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Oral anticoagulation among atrial fibrillation patients with anaemia: an observational cohort study

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Aims To investigate the risk of stroke/thromboembolism (TE) and major bleeding associated with anaemia among patients with atrial fibrillation (AF). Also, to assess the effects of oral anticoagulation (OAC) and time in therapeutic range (TTR) with vitamin K antagonists according to level of haemoglobin (Hb).

Methods and results Through administrative registry databases, we identified all Danish patients diagnosed with AF from 1997 to 2012. We included 18 734 AF patients with recent available data on Hb. Multiple Cox regression analyses were used to estimate hazard ratios and to compute standardized absolute 1-year risks of stroke/TE and major bleeding. Among included patients, 3796 (20%) had mild anaemia (Hb 6.83–7.45 mmol/L for women and Hb 6.83–8.03 mmol/L for men) and 2562 (14%) had moderate/severe anaemia (Hb <6.83 mmol/L). Moderate/severe anaemia was associated with increased risk of major bleeding and 9.1% lower median TTR compared with no anaemia. Use of OAC was associated with reduced risk of stroke/TE among patients without anaemia [standardized absolute 1-year difference -2.5%, 95% confidence interval (CI) -3.8 to -1.7%] or with mild anaemia (-2.3%, 95% CI -2.8 to -1.8%), but not with moderate/severe anaemia, (0.03%, -1.8 to +2.8%, interaction $P = 0.01$). Oral anticoagulation was associated with a 5.3% (95% CI 2.1–8.7%) increased standardized absolute risk of major bleeding among AF patients with moderate/severe anaemia.

Conclusion Anaemia was common in patients with AF and associated with major bleeding and lower TTR. Oral anticoagulation was associated with more major bleeding, but no reduction in risk of stroke/TE among AF patients with moderate/severe anaemia.

Keywords Atrial fibrillation • Anticoagulation • Anaemia

Introduction

Lifetime risk of atrial fibrillation (AF) after age 55 years is more than 35%,[1] and anaemia is common in patients with AF.[2] The prevalence of both AF and anaemia increases with age, and both conditions are increasing in prevalence due to the aging population.[3,4]

Atrial fibrillation is associated with five-fold higher risk of stroke/thromboembolism (TE),[5] and therefore, it is recommended that

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most patients with AF use lifelong oral anticoagulation (OAC) for stroke prevention.[6] Compared with placebo, OAC reduces risk of stroke by 64%, and mortality by 26% among AF patients; however, OAC also increases risk of major bleeding.[7] Patients with moderate to severe anaemia have been excluded from randomized controlled clinical trials of OAC in AF,[8–10] and anaemia has been associated with a two-fold higher risk of major bleeding among AF patients on OAC.[9,10] Uncertainty, therefore, exists about the benefits and risks of OAC in patients with both AF and anaemia, and very limited data exist to guide treatment decisions in this population.

We analysed several Danish nationwide registries to investigate the risks of stroke/TE and major bleeding associated with anaemia in AF, and to assess whether benefit and harms of OAC vary according to haemoglobin (Hb) levels.

Methods

Danish residents have a civil registration number which allows individual-level linkage of administrative registries. We collected data from the following sources: (i) the Danish National Patient Registry,[11] in which every hospital admission is coded according to the International Classification of Disease (ICD) system, (ii) the Danish National Prescription Registry,[12] in which dispensed drugs are coded according to the Anatomical Therapeutic Chemical Classification (ATC) System, (iii) laboratory databases covering ~20% of the Danish population, (iv) the Danish Transfusion Database, which records blood transfusions given in Denmark since 2004, and (v) the Danish Civil Registration System, where data on vital status are recorded.

Study population

We identified all patients discharged with first-time AF hospitalization in Denmark between 1997 and 2012. Follow-up was started 14 days after discharge with AF, because anticoagulation strategy is likely to be changed during first AF hospitalization. We excluded patients with valvular AF,[13] and patients who did not have a measured Hb in the prior 30 days. Patients diagnosed with bleeding in the 180 days before entry were excluded to avoid anaemia caused by recent bleeding. Patients with a CHA_2DS_2-VASc score of <2 were excluded, since these patients do not have definitive recommendation for OAC therapy according to guidelines.[6] Included patients were divided according to World Health Organization (WHO) definition of anaemia; no anaemia (Hb >7.45 mmol/L for women and Hb >8.07 mmol/L for men), mild anaemia (Hb 6.83–7.45 mmol/L women and Hb 6.83–8.07 mmol/L for men), and moderate/severe anaemia (Hb <6.83 mmol/L for women and men).[14]

Baseline comedication and comorbidity

As in prior studies,[15,16] baseline medications were defined by ATC codes for prescriptions claimed during the 180 days prior to inclusion, and comorbidity was defined with ICD codes from hospital contacts during the last 5 years before inclusion. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.[17] The ATC and ICD codes used to define the study population are listed in Supplementary material online, *Table S1*.

Time in therapeutic range

Time in therapeutic range (TTR) was calculated for patients on vitamin K antagonist (VKA) who had at least three available international normalized ratio (INR) values during follow-up. Time in therapeutic range was calculated using the Rosendaal Method,[18] excluding INRs taken during hospitalization and excluding INRs taken in periods off anticoagulation, as in previous studies.[19]

Outcomes

Outcomes were (i) stroke/TE, defined using diagnosis codes for hospitalization with ischaemic stroke, transient ischaemic attack, or systemic embolism[20] and (ii) major bleeding defined using diagnosis codes for hospitalization with intracranial, gastrointestinal, airway, or urogenital bleeding.[21]

