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**Oral anticoagulants in patients with atrial fibrillation at low stroke risk: a multicentre observational study**

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## **Abstract**

**Background:** There is currently no consensus on whether atrial fibrillation (AF) patients at low risk for stroke (1 non-sex-related CHA<sub>2</sub>DS<sub>2</sub>-VASc point) should be treated with an oral anticoagulant.

**Methods and results:** We conducted a multi-country cohort study in Sweden, Denmark, Norway, and Scotland. In total, 59 076 patients diagnosed with AF at low stroke risk were included. We assessed the rates of stroke or major bleeding during treatment with a non-vitamin K antagonist oral anticoagulant (NOAC), a vitamin K antagonist (VKA), or no treatment, using inverse probability of treatment weighted (IPTW) Cox regression. In untreated patients, the rate for ischemic stroke was 0.70 per 100 person-years and the rate for a bleed also 0.70 per 100 person-years. Comparing NOAC to no treatment, the stroke rate was lower (hazard ratio [HR] 0.72; 95% confidence interval [CI] 0.56- 0.94), and the rate for intracranial haemorrhage (ICH) was not increased (HR 0.84; 95% CI 0.54-1.30). Comparing VKA to no treatment, the rate for stroke tended to be lower (HR 0.81; 95% CI 0.59-1.09), and the rate for ICH tended to be higher during VKA treatment (HR 1.37; 95% CI 0.88-2.14). Comparing NOAC to VKA treatment, the rate for stroke was similar (HR 0.92; 95% CI 0.70-1.22), but the rate for ICH was lower during NOAC treatment (HR 0.63; 5% CI 0.42-0.94).

**Conclusion:** These observational data suggest that NOAC treatment may be associated with a positive net clinical benefit compared to no treatment or VKA treatment in patients at low stroke risk, a question that can be tested through a randomised controlled trial.

**Keywords:** Atrial fibrillation, Non vitamin K antagonist oral anticoagulants, vitamin K antagonists, stroke risk

### **One-sentence summary**

These observational data from patients with atrial fibrillation at low stroke risk suggest that treatment with non-vitamin K antagonist oral anticoagulants may be associated with a positive net clinical benefit compared to no treatment and vitamin K antagonist treatment, a question that can be tested through a randomised controlled trial.

## Introduction

Patients with atrial fibrillation (AF) have a five-fold increased risk for stroke. However, risk varies considerably between patients and can be estimated using the CHA<sub>2</sub>DS<sub>2</sub>-VASc score<sup>1,2</sup>. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score is based on five characteristics adding one point: age (65-74), female sex, congestive heart failure, hypertension, vascular disease, and diabetes, and two characteristics adding two points: age  $\geq 75$  and a prior stroke/transient ischemic attack (TIA)/embolism. If this score, and thus the stroke risk, exceeds a certain level, the benefit of treatment with an oral anticoagulant in terms of stroke prevention is considered to outweigh the risks of bleeding associated with treatment. Current guidelines recommend treatment with an oral anticoagulant if a patient has a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of two or higher for males, or three or higher for females<sup>3,4</sup>. For patients at low risk, i.e., having a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 for males, and 2 for females, the guidelines state that treatment with an oral anticoagulant should be individualized based on net clinical benefit and consideration of patient values and preferences<sup>3</sup>.

Some observational studies have shown a positive net clinical benefit of treatment with vitamin K antagonists (VKA) compared to no treatment or antiplatelet treatment in low-risk patients<sup>5,6</sup>. On the other hand, there have also been studies showing no clinical benefit<sup>7</sup>, and there is a class IIa recommendation that treatment for patients at low risk can be considered<sup>8</sup>. However, all studies investigating the effects of anticoagulation therapy compared to no therapy among low-risk patients were conducted prior to the availability of non-vitamin K antagonist oral anticoagulants (NOACs). To the best of our knowledge, there are thus no studies comparing the safety and effectiveness of NOAC treatment to no treatment in low-risk patients, a comparison that represents the clinical decision faced by physicians seeing low-risk AF patients. Unfortunately, there is currently no available randomized trial evidence in this field and no ongoing randomized trial that aims to address this research question either. Given that NOAC treatment has a superior safety and efficacy profile compared to VKA treatment in the overall AF population as documented in randomized clinical trials<sup>9</sup>, as well as in observational studies<sup>10</sup>, the net clinical benefit may be more positive with NOAC treatment in these

low-risk patients, especially given the generally lower risk for intracranial haemorrhage (ICH) with NOAC compared to VKA treatment.

