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Oral anticoagulant treatment in rheumatoid arthritis patients with atrial fibrillation results of an international audit☆

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ABSTRACT

Objective: To describe the prevalence of atrial fibrillation (AF) in patients with rheumatoid arthritis (RA), and to evaluate the proportion of patients with AF receiving guideline-recommended anticoagulation for prevention of stroke, based on data from a large international audit.

Methods: The cohort was derived from the international audit **SU**rvey of cardiovascular disease **R**isk **F**actors in patients with **R**heumatoid **A**rthritis (SURF-RA) which collected data from 17 countries during 2014–2019. We evaluated the prevalence of AF across world regions and explored factors associated with the presence of AF with multivariable logistic regression models. The proportion of AF patients at high risk of stroke (CHA_2DS_2-VASc ≥ 2 in males and ≥ 3 in females) receiving anticoagulation was examined.

Results: Of the total SURF-RA cohort (n = 14,503), we included RA cases with data on whether the diagnosis of AF was present or not (n = 7,665, 75.1% women, mean (SD) age 58.7 (14.1) years). A total of 288 (3.8%) patients had a history of AF (4.4% in North America, 3.4% in Western Europe, 2.8% in Central and Eastern Europe and 1.5% in Asia). Factors associated with the presence of AF were older age, male sex, atherosclerotic cardiovascular disease, heart failure and hypertension. Two-hundred and fifty-five (88.5%) RA patients had a CHA_2DS_2-VASc score indicating recommendation for oral anticoagulant treatment, and of them, 164 (64.3%) were anticoagulated.

Conclusion: Guideline-recommended anticoagulant therapy for prevention of stroke due to AF may not be optimally implemented among RA patients, and requires special attention.

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease affecting 0.8% of the population world-wide [1]. These patients have 1.5–2-fold risk of atherosclerotic cardiovascular disease (CVD) compared to the general population [2]. In addition to an increased prevalence of traditional CVD risk factors such as hyperlipidaemia, hypertension, smoking and diabetes, systemic inflammation in RA plays a key role in the accelerated atherogenesis. Despite the increased CVD risk, it has been shown that patients with RA receive poorer CVD preventive treatment compared to the general population [3,4].

Atrial fibrillation (AF) represents the most common arrhythmia in the general population, affecting more than 3% of people in Europe [5]. The aetiology of non-valvular AF is not completely understood. Chronic systemic inflammation in RA may promote cardiac arrhythmias, including AF [6]. Reports have been inconsistent regarding whether risk of AF is increased in RA patients [7,8], and some report that the risk of AF and stroke in RA patients may be increased by 40% compared to the

☆ The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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general population [9,10]. Cardio-embolic strokes in AF occur most often as a result of thrombus formation in the left atrial appendage. Evidence suggests that RA-related systemic inflammation can further accelerate blood clotting and thus predispose to ischemic stroke [11].

Treatment with oral anticoagulants (OACs) should be considered in patients with AF to prevent thrombus formation in the heart and subsequent cardio-embolic strokes. The benefit of preventing a stroke versus the risk of bleeding by use of OAC treatment should be assessed. Patients with an increased risk of ischaemic stroke and no contraindications for anticoagulation should be treated with OAC [12]. A recommended tool for predicting the risk of stroke and guiding decision initiation of anticoagulation is the CHA_2DS_2-VASc score [i.e. **C**ongestive heart failure, **H**ypertension, **A**ge ≥ 75 years, **D**iabetes mellitus, **S**troke, **V**ascular disease, **A**ge 65–74 years, **S**ex **c**ategory (female) [12]. Underuse of anticoagulants among eligible patients with high stroke risk is a persistent challenge in the general population [13]. To our knowledge there are no reports on stroke prevention with OACs in patients with RA and AF. Thus, it remains uncertain how well the guidelines on stroke prevention and anticoagulation are implemented among RA patients with AF.

The aims of the present evaluation were to describe the prevalence of AF in patients with RA, and to evaluate the proportion of patients with AF receiving guideline-recommended anticoagulation for prevention of stroke using data from the clinical audit, the **SU**rvey of cardiovascular disease **R**isk **F**actors in patients with **R**heumatoid **A**rthritis (SURF-RA).

2. Materials and methods

2.1. Study data

The SURF-RA is an international cross-sectional clinical audit including data from 53 centres/19 countries/3 continents during 2014–2019. Inclusion criteria were 1) patients with clinically-diagnosed RA and 2) age ≥ 18 years. The data was gathered from already established clinical cohorts, as well as from prospective recording with data collection sheets in cardiology and rheumatology clinics. Participating countries were divided into the following world regions: Western Europe, Central and Eastern Europe, North America and Asia (Supplementary Table 1).

