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CLINICAL RESEARCH
Thrombosis and antithrombotic treatment

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

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Abstract

Aims There is currently no consensus on whether atrial fibrillation (AF) patients at low risk for stroke (one non-sex-related CHA_2DS_2-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 ischaemic stroke was 0.70 per 100 person-years and the rate for a bleed was also 0.70 per 100 person-years. Comparing NOAC with 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 with 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 with 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; 95% CI 0.42–0.94).

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

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Key question

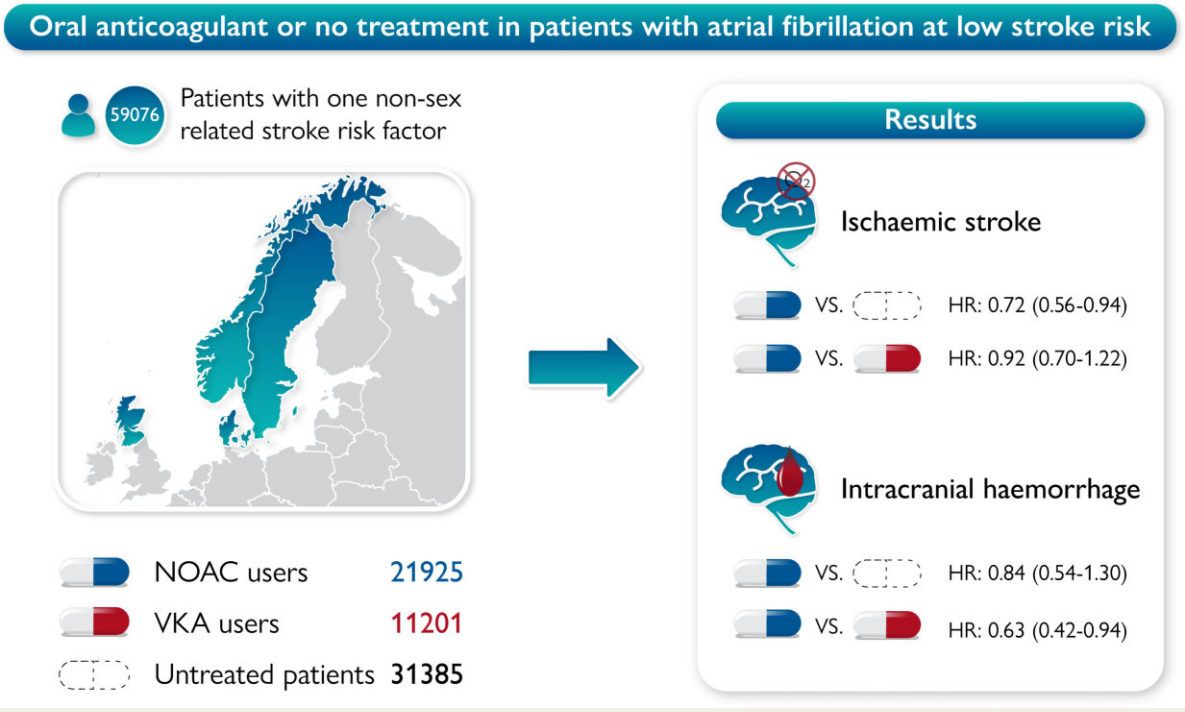
What is the association between anticoagulant treatment and stroke and bleeding rate, in patients with one non-sex-related risk factor for stroke?

Key findings

- Non-vitamin K antagonist oral anticoagulant (NOAC) treatment was associated with a lower stroke rate compared with no treatment.
- Non-vitamin K antagonist oral anticoagulant treatment was associated with a lower rate of intracranial haemorrhage compared with vitamin K antagonist (VKA) treatment.

Take-home message

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



Structured Graphical Abstract In patients with atrial fibrillation at low stroke-risk from Sweden, Denmark, Scotland, and Norway, treatment with a NOAC was associated with a lower stroke rate compared to no treatment and a lower intracranial haemorrhage rate compared to VKA treatment. NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist; HR, hazard ratio; VS, versus.

