076

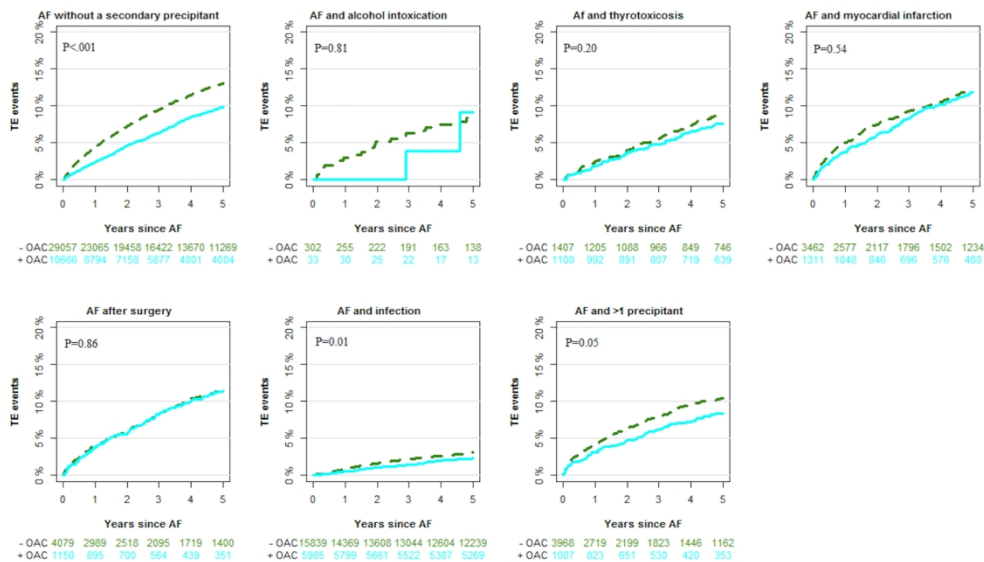
AF without secondary precipitant
N=98,188

Matched population

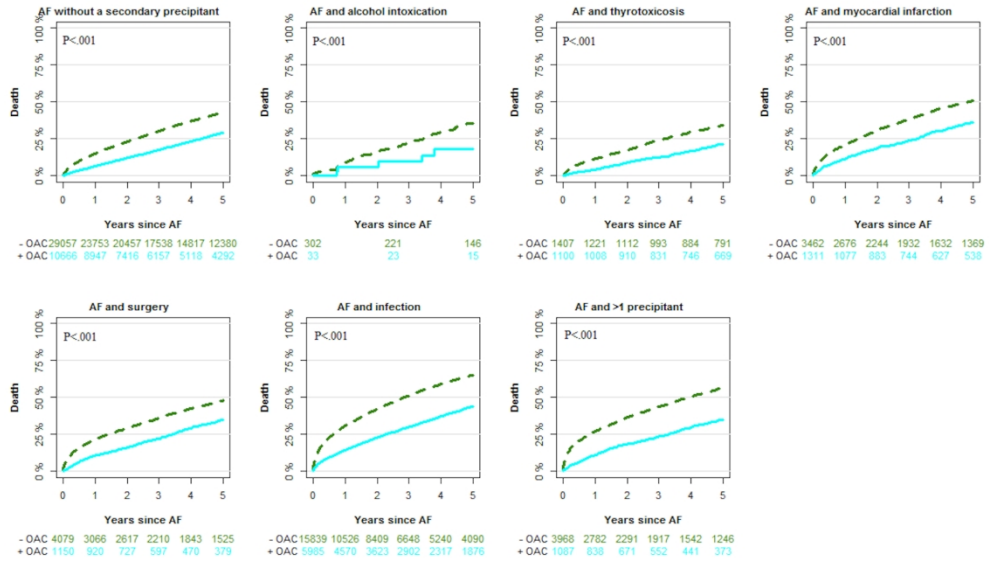
- 39,723 patients with AF with secondary precipitant
 - 335 (0.8%) with alcohol intoxication
 - 2507 (6.3%) with thyrotoxicosis
 - 4773 (12.0%) with myocardial infarction
 - 5229 (13.2%) had had surgery
 - 21,824 (55.0%) with infection
 - 5055 (12.7%) with >1 precipitant
- 39,723 patients with AF without a secondary precipitant