The presence of established CVD, including chronic AF, was recorded based on medical history/known diagnoses. We collected no data on ECG recordings. Other recorded CVD included coronary heart disease,

Table 1
Characteristics of patients with and without chronic atrial fibrillation (AF).

	With atrial fibrillation (n = 288)		Without atrial fibrillation (n = 7377)		P-value*
	Characteristic % (n)	Data available n (%)	Characteristic % (n)	Data available n (%)	
Age mean (SD)	73.4 (8.7)	288 (100%)	58.1 (14)	7377 (100%)	<0.001
Female	54.5% (157)	288 (100%)	75.9% (5597)	7377 (100%)	<0.001
RF-positive	60.4% (163)	270 (93.8%)	64.8% (4444)	6863 (93%)	0.140
World region		288 (100%)		7377 (100%)	<0.001
Western Europe	19.8% (57)		22.0% (1622)		
Central and Eastern Europe	9.0% (26)		12.0% (887)		
North America	67.7% (195)		57.4% (4231)		
Asia	3.5% (10)		8.6% (637)		
DAS-28-ESR	2.5 (1.9, 3.3)	183 (63.5%)	2.5 (1.8, 3.5)	5009 (67.9%)	0.982
Comorbidities and CVD risk factors					
Smoking		267 (92.7%)		6780 (91.9%)	<0.001
Current	6.0% (16)		14.4% (979)		
Previous	41.6% (111)		27.2% (1843)		
Never	52.4% (140)		58.4% (3958)		
Body mass index (kg/m2), median (IQR)	28.3 (24.1,31.7)	224 (77.8%)	27.1 (23.6, 31.4)	5392 (73.1%)	0.077
Atherosclerotic CVD	52.4% (144)	275 (95.5%)	13.3% (927)	6992 (94.8%)	<0.001
History of stroke	13.9% (40)	288 (100%)	2.6% (191)	7377 (100%)	<0.001
Heart failure	27.6% (76)	275 (95.5%)	2.1% (146)	6986 (94.7%)	<0.001
History of venous thromboembolism	19.6% (56)	286 (99.3%)	3.7% (270)	7235 (98.1%)	<0.001
Diabetes (type I and II combined)	22.3% (63)	282 (97.9%)	12.1% (862)	7095 (96.2%)	<0.001
Hyperlipidemia**	61.5% (176)	286 (99.3%)	34.6% (2543)	7341 (99.5%)	<0.001
Hypertension***	89.2% (257)	288 (100%)	47.0% (3460)	7366 (99.9%)	<0.001
History of cancer	18.4% (49)	267 (92.7%)	6.7% (439)	6514 (88.3%)	<0.001
Physical activity		90 (31.2%)		3688 (50.0%)	0.092
Less than moderate	45.6% (41)		42.8% (1579)		
Moderate	46.7% (42)		40.9% (1510)		
More than moderate	7.8% (7)		16.2% (599)		
Medications					
Lipid-lowering treatment	49.7% (143)	288 (100%)	24.6% (1813)	7376 (100%)	<0.001
Antihypertensive medication	84.7% (244)	288 (100%)	42.0% (3099)	7377 (100%)	<0.001
Antidiabetic medication	16.3% (47)	288 (100%)	9.9% (732)	7375 (100%)	<0.001
Any antiplatelet	13.9% (40)	288 (100%)	9.1% (670)	7377 (100%)	0.006
Any OAC	61.5% (177)	288 (100%)	2.5% (183)	7377 (100%)	<0.001
NSAIDs					0.895
DMARDs		288 (100%)		7377 (100%)	0.003
None	14.6% (42)		10.9% (801)		
Any csDMARD	70.5% (203)		66.3% (4890)		
bDMARD ± csDMARDs	14.9% (43)		22.9% (1686)		
Prednisolone	45.3% (130)	287 (99.7%)	39.0% (2836)	7263 (98.5%)	0.057

Abbreviations: RF, rheumatoid factor; DAS28-ESR, Disease Activity Score with 28 joint using erythrocyte sedimentation rate; CVD, cardiovascular disease; OAC, oral anticoagulant; NSAIDs, non-steroidal anti-inflammatory drugs; DMARD, disease-modifying antirheumatic drug; csDMARD, conventional synthetic DMARD; bDMARD, biologic DMARD.

* Chi-squared test for categorical variables and Mann-Whitney *U* test for continuous variables.

** defined as known diagnosis of hyperlipidemia and/or use of lipid-lowering drugs.

*** defined as known diagnosis of hypertension and/or use of any antihypertensive drugs.

stroke, peripheral arterial disease and heart failure. Data on known diagnosis of hypertension, hyperlipidaemia, diabetes, premature CVD in family, and a history of cancer was collected. A patient was considered to have hypertension if they reported either a diagnosis of hypertension and/or the use of an antihypertensive drug. Hyperlipidaemia was defined as either a known diagnosis and/or the use of a lipid-lowering drug.