Even though trials only included a limited number of patients at low risk<sup>11–14</sup>, the meta-analysis of randomized trials by Ruff *et al.*<sup>9</sup> indicated that the point estimate in patients with a CHADS<sub>2</sub> score of 0 or 1 was more in favour of NOAC treatment compared to VKA for both the safety and efficacy outcomes. Because there are currently no data available comparing NOAC to no treatment, and only limited data comparing NOAC to VKA treatment in these patients, observational research is required to provide relevant information for decision making in this setting. Therefore, the aim of the current study was to compare the safety and effectiveness of NOAC, VKA, or no treatment in patients with AF at low stroke risk.

## **Methods**

### *Setting*

We developed a common protocol and used a common data model to analyse and pool results from four Western European databases, namely Denmark, Norway, Scotland, and the Stockholm region in Sweden. Detailed information on the databases can be found elsewhere and a summary overview is given in Appendix Table 1, including available parameters describing the validity of diagnoses of AF and outcomes<sup>15–20</sup>. All databases contain diagnoses from secondary care, both inpatient and outpatient. The Stockholm database also contains diagnoses from primary care. In addition, all databases contain data on medications dispensed at pharmacies.

### *Patient selection*

We selected all patients with a diagnosis of AF from the first of January 2011 until 31<sup>st</sup> of October 2018, the end of data availability. After the date of the first AF diagnosis, we added a 14-day run-in period and considered day 15 as the cohort entry date. This 14-day period was added to avoid including outcomes that are possibly related to the diagnosis of AF, e.g. experiencing a stroke which led to diagnostic workup revealing underlying AF.

As in the clinical trials, we excluded patients if they suffered from a major bleed in the 6 months prior to the cohort entry date since these patients might have a clear indication to withhold anticoagulant treatment. In addition, we excluded patients if they had a diagnosis or procedure code for mechanical valves and/or mitral stenosis in the 5 years prior to the cohort entry date or had immigrated in the 5 years prior to the cohort entry date (see Figure 1, procedure codes were not available in Norway).

We only included patients at low stroke risk, i.e., male patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 and female patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2. We determined age and sex at the cohort entry date and searched for a registration of any of the diagnoses in the 5 years prior to the cohort entry date, to include only patients with one non-sex related single-point stroke risk factor.

As hypertension and diabetes are often solely treated in primary care, and three databases (Norway, Denmark, Scotland) do not contain diagnostic data from primary care, we are likely to underestimate the proportion of patients diagnosed with hypertension and diabetes. Therefore, in those databases, we not only searched for diagnoses in secondary care, but also asserted whether patients had claimed two different antihypertensive drugs in the 5 years prior to the index date to identify hypertension or an antidiabetic drug to identify diabetes. We tested several approaches in the Stockholm database, in which we had access to both primary and secondary care data, and found that this approach led to the best positive predictive value and sensitivity (see Appendix eMethods).

#### *Antithrombotic treatment*

We considered three levels of anticoagulant treatment status: no treatment, NOAC treatment, and VKA treatment. A patient's baseline treatment status was defined in the 90 days prior to the cohort entry date. If a patient did not claim a NOAC or VKA in this period, the patient was considered untreated at baseline.

We excluded all patients claiming both a VKA and a NOAC prescription in the 90 days prior to cohort entry date, and patients claiming a prescription for antiplatelet treatment in the 90 days prior to the index date. In addition, we excluded patients who claimed either a VKA or a NOAC between one year

prior to cohort entry date and 90 days prior to cohort entry date, to only include new users of VKAs and NOACs.

### *Study design*

The main analysis in this study allocated patients to a treatment arm when they claimed at least one prescription of an OAC (mimicking an intention-to-treat analysis). The person time prior to the first claim is considered as untreated status, to avoid immortal time bias. After a patient has claimed his/her first treatment, the patient remained on that treatment status throughout the study period. If a patient did not claim any NOAC or VKA during follow-up, the patient would have the untreated status until the end of the study. Besides the main analysis, we also used a time-varying exposure approach (mimicking an as-treated analysis). In this approach, patients could switch between treatment statuses during follow-up. A patient would switch between NOAC and VKA status after claiming a different prescription, and a treated patient would switch to untreated, if he or she did not claim a new prescription within 180 days after a prior prescription.