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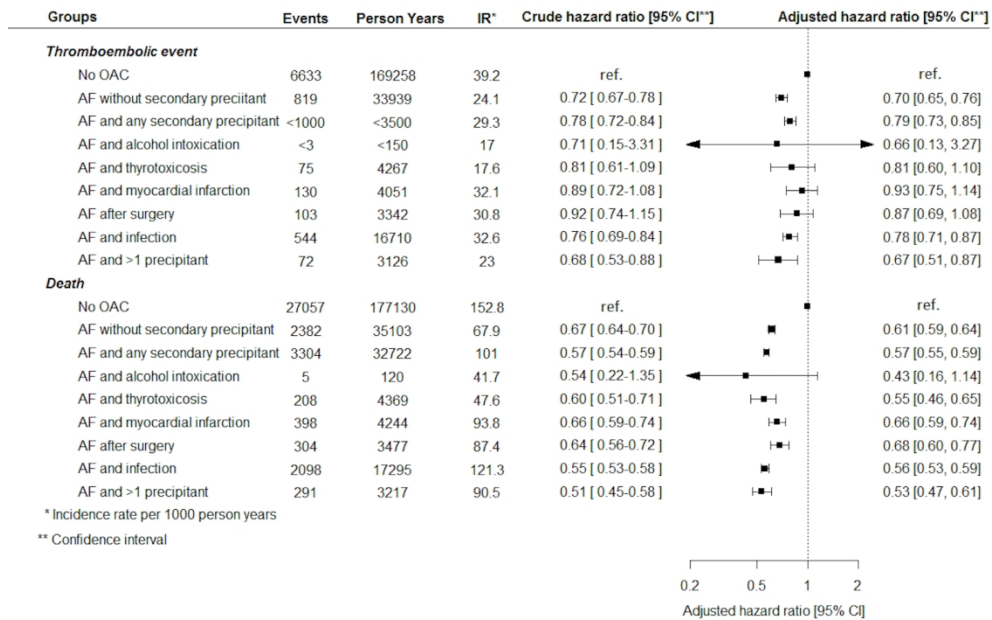


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Supplemental material

Comparative thromboembolic risk in atrial fibrillation with and without a secondary precipitant – a Danish nationwide cohort study

Anna Gundlund, MD, PhD; Thomas Kümler, MD, PhD; Anders N. Bonde, MD; Jawad H. Butt, MD; Gunnar H. Gislason, MD, PhD; Christian Torp-Pedersen, MD, DMSc; Lars Køber, MD, DMSc; Jonas B. Olesen, MD, PhD; Emil L. Fosbøl, MD, PhD

Online Table 1: Specification of diagnoses by international classification of diseases (ICD-8 and ICD-10) codes and pharmacotherapy by anatomical therapeutic chemical classification (ATC) codes.

Online Table 2: Baseline characteristics of the non-matched population, patients initiated on OAC therapy

Online Table 3: Baseline characteristics of the non-matched population, patients not initiated on OAC therapy

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.

Online Table 1: Specification of diagnoses by international classification of diseases (ICD-8 and ICD-10) codes and pharmacotherapy by anatomical therapeutic chemical classification (ATC) codes.

Precipitants	ICD-10 codes and NCSP, NOMESCO Classification of Surgical Procedures
Alcohol intoxication	ICD-10: F100, F103, F104, R780, T51, X65
Infections	ICD-10: Certain infectious and parasitic diseases: A00-B99. Infections in the eye and adnexa: H00, H01, H10, H20, H30, H44, H60, H65-H68, H70, H73.0, H73.1 Infections in the cardiovascular organs: I30, I32, I33, I38-I41 Infections in pulmonary system: J00-J22, J32, J36, J85, J86 Infections in the gastrointestinal system: K12, K20, K35-K37, K57, K65, K67, K81, K85 Infections in the skin, subcutaneous tissue, bones, muscles, and connective tissue: L00-L08, M00, M01, M60, M63.2, M65, M86, M90.0, M90.1, M90.2 Infections in the urogenital system: N00, N01, N05, N30, N70-N77.
Myocardial infarction	ICD-10: I21
Pulmonary embolism	ICD-10: I260, I269, O882D, O882E, T817D
Surgery	NCSP, NOMESCO Classification of Surgical Procedures: KF, KM, KN, KD, KPH, KPJ, KJ, KH, KQ, KB, KC, KL, KE, KA, KG, KK.
Thyrotoxicosis	ICD-10: E05
Outcomes	
Atrial fibrillation re-hospitalization	Hospital admission with primary diagnosis of atrial fibrillation: I48
Thromboembolic event	Ischemic stroke: I63, I64 Death from stroke: I61-I64 Transient ischemic attack: G458, G459 Thrombosis or embolism in arteries: I74
Comorbidities	ICD-8 and ICD-10 codes