Of lifestyle-related CVD risk factors, smoking status (current/ex-smoker/never) and physical activity level (moderate meaning walking or equivalent 30 min 3–5 times/week, less or more than this) were self-reported. Height, weight and body mass index (BMI) were measured.

RA-related factors included rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) status and disease activity as measured by Disease Activity Score with 28 joint using erythrocyte sedimentation rate (DAS28-ESR).

Recorded medications were the current use of OAC (both vitamin K antagonists as well as direct oral anticoagulants), antiplatelet agents, nonsteroidal anti-inflammatory drugs (NSAIDs), antirheumatic agents [methotrexate, other conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs), and biologic DMARDs (bDMARDs)], prednisolone, lipid-lowering agents, antihypertensive medication, and antidiabetic treatment.

2.2. Evaluation of need for OAC in AF

The CHA_2DS_2VASc score is used to evaluate stroke risk among AF patients and guide the initiation of OAC [14]. Common stroke risk factors are incorporated into the CHA_2DS_2VASc score [i.e. **C**ongestive heart failure, **H**ypertension, **A**ge $\geq$ 75 years, **D**iabetes mellitus, **S**troke, **V**ascular disease, **A**ge 65–74 years, **S**ex **c**ategory (female). In calculating CHA_2DS_2VASc score, the presence of congestive heart failure, hypertension, diabetes, vascular disease, age 65–74 years, and female sex yields one point each, and age $\geq$ 75 years and a history of stroke yield two points each, with a maximum score of nine. The 2014 American College of Cardiology/American Heart Association/Heart Rhythm Society (AHA/ACC/HRS) guideline for the management of patients with AF stated that for patients with CHA_2DS_2VASc score $\geq$ 2, treatment with OAC is recommended [15]. The 2012 update of the European Society of Cardiology's (ESC) guidelines for the management of AF also stated that OAC treatment is recommended with CHA_2DS_2VASc score $\geq$ 2, and should be considered with CHA_2DS_2VASc score 1 [16]. These guidelines were further developed, and the 2016 ESC guidelines for the treatment of AF state that OAC treatment is recommended, if CHA_2DS_2VASc score is $\geq$ 2 among males and $\geq$ 3 among females, and should be considered if CHA_2DS_2VASc score is 1 among males and 2 among females. Stroke risk is considered low if CHA_2DS_2VASc score is 0 among males and 1 or lower among females [17]. Of these cut-offs, we chose to apply the most conservative one to our analysis (2016 ESC guidelines). In addition to stroke risk, bleeding risk must also be taken into account when making treatment decisions about anticoagulation for AF patients [17]. We were unable to evaluate bleeding risks and HAS-BLED score due to lack of data on renal or liver disease, alcohol use, prior major or predisposition to neither bleeding nor INR values.

2.3. Statistical analysis

Comorbidities and medications are given as number of observations and percentages. We report the proportion of anticoagulated RA patients with AF stratified by stroke risk, estimated by CHA_2DS_2VASc score. We also report the proportion of anticoagulated RA patients with AF for whom OAC is recommended according to 2016 ESC guidelines as described above. Summary statistics are presented as means or medians, with standard deviation (SD) or interquartile range (IQR). For comparison of baseline characteristics across groups, we used Mann-Whitney *U* test for continuous variables, and $\chi 2$ test for categorical variables. We used univariate and multivariable logistic regression models to identify factors associated with the presence of AF among RA patients. Likewise, we applied univariate and multivariable logistic regression models to identify factors associated with the use of OAC treatment for AF in RA patients for whom OAC is recommended. All logistic regression analyses were carried out for complete cases. Data handling and statistical analyses were performed with R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

2.4. Ethical considerations

The survey was approved by the Data Protection Officer (DPO) at the Oslo University Hospital-Ullevaal (2017/7243), and a general data protection regulation evaluation was performed by the DPO at Diakonhjemmet Hospital (10/10–2018), Oslo, Norway. Each centre was responsible for obtaining the correct regulatory approval for participating in SURF-RA. Due to pseudonymization of data, a Data Protection Impact Assessment was deemed not necessary and informed patient consent was waived due to the quality assurance format of the survey.

3. Results

3.1. Description of the cohort

Of the total SURF-RA cohort (n = 14,503), we included cases with known AF status (n = 7,665 from 32 centers/17 countries). The distribution of the total SURF-RA cohort and the final study cohort across world regions and countries are shown in Supplementary Table 1. Most patients that were excluded from the cohort because data on the diagnosis of AF was missing were from a few countries in Western Europe (all 3,544 Norwegian patients, all 39 Irish patients and 3,110 Greek patients). In Greece, only one centre (Laikon Hospital, Athens) collected data on AF, and all the 176 patients from that center were included in the analysis. From Central and Eastern Europe, North America and Asia, 98.9%, 99.8% and 99.5% of patients were included, respectively.