### *Outcome definition*

We analysed both a composite effectiveness and safety outcome (see ICD-10 codes in Appendix Table 2). The composite effectiveness outcome included ischemic or unspecified stroke. The primary safety outcome was any major bleed. The secondary safety outcomes were gastrointestinal bleeds (GIB) and ICH considered separately. Finally, we included a composite outcome of stroke, major bleed, or death, as was done in the clinical trials of NOACs. All outcomes were included only if they were registered in a secondary care inpatient setting, to only include severe outcomes and reduce misclassification. In addition, we have provided the breakdown of the ICH outcome into intracerebral haemorrhage, subarachnoid haemorrhage, and traumatic ICH, and the stroke outcome into ischemic stroke and unspecified stroke.

### *Net clinical benefit*

We used two approaches to calculate the net clinical benefit comparing the three different treatment arms. First, we used the composite endpoint as described above. Second, we used the method described by Singer *et al.*<sup>21</sup>, using the following formula:

$$\text{Net Clinical Benefit} = (\text{Ischemic Rate}_{\text{off treatment}} - \text{Ischemic Rate}_{\text{on treatment}}) - \text{weight} * (\text{ICH Rate}_{\text{on treatment}} - \text{ICH Rate}_{\text{off treatment}}).$$

We used the full ICH endpoint and both ischemic and unspecified strokes for this calculation. We used the crude rates from the untreated group and multiplied them by the hazard ratio (HR) from the Cox regression to obtain the rates on treatment. We varied the weight given to an ICH with the factors 1.0, 1.5, and 2.0 and considered 1.5 as the main analysis as has been done earlier<sup>21</sup>.

#### *Follow-up time*

Patients were followed from the cohort entry date until censoring at the first occurrence of either the outcome of interest, death, emigration, end of the 2.5-year follow-up, a claim of an antiplatelet prescription, or an increase in the CHA<sub>2</sub>DS<sub>2</sub>-VASc score. A patient's CHA<sub>2</sub>DS<sub>2</sub>-VASc score could increase by passing the age threshold or being newly diagnosed with another component from the risk score.

#### *Covariates*

We defined the use of baseline medication as claiming a prescription in the 6 months prior to the cohort entry date. Baseline medications of interest were prescriptions for antidepressants, antiplatelet agents, beta blockers, calcium channel blockers, corticosteroids, diuretics, insulin, non-steroidal anti-inflammatory drugs, oral diabetic drugs, proton pump inhibitors, renin-angiotensin-aldosterone system inhibitors, and statins (see Appendix Table 2 for ATC codes).

We defined baseline comorbidities as having a registered diagnosis code in the 5 years prior to the cohort entry date. Baseline comorbidities of interest, besides the components of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, were diagnoses of a prior bleed, abnormal liver function, alcohol misuse, anaemia, cancer, chronic obstructive pulmonary disease, dementia, and renal disease (see Appendix Table 2 for ICD-10 codes).

### *Statistical analysis*

We used descriptive statistics to present patient characteristics of the three treatment arms. To contrast the risks for stroke and major bleeds, we used an inverse probability of treatment weighted (IPTW) Cox regression with a robust variance estimator. The probability of treatment was calculated with logistic regression, having age, sex, the year of cohort entry, and the aforementioned baseline medication and comorbidities as independent variables. We calculated the standardized mean differences (SMD) to check whether IPTW yielded comparable cohorts, considering an SMD below 0.1 as indicating satisfactory covariate balance<sup>22</sup>. We calculated the 95% confidence intervals (CI) for the net clinical benefit, by drawing 10.000 bootstrap samples from a normal distribution, with the mean and variance as calculated by the meta-analysis per outcome and per comparison.

### *Subgroup analyses*

We performed several subgroup analyses. First, we stratified by sex. Second, we stratified by age 65 and over or under 65. Third, we stratified by bleeding risk as defined by a HAS-BLED score of 0-1 or more than 1.