Statistics

Continuous covariates are presented as means with standard deviation or medians with interquartile range. Categorical covariates are presented as frequencies with percentages. Comparisons of baseline characteristics were performed using the χ^2 test for categorical covariates and the Kruskal–Wallis test or the Student's *t*-test for continuous covariates. Patients were followed from 14 days after discharge with first-time AF until the first occurrence of stroke, TE, major bleeding, discontinuation or initiation of OAC, death, emigration, or 1 year of follow-up. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox regression models. Subgroups of patients defined by anaemia were analysed separately to estimate the effect of OAC on the hazard rates, and subgroups of OAC status were analysed separately to estimate the effect of anaemia on the hazard rates. The Cox models with stroke/TE as outcome were adjusted for age, cancer, sex, congestive heart failure, hypertension, diabetes, vascular disease, previous stroke, reduced eGFR below 60 or 30 mL/min/1.73 m^2, and use of acetylsalicylic acid and adenosine diphosphate (ADP) receptor blockers. The Cox models with major bleeding as outcome were adjusted for age, sex, previous bleeding, previous stroke, hypertension, chronic liver disease, alcohol abuse, reduced eGFR below 60 and below 30 mL/min/1.73 m^2, and use of acetylsalicylic acid, ADP-receptor blockers, and non-steroid anti-inflammatory drugs. Cox models with restricted cubic splines were used to examine the association between Hb as a continuous variable and the rates of stroke and bleeding. Standardized absolute risks of stroke and bleeding were computed by combining the cause-specific Cox models of the competing events in order to average the predicted absolute risks of each subject.[22] Death without event was considered a competing risk for the calculation of absolute 1-year risks. The absolute risks were standardized using all included patients as the reference population (g-formula). Reported were standardized absolute 1-year risks for each treatment group and risk differences with 95% CI computed using the percentile bootstrap method with 2000 replicates. We performed several sensitivity analyses. First, we repeated analyses of HR of stroke/TE and major bleeding associated with OAC when not censoring at initiation/discontinuation of OAC. Second, we recalculated HR of stroke/TE and major bleeding according to anaemia when reclassifying patients with recent red blood cell transfusion, and we calculated absolute risk of blood transfusion during follow-up according to anaemia status at baseline. Third, we analysed HR of stroke/TE and major bleeding associated with anaemia and OAC when changing the 30-day cut-off for available Hb to 20 and 60 days. Fourth, we assessed HR of stroke/TE and major bleeding associated with anaemia when excluding all patients with prior cancer or prior bleeding. All analyses were performed with SAS version 9.4, and R version 3.4.1.[23]

Ethics

Registry-based studies do not require ethical approval in Denmark, and data were anonymized with no possibility for identification of individual

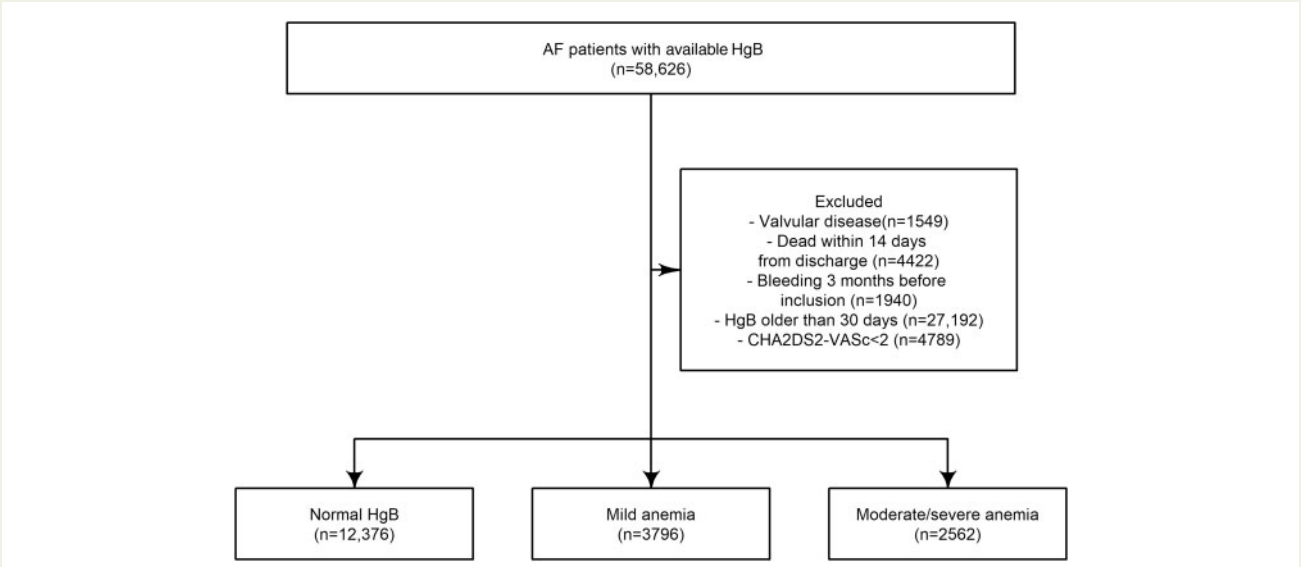


Figure 1 Selection of the study population. Hb, haemoglobin.

patients. The study was approved by the Danish Data Protection Agency (ref.no: 2007-58-0015/GEH-2014-012 I-Suite no: 02729).

Results

Characteristics of the study population

The study population consisted of 18 734 patients with AF and available Hb within the 30 days prior to inclusion (*Figure 1*). A total of 12 376 (66%) patients did not have anaemia, 3796 (20%) had mild anaemia, and 2562 (14%) had moderate/severe anaemia (*Table 1*). Patients with anaemia were more likely to have diagnosed cancer, reduced eGFR, diabetes, previous bleeding, chronic obstructive pulmonary disease, and were more likely to take iron, folate or B_{12} supplements, and less likely to receive OAC. The clinical profile of patients, not covered by our laboratory databases or patients without recent available Hb, were broadly similar to included patients (Supplementary material online, *Table S2*).