Keywords Atrial fibrillation • Non-vitamin K antagonist oral anticoagulants • Vitamin K antagonists • Stroke risk

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_2DS_2-VASc score.[1,2] The CHA_2DS_2-VASc score is based on six characteristics adding one point: age (65–74), female sex, congestive heart failure, hypertension, vascular disease, and diabetes, and two characteristics adding two points: age ≥75 and a prior stroke/transient ischaemic attack (TIA)/embolism. If this score, and thus the stroke risk, exceeds a certain level, the benefit of treatment with an oral anticoagulant (OAC) in terms of stroke prevention is considered to outweigh the risks of bleeding associated with treatment. Current guidelines recommend treatment with an OAC if a patient has a CHA_2Ds_2-VASc score of two or higher for males, or three or higher for females.[3,4] For patients at low risk, i.e. having a CHA_2DS_2-VASc score of 1 for males and 2 for females, the guidelines state that treatment with an OAC should be individualized based on net clinical benefit and consideration of patient values and preferences.[3]

Some observational studies have shown a positive net clinical benefit of treatment with vitamin K antagonists (VKA) compared with no treatment or antiplatelet treatment in low-risk patients.[5,6] On the other hand, there have also been studies showing no clinical benefit,[7] and there is a Class IIa recommendation that treatment for patients at low risk can be considered.[8] However, all studies investigating the effects of anticoagulation therapy compared with no

therapy among low-risk patients were conducted prior to the availability of non-vitamin K antagonist OACs (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 with VKA treatment in the overall AF population as documented in randomized clinical trials,[9] as well as in observational studies,[10] 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 with VKA treatment.

Even though trials only included a limited number of patients at low risk,[11–14] the meta-analysis of randomized trials by Ruff *et al.*[9] indicated that the point estimate in patients with a $CHADS_2$ score of 0 or 1 was more in favour of NOAC treatment compared with VKA for both the safety and efficacy outcomes. Because there are currently no data available comparing NOAC with no treatment, and only limited data comparing NOAC with 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.

Materials and 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 Supplementary material online, *Table S1*, including available parameters describing the validity of diagnoses of AF and outcomes.[15–20] 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 1 January 2011 until 31 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_2DS_2-VASc score of 1 and female patients with a CHA_2Ds_2-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 Supplementary material online, 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.