### *Meta-analysis*

All analyses were performed using the same analytical R script on a local analytical dataset that was transferred into a common data model. This procedure allowed data to stay locally and only results were shared, while ensuring an identical analysis in all databases. The results from the different databases were combined using a meta-analysis and we used Cochran's Q statistic to test whether a fixed or random effects meta-analysis was required. We calculated the number needed to treat for one year (NNT-y) based on the HRs derived from the meta-analysis. We used fixed-effects meta-regression to calculate p-values for subgroup analyses.

### *Additional analyses*

We performed several additional analyses to test the robustness of our findings. First, we used an active comparator-new user design to compare NOAC to VKA treatment. For this analysis, stopping and switching of treatment status were disregarded, and follow-up started at the first claim of a NOAC

or VKA, instead of being anchored to an AF diagnosis. Patients were included if they had an AF diagnosis prior to claiming their treatment, or within 90 days after; all other analyses were performed as in the main analysis. Second, as primary care data was only available in the Stockholm database, we performed an analysis in which we only included data from secondary care in Stockholm, using the proxies for hypertension and diabetes mellitus developed for regions with secondary care data only. Some diagnoses from the CHA<sub>2</sub>DS<sub>2</sub>-VASc score might only be captured in primary care, and hence the patient selection can be affected by this. Third, we used a shorter follow-up of a maximum of one year. Fourth, we used a falsification endpoint, which was a composite of acute upper respiratory infection and osteoarthritis<sup>23</sup>, recorded in inpatient secondary care (see Appendix for ICD-10 codes). These outcomes are not causally linked with any of the treatments but are associated with unmeasured potential confounders, such as frailty. By analysing the falsification endpoint with the same approach as the main analysis, bias from unmeasured confounders may be detected. Finally, we performed two exploratory *post hoc* analyses. First, an analysis to assess the potential for variation in risk estimates across individual components of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score<sup>24</sup>. However, due to low sample size, we were only able to assess the stroke and bleeding rate in the subgroup of individuals with hypertension. In addition, we already performed stratified analyses by age, which is also a component of the score. Second, we performed an analysis in which we pooled the results of the NOAC and the VKA treated patients to assess the group effect of oral anticoagulants compared to no treatment.

## Results

We included 59 076 patients newly diagnosed with AF at low stroke risk: 7352 from Stockholm, 21 272 from Denmark, 19 789 from Norway, and 10 663 from Scotland (see Appendix Figures 1 and 2 for flow-charts of patient selections). In total, 21 926 (37%) of the patients were treated with a NOAC, 11 201 (19%) with a VKA, and 31 385 (53%) were untreated at one time throughout follow-up (Table 1, untreated patients switching to VKA or NOAC were included in both cohorts). Of the patients treated with a NOAC, 47% were treated with apixaban, 29% with rivaroxaban, 23% with dabigatran, and only 1% with edoxaban. In Denmark, only 39% of the patients were untreated at baseline, while

this was 66% in Scotland. In all countries but Scotland, more patients were receiving a NOAC compared to VKA, in Denmark and Norway more than twice as often (Table 2).

There were no large differences in baseline characteristics between the three treatment groups. The mean age was 65.2 years in NOAC treated patients, 64.2 years in VKA treated patients, and 63.5 years in untreated patients. The mean HAS-BLED scores were 1.22, 1.25, and 1.38, respectively. There were more patients with a history of vascular disease in the untreated group, while heart failure was more common amongst VKA users. Of the untreated patients, only 38% received a beta-blocker at baseline, compared to 65% of NOAC treated patients, and 63% of VKA treated patients. In addition, untreated patients more often had aspirin or P2Y12 inhibitor therapy 180 days before baseline. After weighting, all SMDs were below 0.1 in all databases, for all comparisons, and for all covariates (Appendix Table 3).

In total, 432 patients suffered from a stroke during follow-up and 566 suffered a major bleed, of which 146 were an ICH and 250 a GIB (Table 3, see Appendix Table 4 for weighted crude rates). The overall incidence rate (IR) for stroke was 0.58 events per 100 person-years (%/py), 0.76 %/py for all major bleeds, 0.20%/py for ICH, and 0.34%/py for GIB. The highest crude IR for stroke was in the untreated group at 0.70 %/py. The highest IR for bleeds was in the VKA treated group at 0.83%/py, partly driven by the highest rate in ICH as well: 0.25%/py. The breakdown of the different types of ICH and stroke is given in Appendix Table 5.