Risk of stroke/thromboembolism and major bleeding according to anaemia

Decreasing Hb was associated with increased rate of major bleeding, both among patients on OAC and among patients not on OAC (*Figure 2*). Decreasing Hb was not significantly associated with the rate of stroke/TE among patients not on OAC but was associated with increased stroke/TE among patients on OAC. Anaemia status and use of OAC affected the risk of stroke/TE and major bleeding differently (*Figure 3*). Among patients not on OAC, moderate/severe anaemia was associated with an increase in major bleeding (HR 1.46, 95% CI 1.14–1.86), without an effect on stroke/TE (HR 0.97, 95% CI 0.76–1.23). By contrast, among patients on OAC, moderate/severe anaemia was associated with an increase in both major bleeding (HR 1.78, 95% CI 1.30–2.48) and stroke/TE (HR 1.71, 95% CI 1.12–2.61).

Risk of stroke/thromboembolism and major bleeding according to OAC

The standardized, absolute 1-year risk differences between patients on and off OAC were altered by anaemia status (*Table 2*). OAC was associated with a 2.5% (95% CI -2.9 to -1.1%) lower risk of stroke/TE among patients without anaemia, and a 2.3% (95% CI -3.8 to -0.8%) lower risk among patients with mild anaemia, but with a 0.3% (95% CI -1.8 to 2.8%) higher risk of stroke/TE among patients with moderate/severe anaemia (*Table 2*). Oral anticoagulation was associated with a 2.0% (95% CI 1.1–2.9%) higher risk of major bleeding among patients without anaemia, a 1.6% (-0.3 to 3.6%) higher risk among patients with mild anaemia, but with a 5.3% (95% CI 2.1 to 8.7%) higher risk of major bleeding among patients with moderate/severe anaemia. The interaction between OAC and moderate/severe anaemia (compared to no anaemia) for stroke as the outcome was significant ($P = 0.01$), but not for bleeding as outcome ($P = 0.16$). The differential effects of OAC according to anaemia status during the 1 year of follow-up are illustrated in *Figure 4*.

Time in therapeutic range according to haemoglobin

The quality of anticoagulation control declined progressively ($P < 0.01$) with increasing severity of anaemia (*Table 3*). Patients without anaemia had a median TTR of 63.9%, vs. 57.9% among patients with mild anaemia and 54.8% among patients with moderate/severe anaemia.

Sensitivity analyses

We repeated analyses of rate of stroke/TE and major bleeding according to OAC stratified on anaemia without censoring patients at the time of discontinuation of OAC (Supplementary material online, *Table S3*) and had results similar to main analyses. We also repeated analyses of rate of stroke/TE and major bleeding according

Table 1 Baseline characteristics of the study population

	No anaemia	Mild anaemia	Moderate to severe anaemia	*P*-value
Number of patients	12 376	3796	2562	
Age (years), median (IQR)	77.5 (70.5–83.7)	80.5 (74.4–86.0)	80.2 (73.6–86.0)	<0.001
Male (%)	5140 (41.5)	2464 (64.9)	1105 (43.1)	<0.001
Living alone	6072 (49.1)	1861 (49.0)	1425 (55.6)	<0.001
Hb (mmol/L), median (IQR)	8.6 (8.1–9.2)	7.3 (7.1–7.6)	6.4 (6.1–6.7)	<0.001
CHA_2DS_2-VASc, median (IQR)	3 (3–4)	3 (3–4)	4 (3–4)	<0.001
HAS-BLED, median (IQR)	2 (2–3)	2 (2–3)	3 (2–3)	<0.001
eGFR 30–60 (%)	5167 (41.8)	1666 (43.9)	1015 (39.6)	0.003
eGFR<30 (%)	525 (4.2)	397 (10.5)	419 (16.4)	<0.001
Comorbidity				
Hypertension (%)	7666 (61.9)	2204 (58.1)	1475 (57.6)	<0.001
Previous stroke (%)	1508 (12.2)	479 (12.6)	276 (10.8)	0.071
Diabetes	1368 (11.1)	554 (14.6)	402 (15.7)	<0.001
Vascular disease (%)	3037 (24.5)	1312 (34.6)	943 (36.8)	<0.001
Chronic liver disease (%)	65 (0.5)	39 (1.0)	25 (1.0)	0.034
Previous bleeding (%)	294 (2.4)	141 (3.7)	124 (4.8)	<0.001
Cancer (%)	776 (6.3)	467 (12.3)	406 (15.8)	<0.001
Congestive heart failure (%)	3035 (24.5)	1040 (27.4)	575 (22.4)	<0.001
Chronic obstructive pulmonary disease	1360 (11.0)	368 (14.4)	3242 (14.6)	<0.001
Comedication				
Iron supplements	207 (1.7)	212 (5.6)	271 (10.6)	<0.001
Vitamin B_{12}-supplements	523 (4.2)	251 (6.6)	223 (8.7)	<0.001
Folic acid supplements	111 (0.9)	73 (1.9)	63 (2.5)	<0.001
Beta-blocker (%)	7628 (61.6)	2118 (55.8)	1373 (53.6)	<0.001
Loop diuretics	5240 (42.3)	1979 (52.1)	1345 (52.3)	<0.001
Calcium channel blocker (%)	3960 (32.0)	1145 (30.2)	824 (32.2)	0.087
RAS-inhibitor	5760 (46.5)	1756 (46.3)	1204 (47.0)	0.847
Digoxin (%)	5440 (44.0)	1652 (43.5)	951 (37.1)	<0.001
Statin (%)	2940 (23.8)	960 (25.3)	736 (28.7)	<0.001
NSAID (%)	2183 (17.6)	826 (21.8)	618 (24.1)	<0.001
ADP-receptor blocker (%)	405 (3.3)	207 (5.5)	176 (6.9)	<0.001
Acetylsalicylic acid (%)	6082 (49.1)	2123 (55.9)	1422 (55.5)	<0.001
Any oral anticoagulation (%)	5927 (47.9)	1299 (34.2)	606 (23.7)	<0.001
Vitamin K antagonist (%)	5617 (45.4)	1241 (32.7)	575 (22.4)	<0.001
Dabigatran (%)	239 (1.9)	43 (1.1)	20 (0.8)	<0.001
Rivaroxaban (%)	71 (0.6)	15 (0.4)	11 (0.4)	0.325