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Atrial fibrillation	ICD-10: I48 ICD-8: 42793, 42794
Alcohol abuse	ICD-10: E24.4, E52, F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, L27.8A, O35.4, T51, Z71.4, Z72.1. ATC: N07BB
Cancer	ICD-10: C
Chronic kidney disease	ICD-10: E10.2, E11.2, E13.2, E14.2, I12.0, M32.1B, N02-N08, N11, N12, N14, N15.8, N15.9, N16.0, N16.2-N16.4, N16.8, N18, N19, N26, Q61
Chronic obstructive pulmonary disease	ICD-10: J42, J43, J44
Diabetes	ATC: A10 (3 months before index)
Heart failure	ICD-10: I11.0, I42, I50, J81
Hypertension	Usage of a combination of at least two of the seven different drug classes at the same time: <ol style="list-style-type: none"> 1. Non-loop diuretics 2. Loop diuretics 3. Antiadrenergic agents 4. Beta-blockers 5. Vasodilators 6. Calcium channel blockers 7. Renin-angiotensin system inhibitors
Ischemic heart disease	ICD-10: I20-I25
Peripheral artery disease	ICD-10: I70
Prior bleeding	ICD-10: D50.0, D62, G951A, H31.3, H05.2A, H35.6, H43.1, H45.0, I31.2, I60-I62, I85.0, I86.4A, J94.2, K22.8F, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.8A, K62.5, K63.8B, K63.8C, K66.1, K83.8F, K86.8G, K92.0-K92.2, N02, R04, R31, S06.4-S06.6, S36.8D
Thromboembolic event	ICD-10: G45.8, G45.9, I63, I64, I74
Valvular atrial fibrillation	Atrial fibrillation without: ICD-10: I05, I06, I080A, I081A, I082A, I083A, Z952, Z954 ICD-8: 39500-39502, 39508, 39509, 39600-39604, 39608, 39609 Procedures: FKD, FKH, FMD, FMH, FGE, FJE
Pharmacotherapy	ACT-codes

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ADP-receptor blockers	B01AC04, B01AC22, B01AC24
Amiodarone	C01BD01
Antiadrenergic agents	C02A, C02B, C02C
Oral anticoagulation therapy	Vitamin K antagonists: B01AA03, B01AA04 Non-vitamin K antagonist oral anticoagulants: B01AF01, B01AF02, B01AE07
Beta-blockers	C07A, C07B, C07C, C07D, C07F
Calcium channel blockers	C08, C09BB, C09DB
Digoxin	C01AA
Flecainide	C01BC
Loop diuretics	C03C, C03EB
Non-loop diuretics	C02DA, C03EA, C03EB, C02L, C03A, C03B, C03D, C03E, C03X, C07B, C07C, C07D, C08G, C09BA, C09DA, C09XA52
Renin-angiotensin system inhibitors	C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C09XA02, C09XA52
Vasodilators	C02DB, C02DD, C02DG

Online Table 2: Baseline characteristics of the non-matched population, patients initiated on OAC therapy

