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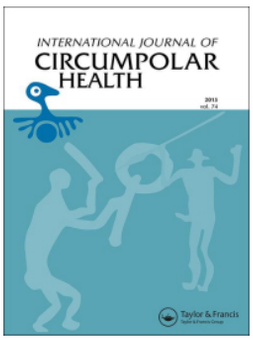

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The prevalence of atrial fibrillation in Greenland: a register-based cross-sectional study based on disease classifications and prescriptions of oral anticoagulants

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ABSTRACT

Previous studies of the prevalence of atrial fibrillation (AF) in Greenland are based on either single-point electrocardiograms (ECGs) or patients admitted with stroke. This study estimates the prevalence of AF based on disease classifications in the electronic medical record system (EMR) and prescriptions of oral anticoagulants (OACs). Patients given a diagnose classification code for AF or atrial flutter or prescribed the vitamin K antagonist Warfarin or the direct-acting oral anticoagulant Rivaroxaban were identified in the EMR. Descriptive data and selected laboratory values were extracted, and a minimum CHA_2DS_2-VASc score was calculated for the 790 patients identified in the EMR (66% men). A total prevalence of AF of 1.4% was found in the general population (1.8% among men and 1.0% among women), with a significantly lower prevalence among women younger than 70 years. There was a significant increase in AF-prevalence with advancing age ($p<0.001$) for both men and women. A minimum CHA_2DS_2-VASc was estimated and app. 10% of the patients may be undertreated with OACs. The prevalence of AF found in this study is higher than that found in previous studies in Greenland and comparable to the prevalence found in other Western countries, indicating that AF is common in Greenland.

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Introduction

Cardiovascular disease (CVD) in the Greenlandic population has been described in more detail during the past decades. It has previously been believed that the traditional Greenlandic diet, including high levels of omega-3 unsaturated fatty acids, protected Inuit against CVD, but no association was found in a prospective cohort study from 2020 [1]. In addition, the prevalence of coronary heart disease (CHD) has been found to correspond to the prevalence in Western countries based on markers of CHD, such as self-reported angina pectoris and ischaemic electrocardiogram (ECG) findings [2]. However, cardiac arrhythmias among the Greenlandic population have not been described in much detail. One study from 2009 based on single-point ECGs from 1963 indicated a low prevalence of atrial fibrillation (AF) among the Greenlandic population [3]. In contrast, a newer study from 2013 based on event recordings among patients admitted with stroke found that 30% of the patients had AF, and most of them were undiagnosed at the time of admission [4]. The latter study additionally found that Greenlanders seemingly suffered their ischaemic stroke at a younger age than stroke patients in Denmark. AF is a significant risk factor for ischaemic strokes [5,6], increasing the relative risk of stroke to 4.5 among the oldest patients [6]. A study from Canada [7] suggests that incident AF is more common at a younger age among the Indigenous people and young Indigenous people from Australia had a higher prevalence when compared to non-Indigenous people [8]. The reason is unknown, but studies from other parts of the world indicate that there are some ethnic differences regarding the risk of incident AF [9] and prevalence of AF [10], and some of these differences may be due to genetics [11,12].

However, it is well-established that the prevalence of several major risk factors for AF are increasing in Greenland. Type 2 diabetes affects between 15–34% of the population older than 65 years [13], 11.4% of the population are treated with antihypertensives [14]

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and the population is getting older. The expected lifetime has increased from 63 and 69 years to 69 and 73 years between 2000 and 2020 for men and women, respectively [15].

This study aims to estimate the prevalence of AF based on disease classification codes and prescribed oral anticoagulants (OACs) among the general population in Greenland.

Methods

Study design

The study was a retrospective cross-sectional based on data extracted from the electronic medical record system (EMR), Cambio COSMIC (Cambio, Sweden). COSMIC is used in all care settings of Greenland except one district in East Greenland and includes 96% of the population.

Data were anonymised and extracted from the EMR to Microsoft Excel® by a statistician (NS) from the Greenlandic Health Care System.