ADP, adenosine diphosphate; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; IQR, interquartile range; NSAID, non-steroid anti-inflammatory drugs; RASi, renin–angiotensin system inhibitor.

to anaemia when reclassifying patients with recent red blood cell transfusion (Supplementary material online, *Table S4*). Patients with recent transfusion had a rate of stroke/TE and major bleeding comparable to patients with moderate/severe anaemia, and rates of stroke/TE and major bleeding for mild or moderate/severe anaemia were not affected by the reclassification of patients with recent transfusions. Analyses of stroke/TE and major bleeding according to anaemia status (Supplementary material online, *Table S5*) and according to OAC status (Supplementary material online, *Table S6*) were not affected by changing the 30-day cut-off for available Hb measurements to 20 or 60 days. Excluding patients with cancer or any previous bleeding did not change main results regarding risk of stroke/TE or major bleeding associated with anaemia (Supplementary material online, *Table S7*). In a gender-stratified analysis, both men (HR 0.62, 95% CI 0.49–0.79) and women (HR 0.50, 95% CI 0.41–0.63) had lower risk of stroke/TE with OAC, and both men (HR 1.23, 95% CI 1.00–1.50) and women (1.52, 95% CI 1.23–1.89) had higher risk of bleeding with OAC. Supplementary material online, *Figure S1* shows absolute risk of red blood cell transfusion during follow-up according to anaemia at baseline. Absolute risk of red blood cell transfusion was 17, 10, and 4% among patients with moderate/severe anaemia, mild anaemia, and no anaemia, respectively.

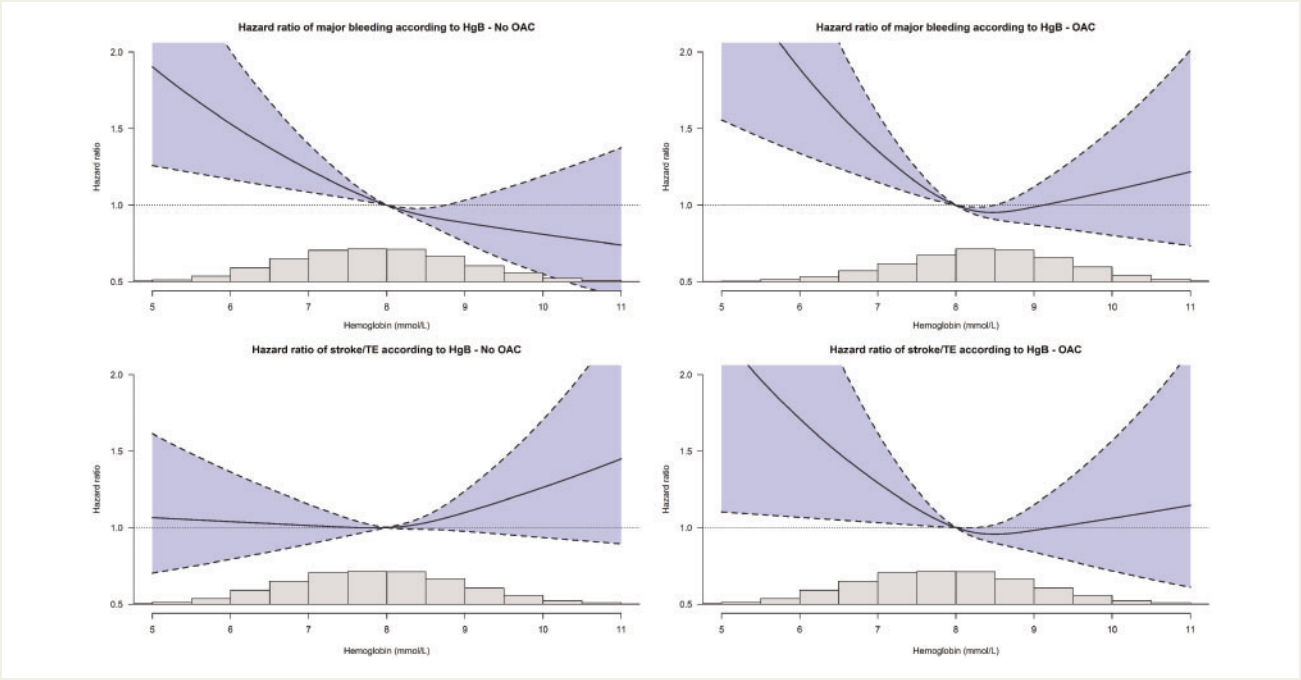


Figure 2 Hazard ratio of major bleeding and stroke/thromboembolism according to haemoglobin and oral anticoagulation among patients with atrial fibrillation. Restricted cubic splines were constructed using fully adjusted Cox models of stroke/thromboembolism and major bleeding divided by oral anticoagulation use with haemoglobin included as a continuous variable. Knots were placed at the 1st, 2nd, and 3rd quartiles of the distribution of haemoglobin. The 95% confidence intervals are displayed by shadow areas, and the histogram on the distribution of haemoglobin is displayed below the hazard ratio curve. Reference value is 8 mmol/L. Hb, haemoglobin; OAC, oral anticoagulation; TE, thromboembolism.