Of the 7,665 patients, 4,426 (57.7%) were from North America, 1,679 (21.9%) from Western Europe, 913 (11.9%) from Central and Eastern Europe, and 647 (8.4%) from Asia. A total of 5,754 (75.1%) were women, and their mean (SD) age was 58.7 (14.1) years. Their median (IQR) RA disease duration was 9 (4–16) years.

3.2. Atrial fibrillation

The prevalence of AF was 3.8% in the total SURF-RA cohort (4.4% in North America, 3.4% in Western Europe, 2.8% in Central and Eastern Europe and 1.5% in Asia). The characteristics and medications of the 288 patients with AF and 7,377 patients without AF are shown in Table 1. Patients with AF were older, more often male, and less often current smokers but more often previous smokers than patients without AF. Several chronic comorbidities were more common among patients with AF compared to patients without AF (atherosclerotic CVD, history of stroke, heart failure, diabetes, hyperlipidemia, hypertension and a history of cancer). The characteristics of patients with and without AF by world region are shown in Supplementary Table 2. In addition to the lower prevalence of AF in Asia, patients in Asia were somewhat younger than patients from other continents, had less often a history of a stroke (3.1% in North America, 3.2% in Western Europe, 2.7% in Central and Eastern Europe, and 2.3% in Asia), and a lower prevalence of hypertension (50.1% in North America, 40.6% in Western Europe, 63.7% in Central and Eastern Europe and 37.3% in Asia). Diabetes was most common in North America, 14.2% (9.6% in Western Europe, 11.8% in Central and Eastern Europe, and 10.5% in Asia).

AF was more common among older adults (greater than70 years) with RA compared to younger patients, and was more frequent among men compared to women. There were no AF cases among women aged < 50 (Supplementary Figure 1).

Factors that were associated with the presence of AF in univariate

Table 2
Results of the univariate and multivariable logistic regression models for the presence of AF as the outcome.

	Univariate		Multivariable (n = 6250)	
Characteristic	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Age (per 10-year increase)	2.81 (2.50–3.17)	<0.001	2.16 (1.86–2.52)	<0.001
Male sex (reference female sex)	2.62 (2.06–3.33)	<0.001	2.29 (1.70–3.08)	<0.001
Region (reference North America)				
Western Europe	0.76 (0.56–1.02)	0.077	0.95 (0.64–1.39)	0.799
Central and Eastern Europe	0.64 (0.41–0.95)	0.033	0.84 (0.51–1.33)	0.468
Asia	0.34 (0.17–0.61)	<0.001	0.68 (0.33–1.28)	0.270
Atherosclerotic CVD*	7.19 (5.62–9.21)	<0.001	1.84 (1.34–2.52)	<0.001
Heart failure	17.89 (13.07–24.37)	<0.001	6.01 (4.07–8.83)	<0.001
Diabetes (type I and II combined)	2.08 (1.54–2.76)	<0.001	0.99 (0.69–1.39)	0.944
Hypertension**	9.36 (6.54–13.89)	<0.001	2.92 (1.91–4.61)	<0.001
Never smoker (reference ever smoker)	0.79 (0.62–1.00)	0.054	1.38 (1.03–1.86)	0.032
Current prednisolone use	1.29 (1.02–1.64)	0.034	0.99 (0.75–1.31)	0.956
Current DMARD treatment (reference bDMARD user)				
None	2.06 (1.33–3.18)	0.001	0.81 (0.47–1.39)	0.440
csDMARD user	1.63 (1.18–2.30)	0.004	0.91 (0.61–1.40)	0.662

Abbreviations: OR, odds ratio; CVD, cardiovascular disease; DMARD, disease-modifying antirheumatic drug; csDMARD, conventional synthetic DMARD; bDMARD, biologic DMARD.

* Stroke, peripheral artery disease or coronary heart disease.

** Defined as known diagnosis of hypertension or use of any antihypertensive drugs.

logistic regression models included older age, male sex, having atherosclerotic CVD, heart failure, diabetes, hypertension, and current use of prednisolone (Table 2). Compared to bDMARD users, those with only csDMARD treatment or no DMARD treatment had a higher risk of AF. In addition, being from Asia or Central and Eastern Europe was associated with a lower risk of AF compared to being from North America in univariate analysis. In multivariable logistic regression (n = 6250 complete cases), AF was positively associated with older age, male sex, atherosclerotic CVD, heart failure and hypertension, whereas there were no significant associations between AF and the current use of prednisolone or DMARDs nor world regions. DAS28-ESR was not associated with the presence of AF (univariate OR 0.98 [95% CI 0.89–1.09], p = 0.789; multivariable logistic regression results shown in Supplementary Table 3).