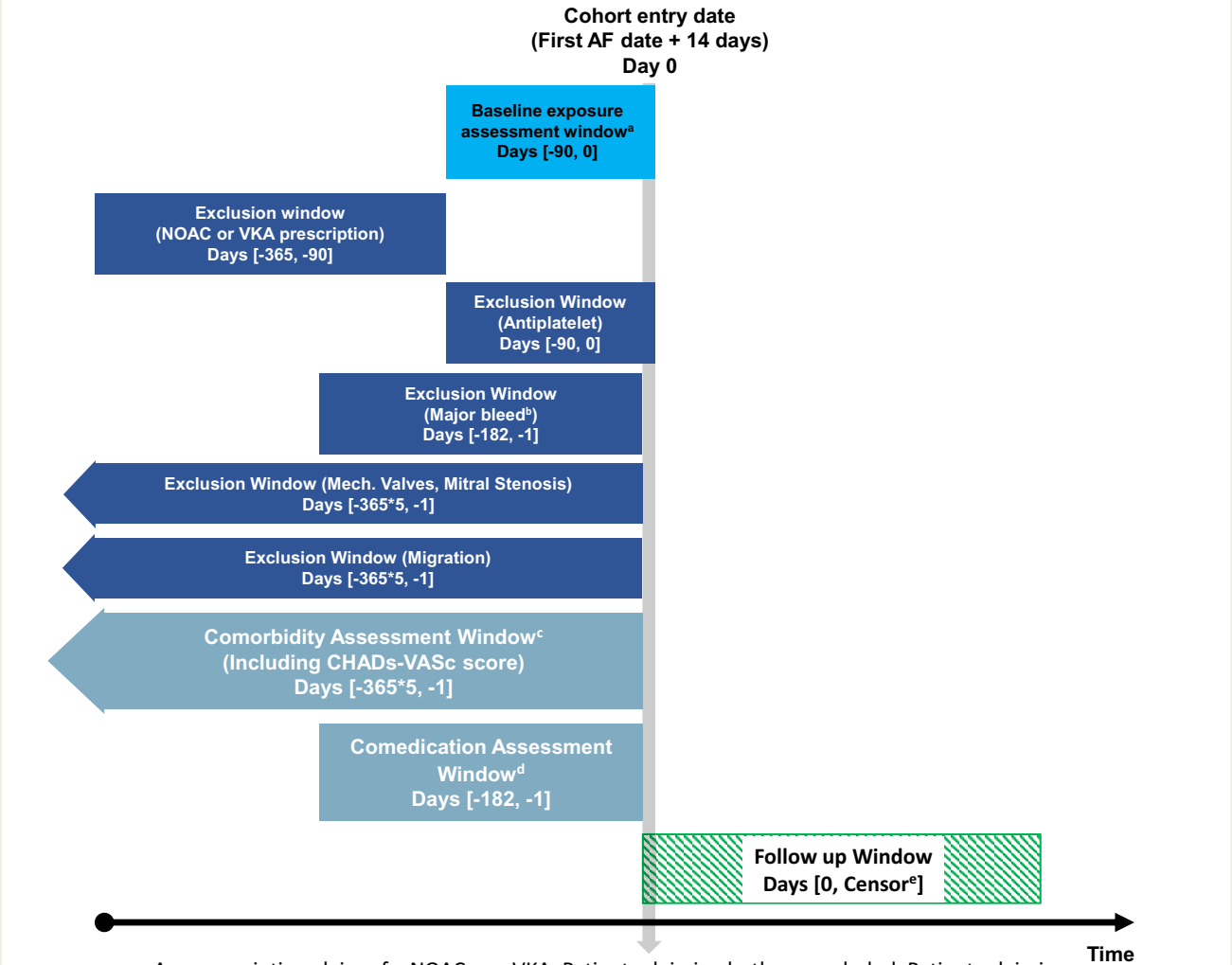
We excluded all patients claiming both a VKA and a NOAC prescription in the 90 days prior to cohort entry date, and patients claiming a prescription for antiplatelet treatment in the 90 days prior to the index date. In addition, we excluded patients who claimed either a VKA or a NOAC between 1 year prior 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 Supplementary material online, *Table S2*). The composite effectiveness outcome included ischaemic or unspecified stroke. The primary safety outcome was any major



a. Any prescription claim of a NOAC or a VKA. Patients claiming both are excluded. Patients claiming none are considered untreated. After the cohort entry date, untreated patients could switch to treated once.
b. The same definition and ICD-10 codes for a major bleed were used as for defining the outcome.
c. Baseline comorbidities are: alcoholism, anaemia, cancer, COPD, dementia, diabetes, heart failure, hypertension, renal disease, stroke/TIA/embolism, and vascular disease
d. Baseline comedications are: aspirin, antidepressants, beta blockers, calcium channel blockers, corticosteroids, diuretics, insulin, NSAIDs, oral diabetic drugs, P2Y12-inhibitors, proton pump inhibitors, RAAS inhibitors, and statins.
e. Censoring at an earliest of: outcome of interest, death, emigration, end of study period, or CHADs-VASc score increase.

Figure 1 Graphical representation of patient inclusion; starting on top and going down the boxes mean the following. Patients enter the cohort at 14 days after their atrial fibrillation diagnosis. The baseline exposure window is 90 days prior to the cohort entry date. Patients are excluded if (i) they have claimed a non-vitamin K antagonist oral anticoagulant or vitamin K antagonist 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.

bleed. The secondary safety outcomes were gastrointestinal bleeds (GIBs) 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 ischaemic stroke and unspecified stroke.