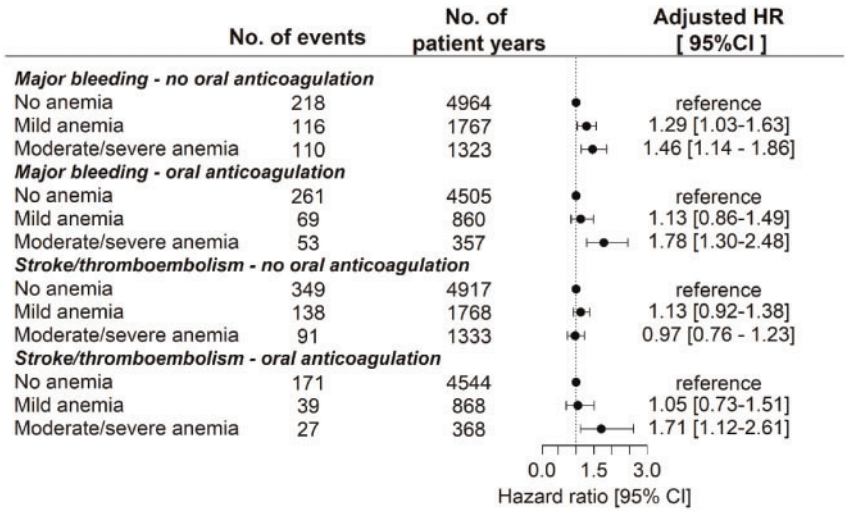


Figure 3 Adjusted hazard ratio of stroke/thromboembolism and major bleeding according to anaemia and oral anticoagulation among atrial fibrillation patients. CI, confidence interval.

Discussion

This was a large observational cohort study including real-world patients with first-time hospitalization for AF and with indication of OAC. We had the following major findings: (i) one-third of AF patients had anaemia; (ii) anaemia had a strong association with major bleeding; and (iii) among patients with moderate/severe anaemia, the effect of OAC on stroke/TE was significantly attenuated, but the effect on major bleeding was greater.

Table 2 Stroke/thromboembolism and major bleeding according to haemoglobin and oral anticoagulation

	Number of events	Adjusted hazard ratio (95% CI)	Non-standardized absolute risk (95%CI)	Standardized absolute 1-year risk (95% CI), %	Standardized absolute 1-year risk difference (95% CI), %
Stroke/thromboembolism					
No anaemia					
No OAC	352	1.00 (reference)	5.9 (5.3–6.5)	5.9% (5.3–6.6%)	Reference
OAC	171	0.52 (0.43–0.63)	3.4 (2.9–3.9)	3.4% (2.9–3.9%)	-2.5% (-3.4 to -1.7%)
Mild anaemia					
No OAC	138	1.00 (reference)	5.9 (4.9–6.8)	5.9% (5.0–6.9%)	Reference
OAC	39	0.56 (0.39–0.80)	3.8 (2.6–5.0)	3.6% (2.5–4.8%)	-2.3% (-3.8 to -0.8%)
Moderate/severe anaemia					
No OAC	88	1.00 (reference)	4.9 (3.8–5.8)	5.0% (3.9–6.0%)	Reference
OAC	27	0.98 (0.62–1.55)	5.4 (3.9–7.5)	5.3% (3.4–7.5%)	0.3% (-1.8 to 2.8%)
Major bleeding					
No anaemia					
No OAC	221	1.00 (reference)	3.7 (3.2–4.2)	3.6% (3.1–4.1%)	Reference
OAC	261	1.46 (1.20–1.78)	5.3 (4.7–5.9)	5.5% (4.9–6.3%)	2.0% (1.1–2.9%)
Mild anaemia					
No OAC	122	1.00 (reference)	5.3 (4.3–6.2)	5.3% (4.4–6.2%)	Reference
OAC	71	1.20 (0.88–1.64)	7.1 (5.4–8.7)	6.9% (5.4–8.6%)	1.6% (-0.3 to 3.6%)
Moderate/severe anaemia					
No OAC	101	1.00 (reference)	5.5 (4.5–6.6)	5.5% (4.3–6.6%)	Reference
OAC	51	1.84 (1.29–2.64)	10.2 (7.5–12.9)	10.8% (8.0–13.9%)	5.3% (2.1–8.7%)

CI, confidence interval; Hb, haemoglobin; HR, hazard ratio; OAC, oral anticoagulation.

