ESC European Society of Cardiology

European Heart Journal (2018) **39**, 453–460
doi:10.1093/eurheartj/ehx579

Less dementia with oral anticoagulation in atrial fibrillation

Leif Friberg* and Mårten Rosenqvist

Department of Clinical Sciences, Karolinska Institutet at Danderyd University Hospital, Storskogsvägen 5, SE-167 65 Stockholm, Sweden

Received 6 March 2017; revised 6 July 2017; editorial decision 21 September 2017; accepted 27 September 2017; online publish-ahead-of-print 24 October 2017

See page 461 for the editorial comment on this article (doi: 10.1093/eurheartj/ehx649)

Aims The association between atrial fibrillation (AF) and dementia is well documented, but it is not clear if oral anticoagulant treatment offers protection. The aim of the study is therefore to compare the incidence of new dementia in patients with AF with and without oral anticoagulants, and to explore if there is a difference between novel anticoagulants and warfarin in this respect.

Methods and results Retrospective registry study of all patients with hospital diagnosis of AF and no previous diagnosis of dementia in Sweden between 2006 and 2014. Propensity score matching, falsification endpoints, and analyses according to intention to treat as well as on-treatment principles were used. The study included 444 106 patients and over 1.5 million years at risk. Patients on anticoagulant treatment at baseline was associated with 29% lower risk of dementia than patients without anticoagulant treatment [hazard ratio (HR) 0.71, 95% confidence intervals (95% CI) 0.68–0.74] and 48% lower risk analysed on treatment (HR 0.52, 95% CI 0.50–055). Direct comparison between new oral anticoagulants and warfarin showed no difference (HR 0.97, 95% CI 0.67–1.40).

Conclusion The risk of dementia is higher without oral anticoagulant treatment in patients with AF. This suggests that early initiation of anticoagulant treatment in patients with AF could be of value in order to preserve cognitive function.

Keywords Atrial fibrillation • Dementia • Oral anticoagulation

Introduction

It is well known that atrial fibrillation (AF) carries an increased risk for stroke,[1] and that this risk can be significantly reduced by oral anticoagulation (OAC).[2] The association between AF and dementia is also well documented,[3–5] but it is not clear if AF-related dementia can be prevented by OAC treatment. The thought being that, if OAC protects against large emboli which causes stroke, OAC treatment also ought to protect against small emboli which causes microinfarctions that eventually lead to cognitive deterioration. Imaging studies have shown that structural cerebral changes are common in patients with AF even when there is no history of cerebral infarction.[6,7]

A recent systematic review of 19 studies including 15 876 patients suggested that OAC treatment may be associated with cognitive decline over time, but the evidence was inconclusive.[8] One study reported an inverse correlation between the quality of warfarin treatment and incidence of dementia.[9] Another study reported higher risk of dementia in warfarin treated patients with AF, than in patients with other indications for warfarin treatment.[10] A recent study showed lower incidence of dementia among patients treated with non-vitamin K oral anticoagulants (NOAC) than among patients treated with warfarin.[11]

A randomized placebo controlled trial with this purpose would of course be ideal to answer this question, but such a study will never be done due to ethical reasons; it is not possible to treat AF patients at risk of stroke with placebo. A study randomizing AF patients to either dabigatran or warfarin which has incident dementia as primary endpoint was launched earlier this year and is expected to be completed in 2021 (ClinicalTrials.gov Identifier NCT03061006).

Our aim was to study the incidence of dementia among AF patients with and without OAC treatment. We also wanted to investigate if there is a difference between novel anticoagulants and warfarin in this respect.

* Corresponding author. Tel: +4 670 173 0519, Email: leif.friberg@ki.se

Methods

This is a retrospective cohort study using data from the Swedish Patient register and the Dispensed Drug register, cross-linked by individual civic registration numbers.

The Patient register carries detailed information about all hospitalizations in the country since 1987, and about all visits in specialized open care since 2001. Laboratory values and results of examinations are not available.

The Drug register stores details about all dispensed prescriptions in Sweden since 1 July 2005. All pharmacies are required to participate by law, and information is transferred electronically whenever a drug is dispensed. It does not include information about prescriptions that have not been dispensed, drugs used during short-time hospital stay and over-the-counter drugs.

These Swedish registers have frequently been used for epidemiological and outcome studies, and the general quality of data are good according to validation studies.[12–17]

Identification of study population

All individuals with a diagnosis of AF during 2006–14 were identified from the Patient register. Individuals with a previous diagnosis of dementia were excluded. No other exclusions were made. Diagnoses given, and prescriptions filled, up to 30 days after the first contact with AF during the inclusion period were considered as baseline conditions. Subsequently, time at risk was counted from Day 31. The codes used to define dementia and comorbidity are listed in Supplementary material online, *Table S1*. The Patient register was also used to detect incident new dementia during follow-up.