	AF with a secondary precipitant N=10,673						AF without a secondary precipitant N=37,827
	Alcohol intoxication N=33	Thyro- toxicosis N=1103	Myocardial infarction N=1312	Surgery N=1151	Infection N=5987	>1 precipitant N=1087	
Demographics							
Age, median (IQR*)	64 (55-68)	72 (64-79)	75 (68-81)	74 (67-81)	77 (69-83)	75 (68-81)	72 (64-79)
Male, n (%)	28 (84.8)	259 (23.5)	842 (64.2)	667 (57.9)	3189 (53.3)	634 (58.3)	21,386 (56.5)
Comorbidities, n (%)							
Cancer	≤3	114 (10.3)	146 (11.1)	239 (20.8)	927 (15.5)	171 (15.1)	4617 (12.2)
Chronic kidney disease	4 (12.1)	23 (2.1)	62 (4.7)	65 (5.6)	372 (6.2)	59 (5.4)	1011 (2.7)
COPD†	≤3	106 (9.6)	133 (10.1)	128 (11.1)	1251 (20.9)	157 (14.4)	3426 (9.1)
Diabetes	≤3	84 (7.6)	159 (12.1)	111 (9.6)	712 (11.9)	112 (10.3)	3384 (8.9)
Heart failure	6 (18.2)	236 (21.4)	464 (35.4)	228 (19.8)	1440 (24.1)	359 (33.0)	6791 (18.0)
Hypertension	11 (33.3)	658 (59.7)	982 (74.8)	687 (59.7)	3652 (61.0)	723 (66.5)	23,057 (61.0)
IHD‡	5 (15.2)	129 (11.7)	1312 (100)	434 (37.7)	1202 (20.1)	744 (68.4)	7360 (19.5)
PAD§	≤3	29 (2.6)	83 (6.3)	101 (8.8)	353 (5.9)	77 (7.1)	1258 (3.3)
Prior bleeding event	7 (21.2)	86 (7.8)	150 (11.4)	213 (18.5)	966 (16.1)	182 (16.7)	4564 (12.1)
Prior thromboembolic event	≤3	60 (5.4)	142 (10.8)	153 (13.3)	672 (11.2)	133 (12.2)	3313 (8.8)
Risk scores							
CHA ₂ DS ₂ -VASc							
Median (IQR*)	1 (0-2)	3 (2-4)	4 (3-5)	3 (2-4)	3 (2-4)	4 (3-5)	3 (2-4)
0	11 (33.3)	134 (12.2)	0	74 (6.4)	269 (4.5)	28 (2.6)	3592 (9.5)
1-2	16 (48.5)	263 (23.8)	181 (13.8)	289 (25.1)	1493 (24.9)	181 (16.6)	12,341 (32.6)
≥3	6 (18.2)	706 (64.0)	1131 (86.2)	788 (68.5)	4225 (70.6)	878 (80.8)	21,894 (57.9)
HAS-BLED#							
Median (IQR*)	2 (1-3)	2 (1-2)	3 (2-3)	2 (1-3)	2 (1-3)	2 (2-3)	2 (1-3)
0	0	128 (11.6)	32 (2.4)	60 (5.2)	259 (4.3)	33 (3.0)	3361 (8.9)
1-2	21 (63.6)	706 (64.0)	571 (43.5)	611 (53.1)	3433 (57.3)	515 (47.4)	22,792 (60.3)
≥3	12 (36.4)	269 (24.4)	709 (54.0)	480 (41.7)	2295 (38.3)	539 (49.6)	11,674 (30.9)
Pharmacotherapy, n (%)							

Amiodarone	0	19 (1.7)	104 (7.9)	181 (15.7)	261 (4.4)	141 (13.0)	1493 (3.9)
Digoxin	11 (33.3)	605 (54.9)	437 (33.3)	312 (27.1)	2847 (47.6)	368 (33.9)	14,803 (39.1)
Flecainide	0	5 (0.5)	≤3	≤3	10 (0.2)	≤3	248 (0.7)

*IQR: interquartile range. †COPD: chronic obstructive pulmonary disease. ‡IHD: ischemic heart disease. §PAD: peripheral artery disease. ||CHA₂DS₂-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.

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Online Table 3: Baseline characteristics of the non-matched population, patients not initiated on OAC therapy