3.3. Implementation of guideline-recommended OAC among patients with AF

Out of 288 AF patients, 255 (88.5%) had a CHA_2DS_2VASc score for which anticoagulation is recommended (≥2 for men and ≥ 3 for women). Of them, 164 (64.3%) were anticoagulated, and 91 (35.7%) were not. These proportions varied across world regions (highest anticoagulation rates in North America, lowest in Central and Eastern Europe) (Fig. 1 A). Number and percentage of patients with and without OAC by CHA_2DS_2VASc score is shown in Fig. 1 B. Even among the patients with CHA_2DS_2VASc scores of ≥ 4, only approximately 70% received OAC treatment.

The characteristics of patients with AF for whom OAC treatment was recommended and who were or were not anticoagulated are shown in Table 3. Patients receiving OAC treatment were slightly older, had more often heart failure, and had on average higher CHA2DS2VASc score than patients who were not anticoagulated. Similar data by world region is shown in Supplementary Table 4. In the logistic regression model among AF patients for whom OAC is recommended, presence of heart failure was associated with the use of OAC treatment (Supplementary Table 5). Older age was associated with the use of OAC in univariate analysis, but the association was no longer significant in multivariable analysis.

Of the 91 AF patients who did not receive OAC treatment despite having a CHA_2DS_2VASc score of ≥ 2 among men and ≥ 3 among women, 25 (27.5%) used an antiplatelet agent (Table 3). Thus, a total of 66 (25.9%) AF patients for whom OAC is recommended did not receive any antithrombotic treatment (OAC or antiplatelet agents).

4. Discussion

Contemporary data from the last decade derived from the SURF-RA revealed that AF is common in patients with RA. AF patients are at high risk of stroke [9,10], and an essential part of stroke prevention in AF patients is OAC treatment. There has been a knowledge gap regarding OAC treatment in AF patients with RA, and in this study, we show for the first time that a considerable proportion of these patients may not receive recommended anticoagulation.

The overall prevalence of AF in RA patients in the SURF-RA is comparable to the level previously reported in the general population [18]. Previous evaluations point towards an approximately 30% increase in the risk of AF in patients with RA compared to non-RA controls [19]. In general, the risk of AF is related to several comorbidities, such as heart failure, coronary heart disease and hypertension, which are more prevalent in RA patients compared to the general population [20]. In many of the studies, the excess risk of AF among RA patients has been diminished when adjusted for cardiovascular comorbidities and other confounding factors [6]. This suggests that the increased risk of AF related to RA may result partly from the increased prevalence of structural CVD. The well-recognized associations of AF with heart failure, atherosclerotic CVD, and hypertension were apparent also in our RA cohort.

The presence of AF and its risk factors increases with age in the general population, which conforms to the observed increased occurrence of AF with age in our population. Furthermore, AF is more common in males compared to females in the general population, which is compatible with the sex distribution of AF in RA patients in this audit. Lifetime risk of AF varies between the world regions [12], which was also apparent in the SURF-RA cohort. The reasons for the higher occurrence of AF in North America compared to Asia may be related to differences in the presence of risk factors for AF, such as older age, male sex, alcohol use, hypertension, diabetes, and CVDs. In addition, factors such as genetics, ethnic factors (higher AF incidence in Caucasian vs. non-Caucasian populations), obesity and physical activity may play a role [12]. After accounting for differences in sex, age, smoking, and comorbidities in the multivariable logistic regression model (Table 2), there were no significant differences in the odds for AF between the world regions.

Systemic inflammation may induce AF by promoting structural and electrical atrial remodeling for example via atrial fibroblast activation and interfering with intracellular calcium-handling [6]. Low-grade inflammation as measured by high-sensitivity CRP is associated with an increased risk of AF, irrespective of other risk factors for AF [6]. It has been postulated that systemic inflammation and disease activity may be associated with AF in RA patients, and that reduction of inflammation by use of anti-rheumatic medication might influence this propensity [6]. In SURF-RA, anti-rheumatic treatment with csDMARDs (with partly unclear and multifaceted mechanisms of action) or no DMARD treatment