The results from the meta-analyses of all databases showed that NOAC treatment was associated with a lower rate of stroke compared to no treatment (hazard ratio  $[HR]_{\text{stroke}}$  0.72; 95% confidence interval [CI] 0.55–0.94; NNT-y: 511), but a higher rate of bleeds ( $HR_{\text{bleed}}$  1.26; 95% CI 1.00 – 1.58; NNT-y: 475) (Table 4). This higher rate of bleeds was mainly driven by an increased GIB rate ( $HR_{\text{GIB}}$  1.48; 95% CI 1.05 – 2.08; NNT-y: 675), and not by the ICH rate ( $HR_{\text{ICH}}$  0.84; 95% CI 0.54 – 1.30; NNT-y: 3473). This yielded a statistically significant positive net clinical benefit for NOAC treatment, at each weight given to an ICH.

Comparing VKA treatment to no treatment showed tendencies towards a lower stroke rate ( $HR_{\text{stroke}}$  0.81; 95% CI 0.59 – 1.09; NNT-y: 754) and a higher bleeding rate ( $HR_{\text{bleed}}$  1.44; 95% CI 0.82 – 2.50;

NNT-y: 324). The rate of ICH tended to be higher on VKA treatment ( $HR_{ICH}$  1.37; 95% CI 0.88 – 2.14; NNT-y: 1501), which yielded a neutral net clinical benefit at each weight given to an ICH.

Comparing NOAC to VKA treatment showed no statistically significant difference in either the stroke or the bleeding rate ( $HR_{stroke}$  0.92; 95% CI 0.70 – 1.22; NNT-y: 2506);  $HR_{bleed}$  0.85; 95% CI 0.69 – 1.06; NNT-y: 807). However, NOAC treatment was associated with a significantly lower rate of ICH ( $HR_{ICH}$  0.63; 95% CI 0.42 – 0.94; NNT-y: 1096). The net clinical benefit calculation showed that there was a positive net clinical benefit for NOACs compared to VKA, which was statistically significant in two of the three weights given to an ICH in the net clinical benefit calculation. The composite endpoint of stroke, bleed, and death showed no significant differences (HR 0.87; 95% CI 0.68 – 1.11).

The time-varying analysis showed similar results as the main analysis. The rate for stroke was lower in NOAC treated patients compared to untreated patients without a higher rate of ICH, yielding a statistically significant positive net clinical benefit. Comparing VKA to no treatment showed a lower stroke rate, but a higher ICH rate and therefore no positive net clinical benefit. In NOAC versus VKA treated patients, the rate for stroke was not different, while there was statistically significant lower rate of ICH during NOAC treatment. The net clinical benefit for NOAC treatment was positive, although not statistically significant.

#### *Subgroup analyses*

There were no significant differences between subgroups (Table 5). However, comparing NOACs to VKA, the HR for stroke was lower for female than for male patients (0.68 for female, 1.15 for male). In addition, when comparing VKA to no treatment for stroke, the protective effect was only visible in male patients (HR: 1.06 for female, 0.68 for male). Of interest, age 65-74 years was the most common component of the  $CHA_2DS_2-VASc$  score in low risk patients (59.5%). The results were similar in the age group 65-74 years compared to patients < 65 years with one comorbidity component of the  $CHA_2DS_2-VASc$  score (Table 5).

#### *Additional analyses*

In the new-user active comparator design analysis there was no statistically significant difference in stroke rate between users of NOACs and VKAs ( $HR_{\text{stroke}} 0.85$ ; 95% CI 0.64 – 1.14), but a lower rate for bleeding in NOAC treated patients compared to VKA treated patients ( $HR_{\text{bleed}} 0.80$ ; 95% CI 0.64 – 0.99), which was mainly driven by a lower risk for ICH ( $HR_{\text{ICH}} 0.55$ ; 95% CI 0.37 – 0.81).

None of the falsification endpoints was significantly associated with any of the treatment arms in any comparison (Appendix Table 6). Censoring patients at one year of follow-up yielded similar results. Patients with hypertension and an age below 65 years had the lowest crude rates of stroke and bleeding (Appendix Table 7). In patients with hypertension, the stroke rates were significantly lower in NOAC treated patients compared to untreated patients ( $HR 0.57$ ; 95% CI 0.33 – 0.97). Associations between other treatment strategies and other outcomes in these patients were generally comparable to those obtained in the full population, albeit not reaching statistical significance. The pooled results of the NOAC and VKA treated patients compared to untreated patients showed an association of a lower rate of ischemic stroke ( $HR 0.76$ ; 95% CI 0.62 – 0.92), with a non-significantly higher major bleeding rate ( $HR 1.31$ ; 95% CI 0.93 – 1.85) as well as for ICH ( $HR 1.07$ ; 95% CI: 0.78 – 1.46) and for GIB ( $HR 1.30$ ; 95% CI 0.75 – 2.26).