Setting and population

Greenland is a self-governing part of the kingdom of Denmark and home to 56,000 people. One-third of the population lives in the capital Nuuk, while the rest live in towns and settlements along the west, east and south coast.

Larger towns in Greenland have primary health care clinics with facilities allowing minor surgery and treatment for medical diseases such as infections, and settlements and small towns usually have a health care station with trained personnel. The only hospital in Greenland is located in Nuuk.

In Greenland, diseases are classified in the EMR by either the International Classification of Primary Care (ICPC) or the International Classification of Diseases, 10th revision (ICD −10). Patients are not always given disease classifications in the primary care settings in Greenland but consistently when discharged from hospitals in either Greenland or Denmark. Cardiovascular classifications in the EMR have been validated and agreed between 92% and 99% with patient records in Greenland [16].

Data extraction by disease classification

Data were extracted on patients classified with ICPC as having K78 (AF or atrial flutter (AFL)) or with ICD-10 as having DI48 (AF or AFL), DI480 (paroxysmal AF), DI481 (persistent AF), DI482 (chronic AF), DI483 (typical AFL), DI484 (atypical AFL) or DI489 (unspecified AF or AFL).

CHA_2DS_2-VASc -score and anticoagulant treatment

The CHA_2DS_2-VASc score is an ischaemic stroke risk factor assessment tool intended for patients with AF. It includes common risk factors for stroke: congestive heart failure, hypertension, age, diabetes, stroke, vascular disease and gender [17]. It is generally accepted that a score of zero among males and one among females (female sex being an age-dependent risk factor) equals a low risk of ischaemic strokes and mortality, and these patients may not need anticoagulant treatment. However, treatment should be considered when definitive risk factors are present (previous stroke, embolism or transient ischaemic attack and age ≤ 75 years) or in male patients with a score of one and females with a score of two. Treatment with an OAC is recommended at higher scores [17].

The CHA_2DS_2-VASc score stated in the results is not the exact score but the minimum score for the study population, as data on vascular disease and congestive heart failure were not available for extraction.

Oral anticoagulant treatment includes the vitamin K antagonist (VKA) Warfarin and direct-acting oral anticoagulant (DOAC) Rivaroxaban, both of which reduce the risk of stroke and mortality in patients with AF [18,19]. Patients prescribed either Warfarin or Rivaroxaban were included in our study to minimise the loss of patients due to lack of disease classification, as Warfarin and Rivaroxaban are the only two oral anticoagulants available in Greenland. All active prescriptions in Greenland are registered in the EMR, and patients prescribed either drug were identified by searching the EMR using the drugs' Anatomical Therapeutic Chemical (ATC) codes B01AA03 and B01AF01.

Risk factors and comorbidities

To assess well-known risk factors for AF and the prevalence of other diseases that may be caused by AF or treated with an oral anticoagulant, the most recent information on age, gender, smoking status, and blood pressure (BP) measurements were extracted from the EMR. ICD-10 classifications supplemented These data were supplemented by ICD-10 classification for pumonary embolism (PE) (I260, I269, I269A), stroke (I631-I639, I649), transient ischaemic attack (TIA) (G459), deep venous thrombosis (DVT) (I800-I809) and presence of a prosthetic heart valve (Z952, Z954) and ICPC- and ICD-10 classifications for diabetes (T89, T90 and E100-E109, E110-E119). In addition, laboratory results for thyroid-stimulating hormone (TSH), cholesterol and glycated haemoglobin (HbA1c) were included. ATC-codes

Table 1. The estimated prevalence of AF/AFl in the Greenlandic population according to age and gender. The p-value relates to the test for differences between men and women.