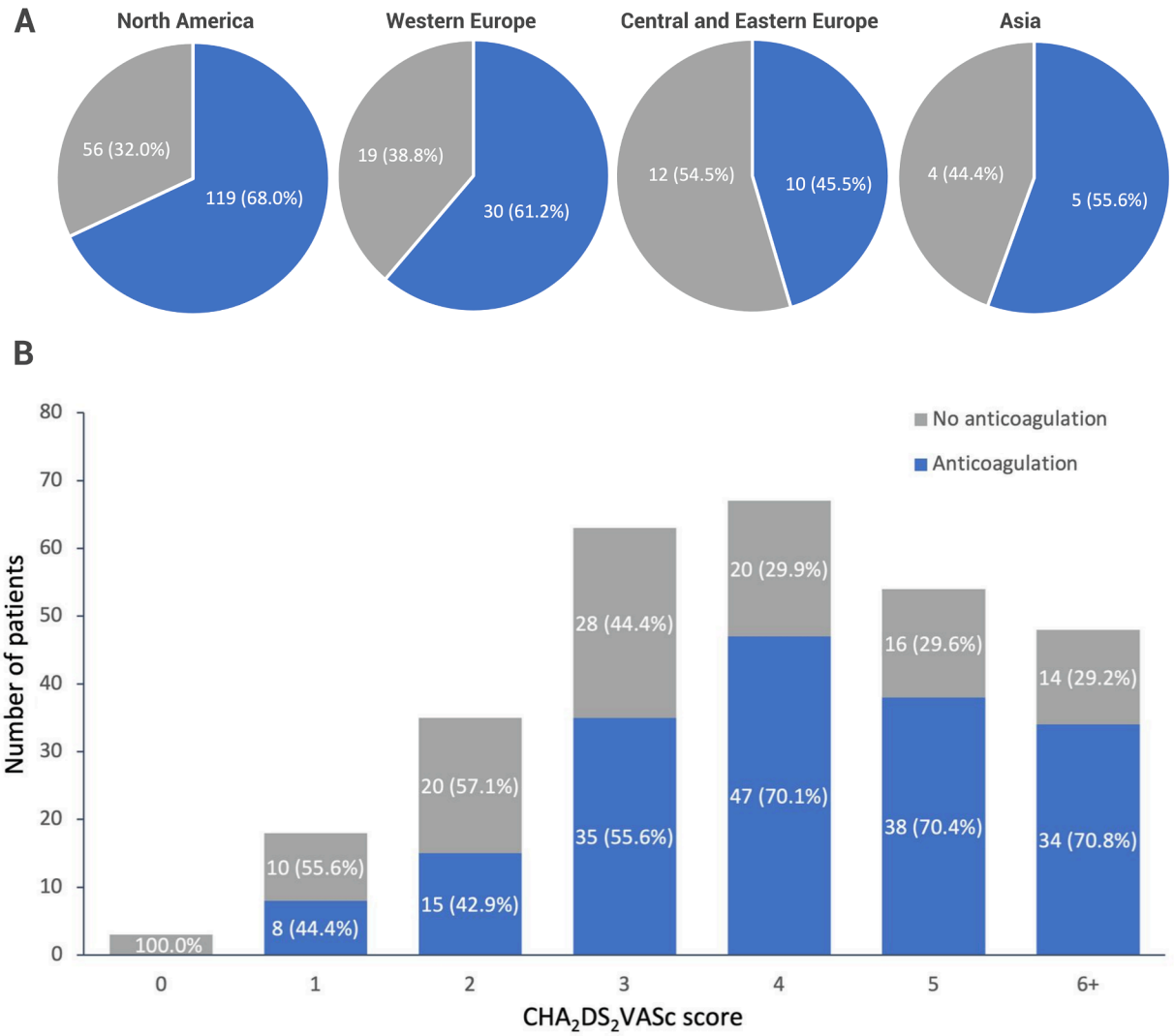

Fig. 1. Number (%) of patients with atrial fibrillation with and without OAC A] by world region in those for whom OAC is recommended (CHA_2DS_2-VASc $\geq$ 2 for men and $\geq$ 3 for women) and B) by CHA_2DS_2-VASc score in the whole cohort.

was associated with the presence of AF compared to treatment with bDMARDs (that target immune system pathways) in univariate logistic regression, but these associations disappeared after accounting for age, sex, and comorbidities in multivariable models. This may be related to selection bias because healthier and younger patients with less AF risk factors are more likely to receive bDMARD treatment for RA. We were not able to demonstrate an association between the presence of AF and RA disease activity. Since SURF-RA was a cross-sectional survey, disease activity was measured only at one point in time which may not reflect disease activity burden over time. Thus, we cannot conclude that an association between inflammation and disease activity burden and risk of AF does not exist. Longitudinal studies with information on cumulative disease activity, inflammatory markers over time, and DMARD treatments are needed to further explore these associations.

The risk of ischemic stroke, a common complication of AF, is markedly increased among RA patients compared to the general population, as shown by several observational studies [21]. Besides traditional CVD risk factors, stroke risk among patients with RA may be enhanced by prothrombotic changes involving endothelial activation, platelet function, coagulation and fibrinolysis factors as well as clot thrombodynamics [11].