Statistical methods

Baseline characteristics are presented descriptively and differences tested with Wilcoxon's signed rank test and Pearson's χ^2 test as appropriate. Incidences are reported as number of newly diagnosed dementia per 100 patient years at risk, with 95% confidence intervals (95% CI).

Propensity scores for the likelihood of any oral anticoagulant treatment at baseline were obtained by logistic regression. The cofactors used in the regression are listed in a footnote to Supplementary material online, *Table S2*. Another set of propensity scores were obtained for the likelihood of obtaining a NOAC rather than warfarin for patients using an oral anticoagulant at baseline.

Patients were matched according to propensity scores in order to produce as similar cohorts as possible on measurable cofactors. Matching was made 1:1 without replacement and with caliper of 0.000001. The matched cohorts were compared on the individual variables in the search of remaining imbalances. Cofactors that had not been balanced by this process (see Supplementary material online, *Tables S2* and *S3*) were introduced as cofactors in subsequent multivariable Cox regression procedures used to evaluate the association between treatment and incident dementia.

The main analyses were performed in analogy to the intention to treat principle, i.e. analyses were made according to each patient's treatment at baseline regardless of subsequent changes. We also made analyses in analogy with the on-treatment principle, whereby we restricted the analysis to propensity score matched patients with either access to anticoagulants covering 80% of the time at risk or non-OAC patients who never were exposed to OAC during follow-up.

For determination of the number of days NOACs would last, we used the information about dispensed quantities and the standard dose for the strength of the drug. For warfarin, which has no fixed dose, we assumed that all days between two subsequent purchases were days on treatment as long as the interval did not exceed 6 months. If it exceeded 6 months, or if there were no more purchases, treatment was assumed to have stopped after 3 months.

In order to further assess the likelihood of confounding by indication we used four falsification endpoints[18] which we considered unlikely to be causally affected by anticoagulant treatment; influenza, hospitalization for fall accident, new diagnosis of diabetes, and new diagnosis of chronic obstructive pulmonary disease. The rationale for using a falsification endpoint is that if an association is found between a treatment and a falsification endpoint, and if it can be postulated that the treatment is not the cause of the outcome, the result has to be due to unknown factor(s), which the analysis was unable to adjust for. A finding of an association between OAC treatment and these falsification endpoints would therefore indicate the presence of unaccounted confounding and the strength of that association would indicate to which extent a finding of an association between OAC treatment and dementia is a result of confounding.

P-values <0.05 were considered significant. All analyses were performed by using Stata version 14.0 (Stata Corp., 4905 Lakeway Dr, College Station TX 77856, USA). The Forest plots were produced in R 3.3.0.

The study was approved by the local ethics committee (approvals # 2014/894-31, #2014/876-31/4, #2014/1065-31) and conformed to the Declaration of Helsinki.

Results

The number of patients identified with a diagnosis of AF during the inclusion period was 456 960. Among these, 12 854 already had a diagnosis of dementia and were therefore excluded, leaving 444 106 patients for the study. During over 1.5 million years of follow-up, 26 210 patients received a new diagnosis of dementia (1.73 per 100 years at risk).

At baseline, 241 160 patients (54.3%) were without oral anticoagulant treatment (OAC), 190 570 patients (42.9%) used warfarin, 199 patients (0.04%) used phenprocuomon, and 12 916 patients (2.9%) used a NOAC.

Patients who developed dementia were older and had more comorbidity than patients who did not develop dementia (*Table 1*). The strongest predictors for dementia were age [hazard ratio (HR) per decade 2.19, 95% CI 2.16–2.22], Parkinson's disease (2.46, 95% CI 2.25–2.69), absence of OAC treatment (HR 2.08, 95% CI 1.73–2.53), and alcohol abuse (HR 1.53, 95% CI 1.41–1.66) (*Table 2*).

Anticoagulation vs. no anticoagulation

The incidence rate of dementia among patients with OAC was lower than among patients without OAC (1.14 vs. 1.78 per 100 patient