## Discussion

These observational data from 59 076 patients, newly diagnosed with AF at low stroke risk from Denmark, Norway, Scotland, and the Stockholm region in Sweden, suggest that NOAC treatment may be associated with positive net clinical benefit compared to both VKA and to no treatment, a question that can be tested through a randomised controlled trial. Compared to no treatment, NOAC treatment was associated with a 28% lower rate of stroke, but also a 26% higher rate of bleeding. This higher bleeding rate was not driven by ICH, but by a surplus of GIB in the NOAC treated group. When comparing VKA to no treatment, VKA treatment was associated with a lower rate for strokes, but a higher rate for bleeds, especially ICH, and therefore there was no net clinical benefit when comparing VKA to no treatment. Compared to VKA, NOAC treatment was associated with a 37% lower rate of ICH, with similar rates of strokes and other bleeds (Graphical abstract). However, the absolute rates of events was low at 0.58%/py for strokes and 0.76%/py for bleeds in the entire population and 0.70%/py

for strokes and also 0.70%/py for bleeds among untreated patients. This yielded relatively high NNT-y, although it should be noted that these are the numbers needed to treat for only one year, while treatment with oral anticoagulants is often life-long.

Previous observational studies have assessed the clinical benefit of VKA treatment compared to no treatment in patients with AF at low stroke risk, with conflicting results<sup>5-7</sup>. After the introduction of NOACs, an observational study from Denmark compared the safety and effectiveness of the different NOACs and VKA. However, this study was relatively small, making it difficult to draw conclusions<sup>25</sup>. An observational study from the United States comparing rivaroxaban to VKA treatment showed both a lower risk for stroke and a lower risk for ICH in rivaroxaban treated patients<sup>26</sup>.

Post-hoc analyses of randomised controlled trials comparing NOACs to VKA in low-risk patients show similar results; small differences in stroke reduction, but a substantially lower risk for ICH. In a post-hoc analysis of patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 in the ARISTOTLE trial, the HR for ischemic stroke was 1.13 (95% CI 0.68 – 1.90), and the HR for ICH was 0.45 (95% CI 0.24 – 0.82)<sup>27</sup>. In the RE-LY trial, in patients with a CHADS<sub>2</sub> score of 0-1, dabigatran 150 mg performed better than warfarin for stroke prevention (HR 0.61, 95% CI 0.37 – 0.99), whereas dabigatran 110 mg did not (HR 0.98, 95% CI 0.63 – 1.51), and both markedly reduced the risk for ICH (HR<sub>110</sub> 0.37, 95% CI 0.16 – 0.83; HR<sub>150</sub> 0.37, 95% CI 0.16 – 0.84)<sup>28</sup>. These results are in line with our results, a similar stroke rate with NOAC treatment, but with a lower rate of ICH. The current study adds to the knowledge that NOAC treatment does not substantially increase the rate of an ICH compared to no treatment, while VKA treatment does. This yielded a positive net clinical benefit of treating patients with a NOAC compared to no treatment and compared to VKA treatment.

To the best of our knowledge, we are the first to investigate the question whether low-risk patients would benefit from treatment with a NOAC, a VKA, or no treatment. Prior to the NOAC introduction it was uncertain whether VKA or no treatment should be recommended in low-risk patients. There was already compelling evidence that NOACs are safer and more effective than VKAs in the general AF population, but it has previously not been shown that this would also shift the balance towards a positive net clinical benefit in low-risk patients, indicating that these patients may benefit from being

treated with a NOAC. To put the net clinical benefit findings into context, previous work by Friberg *et al.*<sup>29</sup>, comparing VKA to no treatment using the same definition to calculate the net clinical benefit, found a net clinical benefit of -0.6 for patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0, and 0.0 for a score of 1. In patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2 the net clinical benefit was 1.1 and increased to 11.5 for a score of 9. These numbers can be interpreted as the number of ischemic strokes prevented without causing excess ICH after 100 treatment-years.