Underuse of OAC is a substantial problem in the prevention of stroke among AF patients in the general population [13]. In large international studies representing the general population with AF such as GLORIA-AF, the PREFER in AF and the EORP-AF survey, approximately 80% of AF patients with an indication for OAC were anticoagulated [18,22,23]. In the SURF-RA audit, a lower proportion of AF patients with RA, for whom OAC is recommended, received OAC (63%). Thus, an unmet need for OAC treatment may exist among RA patients with AF.

A possible reason for RA patients with AF not being anticoagulated may be that, due to their chronic disease being treated regularly in specialized healthcare, these patients do not see their general practitioner as often as the general population [24]. Polypharmacy is common in RA patients and may influence drug compliance. Furthermore, polypharmacy may have an impact on safety and effectiveness on use of OAC [25]. RA patients are recommended to undergo CVD risk evaluation regularly and at least once every 5 years [20]. Despite this, RA patients have been reported to receive less CVD preventive medication both before and after a CVD event compared to the general population and to other high-risk patients [3,4,26]. Other reasons for the low rates of OAC use may be related to major bleeding risks, including history of or significant predisposing conditions to severe bleeding. Moreover, the frequent use of NSAIDs and or corticosteroids, which commonly induce hemorrhagic gastric ulcer, may affect the inclination of physicians to prescribe OAC for RA patients with AF. It is recommended that NSAIDs should be used with caution among RA patients with documented CVD or risk factors, and corticosteroid dosage and length of treatment should be kept to a minimum. We hypothesize that with the improvements in

Table 3
Characteristics of patients with AF for whom OAC is recommended (CHA_2DS_2VASc score ≥ 2 for males and ≥ 3 for females) with or without OAC treatment.

	With OAC (n = 164)		Without OAC (n = 91)		P-value*
	Characteristic % (n)	Data available n (%)	Characteristic % (n)	Data available n (%)	
Age, mean (SD)	75.7 (7.9)	164 (100%)	73.5 (7.8)	91 (100%)	0.008
Female	53.7% (88)	164 (100%)	58.2% (53)	91 (100%)	0.481
World region		164 (100%)		91 (100%)	0.176
Western Europe	18.3% (30)		20.9% (19)		
Central and Eastern Europe	6.1% (10)		13.2% (12)		
North America	72.6% (119)		61.5% (56)		
Asia	3.0% (5)		4.4% (4)		
Comorbidities and CVD risk factors					
Smoking		151 (92.1%)		86 (94.5%)	0.788
Current	5.3% (8)		7.0% (6)		
Previous	44.4% (67)		40.7% (35)		
Never	50.3% (76)		52.3% (45)		
Body mass index (kg/m2), median (IQR)	28.7 (25.1, 31.7)	128 (78%)	28.9 (24.0, 32.0)	75 (82.4%)	0.842
Atherosclerotic CVD	60.1% (95)	158 (96.3%)	53.5% (46)	86 (94.5%)	0.316
History of stroke	17.7% (29)	164 (100%)	12.1% (11)	91 (100%)	0.239
Heart failure	36.1% (57)	158 (96.3%)	22.1% (19)	86 (94.5%)	0.024
History of venous thromboembolism	21.5% (35)	163 (99.4%)	16.5% (15)	91 (100%)	0.338
Diabetes (type I and II combined)	23.9% (39)	163 (99.4%)	27.3% (24)	88 (96.7%)	0.560
Hyperlipidemia**	67.5% (110)	163 (99.4%)	58.9% (53)	90 (98.9%)	0.172
Hypertension***	94.5% (155)	164 (100%)	92.3% (84)	91 (100%)	0.487
History of cancer	19.5% (30)	154 (93.9%)	20.7% (17)	82 (90.1%)	0.819
Physical activity		40 (24.4%)		36 (39.6%)	0.276
Less than moderate	55% (22)		44.4% (16)		
Moderate	42.5% (17)		44.4% (16)		
More than moderate	2.5% (1)		11.1% (4)		
CHA2DS2VASc score, mean (SD)	4.4 (1.3)	164 (100%)	4.0 (1.5)	91 (100%)	0.013
Medications					
Lipid-lowering treatment	54.3% (89)	164 (100%)	49.5% (45)	91 (100%)	0.461
Antihypertensive medication	91.5% (150)	164 (100%)	87.9% (80)	91 (100%)	0.361
Antidiabetic medication	15.2% (25)	164 (100%)	24.2% (22)	91 (100%)	0.078
Any antiplatelet	5.5% (9)	164 (100%)	27.5% (25)	91 (100%)	<0.001
NSAIDs	44.9% (71)	158 (96.3%)	61.1% (55)	90 (98.9%)	0.014
DMARDs		164 (100%)		91 (100%)	0.123
None	17.1% (28)		11% (10)		
Any csDMARD	71.3% (117)		69.2% (63)		
bDMARD ± csDMARDs	11.6% (19)		19.8% (18)		
Prednisolone	45.7% (75)	164 (100%)	47.8% (43)	90 (98.9%)	0.950

Abbreviations: OAC; oral anticoagulant; CVD, cardiovascular disease; NSAIDs, non-steroidal anti-inflammatory drugs; DMARD, disease-modifying antirheumatic drug; csDMARD, conventional synthetic DMARD; bDMARD, biologic DMARD.