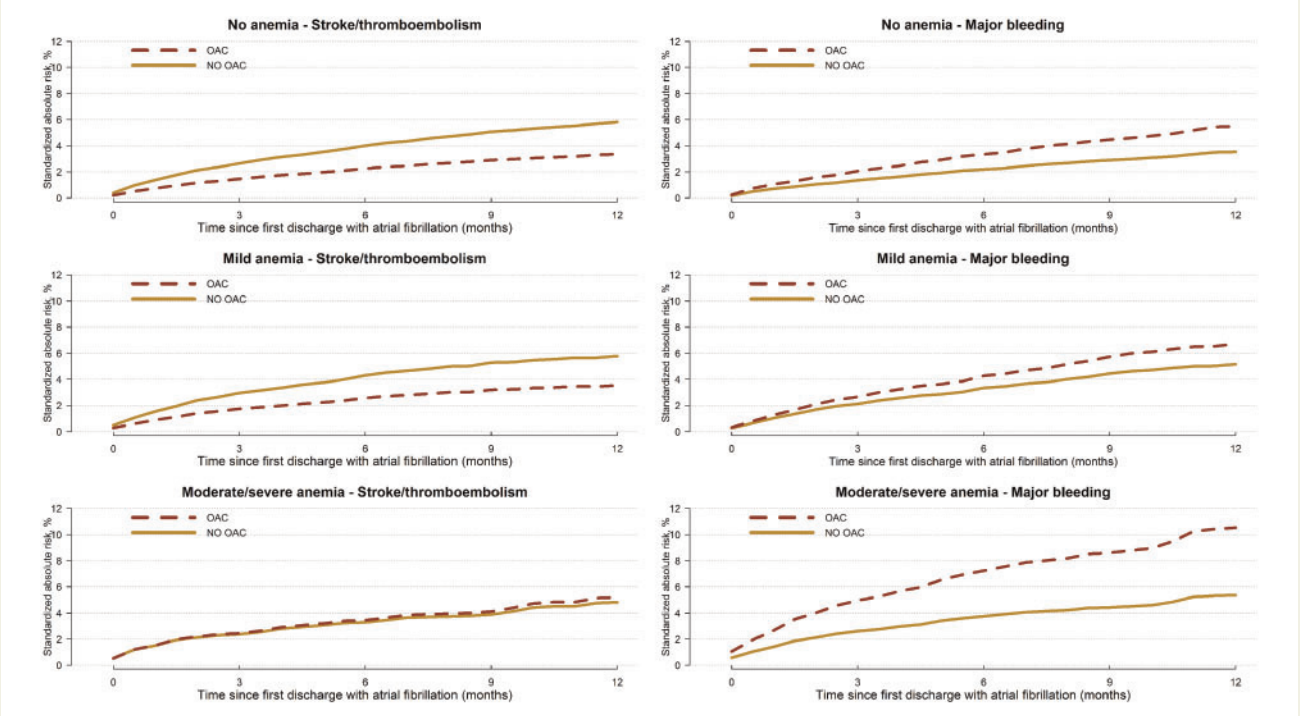
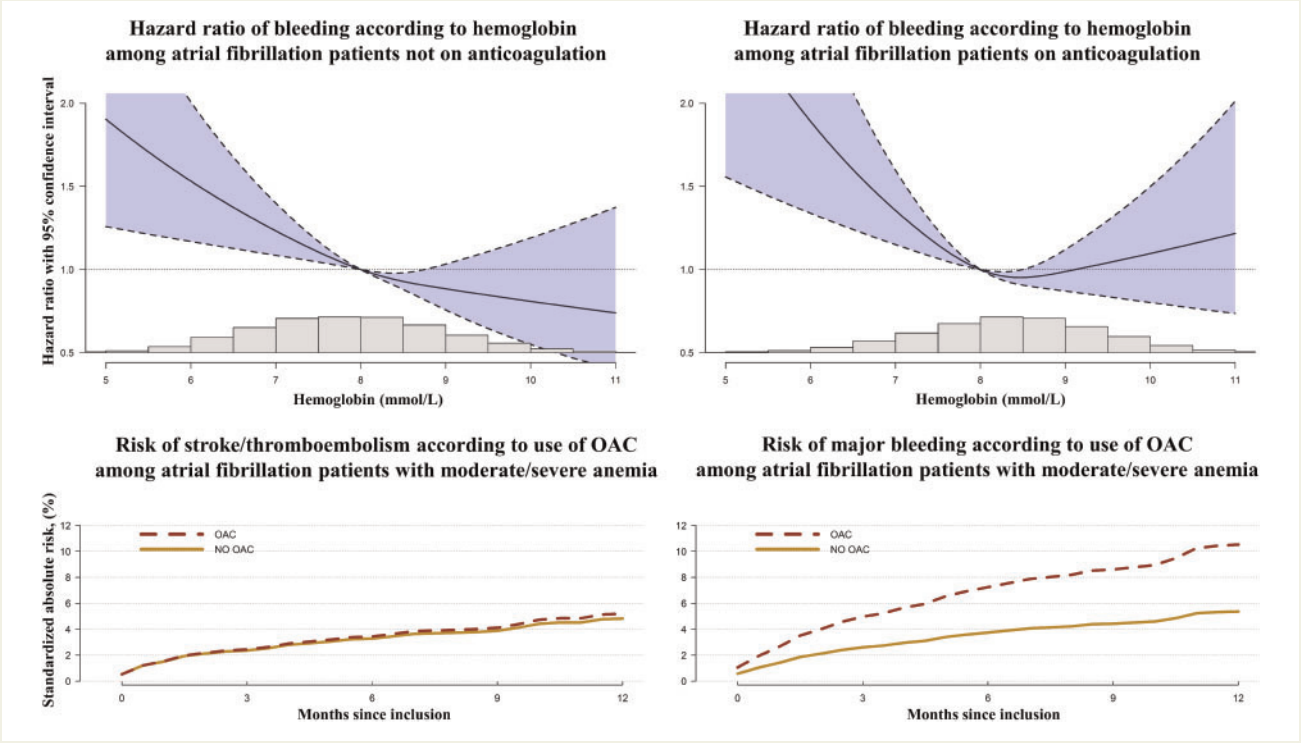


Figure 4 Standardized 1-year absolute risk of stroke/thromboembolism and major bleeding according to haemoglobin and oral anticoagulation among patients with atrial fibrillation. OAC, oral anticoagulation.

Table 3 Anticoagulation control according to haemoglobin among patients on vitamin K antagonist with available international normalized ratio values

	No anaemia	Mild anaemia	Moderate/severe anaemia	*P*-value
Number of patients with at least three available INR values during follow-up (% of anticoagulated patients)	3169 (56.4)	715 (57.6)	310 (53.9)	0.334
Number of INRs during the 1st year after inclusion, median (IQR)	10 (6–15)	9 (5–14)	9 (5–14)	0.052
Time in therapeutic range, median (IQR)	63.9 (36.3–84.8)	57.9 (26.8–81.8)	54.8 (19.5–79.7)	<0.001
Percent of time with INR below 2.00, median (IQR)	15.1 (3.1–38.7)	17.0 (3.3–45.6)	23.3 (3.7–52.3)	<0.001
Percent of time spend with INR above 3.00, median (IQR)	5.4 (0–19.3)	6.5 (0–22.2)	4.8 (0–20.3)	0.342

Hb, haemoglobin; INR, international normalized ratio; IQR, interquartile range.



Take home figure Risk of major bleeding according to haemoglobin level among atrial fibrillation patients with or without OAC, and risk of stroke/thromboembolism and major bleeding according to use of OAC among atrial fibrillation patients with moderate/severe anaemia. OAC, oral anticoagulation.

Risk of stroke/thromboembolism and major bleeding according to haemoglobin

Anaemia has previously been associated with increased rate of bleeding among patients with AF,[2,9,10] and is therefore, included in most bleeding risk scores.[24] Anaemia is likely to be a good marker for several different causes of bleeding, including chronic kidney disease and associated haemostatic dysfunction, bone marrow insufficiency, and associated thrombocytopenia and could be found in relation to minor bleedings caused by undiagnosed gastrointestinal cancer. There is also available evidence to suggest an association between anaemia and low platelet function related to lower tendency for platelets to marginate.[25] Anaemia was associated with increased bleeding both in the RE-LY and in the ARISTOTLE randomized trials, although they excluded patients with severe anaemia (Hb of <10 g/dL or 9 g/dL, respectively).[8–10] Furthermore, they offered no opportunity to study patients that did not receive OAC or to assess the prevalence of anaemia in real-world AF patients.