Table 1 Baseline characteristics of the full cohort

	Developed dementia		Oral anticoagulant	
	During follow-up		At baseline	
	Yes (n = 26 210)	No (n = 417 896)	Yes (n = 202 946)	No (n = 241 160)
Age, mean (years)	81.4	74.4	73.7	75.7
Female sex (%)	53.5	44.1	40.6	48.1
Years since first AF diagnosis, mean (years)	2.14	1.64	1.88	1.50
CHA_2DS_2-VASc risk factors				
Score, mean	4.20 points	3.42 points	3.43 points	3.49 points
Heart failure (%)	33.0	29.9	31.0	29.2
Hypertension (%)	51.8	50.4	53.2	48.1
Age 65–74 years (%)	13.1	25.0	30.2	19.4
Diabetes (%)	19.6	18.1	19.2	17.3
Stroke/systemic emboli/TIA (%)	27.8	20.5	21.9	20.1
Vascular disease (%)	23.0	23.1	21.1	24.8
Age ≥ 75 years (%)	85.4	55.1	52.0	61.0
Additional HASBLED bleeding risk factors				
Score, mean	2.61 points	2.26 points	2.09 points	2.43 points
Renal disease (%)	3.4	4.6	3.4	5.4
Liver disease (%)	0.9	1.4	0.9	1.8
Stroke (bleeding or ischaemic) (%)	22.5	16.1	16.1	16.7
Prior bleed or anaemia (%)	17.4	16.0	12.2	19.3
Age > 65 years (%)	98.4	80.1	82.1	80.4
Antiplatelet drug/NSAID (%)	64.7	54.3	39.7	67.7
Alcohol (%)	2.3	2.9	1.8	3.7
Other comorbidity/history				
Ischaemic stroke (%)	19.3	14.1	14.4	14.4
Systemic embolism (%)	1.5	1.3	1.6	1.1
TIA (%)	8.5	6.2	7.4	5.5
Venous thrombo-embolism (%)	4.7	4.9	6.3	3.7
Intracranial bleed (%)	3.5	2.5	1.7	3.3
Intracerebral (%)	1.4	1.1	0.7	1.5
Subarachnoidal (%)	0.4	0.3	0.2	0.4
Subdural or traumatic (%)	1.6	1.1	0.7	1.5
Myocardial infarction (%)	18.3	18.3	16.5	19.8
Peripheral artery disease (%)	6.8	7.3	6.8	7.7
Mitral stenosis (%)	0.4	0.5	0.8	0.3
Mechanical heart valve (%)	0.5	0.7	1.4	0.1
Other valvular disease (%)	9.9	10.6	13.2	8.3
Pacemaker/ICD (%)	8.5	7.4	8.7	6.5
Hypothyroidism (%)	6.6	5.5	5.0	6.0
Thyrotoxicosis (%)	1.8	1.6	1.7	1.6
Chronic obstructive pulmonary disease (%)	6.6	7.7	6.8	8.3
Parkinson's disease (%)	1.9	0.7	0.6	1.0
Cancer (%)	8.9	11.9	9.3	13.7
Frequent falls (%)	9.1	5.7	3.4	8.0
Medicine use at baseline				
ACE inhibitor or ARB (%)	46.5	49.0	57.9	41.2
Statin (%)	28.7	31.6	37.9	26.0
Beta blocker (%)	67.4	70.7	79.1	63.2
Class 1 or 3 antiarrhythmic (%)	6.4	7.6	7.9	7.2
Digoxin (%)	25.3	18.2	22.4	15.4
Diuretic (%)	55.1	48.3	50.6	47.0
Vitamin K antagonist (%)	35.8	43.2	93.6	—
NOAC (%)	0.4	3.1	6.4	—
Acetacetylic acid (%)	58.0	45.7	30.5	59.7

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; ICD, implantable cardioverter/defibrillator; NSAID, non-steroidal anti-inflammatory drug.

Table 2 Assocation between cofactors and risk of dementia among 444 106 patients with atrial fibrillation and no previous diagnosis of dementia