* Chi-squared test for categorical variables and Mann-Whitney *U* test for continuous variables.

** defined as known diagnosis of hyperlipidemia and/or use of lipid-lowering drugs.

*** defined as known diagnosis of hypertension and/or use of any antihypertensive drugs.

DMARD treatment strategies and concurrent decreases in NSAID and corticosteroid use, OAC treatment may safely be initiated to an increasing number of patients with RA and AF. Unfortunately, side effects or contraindications for anticoagulation therapy were not recorded in the SURF-RA, and we were not able to assess the HAS-BLED score due to no data on renal or liver disease, alcohol use, prior major or predisposition to neither bleeding nor INR values. Future studies are encouraged to shed light upon these factors and their associations with initiation of OAC treatment in RA.

In our logistic regression model, we failed to find predictors of OAC use among RA patients with AF and $CHA_2DS_2VASc \geq 2$ among men and ≥ 3 among women, with the exception of heart failure. This may be related to the uneven distribution of covariates among these patients (e.g., hypertension was present in over 90%) and relatively low number of patients, but may also indicate that unmeasured factors beyond the presence of CVD and CVD risk factors (such as estimated bleeding risk and drug compliance) affect OAC use.

The data collection in the SURF-RA did not include specification of OACs and thus we cannot elucidate how many of those treated with OACs were using vitamin K antagonist (VKA) or direct oral anticoagulants (DOACs), which could have revealed the adaptions to the newer recommended OAC treatment regimens in AF patients. Our results indicate that more focus on stroke prevention among RA patients with AF is warranted.

Audits are not epidemiologic studies and lack control groups, which applies also to the SURF-RA audit. Thus, we were not able to analyze how much of the AF burden is attributable to RA, nor directly compare OAC use rates in RA patients with AF to that in non-RA subjects. Nevertheless, indirect comparison to previous studies shows that the use of OACs in stroke prevention in the SURF-RA appears lower than in unselected AF populations [18,22,23]. Another important limitation is that the presence/absence of AF was identified from known medical history, and ECG recordings were not collected as a part of this study. Therefore, it is likely that some patients with asymptomatic or nearly asymptomatic AF have not been identified, and this may cause underestimation of AF prevalence. In addition, we did not collect information on the duration or pattern of AF. However, our main conclusion, which is that a considerable proportion of patients with AF and RA with an indication to OACs did not receive OACs, should not be affected by these limitations. We acknowledge the limitation of the SURF-RA's generalizability related to that the centres participating in the SURF-RA may not represent the situation in each country. In addition, the numbers of AF patients in total were rather low, and most AF patients were from North America with only quite small numbers of AF patients from other world regions. This may reduce the generalizability of our results in a global perspective.

5. Conclusion

In this international clinical audit, a considerable proportion of RA patients with AF who had a high estimated stroke risk by CHA_2DS_2VASc score did not receive OACs. Our findings suggest that stroke prevention with OAC might not be optimally implemented according to guidelines in these high-risk patients, although further studies with data on contraindications for anticoagulation are warranted. Moreover, prospective studies on the impact of OAC on stroke incidence in patients with RA and AF would be essential. Our findings call for attention to ensure appropriate initiation of OAC treatment among RA patients with AF.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' Contributions

A.G.S. contributed to conception, design, acquisition, analysis, interpretation, and drafted including critically revised and gave final approval of the manuscript, A.K. and S.R. contributed to conception and design of the analyses, interpretation, drafted, critically revised and gave final approval of the manuscript, J.S. contributed to design, acquisition, analysis, interpretation, critically revised and gave final approval of the manuscript, E.I., contributed to conception, acquisition, interpretation, critically revised and gave final approval of the manuscript, I.G., P. van R., G.K., C.S.C. contributed to conception, design, interpretation, critically revised and gave final approval of the manuscript.

Data availability statement

No data are available. All data relevant to the study are included in the article or uploaded as supplementary information. The data were pseudonymised by each centre before transferred to the data handling centre at Diakonhjemmet hospital, where it is stored on a central server. The data handling manager is Joe Sexton (joesexton0@gmail.com) and the data centre leader is Anne Grete Semb (a-semb@diakonsyk.no).

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2022.101117.

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