Net clinical benefit

We used two approaches to calculate the net clinical benefit by 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.*,[21] using the following formula:

$$\text{Net clinical benefit} = (\text{ischaemic rate}_{\text{off treatment}} - \text{ischaemic rate}_{\text{on treatment}}) - \text{weight} \times (\text{ICH rate}_{\text{on treatment}} - \text{ICH rate}_{\text{off treatment}}).$$

We used the full ICH endpoint and both ischaemic 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.[21]

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_2DS_2-VASc score. A patient's CHA_2DS_2-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 Supplementary material online, *Table S2* 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_2DS_2-VASc score, were diagnoses of a prior bleed, abnormal liver function, alcohol misuse, anaemia, cancer, chronic obstructive pulmonary disease, dementia, and renal disease (see Supplementary material online, *Table S2* 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 (SMDs) to check whether IPTW yielded comparable cohorts, considering an SMD below 0.1 as indicating satisfactory covariate balance.[22] We calculated the 95% confidence intervals (CIs) 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 1 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 were 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_2DS_2-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 1 year. Fourth, we used a falsification endpoint, which was a composite of acute upper respiratory infection and osteoarthritis,[23] recorded in inpatient secondary care (see Supplementary material online, 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_2DS_2-VASc score.[24] However, due to the 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 OACs compared with 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 Supplementary material online, *Figures S1* and *S2* 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 with 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 65.3 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 1.23, 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 among VKA users. Of the untreated patients, only 38% received a beta-blocker at baseline, compared with 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 (Supplementary material online, *Table S3*).

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 Supplementary material online, *Table S4* 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 Supplementary material online, *Table S5*.

The results from the meta-analyses of all databases showed that NOAC treatment was associated with a lower rate of stroke compared with no treatment (HR_{stroke} 0.72; 95% CI 0.55–0.94; NNT-y: 511), but a higher rate of bleeds (HR_{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_{GIB} 1.48; 95% CI 1.05–2.08; NNT-y: 675), and not by the ICH rate (HR_{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 with no treatment showed tendencies towards a lower stroke rate (HR_{stroke} 0.81; 95% CI 0.59–1.09; NNT-y: 754) and a higher bleeding rate (HR_{bleed} 1.44; 95% CI 0.83–2.50; 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 with 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 with 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 with untreated patients without a higher rate of ICH, yielding a statistically significant positive net clinical benefit. Comparing VKA with no treatment showed a lower stroke rate, but a higher ICH rate and therefore no positive net clinical benefit. In NOAC vs. 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 with 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 with 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 with 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_{stroke} 0.85; 95% CI 0.64–1.14), but a lower rate for bleeding in NOAC-treated patients compared with VKA-treated patients (HR_{bleed} 0.80; 95% CI 0.64–0.99), which was mainly driven by a lower risk for ICH (HR_{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 (Supplementary material online, *Table S6*). Censoring patients at 1 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 (Supplementary material online, *Table S7*). In patients with hypertension, the stroke rates were significantly lower in NOAC-treated patients compared with 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 with untreated patients showed an association of a lower rate of ischaemic 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).

Table 1 Baseline characteristics

	NOAC	VKA	No treatment
Number of patients	21 925 (34%)	11 201 (17%)	31 385 (49%)
Age, years (mean)	65.3	64.2	63.5
Female sex	8380 (38%)	4053 (36%)	11 829 (38%)
HAS-BLED (mean)	1.23	1.25	1.38
NOAC			
Apixaban	10 284 (47%)	—	—
Dabigatran	4975 (23%)	—	—
Edoxaban	220 (1%)	—	—
Rivaroxaban	6446 (29%)	—	—
Comorbidities			
Hypertension	4969 (23%)	2687 (24%)	7325 (23%)
Heart failure	1542 (7%)	1180 (11%)	1601 (5%)
Vascular disease	762 (3%)	563 (5%)	3571 (11%)
Diabetes	557 (3%)	251 (2%)	1113 (4%)
Abnormal liver function	219 (1%)	115 (1%)	911 (3%)
Alcoholism	551 (3%)	342 (3%)	2101 (7%)
Anaemia	436 (2%)	268 (2%)	1732 (6%)
Prior bleed	1119 (5%)	520 (5%)	2056 (7%)
Cancer	2393 (11%)	1073 (10%)	5741 (18%)
COPD	1259 (6%)	710 (6%)	2958 (9%)
Dementia	75 (0%)	25 (0%)	233 (1%)
Renal disease	181 (1%)	252 (2%)	806 (3%)
Baseline medication			
Aspirin[a]	3271 (15%)	2401 (21%)	8297 (26%)
Antidepressant	1810 (8%)	987 (9%)	3717 (12%)
Beta-blocker	14 325 (65%)	7066 (63%)	11 952 (38%)
Calcium channel blocker	3381 (15%)	1884 (17%)	4024 (13%)
Corticosteroid	1687 (8%)	1049 (9%)	3873 (12%)
Diuretic	3769 (17%)	2493 (22%)	4278 (14%)
Insulin	145 (1%)	76 (1%)	365 (1%)
NSAID	3761 (17%)	1907 (17%)	5610 (18%)
Oral antidiabetics	736 (3%)	342 (3%)	898 (3%)
P2Y12 inhibitor[a]	346 (2%)	226 (2%)	1336 (4%)
PPI	3964 (18%)	2042 (18%)	7608 (24%)
RAAS inhibitor	7291 (33%)	3656 (33%)	7436 (24%)
Statin	4726 (22%)	2588 (23%)	7274 (23%)