	Incidence rate Per 100 years at risk (95% CI)	Multivariable HR (95% CI)
Age		
<65 years	0.11 (0.10–0.12)	Reference
65–74 years	0.79 (0.76–0.82)	7.75 (7.00–8.58)
≥75 years	3.26 (3.22–3.31)	28.04 (25.43–30.93)
Per incremental decade	—	2.19 (2.16–2.22)
Gender		
Male	1.39 (1.37–1.42)	Reference
Female	2.19 (2.15–2.22)	1.04 (1.02–1.07)
Years since first AF diagnosis		
0–1	1.66 (1.63–1.68)	Reference
1–3	1.58 (1.51–1.66)	0.97 (0.92–1.02)
3–5	1.75 (1.68–1.83)	1.03 (0.98–1.07)
≤5	2.04 (1.99–2.10)	1.09 (1.06–1.13)
CHA_2DS_2-VASc risk factors		
Heart failure	2.34 (2.30–2.39)	1.17 (1.14–1.21)
Hypertension	1.93 (1.90–1.97)	1.00 (0.98–1.03)
Diabetes	2.15 (2.09–2.21)	1.22 (1.18–1.26)
Stroke/systemic emboli/TIA	2.82 (2.76–2.89)	1.34 (1.30–1.38)
Vascular disease	2.09 (2.04–2.15)	0.94 (0.91–0.97)
Additional HASBLED bleeding risk factors		
Renal disease	2.39 (2.23–2.55)	1.01 (0.94–1.08)
Liver disease	1.49 (1.31–1.69)	0.91 (0.80–1.03)
Stroke (bleeding or ischaemic)	3.03 (2.95–3.10)	1.48 (1.37–1.59)
Prior bleeding hospitalization	2.59 (2.51–2.67)	1.04 (1.00–1.07)
Antiplatelet drug/NSAID	2.11 (2.08–2.14)	1.07 (1.04–1.10)
Alcohol	1.53 (1.41–1.66)	1.53 (1.41–1.66)
Other comorbidity/history		
Ischaemic stroke	2.95 (2.87–3.04)	1.33 (1.29–1.37)
Systemic embolism	2.57 (2.32–2.84)	1.15 (1.04–1.27)
TIA	2.60 (2.49–2.71)	1.15 (1.10–1.20)
Venous thromboembolism	2.06 (1.95–2.18)	1.05 (0.99–1.11)
Intracranial bleed	3.27 (3.06–3.48)	1.20 (1.12–1.29)
Intracerebral	3.18 (2.87–3.52)	1.19 (1.07–1.32)
Subarachnoidal	2.24 (1.82–2.74)	1.04 (0.84–1.28)
Subdural or traumatic	3.54 (3.21–3.89)	1.14 (1.03–1.26)
Myocardial infarction	2.08 (2.02–2.14)	0.94 (0.91–0.97)
Peripheral artery disease	2.18 (2.08–2.28)	1.00 (0.96–1.05)
Mitral stenosis	1.31 (1.09–1.59)	0.95 (0.78–1.15)
Mechanical heart valve	0.97 (0.82–1.16)	1.21 (1.01–1.44)
Other valvular disease	1.71 (1.64–1.78)	0.96 (0.92–1.00)
Pacemaker/ICD	1.90 (1.82–1.98)	0.92 (0.88–0.96)
Hypothyroidism	2.39 (2.28–2.51)	1.00 (0.95–1.05)
Thyrotoxicosis	1.96 (1.80–2.15)	1.12 (1.02–1.22)
Chronic obstructive pulmonary disease	2.07 (1.97–2.17)	0.93 (0.88–0.97)
Parkinson's disease	6.43 (5.89–7.02)	2.46 (2.25–2.69)
Cancer	1.80 (1.73–1.88)	0.84 (0.80–0.87)
Frequent falls	4.44 (4.26–4.62)	1.42 (1.36–1.49)
Medicine use at baseline		
ACE inhibitor or ARB	1.69 (1.66–1.72)	0.86 (0.84–0.89)
Statin	1.50 (1.47–1.54)	0.85 (0.82–0.87)
Beta blocker	1.64 (1.61–1.66)	0.88 (0.86–0.90)
Class 1 or 3 antiarrhythmic	0.99 (0.95–1.04)	0.72 (0.68–0.75)
Digoxin	2.33 (2.27–2.39)	1.17 (1.13–1.20)
Diuretic	2.21 (2.17–2.24)	0.98 (0.96–1.01)
Vitamin K antagonist	1.26 (1.24–1.29)	0.62 (0.60–0.64)
NOAC	1.13 (0.93–1.36)	0.48 (0.40–0.58)
Acetacetylic acid	2.28 (2.24–2.31)	1.15 (1.12–1.18)
All patients	1.73 (1.71–1.75)	—

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; ICD, implantable cardioverter/defibrillator; NSAID, non-steroidal anti-inflammatory drug.

years at risk, $P < 0.001$) (*Figure 1*). This difference was present in all subgroups (*Figure 2*).

Patients with OAC at baseline were younger and healthier than patients without OAC, e.g. regarding previous hospitalization with bleeding diagnoses (12.2% vs. 19.3%, $P < 0.001$), intracranial bleeds (1.7% vs. 3.3%, $P < 0.001$), and recurrent fall accidents (3.4% vs. 8.0%, $P < 0.001$). See Supplementary material online, *Tables S2 and S3* for a detailed account of these differences.

Propensity score matching was applied, and two cohorts of 80 948 patients with and without oral anticoagulant treatment were created, which were similar on observable cofactors (see Supplementary material online, *Table S2*). Comparison of these cohorts showed that patients with OAC treatment had 29% lower risk of dementia than patients without OAC treatment at baseline (HR 0.71, 95% CI 0.68–0.74) (*Figure 2*, see Supplementary material online, *Table S5*). There was an interaction between OAC and the time since the first diagnosis of AF suggesting that the benefit of treatment may be larger if initiated early rather than late.

The percentage of time at risk with access to an oral anticoagulant was 72% in the OAC group and 25% in the group without OAC. Thus, there was substantial crossover between treatment groups. Data were therefore re-analysed according to the on-treatment principle excluding patients in the non-OAC cohort who later received OAC, and OAC patients with who had collected less OAC than needed to cover at least 80% of the time at risk. This accentuated the apparent benefit of OAC so that OAC patients now had 48% lower risk of dementia than non-OAC patients (HR 0.52, 95% CI 0.50–0.55) (*Figure 3*, see Supplementary material online, *Table S6*).

We found no significant association between OAC treatment and the falsification endpoints influenza (HR 0.87, 95% CI 0.70–1.06) and fall accidents (HR 0.98, 95% CI 0.95–1.00). For incident diabetes (HR 1.09, 95% CI 1.04–1.14) and chronic obstructive pulmonary disease (HR 1.08, 95% CI 1.03–1.15), there were week associations with OAC treatment, but in opposite direction to that of dementia.

