

Risk profile, antithrombotic treatment and clinical outcomes of patients in Nordic countries with atrial fibrillation – results from the GARFIELD-AF registry

Marita Knudsen Pope, Dan Atar, Arne Svilaas, Torstein Hole, Jørn Dalsgaard Nielsen, Ulrik Hintze, Milita Crisby, Pekka Raatikainen, K. E. Juhani Airaksinen, Saverio Virdone, Karen Pieper, Gloria Kayani, Jean-Yves Le Heuzey, Jan Steffel, Janina Stepinska, Jean-Pierre Bassand, A. John Camm & for the GARFIELD-AF Investigators

To cite this article: Marita Knudsen Pope, Dan Atar, Arne Svilaas, Torstein Hole, Jørn Dalsgaard Nielsen, Ulrik Hintze, Milita Crisby, Pekka Raatikainen, K. E. Juhani Airaksinen, Saverio Virdone, Karen Pieper, Gloria Kayani, Jean-Yves Le Heuzey, Jan Steffel, Janina Stepinska, Jean-Pierre Bassand, A. John Camm & for the GARFIELD-AF Investigators (2021) Risk profile, antithrombotic treatment and clinical outcomes of patients in Nordic countries with atrial fibrillation – results from the GARFIELD-AF registry, *Annals of Medicine*, 53:1, 485-494, DOI: [10.1080/07853890.2021.1893897](https://doi.org/10.1080/07853890.2021.1893897)

To link to this article: <https://doi.org/10.1080/07853890.2021.1893897>



© 2021 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.



[View supplementary material](#)



Published online: 05 Apr 2021.



[Submit your article to this journal](#)



Article views: 154





[View related articles](#)



[View Crossmark data](#)

Risk profile, antithrombotic treatment and clinical outcomes of patients in Nordic countries with atrial fibrillation – results from the GARFIELD-AF registry

Marita Knudsen Pope^{a,b}, Dan Atar^{a,c} , Arne Svilaas^{d,e}, Torstein Hole^{f,g}, Jørn Dalsgaard Nielsen^h, Ulrik Hintzeⁱ, Milita Crisby^j, Pekka Raatikainen^k, K. E. Juhani Airaksinen^l , Saverio Virdone^m, Karen Pieper^m, Gloria Kayani^m, Jean-Yves Le Heuzeyⁿ, Jan Steffel^o, Janina Stepinska^p, Jean-Pierre Bassand^{m,q}, and A. John Camm^r; for the GARFIELD-AF Investigators*

^aInstitute of Clinical Medicine, University of Oslo, Oslo, Norway; ^bHamar Hospital, Innlandet Hospital Trust, Hamar, Norway; ^cDepartment of Cardiology, Oslo University Hospital, Ullevål, Oslo, Norway; ^dNymoan Medical Centre, Kongsberg, Norway; ^eLipid Clinic, Oslo University Hospital, Oslo, Norway; ^fClinic of Medicine and Rehabilitation, More and Romsdal Hospital Trust, Alesund, Norway; ^gDepartment of Circulation and Medical Imaging, Faculty of Medicine and Health Sciences, NTNU – Norwegian University of Science and Technology, Trondheim, Norway; ^hDepartment of Cardiology, Copenhagen University Hospital, Copenhagen University, Copenhagen, Denmark; ⁱDepartment of Cardiology, Hospital of South West Jutland, Esbjerg, University of Southern Denmark, Denmark; ^jDepartment of Neurobiology, Care Science and Society, Karolinska University Hospital, Stockholm, Sweden; ^kDepartment of Cardiology, Heart and Lung Center, Helsinki University Hospital, Tampere, Finland; ^lHeart Centre, Turku University Hospital and University of Turku, Turku, Finland; ^mThrombosis Research Institute, London, UK; ⁿGeorges Pompidou Hospital, René Descartes University, Paris, France; ^oDivision of Electrophysiology and Pacing, Department of Cardiology, University Heart Center Zurich, Zurich, Switzerland; ^pInstitute of Cardiology, Intensive Cardiac Therapy Clinic, Warsaw, Poland; ^qUniversity of Besançon, Besançon, France; ^rCardiology Clinical Academic Group Molecular & Clinical Sciences Research Institute, St. George's University of London, London, UK

ABSTRACT

Aims: The objective was to evaluate the clinical characteristics, management and two-year outcomes of patients with newly diagnosed non-valvular atrial fibrillation at risk for stroke in Nordic countries.