	AF with a secondary precipitant N=29,403						AF without a secondary precipitant N=60,361
	Alcohol intoxication N=302	Thyro- toxicosis N=1408	Myocardial infarction N=3508	Surgery N=4101	Infection N=16,079	>1 precipitant N=4005	
Demographics							
Age, median (IQR*)	58 (48-66)	74 (62-82)	78 (69-84)	76 (67-82)	80 (72-87)	76 (68-83)	69 (58-80)
Male, n (%)	248 (82.1)	263 (18.7)	1907 (54.4)	2069 (50.5)	7352 (45.7)	2073 (51.8)	31,074 (51.5)
Comorbidities, n (%)							
Cancer	15 (5.0)	174 (12.4)	454 (12.9)	1115 (27.2)	3474 (21.6)	795 (19.9)	7915 (13.1)
Chronic kidney disease	7 (2.3)	38 (2.7)	236 (6.7)	289 (7.0)	1223 (7.6)	375 (9.4)	1733 (2.9)
COPD†	26 (8.6)	128 (9.1)	495 (14.1)	539 (13.1)	3493 (21.7)	765 (19.1)	4544 (7.5)
Diabetes	24 (7.9)	105 (7.5)	417 (11.9)	396 (9.7)	1473 (9.2)	387 (9.7)	3566 (5.9)
Heart failure	18 (6.0)	209 (14.8)	1218 (34.7)	744 (18.1)	3752 (23.3)	1231 (30.7)	6328 (10.5)
Hypertension	53 (17.5)	653 (46.4)	2348 (66.9)	1808 (44.1)	6942 (43.2)	1991 (49.7)	22,309 (37.0)
IHD‡	38 (12.6)	207 (14.7)	3508 (100)	1326 (32.3)	3558 (22.1)	2354 (58.8)	11,528 (19.1)
PAD§	6 (2.0)	49 (3.5)	298 (8.5)	371 (9.0)	1057 (6.6)	374 (9.3)	1913 (3.2)
Prior bleeding event	74 (24.5)	157 (11.2)	585 (16.7)	1062 (25.9)	3420 (21.3)	998 (24.9)	7616 (12.6)
Prior thromboembolic event	22 (7.3)	78 (5.5)	350 (10.0)	422 (10.3)	2029 (12.6)	478 (11.9)	4301 (7.1)
Risk scores							
CHA₂DS₂-VASC							
Median (IQR*)	1 (0-2)	3 (2-4)	4 (3-5)	3 (2-4)	3 (2-4)	4 (2-5)	2 (0-4)
0	147 (48.7)	271 (19.2)	0	317 (7.7)	1059 (6.6)	241 (6.0)	15,957 (26.4)
1-2	102 (33.8)	270 (19.2)	489 (13.9)	1119 (27.3)	3671 (22.8)	824 (20.6)	17,513 (29.0)
≥3	53 (17.5)	867 (61.6)	3019 (86.1)	2665 (65.0)	11,349 (70.6)	2940 (73.4)	26,891 (44.6)
HAS-BLED[#]							
Median (IQR*)	2 (1-3)	2 (1-3)	3 (2-3)	2 (1-3)	2 (1-3)	2 (2-3)	2 (1-3)
0	0	228 (16.2)	102 (2.9)	229 (5.6)	745 (4.6)	175 (4.4)	12,875 (21.3)
1-2	211 (69.9)	756 (53.7)	1424 (40.6)	2265 (55.2)	8795 (54.7)	1924 (48.0)	31,914 (52.9)
≥3	91 (30.1)	424 (30.1)	1982 (56.5)	1607 (39.2)	6539 (40.7)	1906 (47.6)	15,572 (25.8)