NOAC vs. warfarin

When NOACs and warfarin were compared to no treatment, the risk of dementia appeared to be lower with NOAC (HR 0.48, 95% CI 0.40–0.58) than with warfarin (HR 0.62, 95% CI 0.60–0.64) (*Table 2*).

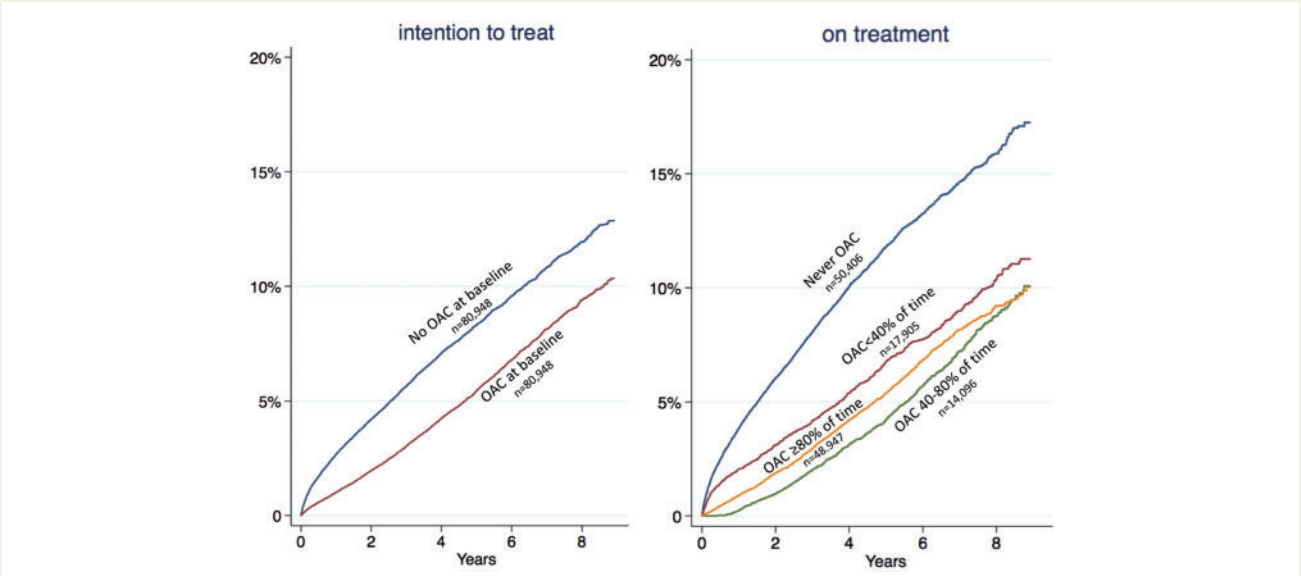

Figure 1 Unadjusted incidence of dementia in relation to oral anticoagulant treatment among 161 896 patients with atrial fibrillation and no previous diagnosis of dementia who were propensity score matched for the likelihood of oral anticoagulation treatment at baseline.

This was also true in the on-treatment analysis (NOAC HR 0.30, 95% CI 0.22–0.42 vs. VKA HR 0.53, 95% CI 0.50–0.56).

However, the NOAC and the VKA group differed in several of the baseline characteristics as can be seen from Supplementary material online, *Tables S3 and S4*. A direct comparison between NOACs and warfarin, made after another propensity score matching for the likelihood of either treatment, showed no difference regarding dementia risk (HR 0.97, 95% CI 0.67–1.40) (*Figure 4*).

The falsification endpoints showed no significant associations between NOAC use rather than warfarin use and influenza (HR 0.30, 95% CI 0.03–2.63), fall accidents (HR 0.99, 95% CI 0.79–1.24), incident diabetes (0.92, 95% CI 0.70–1.20), or chronic obstructive pulmonary disease (HR 0.80, 95% CI 0.56–1.13).

Discussion

In this register-based study of nearly half a million patients with AF, we found that OAC treatment was associated with 29% lower dementia risk in the intention to treat analysis, and 48% lower dementia risk in the on-treatment analysis.

There was a considerable crossover between the treatment groups, defined by treatment at baseline, which acts to attenuate associations between treatment and outcome. It is therefore natural that the association became much stronger when the analysis was made according to the on-treatment principle. It must however be pointed out that the information about drug exposure from dispensed prescriptions alone is inexact, especially regarding warfarin where individual dosages vary widely. The frequency of refills is a surrogate measure that is apt to overestimate the true exposure in patients with short follow-up and few dispensations. Exclusion of patients in the non-OAC cohort who later received OAC is however very reliable, since all dispensed OAC purchases in the country are recorded. Thus, the on-treatment analysis may underestimate the relation between treatment and outcome due to attenuation.