Our study provides important new information, as one-third of AF patients with indication for OAC had anaemia, and we found a dose-response relation between reduced Hb levels and an increase in rate

of major bleeding, irrespective of OAC use. In contrast to the rate of bleeding associated with anaemia in AF, much less evidence exists regarding the association between anaemia and stroke/TE. Some studies of AF patients on OAC found anaemia to be associated with increased rate of stroke/TE,[9] while others did not.[10] Stroke risk ideally is investigated among patients that do not receive OAC, since the risk is not influenced by quality of oral anticoagulation control in this population. We found no association between anaemia and stroke risk among AF patients without OAC treatment, but we found a linearly increased rate of bleeding associated with lower Hb, both among patients on OAC and not on OAC. This association could indicate that patients with lower Hb are more prone to bleeding than TE.

Benefit with oral anticoagulation according to anaemia

Anticoagulation in AF must balance the benefits of reducing stroke against the risk of increasing bleeding. Identification of patients in whom harms of OAC outweigh the benefits could improve outcomes. Since lower Hb values are associated with more bleeding on OAC, but no change in the risk of stroke/TE, the balance of benefit and risk from OAC may be reversed in patients with moderate/severe anaemia. Oral anticoagulation was associated with an ~50% reduced risk of stroke/TE among patients without anaemia in our study, a reduction close to the risk reduction found in randomized controlled clinical trials. However, we found a significant attenuation in the stroke risk reduction associated with OAC among patients with moderate/severe anaemia (interaction $P = 0.01$), to the point that there was no effect of OAC (*Table 2*). Furthermore, OAC was associated with a 5.3% higher risk of major bleeding among patients with moderate/severe anaemia (*Table 2*). There are several possible reasons why OAC was not associated with reduced stroke/TE in this population. First, patients with moderate/severe anaemia had worse anticoagulation control on a VKA, with a median TTR of 54.8% during follow-up. The benefit of a VKAs declines progressively with lower achieved TTR,[26] and may be non-existent once TTR is <58–60%.[27] Patients with moderate/severe anaemia spend more time with INR below 2.00 than patients without anaemia, and it is also possible that some physicians aimed at a lower target INR for these patients. If so, this approach did not result in significantly lower time above INR 3.00 or lower risk of bleeding compared to patients without anaemia on VKA. Second, it is possible that a larger proportion of patients with AF and anaemia had poor compliance with OAC or discontinued OAC during follow-up; however, results obtained when censoring at discontinuation showed even less benefit with OAC compared with analyses not censored at discontinuation. Third, although <10% of strokes in the Danish registries are of haemorrhagic origin,[20] in a population with very high baseline bleeding risk, such as patients with AF on OAC with anaemia, it is possible that a larger proportion of the strokes might have been of haemorrhagic origin. Fourth, warfarin has previously been associated with increased vascular calcification due to inhibition of carboxylation of matrix G protein, which prevents arterial calcification,[28] and patients with anaemia could be more susceptible to these effects of warfarin.

Should patients with AF and moderate/severe anaemia not receive OAC? Randomized controlled trials provide no data to answer this question. In this large, national population cohort, we found markedly increased risk of major bleeding, low TTR, and little to no effect on stroke from OAC in patients with moderate/severe anaemia. Our results suggest that physicians should carefully weigh the potential risks and benefits of OAC in patients with AF and moderate/severe anaemia; closer follow-up, tighter anticoagulation control, strenuous efforts to investigate (and treat the reversible causes of) the anaemia, and sometimes, lack of initiation or discontinuation of OAC may be options in this population.

Strengths and limitations

The main strength of our study is the real-world nature of the cohort and inclusion of patients irrespective of OAC, age, sex and participation in a health insurance programme. We have practically no loss to follow-up. Of patients with a diagnosis of AF in the Danish registries, 99% had documentation of AF with Holter or electrocardiogram in an earlier validation study.[29] The

diagnosis of stroke has been validated with a positive predictive value of more than 90%,[20] and the majority of diagnoses have been validated in the Danish registries.[30] Furthermore, we had access to a large sample of laboratory values including INR, Hb, and creatinine which are usually not available in administrative registries. Our study also has limitations. First, our study was observational, so our results should ideally be validated in a randomized setting. Second, there have been many changes in management of AF during our 15-year study period from 1997 to 2012, and data regarding Hb were not available after 2012. For this reason, few patients in our study received non-VKA oral anticoagulants, and we do not know if our findings are restricted only to patients on VKA. Third, we only had recent Hb for a subpopulation of our nationwide cohort, but age and sex distribution as well as stroke and bleeding risks were similar between patients with available Hb and patients not covered by our laboratory databases, and we have no reason to believe that we have introduced selection bias. Fourth, we could not characterize the cause of anaemia in our study, and the effect of OAC might differ between causes. Fifth, as a real-world cohort, cerebral imaging was not uniformly available for our population and it was not always possible for us to distinguish between ischaemic and haemorrhagic strokes. Sixth, we included only patients with incident AF hospitalization in order to homogenize our study population and in order to prevent survivor bias among prevalent AF patients, but our findings might not be generalizable to other presentations of AF.

Conclusions

In a large real-world observational study of patients with AF, one-third of patients had anaemia, which was associated with increased rate of major bleeding and low TTR. Oral anticoagulation was associated with reduced risk of stroke/TE among patients with no anaemia or mild anaemia, but not among patients with moderate/severe anaemia. Caution with OAC might be warranted among patients with AF and moderate/severe anaemia, who require careful evaluation of the balance between harm or benefit of treatment.