In the current study, we performed exploratory analyses to assess the heterogeneity regarding stroke and bleeding risk per component of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score<sup>24</sup>. While the study lacked sample size to assess the net clinical benefit for each component, we found comparable estimates in patients included for hypertension compared to the overall population. Age is a continuous variable, and it is reasonable to believe that its weight gradually increases in the age span of 65-74 years. Future research, in even larger study samples, should further assess the optimal treatment strategy per component of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score.

Our study has some limitations. First, this is not a randomized study and thus no causal conclusions can be drawn from this study. We used IPTW to correct for measured confounders, but residual and unknown confounding will always be a threat to observational studies. The numerically lower rate of ICH in the NOAC group compared to the untreated group is probably a result of this, as well as the markedly increased rate of death in the no treatment group. Near the end of life of a patient, it is likely that treatment is withheld and thus we saw such a markedly increased risk of dying in untreated patients. Therefore, we have not considered the composite which included mortality in the interpretation of our results comparing no treatment to NOAC and VKA treatment. Second, the absolute stroke rate in this study was low, at 0.70%/py in untreated patients, and the estimated absolute NCB was limited which should be considered when considering oral anticoagulant treatment in low-risk AF patients. Third, only one database had access to primary care diagnoses. Since covariates from the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, such as hypertension and diabetes, are often only diagnosed in primary care we might have underestimated the true CHA<sub>2</sub>DS<sub>2</sub>-VASc score and included patients who actually had a higher risk score<sup>15</sup>. We tried to avoid this by adding diagnoses based on

an algorithm that searched for prescriptions for antihypertensive and antidiabetic drugs in the years before the cohort entry date, and validated this procedure in the Stockholm database, which had access to primary care data. Besides the covariates from the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, some patients with AF may also have been missed in only secondary care, which may have introduced some selection bias<sup>30</sup>. However, we performed an additional analysis in which we removed the primary care data from the Stockholm database, and this yielded similar results as the analysis with primary care data. Fourth, we have excluded patients receiving antiplatelet prescriptions, which should be kept in mind when considering the generalizability of the study. However, the absence of patients receiving antiplatelet treatment increases the validity of the comparison between NOAC, VKA, or no treatment in these patients, which is the clinically relevant comparison studied here. Fifth, it is possible that some patients were more prone to healthcare avoidance, which also increases the chance of being untreated, potentially leading to additional residual confounding.

Our study also has some strengths. First, the study relies on data from four countries, which adds to the generalizability of the results. Second, we performed multiple additional analyses which all yielded similar results, indicating that the results in this study are robust to several changes in study design choices. In addition, the number of events per person year were similar to those found in the randomized trials, indicating the validity of the outcomes in our study<sup>27,28</sup>.

In conclusion, in 59 076 patients with AF at low stroke risk from four countries, the absolute rates of both strokes and bleeds were low. These observational data suggest that NOAC treatment may be associated with a positive net clinical benefit compared to no treatment or VKA treatment in patients at low stroke risk, a question that can be tested through a randomised controlled trial. Compared to no treatment, NOAC treatment was associated with a lower stroke rate, without a higher rate of ICH, and compared to VKA treatment, NOAC treatment was associated with similar stroke rate, but a lower ICH rate.

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## **Data availability statement**

Ethical and privacy reasons prohibit sharing of data from all four databases.

## **Disclosures**

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### **Figure Legends**

**Figure 1.** Graphical representation of patient inclusion; starting on top and going down the boxes mean the following. Patients enter cohort at 14 days after their AF diagnosis. The baseline exposure window is 90 days prior to cohort entry date. Patients are excluded if (i) they have claimed a NOAC or VKA in the 365 to 90 days prior to cohort entry; (ii) they have claimed an antiplatelet prescription in the 90 days prior to cohort entry; (iii) they suffered from a major bleed in the 182 days prior to cohort entry; (iv) they have a diagnosis or procedure code for mechanical valves or mitral stenosis in the 5 years prior to cohort entry; and (v) they immigrated in the 5 years prior to cohort entry. Baseline comorbidities were assessed in the 5 years prior to cohort entry. Baseline comedication was assessed in the 182 days prior to cohort entry. Patients were followed from cohort entry until censored.