Absence of OAC was an independent risk factor for dementia along with more established risk factors such as age, Parkinson's disease, earlier stroke, and alcohol abuse. The benefit of OAC treatment appeared to be more pronounced among patients were treatment had been initiated early after the first diagnosed AF episode suggesting a dose response relationship between unprotected time in AF and development of dementia. Likewise there was a trend towards more benefit from treatment in patients with higher CHA_2DS_2-VASc scores suggesting that microembolization indeed might be a cause of dementia in AF patients.

Cerebral microbleeds are common in AF patients irrespective of whether they are treated with OAC or not.[19] It has been suggested that NOACs would be a better choice for prevention of dementia than warfarin due to the fact that these consistently show a lower rate of intracerebral bleeding.[20] We could not confirm earlier observations that the risk of dementia should be lower with NOACs than with warfarin.[11]

Results from Swedish patients enrolled in clinical trials[21,22] as well as non-selected patients in general practice or at anticoagulation clinics[23,24] have repeatedly shown mean time in therapeutic range (TTR) to be well above 70%. It is therefore possible that NOACs may offer better protection than warfarin in places with less well-managed warfarin treatment than in Sweden.

Our study showed that only 45% of Swedish AF patients collected an oral anticoagulant in a pharmacy within a month after AF had been diagnosed for the first time. Our findings regarding dementia protection may provide a second argument for initiation of treatment among untreated AF-patients. Since the time from diagnosis to start of treatment appears to be an independent risk factor, early initiation of treatment is desirable in order to preserve cognitive function.

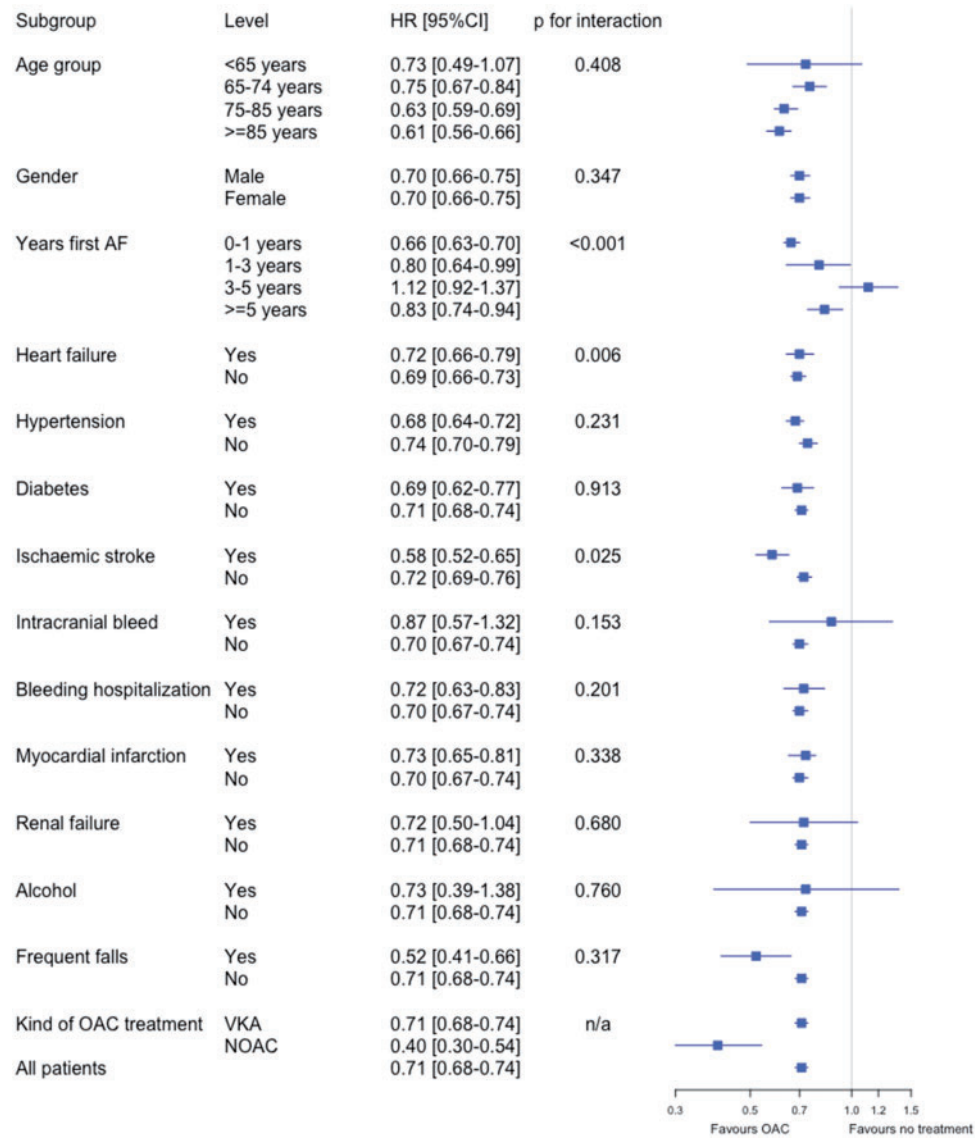

Figure 2 Risk of dementia with and without oral anticoagulation treatment at baseline ('intention to treat'). Multivariable Cox regression on propensity score matched cohorts.