Methods: We examined the baseline characteristics, antithrombotic treatment, and two-year clinical outcomes of patients from four Nordic countries.

Results: A total of 52,080 patients were enrolled in the GARFIELD-AF. Out of 29,908 European patients, 2,396 were recruited from Nordic countries. The use of oral anticoagulants, alone or in combination with antiplatelet (AP), was higher in Nordic patients in all CHA₂DS₂-VASc categories: 0–1 (72.8% vs 60.3%), 2–3 (78.7% vs 72.9%) and ≥4 (79.2% vs 74.1%). In Nordic patients, NOAC±AP was more frequently prescribed (32.0% vs 27.7%) and AP monotherapy was less often prescribed (10.4% vs 18.2%) when compared with Non-Nordic European patients. The rates (per 100 patient years) of all-cause mortality and non-haemorrhagic stroke/systemic embolism (SE) were similar in Nordic and Non-Nordic European patients [3.63 (3.11–4.23) vs 4.08 (3.91–4.26), *p* value = .147] and [0.98 (0.73–1.32) vs 1.02 (0.93–1.11), *p* value = .819], while major bleeding was significantly higher [1.66 (1.32–2.09) vs 1.01 (0.93–1.10), *p* value < .001].

Conclusion: Nordic patients had significantly higher major bleeding than Non-Nordic-European patients. In contrast, rates of all-cause mortality and non-haemorrhagic stroke/SE were comparable.

Clinical Trial Registration: Unique identifier: NCT01090362. URL: <http://www.clinicaltrials.gov>.

Key Message: Nordic countries had significantly higher major bleeding than Non-Nordic-European countries. Rates of mortality and non-haemorrhagic stroke/SE were similar.

ARTICLE HISTORY

Received 14 October 2020
Revised 9 February 2021
Accepted 16 February 2021



KEYWORDS

Atrial fibrillation; stroke prevention; antithrombotic treatment; Nordic countries


Introduction

One in four individuals is expected to develop atrial fibrillation (AF) after the age of 40 [1–3], and the

prevalence and incidence of patients with this condition are predicted to rise considerably in the next few decades. The exact reasons are unknown, but it has

CONTACT Dan Atar  dan.atar@medisin.uio.no  Institute of Clinical Medicine, University of Oslo, Oslo, Norway

*A complete list of the investigators and NORDIC countries investigators are given in [Appendix](#).

 Supplemental data for this article can be accessed [here](#).

© 2021 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

been partly explained by an increase in comorbidities and cardiovascular risk factors, and an ageing population [4–6]. AF is related to higher risk of mortality and morbidity, the risk of stroke being nearly fivefold increased [7–11] and the severity of these cardioembolic strokes tends to be greater than atherosclerotic strokes [12,13]. Oral anticoagulation (OAC) can prevent major ischaemic events and prolong patient lives and is, therefore, an integral part of the clinical management of AF patients [1,12].

Non-vitamin K antagonist oral anticoagulants (NOACs) have been shown to reduce the rate of all-cause mortality, stroke/systemic embolism (SE) and intracranial haemorrhage when compared to vitamin K-antagonists (VKA) in patients with non-valvular AF, with a faster onset of action, fewer interactions and no requirement for INR-monitoring [14–17]. Treatment with antiplatelet drugs (AP) has been shown to be substantially less effective than OAC while bleeding risk is similar [18,19]. Consequently, for stroke prevention in the non-valvular AF patient population, European, American, Canadian and Asia-Pacific guidelines consider NOACs the first choice in antithrombotic treatment, while AP therapy is not recommended [1,20,21].

The Global Anticoagulant Registry in the FIELD-AF (GARFIELD-AF) is a prospective, international, multi-centre registry of adult patients with newly diagnosed non-valvular atrial fibrillation (NVAF) and one or more additional risk factors for stroke. The main goal of the registry is to identify best practices as well as differences in stroke prevention strategies for AF patients. There might be substantial regional and intraregional differences among baseline characteristics and use of antithrombotic therapies in patients with new NVAF [22,23]. To our knowledge, no studies have investigated the combined Nordic AF patient population apart from a few individual national studies [8,13,24]. All the Nordic countries are followers of the welfare state concept with similar healthcare systems and some individual differences [25]. Therefore, we aimed to assess the baseline characteristics, antithrombotic treatment and clinical outcomes through 24 months for patients in Nordic countries, and the results were compared with patients from Non-Nordic European countries. For clinical outcomes, results were also compared with Non-European countries.