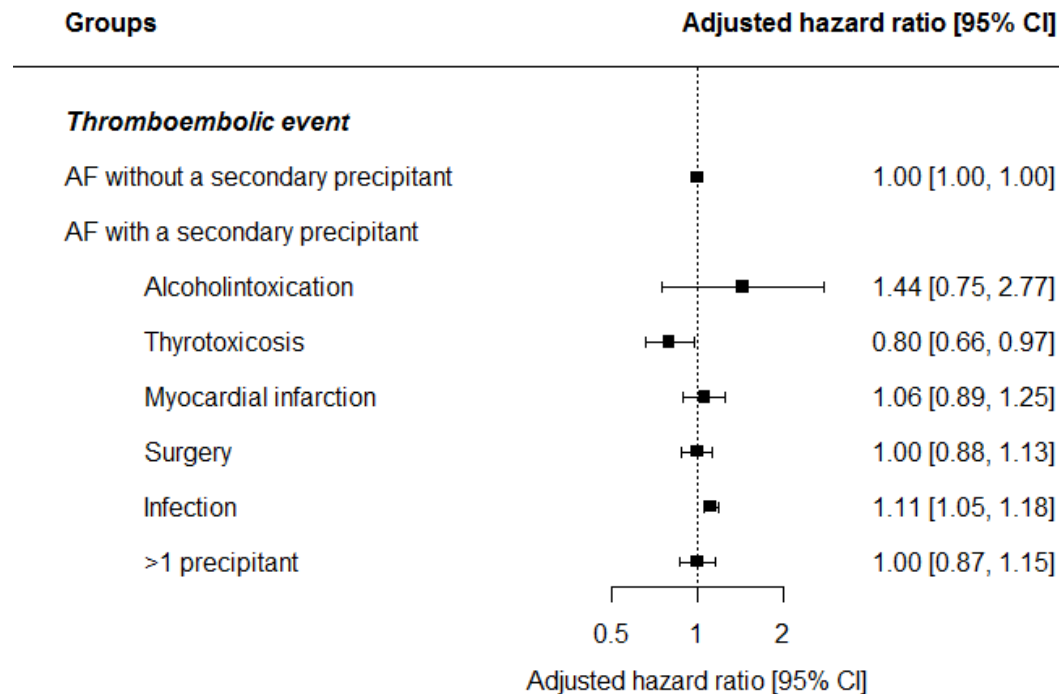
Pharmacotherapy, n (%)							
Amiodarone	≤3	14 (1.0)	259 (7.4)	262 (6.4)	361 (2.2)	278 (6.9)	1133 (1.9)
Digoxin	38 (12.6)	398 (28.3)	784 (22.3)	782 (19.1)	5210 (32.4)	828 (20.7)	10,336 (17.1)
Flecainide	0	8 (0.6)	8 (0.2)	10 (0.2)	30 (0.2)	5 (0.1)	786 (1.3)

*IQR: interquartile range. †COPD: chronic obstructive pulmonary disease. ‡IHD: ischemic heart disease. §PAD: peripheral artery disease. ¶CHA₂DS₂-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.

For peer review only

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.



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract YES, p.1 and 3. (b) Provide in the abstract an informative and balanced summary of what was done and what was found YES, p. 3.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported YES, p. 5
Objectives	3	State specific objectives, including any prespecified hypotheses YES, p. 5
Methods		
Study design	4	Present key elements of study design early in the paper YES, p. 5-7.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection YES, p. 5-7.
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up YES, p. 6-7. <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed YES, p. 8. <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable YES, p. 7-8. Figure 3. Specification of diagnosis can be found in the Online Table 1.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group YES, p. 5-6 and eTable 1.
Bias	9	Describe any efforts to address potential sources of bias YES, p. 8.
Study size	10	Explain how the study size was arrived at YES, p. 6-7, figure 1.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why

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YES, p. 6-7.

Statistical methods

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(a) Describe all statistical methods, including those used to control for confounding

YES, p. 7-8.

(b) Describe any methods used to examine subgroups and interactions

YES, p. 7-8.

(c) Explain how missing data were addressed

No missing data

(d) *Cohort study*—If applicable, explain how loss to follow-up was addressed

No loss to follow-up.

Case-control study—If applicable, explain how matching of cases and controls was addressed

Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy

(e) Describe any sensitivity analyses

YES, p. 7.

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Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed YES, p. 8-9 and Figure 1.
		(b) Give reasons for non-participation at each stage YES, p. 8-9 and Figure 1.
		(c) Consider use of a flow diagram YES, Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders YES, p. 9, Table 1.
		(b) Indicate number of participants with missing data for each variable of interest No missing data
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) YES, Figure 2.
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time YES, p. 10 and Figure 2, 3.
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included YES, Figure 3.
		(b) Report category boundaries when continuous variables were categorized Continuous variables were not categorized.
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses YES, p. 11.
Discussion		
Key results	18	Summarise key results with reference to study objectives YES, p. 11.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias YES, p. 13-14.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence YES, p. 12-13.
Generalisability	21	Discuss the generalisability (external validity) of the study results YES, p. 14.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

1
2 YES, p. 14.
3

4 *Give information separately for cases and controls in case-control studies and, if applicable, for exposed and
5 unexposed groups in cohort and cross-sectional studies.
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8 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and
9 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely
10 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
11 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
12 available at www.strobe-statement.org.
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