	Men	Women	Total	p-value
All participants, % (95% CI)	1.8 (1.6;1.9)	1.0 (0.9;1.11)	1.4 (1.3;1.5)	<0.001
Age <60 years, % (95% CI)	0.6 (0.5;0.7)	0.3 (0,2;0.4)	0.4 (0.4;0.5)	<0.001
Age 60–69 years% (95% CI),	5.9 (5.1;6.7)	2.6 (2.0;3.3)	4.5 (3.9;5,1)	<0.001
Age 70+, % (95% CI)	11.9 (10.3;13.6)	10.1 (8.6;11.8)	11.0 (9.9;12.2)	0.077

were used to identify active prescriptions for antithyroid (H03BB02), antihypertensive (C03, C04, C07, C08, C09), lipid-lowering (C10) and antidiabetic drugs (A10).

Statistics

Normality of distribution was confirmed by inspection of QQ-plots. Parametric data is described with means and standard deviations (SD) and tested with ANOVA when testing for differences between more than two groups and the unpaired t-test when testing between two groups. Non-parametric data is described with medians and the interquartile range (IQR) and tested with the Wilcoxon Signed Rank Test when testing for differences between more than two groups and with the Wilcoxon Mann-Whitney Test when testing for differences between two groups. Binary data is described with frequencies and 95% confidence intervals (CI) and tested using the Chi-Square Test.

Prevalence is calculated based on data on population size from Statistics Greenland [15].

Statistical analyses were performed in STATA® (version 16). A p-value less than 0.05 was considered significant.

Ethics

The study was approved by Health Research Ethics Committee in Greenland (KVUG 2020–18) and the health authorities in Greenland and was conducted according to the Helsinki declaration. No informed consent from the participants was needed as all data from the EMR was anonymised upon extraction.

Results

A total of 790 patients (66% men) were identified by either ICD10- or ICPC-code or as having a prescription for either Warfarin or Rivaroxaban. Of these, 399 (145 female and 254 male, p = 0.38) were prescribed an OAC without being classified as having AF or AFL, and 105 (28 female and 77 male, p = 0.14) patients had an AF-/AFl-classification but were not prescribed an OAC. The remaining 286 (94 female and 192 male, p = 0.78) patients were classified as having AF or AFL in the EMR and prescribed an OAC.

The estimated prevalence of AF/AFL in the Greenlandic population is shown in Table 1. We found a significant increase in prevalence for both female and male participants with advancing age (p < 0.001 when comparing participants aged <60 years with 60–69-year -old participants and participants aged 60–69 years with those aged 70 years or older) and a higher prevalence among males than females among the population younger than 70 years.

A description of all participants and a comparison of the characteristics between men and women are shown in Table 2. The comparison indicates that the female participants had a lower diastolic BP but were older and had higher cholesterol levels than the men. The female participants also had a higher prevalence of stroke, pulmonary embolism, diabetes and were more often prescribed antithyroid medication.

Among the 105 patients with a disease classification for AF or AFL and no active prescription for either Warfarin or Rivaroxaban, 21 females had a CHA_2DS_2-VASc score of at least two, and 56 males had a score of at least one.

Discussion

We found a prevalence of AF of 1.4% among the general population in Greenland. Our results contrast the prevalence of only 0.6% seen in a study based on single-point ECGs from East Greenland from 1963 [3], but the lifestyle in Greenland has changed since 1963, including levels of physical activity, smoking and dietary habits [20], as well as an increase in the life expectancy has been seen [15]. Therefore, the prevalence of AF in Greenland may have increased since 1963, but it has been shown elsewhere that prevalence calculated based on single-point ECGs is more likely to miss cases with paroxysmal AF and consequently underestimate the true prevalence of total AF [21]. Thus, as our study is based on disease classification codes and medication, it is more likely to include patients with all AF types, although our study setup only allows us to include patients already diagnosed or treated for AF and therefore misses undiagnosed patients. However, our

Table 2. Characteristics and comparison of the participants.