Methods

Study design and participants

The Global Anticoagulant Registry in the FIELD in AF (GARFIELD-AF) is an international registry of adult

patients with newly diagnosed non-valvular (AF) with at least one additional risk factor for stroke [22,23]. Patients were enrolled prospectively and consecutively in 35 countries and 5 consecutive cohorts of approximately 10,000 patients with intended 2-year follow-up. A total of 52,080 patients were prospectively enrolled (2010–2016) from 35 countries and 29,908 patients were registered from Europe, and of these 2,396 from the four Nordic countries (Sweden, Denmark, Finland and Norway). The sites were randomly selected and when random site selection did not generate the required number of sites in a given country, the national lead investigators were asked to recommend sites to make up the numbers (18 out of 1317 sites). The sites represent different care settings in each participating country (office-based practice; hospital departments including neurology, cardiology, geriatrics, internal medicine, and emergency; anticoagulation clinics; and general or family practice)

Data collection

Data collection at baseline included patient demographics, medical history, care setting, type of AF (also collected during follow-up), and antithrombotic treatment (vitamin K antagonists, non-vitamin K antagonist oral anticoagulants, and antiplatelet treatment). Data on components of the CHA₂DS₂-VASc and HAS-BLED risk stratification schemes were used to assess the risks of stroke and bleeding, retrospectively. HAS-BLED scores were calculated excluding fluctuations in the international normalized ratio. In addition, the risks of death, stroke/SE and major bleeding were assessed at baseline with the recently described GARFIELD-AF risk calculator [26].

Patients were contacted at 4-monthly intervals *via* telephone or postal mail. Data were collected using an electronic case report form and were examined for completeness and accuracy by the coordinating centre (Thrombosis Research Institute, London, UK). In accordance with the study protocol, 20% of all data submitted electronically were monitored against source documentation [27].

Initiated antithrombotic treatments were categorized as VKA, NOACs [Factor Xa inhibitors (FXa) and Direct Thrombin inhibitors (DTI)], and AP, alone or in combination. The incidences of stroke/systemic embolism, major bleeding, all-cause death, cardiovascular and non-cardiovascular death, acute coronary syndromes, and congestive heart failure were recorded over two years. Only the first occurrence of an event was considered. Data used in this analysis were

extracted from the GARFIELD-AF registry in November 2018.

Clinical events were defined using standardized definitions, which have been reported previously [22,23]. Vascular disease included peripheral artery disease and/or coronary artery disease. Chronic kidney disease was classified according to National Kidney Foundation guidelines into two groups; moderate-to-severe (stages 3–5), or mild (stages 1 and 2) or none [28]. Congestive heart failure was defined as current/prior history of congestive heart failure or left ventricular ejection fraction of <40%.

Ethics statement

All patients signed written informed consent to participate prior to enrolment. Approvals for the registry protocol were obtained from independent ethics committees and/or hospital-based institutional boards. The database is being conducted according to the principles of the Declaration of Helsinki and the International Conference on Harmonisation – Good Pharmaco-epidemiological and Clinical Practice guidelines.

Statistical analyses

Categorical variables were expressed as percentages and frequency, and continuous variables as mean \pm standard deviation (SD). Clinical outcomes were presented as person-time event rates (per 100 person-years) with 95% confidence intervals. Differences in baseline characteristics were performed using chi-square tests for categorical variables and Wilcoxon sign-rank tests for continuous variables. Statistical analyses were performed using SAS[®] software version 9.4 (SAS Institute Inc., Cary, NC, USA.)

Results

A total of 2,396 patients from four Nordic countries, Sweden ($n=1,233$), Denmark ($n=532$), Finland ($n=359$) and Norway ($n=272$), were included in the study. From Non-Nordic-European countries, 27,512 patients were enrolled from Austria, Belgium, The Czech Republic, France, Germany, Hungary, Italy, the Netherlands, Poland, Russia, Spain, Switzerland, Turkey, Ukraine and the United Kingdom (Figure 1).