Limitations

Being a retrospective and non-randomized study, it cannot prove or disprove causal relationships. Multivariable analysis and propensity score matching can compensate for known cofactors, but not for things doctors see but do not document in code. When such observations affect treatment decisions, confounding by indication follows. For example, elderly patients with cognitive difficulties, but without an outright diagnosis of dementia, may not be offered OAC treatment as often as other patients in the same situation.

We used four falsification endpoints for which OAC treatment does not have a known causal relationship. When a falsification endpoint shows a significant relationship to the given treatment, one therefore must draw the conclusion the association is due to some unknown factor which it had not been possible to adjust for. In our study, OAC treatment showed no association with two of these falsification outcomes, and a week association with the two other falsification outcomes. The direction of the effect in these were however opposite to that between OAC treatment and dementia, which in our view indicate that although there may be unknown cofactors affecting the results, these works to attenuate rather than to accentuate the beneficial role of OAC treatment.

It is in the nature of registry studies that the knowledge about study subjects is incomplete. Patients may have diseases about which there is no information. It is uncommon for registries to give false diagnoses. The Swedish registries are of high standard and have frequently been used and validated, for research.[12–17] A validation study of 498 twins aged 70–81 showed a sensitivity of 26% and a specificity of 97% for a discharge diagnosis of dementia compared to the diagnosis made at a consensus conference with access to full test results.[17] The low sensitivity means that patients with pre-existing dementia

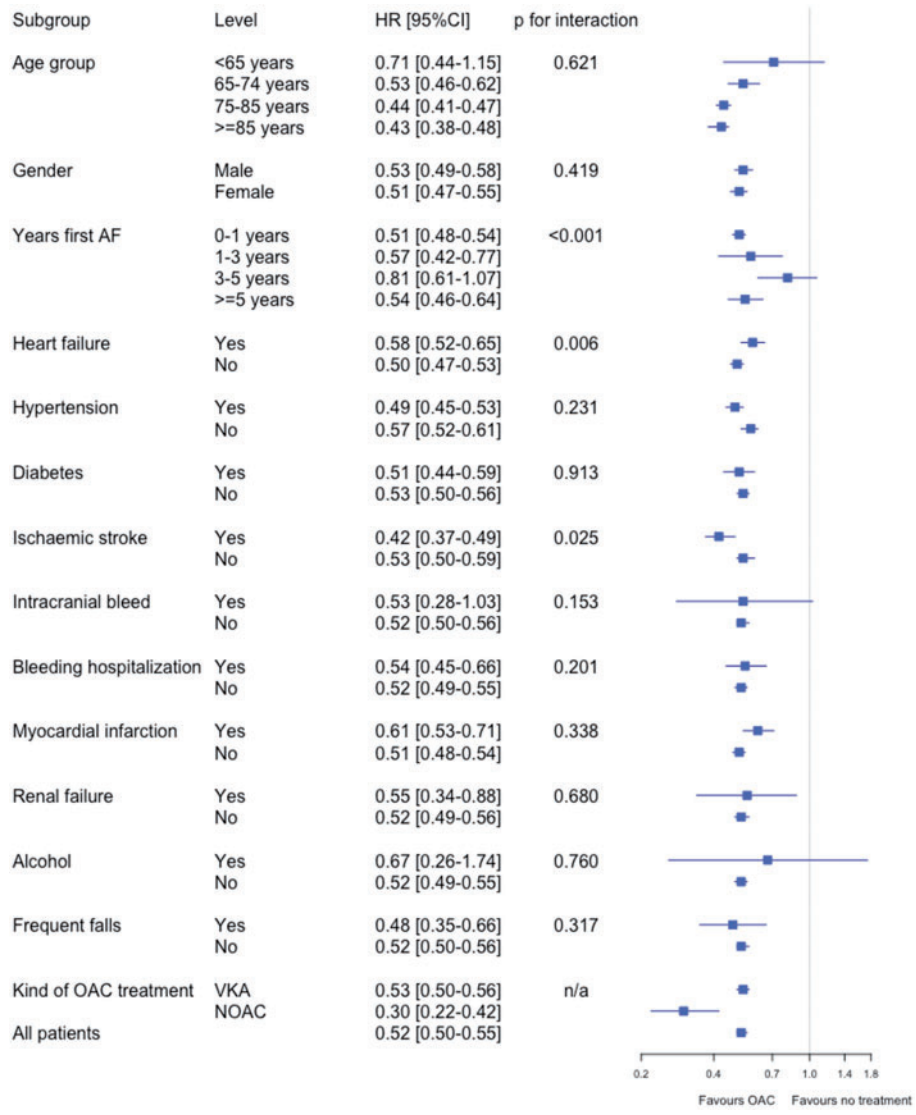

Figure 3 Risk of dementia with and without oral anticoagulation treatment ('on treatment'). Multivariable Cox regression on propensity score matched cohorts.

may have included in the study contributing to confounding by indication. The high specificity confers high validity to the dementia endpoint during follow-up.