	Men	N	Women	N	p-value	Total	N
Age, years (SD)	64.6 (11.3)	523	68.7 (12.4)	267	<0.001	66.0 (11.8)	790
BMI, kg/m^2 (SD)	31.3 (6.9)	288	31.2 (7.0)	167	0.890	31.3 (6.9)	455
Daily smokers, n (%)	123 (41.4)	297	61 (35.3)	173	0.187	39.2 (34.7;43.7)	470
Systolic BP, mmHg (SD)	136.5 (14.3)	206	135.6 (18.8)	142	0.64	136.1 (16.3)	348
Diastolic BP, mmHg (SD)	83.3 (10.3)	206	77.7 (9.9)	142	<0.001	81.0 (10.5)	348
TSH U/L, (IQR)	0.9 (0.6;1.4)	412	0.9 (0.5;1.4)	223	0.154	0.9 (0.6;1.4)	635
HbA1c, mmol/mol (IQR)	42 (39;46)	483	43 (40;47)	246	0.091	43 (39;46)	729
Total cholesterol, mmol/l (SD)	4.3 (1.1)	478	4.8 (1.2)	241	<0.001	4.5 (1.2)	719
LDL, mmol/L (SD)	2.3 (1.1)	476	2.5 (1.2)	241	0.004	2.4 (1.2)	717
HDL, mmol/l (SD)	1.0 (0.4)	479	1.2 (0.4)	241	<0.001	1.1 (0.4)	720
ICD-10/ICPC-codes							
AF/AFl, n (%)	269 (51.4)	523	122 (45.7)	267	0.127	391 (49.5)	790
Diabetes, n (%)	89 (17.0)	523	65 (24.3)	267	0.014	154 (19.5)	790
Stroke, n (%)	59 (11.3)	523	44 (16.5)	267	0.040	103 (13.0)	790
TIA, n (%)	11 (2.1)	523	10 (3.8)	267	0.175	21 (2.7)	790
DVT, n (%)	6 (1.2)	523	2 (0.8)	267	0.597	8 (1.0)	790
PE, n (%)	0 (0.0)	523	3 (1.1)	267	0.015	3 (0.4)	790
Prosthetic heart valve, n (%)	11 (2.1)	523	6 (2.3)	267	0.895	17 (2.2)	790
Medication							
Warfarin, n (%)	55 (10.5)	523	25 (9.4)	267	0.611	80 (10.1)	790
Rivaroxaban, n (%)	391 (74.8)	523	214 (80.1)	267	0.091	605 (76.6)	790
Antidiabetic drugs, n (%)	64 (12.2)	523	39 (14.6)	267	0.349	103 (13.0)	790
Antihypertensive drugs, n (%)	425 (81.3)	523	224 (83.9)	267	0.361	649 (82.2)	790
Lipid-lowering drugs, n (%)	247 (47.2)	523	114 (42.7)	267	0.227	361 (45.7)	790
Antithyroid drugs, n (%)	3 (0.6)	523	14 (5.2)	267	<0.001	17 (2.2)	790

findings are in line with studies from other parts of the world, as the worldwide prevalence of AF in adults is estimated to be between two and four per cent [22], between one and two per cent in the Canadian and the general US population [10,23] and between 0.5% and three per cent in most low- and middle-income countries [24].

The prevalence of AF found in our study was higher among men than women, as described in other studies [25]. However, the gender difference was only prominent among those younger than 70 years. Similarly, no difference between the genders was found in the prevalence of AF among Italian nonagenarians [26], and the highest prevalence in the US was found among females older than 75 years [27]. The catching up in prevalence may be explained by the longer life expectancy among women, as the total number of women living with AF may exceed the number of men [27–29]. Moreover, with lifetime expectancies app. eight years shorter than in the US [15,30] and ten years shorter than in Denmark [31], this may become evident already at 70 years in Greenland as only five per cent of the Greenlandic population are older than 70 years [15].