Characteristics of the patients included in the cohort at the cohort entry date. Patients switching from untreated status to treated status were included twice in this table. NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist; COPD, chronic obstructive pulmonary disease; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; RAAS, renin–angiotensin–aldosterone system.

[a]Aspirin and P2Y12 inhibitor use is measured from Days 180 to 90 prior to the cohort entry date, as patients claiming one of these drugs in the 90 days prior to the cohort entry date were excluded from the cohort.

Table 2 Treatment per database

	Stockholm	Denmark	Norway	Scotland
Untreated	4115 (51%)	8962 (39%)	9969 (48%)	8339 (66%)
VKA	1622 (20%)	4348 (19%)	2947 (14%)	2284 (18%)
NOAC	2389 (29%)	9592 (42%)	7927 (38%)	2017 (16%)
Apixaban	1613 (68%)	2989 (31%)	4413 (56%)	1269 (63%)
Dabigatran	477 (20%)	2857 (30%)	1570 (20%)	71 (4%)
Edoxaban	5 (%)	147 (2%)	63 (1%)	5 (%)
Rivaroxaban	294 (12%)	3599 (38%)	1881 (24%)	672 (33%)

The number of patients in the different treatment arms per database. Patients switching from untreated status to treated status were included twice in this table. NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist.

Table 3 Crude event rates

Follow-up time (years)	NOAC		VKA		Untreated	
	29 801		17 444		27 230	
	n events	IR (%/year)	*n* events	IR (%/year)	*n* events	IR (%/year)
Stroke	155	0.52	87	0.50	190	0.70
Bleed	231	0.78	144	0.83	191	0.70
ICH	54	0.18	43	0.25	49	0.18
GIB	108	0.36	58	0.33	84	0.31
Stroke/bleed/death	857	2.88	528	3.03	2607	9.57

The number of events per treatment arm and the corresponding incidence rate, given in the number of events per 100 person-years (%/py). NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist; IR, incidence rate; ICH, intracranial haemorrhage; GIB, gastrointestinal bleed.

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 with both VKA and to no treatment, a question that can be tested through a randomized controlled trial. Compared with 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 with 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 with no treatment. Compared with VKA, NOAC treatment was associated with a 37% lower rate of ICH, with similar rates of strokes and other bleeds (*Structured Graphical Abstract*). However, the absolute rates of events were 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 1 year, while treatment with OACs is often lifelong.

Previous observational studies have assessed the clinical benefit of VKA treatment compared with no treatment in patients with AF at low stroke risk, with conflicting results.[5–7] 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.[25] An observational study from the USA comparing rivaroxaban with VKA treatment showed both a lower risk for stroke and a lower risk for ICH in rivaroxaban-treated patients.[26]

Post hoc analyses of randomized controlled trials comparing NOACs with 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_2DS_2-VASc score of 1 in the ARISTOTLE trial, the HR for ischaemic stroke was 1.13 (95% CI 0.68–1.90), and the HR for ICH was 0.45 (95% CI 0.24–0.82).[27] In the RE-LY trial, in patients with a $CHADS_2$ 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_{110} 0.37, 95% CI 0.16–0.83; HR_{150} 0.37, 95% CI 0.16–0.84).[28] These results are in line with our results, a similar stroke rate with NOAC treatment, but with a lower rate of ICH. The