The information about the exposure to vitamin K antagonists (VKA) had to be assessed through the frequency of refill dispensings rather than on dispensed tablets and prescribed dosages since individual dosages were not known. This makes information about the exposure less exact than desired. For all drugs there is a possibility that patients did not take all drugs they collected. The effect on the results would most likely be one of attenuation and a bias towards null.

Access to detailed information about medical history, comorbidity, and medication over many years prior to study entry made it possible for us to create, through propensity score matching, cohorts that were balanced on as many as 40 covariates. With likeness in so many dimensions, fundamental differences on unknown cofactors are less likely, and thus the potential damage from confounding by indication.

The dementia endpoint in this study was not adjudicated. We had to rely on the use of clinical diagnoses. Two previous validation studies of dementia diagnoses in the Swedish patient register have shown a specificity of 97% and 98%, respectively[17,25] while data on sensitivity, which requires screening of undiagnosed subjects, is less exact. It is likely that dementia is under-reported in the clinical setting thus making the true prevalence of dementia higher.

We did not perform separate analyses with respect to whether AF was permanent or intermittent as register data doesn't offer reliable distinction in that aspect, and because AF is a progressive disorder and patients during a follow-up period of up to almost 9 years were likely to progress from paroxysmal AF to permanent AF.

Neither did we attempt to analyse whether different types of dementia could have influenced the results because the most commonly used code was the code for unspecified dementia, not the more specific codes for the different forms of dementia.

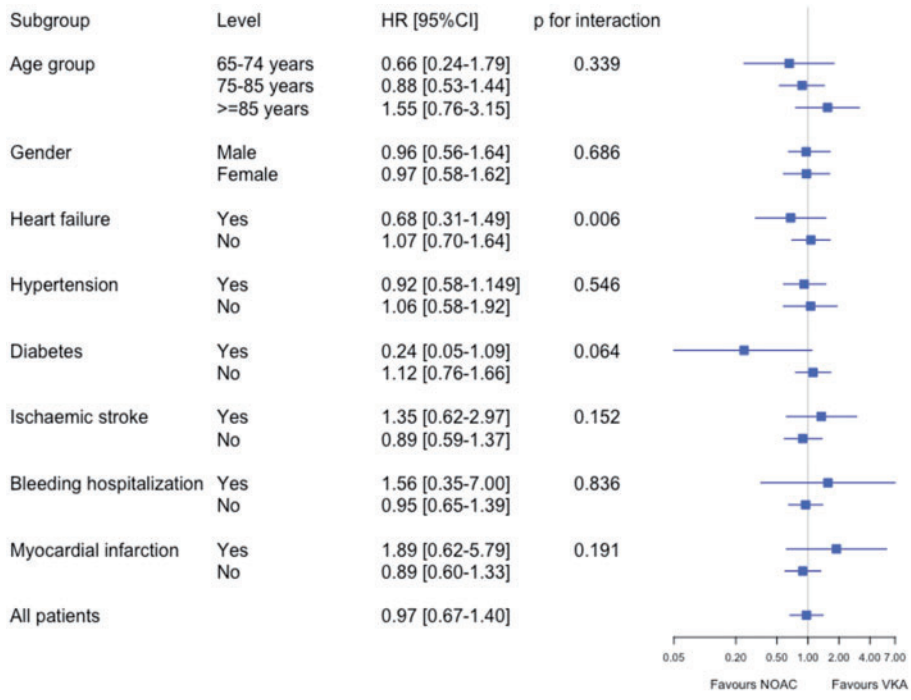

Figure 4 Risk of dementia with non-vitamin K oral anticoagulants (NOAC) compared to warfarin. Propensity score matched according to likelihood of receiveing a NOAC rather than warfarin.

Our results strongly suggest that OAC treatment protects against dementia in AF. In order to prove this assumption, randomized placebo controlled trials would be needed, but a previously pointed out, such studies cannot be done because of ethical reasons. It is not possible to give placebo to AF patients and then wait for dementia or stroke to occur. Therefore, we have to do the second best, which is to use the information in population-wide health databases for retrospective studies while trying to control for biases and confounders the best we can. More registry studies in this field are therefore important in order to confirm or reject our findings.

Conclusions

The risk of dementia is higher without oral anticoagulant treatment in patients with AF. This suggests that early initiation of anticoagulant treatment in patients with AF could be of value in order to preserve cognitive function.

Supplementary material

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

Conflict of interest: Neither of the authors have any potential conflicts of interest in relation to the present study. Outside of this, LF has received consultancy fees from Bayer, BMS, Pfizer and Sanofi. MR has received grants and/or consultancy fees from Bayer, Boehringer-Ingelheim, BMS, Medtronic, Pfizer, Roche, Sanofi, St Jude Medical and Zenicor.

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