Hypertension, diabetes and smoking are common in Greenland [13,14,32]. Compared to the female participants, the men in our study were more often smokers. In addition, men had lower total cholesterol, which has been found to have an inverse relationship with the risk of AF [33]. Prescriptions for antithyroid medication were more common among women, as was diabetes. Hyperthyroidism has been found to increase the risk of AF up to 42% [34], and the odds ratio for developing AF with diabetes is between 1.4 and 1.6 for men and women, respectively [35]. Thus, although women in Greenland appear to have a lower prevalence of AF until the age of 70 years, they still carry a high burden of risk factors.

Men and women with AF have been found to have different risk profiles [36,37], and women are more likely to present atypical symptoms for AF than men, which may delay diagnosis [37]. This may also be the case in Greenland, as the difference in prevalence is not likely to be attributed to healthcare-seeking behaviour as women in Greenland have more contacts with the primary health care system than men [38]. In addition, we found that the women in our study had a higher prevalence of stroke than men. Generally, women older than 65 years with AF have a higher rate of ischaemic strokes than men with AF [29,39,40], and our results may indicate that women in Greenland more often suffer a stroke before being diagnosed with AF.

Finally, we found the minimum percentage of the study population with no prescription for OACs despite having a CHA_2DS_2-VASc score of at least one for men and two for women to be almost ten per cent. The setup of our study does not allow us to evaluate whether OACs were contraindicated for these patients or, for example, discontinued because of side effects, and as we were not able to include all parameters used in calculating the total CHA_2DS_2-VASc score, the actual percentage may be higher.

However, when comparing our results to those found by Gamra et al. in their study from 2014 [41], our results suggest a relatively high treatment rate in Greenland. Gamra et al. found that the treatment rate with OACs across 26 countries ranged between 31.7% and 66.7% among patients with a CHA_2DS_2-VASc score of two or more, with the highest coverage rate being in the Middle East/Africa [41]. However, as stated above, our results must be interpreted with caution.

Strengths and limitations

Strengths

Ours is the first study of the prevalence of AF among the general population in Greenland, as the EMR COSMIC is used in almost all of Greenland and covers 96% of the population. It is also the first study of AF in Greenland based on OAC-prescription and disease classification codes, including patients diagnosed in different settings.

Limitations

First and foremost, we may have missed some patients diagnosed with AF, as disease classification has not been done consequently in Greenland's primary health care sector but has become a point of focus in recent years. However, including prescription history and other diagnoses requiring OACs enables us to identify most patients with AF, as ICD-10 disease classification codes are registered in the EMR when discharging patients from the hospital, as are all prescriptions from primary and secondary health care sectors.

This setup only allows us to include patients diagnosed, registered or medically treated as having AF. The number of undiagnosed Greenlanders with AF remains unknown and must be explored using different methods. In addition, as some included patients had multiple ICD-10 codes for AF type and the ICPC codes does not specify which kind of AF the patient is suffering from, it is not possible to give an accurate estimation of the distribution of paroxysmal AF, chronic AF and persistent AF among the included patients.

Our results do not offer any estimations on possible genetic effects on the prevalence of AF in Greenland, as COSMIC covers all residents with a permanent address in Greenland, including residents of other nationalities and ethnicities. The risk factors for AF are extracted after the participant was either diagnosed with AF or had started treatment with an OAC. This may cause us to over- or underestimate the prevalence of the included risk factors regarding AF, as some conditions may no longer have been present or treated at the time of the study, and some may have occurred or started treatment after the diagnosis of AF were given.

Finally, our data does not include information on congestive heart failure or vascular disease; however, our data allows us to estimate a minimum number of patients with a CHA_2DS_2-VASc score above zero for males and one for females, and consequently a minimum number of potentially undertreated patients.

Conclusion

In conclusion, we found a prevalence of AF and a pattern of AF comparable to other Western countries. Our findings suggest that AF poses the same challenges in Greenland as elsewhere, as Greenland's life expectancy and the prevalence of risk factors is increasing. Early detection and timely treatment with OACs should be a point of focus in the future to decrease the risk of stroke and AF-related morbidity and -mortality, and further studies should evaluate whether AF and AFL carry the same disease burden in Greenland as elsewhere.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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