Table 4 Estimated hazard ratios and net clinical benefits from the different associations

	NOAC vs. no treatment		VKA vs. no treatment		NOAC vs. VKA	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Main analysis						
Stroke	0.63 (0.41–0.98)	0.72 (0.56–0.94)	0.76 (0.59–0.99)	0.81 (0.59–1.09)	0.94 (0.72–1.24)	0.92 (0.70–1.22)
Bleed	1.08 (0.88–1.31)	1.26 (1.00–1.58)	1.30 (0.89–1.90)	1.44 (0.83–2.50)	0.82 (0.67–1.02)	0.85 (0.69–1.06)
GIB	1.20 (0.88–1.62)	1.48 (1.05–2.08)	1.22 (0.64–2.34)	1.20 (0.62–2.32)	0.95 (0.69–1.33)	1.00 (0.72–1.39)
ICH	0.94 (0.64–1.39)	0.84 (0.54–1.30)	1.41 (0.94–2.13)	1.37 (0.88–2.14)	0.68 (0.45–1.01)	0.63 (0.42–0.94)
Stroke/bleed/death	0.32 (0.29–0.34)	0.45 (0.41–0.50)	0.38 (0.28–0.50)	0.50 (0.41–0.62)	0.85 (0.67–1.08)	0.87 (0.68–1.11)
Net clinical benefit						
ICH × 1	0.31 (0.02–0.75)	0.24 (0.06–0.48)	0.08 (−0.08 to 0.28)	0.05 (−0.12 to 0.29)	0.12 (−0.05 to 0.33)	0.15 (−0.02 to 0.38)
ICH × 1.5	0.32 (0.01–0.78)	0.25 (0.05–0.54)	0.04 (−0.13 to 0.27)	0.02 (−0.17 to 0.29)	0.16 (−0.03 to 0.42)	0.21 (0.01–0.48)
ICH × 2	0.32 (0.01–0.79)	0.27 (0.04–0.59)	0.01 (−0.19 to 0.26)	−0.01 (−0.23 to 0.29)	0.21 (−0.02 to 0.52)	0.26 (0.02–0.61)
Time-varying analysis						
Stroke	0.77 (0.62–0.96)	0.75 (0.59–0.95)	0.74 (0.57–0.98)	0.84 (0.62–1.14)	1.00 (0.74–1.35)	1.00 (0.73–1.36)
Bleed	1.12 (0.93–1.35)	1.31 (1.06–1.63)	1.31 (1.05–1.64)	1.53 (0.95–2.47)	0.85 (0.68–1.06)	0.87 (0.69–1.09)
GIB	1.32 (0.99–1.75)	1.59 (1.16–2.18)	1.07 (0.75–1.54)	1.10 (0.74–1.63)	1.18 (0.83–1.69)	1.22 (0.85–1.75)
ICH	0.94 (0.65–1.35)	0.89 (0.60–1.33)	1.38 (0.91–2.10)	1.39 (0.88–2.18)	0.63 (0.41–0.99)	0.62 (0.40–0.97)
Stroke/bleed/death	0.28 (0.25–0.30)	0.37 (0.34–0.41)	0.29 (0.26–0.33)	0.38 (0.33–0.43)	0.94 (0.82–1.07)	0.96 (0.84–1.10)
Net clinical benefit						
ICH × 1	0.15 (0.02–0.36)	0.20 (0.03–0.41)	0.19 (−0.07 to 0.33)	0.02 (−0.14 to 0.26)	0.10 (−0.07 to 0.34)	0.11 (−0.07 to 0.35)
ICH × 1.5	0.14 (0.01–0.38)	0.21 (0.02–0.45)	0.19 (−0.12 to 0.31)	−0.01 (−0.19 to 0.25)	0.16 (−0.05 to 0.46)	0.16 (−0.05 to 0.47)
ICH × 2	0.13 (0.01–0.42)	0.22 (0.01–0.49)	0.20 (−0.17 to 0.31)	−0.05 (−0.25 to 0.25)	0.21 (−0.04 to 0.58)	0.22 (−0.04 to 0.59)