Supplementary material

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

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References

1. Staerk L, Wang B, Preis SR, Larson MG, Lubitz SA, Ellinor PT, McManus DD, Ko D, Weng L, Lunetta KL, Frost L, Benjamin EJ, Trinquart L. Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. *BMJ* 2018;**361**:k1453.
2. Puurunen M, Kiviniemi T, Nammas W, Schlitt A, Rubboli A, Nyman K, Karjalainen P, Kirchhof P, Lip GY, Airaksinen J. Impact of anaemia on clinical outcome in patients with atrial fibrillation undergoing percutaneous coronary intervention: insights from the AFCAS registry. *BMJ Open* 2014;**4**:e004700.
3. Gaskell H, Derry S, Andrew Moore R, McQuay HJ. Prevalence of anaemia in older persons: systematic review. *BMC Geriatr* 2008;**8**:1.
4. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med* 1995;**155**:469–473.
5. Lip GYH, Freedman B, Caterina RD, Potpara TS. Stroke prevention in atrial fibrillation: past, present and future. *Thromb Haemost* 2017;**60**: 1230–1239.
6. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Putte BV, Vardas P. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: the Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC). Developed with the special contribution of the Europea. *Eur Hear J* 2016;**356**:2893–2962.
7. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;**146**:857–867.
8. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014; **383**:955–962.
9. Westenbrink BD, Alings M, Connolly SJ, Eikelboom J, Ezekowitz MD, Oldgren J, Yang S, Pongue J, Yusuf S, Wallentin L, van Gilst WH. Anemia predicts thromboembolic events, bleeding complications and mortality in patients with atrial fibrillation: insights from the RE-LY trial. *J Thromb Haemost* 2015;**13**:699–707.
10. Westenbrink BD, Alings M, Granger CB, Alexander JH, Lopes RD, Hylek EM, Thomas L, Wojdyla DM, Hanna M, Keltai M, Steg PG, Caterina RD, Wallentin L, van Gilst W. Anemia is associated with bleeding and mortality, but not stroke, in patients with atrial fibrillation: insights from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. *Am Heart J* 2017;**185**:140–149.
11. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National patient registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;**7**:449–490.
12. Gaist D, Sørensen HT, Hallas J. The Danish prescription registries. *Dan Med Bull* 1997;**44**:445–448.
13. De Caterina R, Camm AJ. What is "valvular" atrial fibrillation? A reappraisal. *Eur Hear J* 2014;**35**:3328–3335.
14. WHO, Camm AJ. *Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity*. Geneva, Switzerland: World Health Organization; 2011. p1–6.
15. Bonde AN, Lip GY, Kamper AL, Hansen PR, Lamberts M, Hommel K, Hansen ML, Gislason GH, Torp-Pedersen C, Olesen JB. Net clinical benefit of antithrombotic therapy in patients with atrial fibrillation and chronic kidney disease: a nationwide observational cohort study. *J Am Coll Cardiol* 2014;**64**:2471–2482.
16. Staerk L, Lip GY, Olesen JB, Fosbol EL, Pallisgaard JL, Bonde AN, Gundlund A, Lindhardt TB, Hansen ML, Torp-Pedersen C, Gislason GH. Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation: nationwide cohort study. *BMJ* 2015; **351**:h5876.
17. Skali H, Uno H, Levey AS, Inker LA, Pfeffer MA, Solomon SD. Prognostic assessment of estimated glomerular filtration rate by the new Chronic Kidney Disease Epidemiology Collaboration equation in comparison with the Modification of Diet in Renal Disease Study equation. *Am Hear J* 2011;**162**:548–554.
18. Rosendaal FR, Cannegieter SC, van der Meer F, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost* 1993;**69**: 236–239.
19. Bonde AN, Lip GYH, Kamper A-L, Staerk L, Torp-Pedersen C, Gislason GH, Olesen JB. Effect of reduced renal function on time in therapeutic range among anticoagulated atrial fibrillation patients. *J Am Coll Cardiol* 2017;**69**:752–753.
20. Krarup LH, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. *Neuroepidemiology* 2007;**28**:150–154.
21. Poulton R, Caspi A, Milne BJ, Thomson WM, Taylor A, Sears MR, Moffitt TE. An automated database case definition for serious bleeding related to oral anticoagulant use. *Pharmacoepidemiol Drug Saf* 2013;**360**:1640–1645.
22. Ozenne B, Sørensen AL. Scheike T, Torp-Pedersen C. riskRegression: predicting the risk of an event using Cox regression models. *R Journal* 2007;**9**:440–460.
23. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Core Team; 2017. http//wwwR-project.org/2017 (25 July 2018).
24. Apostolakis S, Lane DA, Guo Y, Buller H, Lip GYH. Performance of the HEMORR(2)HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation: the AMADEUS (evaluating the use of SR34006 compared to warfarin or acenocoumarol in patients with atrial fibrillation) study. *J am Coll Cardiol* 2012;**60**:861–867.
25. Spann AP, Campbell JE, Fitzgibbon SR, Rodriguez A, Cap AP, Blackbourne LH, Shaqfeh E. The effect of hematocrit on platelet adhesion: experiments and simulations. *Biophys J* 2016;**111**:577–588.
26. Björck F, Renlund H, Lip GYH, Wester P, Svensson PJ, Själander A. Outcomes in a warfarin-treated population with atrial fibrillation. *JAMA Cardiol* 2016;**1**:172.
27. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, Healey JS, Yusuf S. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation* 2008;**118**:2029–2037.
28. Poterucha TJ, Goldhaber SZ. Warfarin and vascular calcification. *Am J Med* 2016; **129**:635e1–635e4.
29. Frost L, Andersen LV, Vestergaard P, Husted S, Mortensen LS. Trend in mortality after stroke with atrial fibrillation. *Am J Med* 2007;**120**:47–53.
30. Sundbøll J, Adelborg K, Munch T, Frøslev T, Sørensen HT, Bøtker HE, Schmidt M. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open* 2016;**6**:e012832.