Estimated hazard ratios and 95% confidence intervals resulting from the meta-analysis comparing the different treatment arms and the different outcomes. The upper half of the table shows the results from the main analysis, and the lower half of the table shows the results from the time-varying analysis. The estimated net clinical benefit is calculated using the formula in the text and can be interpreted as how many strokes are prevented without causing excess intracranial haemorrhages after 100 treatment-years. NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist; GIB, gastrointestinal bleed; ICH, intracranial haemorrhage.

current study adds to the knowledge that NOAC treatment does not substantially increase the rate of an ICH compared with no treatment, while VKA treatment does. This yielded a positive net clinical benefit of treating patients with a NOAC compared with no treatment and compared with VKA treatment.

To the best of our knowledge, we are the first to investigate the question of 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.*,[29] comparing VKA with 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_2DS_2-VASc score of 0, and 0.0 for a score of 1. In patients with a CHA_2DS_2-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 ischaemic 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_2DS_2-VASc score.[24] 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 with 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_2DS_2-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 with the untreated group is probably a result of this, as well as the markedly increased rate of death in the no treatment group.

Table 5 Stratified results

	NOAC vs. no treatment	*P* for interaction	VKA vs. no treatment	*P* for interaction	NOAC vs. VKA	*P* for interaction
Stroke		0.591		0.140		0.071
Female	0.65 (0.43–0.98)		1.06 (0.67–1.68)		0.68 (0.44–1.06)	
Male	0.57 (0.29–1.13)		0.68 (0.46–1.00)		1.15 (0.80–1.66)	
Bleed		0.179		0.877		0.337
Female	1.54 (1.07–2.22)		1.37 (0.89–2.11)		0.98 (0.67–1.42)	
Male	1.12 (0.84–1.49)		1.43 (1.06–1.93)		0.78 (0.6–1.02)	
Stroke		0.984		0.979		0.404
<65 years	0.58 (0.26–1.30)		0.81 (0.49–1.36)		1.15 (0.67–1.95)	
≥65 years	0.73 (0.54–1.00)		0.81 (0.56–1.16)		0.88 (0.63–1.22)	
Bleed		0.471		0.577		0.980
<65 years	1.42 (0.95–2.12)		1.26 (0.82–1.94)		0.86 (0.58–1.28)	
≥65 years	1.19 (0.90–1.56)		1.47 (1.08–1.99)		0.85 (0.66–1.10)	
Stroke		0.784		0.570		0.398
Has low	0.73 (0.53–1.01)		0.87 (0.60–1.26)		0.84 (0.60–1.19)	
Has high	0.50 (0.22–1.13)		0.73 (0.44–1.20)		1.08 (0.68–1.73)	
Bleed		0.815		0.172		0.270
Has low	1.25 (0.92–1.70)		1.62 (1.17–2.24)		0.77 (0.58–1.01)	
Has high	1.19 (0.85–1.65)		1.08 (0.54–2.14)		0.98 (0.70–1.38)	

Hazard ratios from the meta-analyses of the stratified analyses. NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist; Has low, HAS-BLED score of 0 or 1; Has high, HAS-BLED score above 1.

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 with 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 net clinical benefit was limited which should be considered when considering OAC treatment in low-risk AF patients. Third, only one database had access to primary care diagnoses. Since covariates from the CHA_2DS_2-VASc score, such as hypertension and diabetes, are often only diagnosed in primary care we might have underestimated the true CHA_2DS_2-VASc score and included patients who actually had a higher risk score.[15] 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_2DS_2-VASc score, some patients with AF may also have been missed in only secondary care, which may have introduced some selection bias.[30] 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 was similar to those found in the randomized trials, indicating the validity of the outcomes in our study.[27,28]

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 with no treatment or VKA treatment in patients at low stroke risk, a question that can be tested through a randomized controlled trial. Compared with no treatment, NOAC treatment was associated with a lower stroke rate, without a higher rate of ICH, and compared with VKA treatment, NOAC treatment was associated with a similar stroke rate, but a lower ICH rate.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

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

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