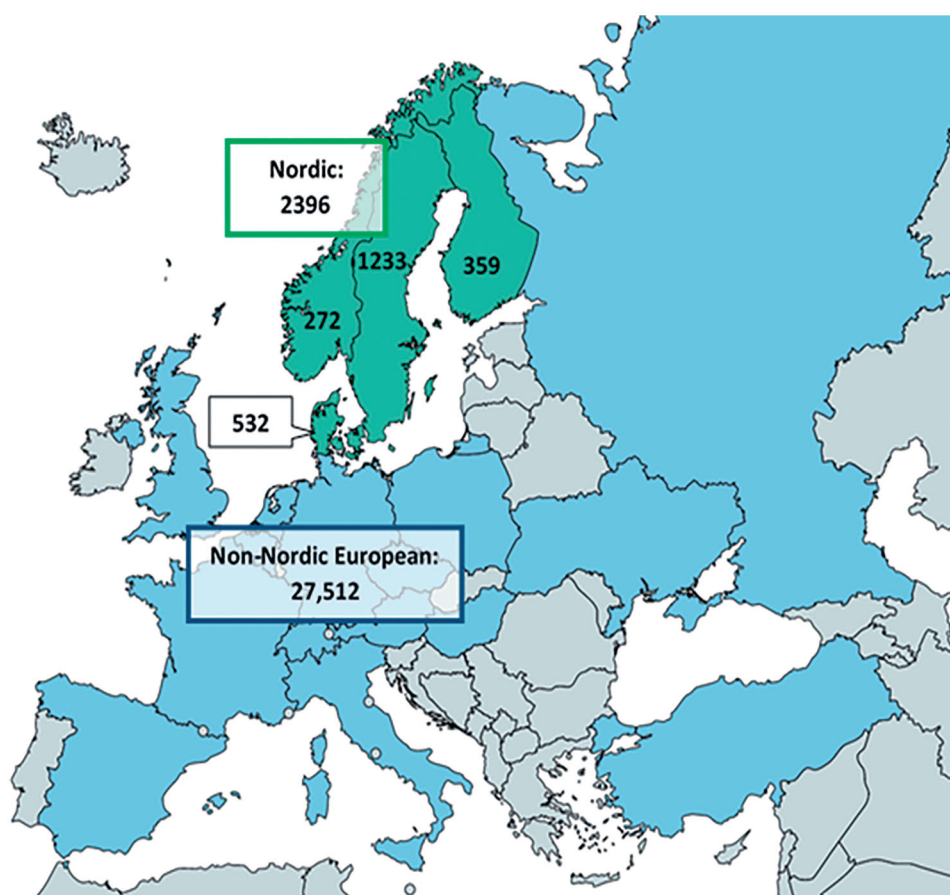


Figure 1. Nordic and Non-Nordic European countries with number of patients included.

Care setting

In Nordic countries, care-setting speciality at diagnosis was cardiology (45.4%), primary care/general practice (27.9%), followed by internal medicine (23.3%). In Non-Nordic-European countries, speciality at diagnosis was cardiology (57.3%), internal medicine (20.9%) followed by general practitioners (19.3%) (Table 1).

Patient characteristics

Nordic countries patients were older (mean age 71.7 years) than those in Non-Nordic European countries (mean age 70.6 years), and a larger group were

≥65 years (Nordic 80.1%, Non-Nordic European 72.6%) (Table 2).

The number of patients with a history of hypertension, hypercholesterolaemia and vascular disease was lower in the Nordic patients than in the Non-Nordic European patients (69.4% vs 80.5%, 36.1% vs 47.2%, 15.9% vs 28.7% respectively). Congestive heart failure (CHF) and moderate to severe chronic kidney disease (CKD) were also less common in Nordic patients (14.5% vs 23.6%) and (7.9% vs 12.8%).

The mean CHA₂DS₂ and CHA₂DS₂-VASc scores in Nordic countries were 1.8 and 3.2, and in Non-Nordic European patients 1.9 and 3.4, respectively. Almost 9 out of 10 patients in Nordic and Non-Nordic European

Table 1. Care-setting speciality at diagnosis in Nordic and Non-Nordic European countries, and in the four Nordic countries Sweden, Denmark, Finland and Norway.

Care-setting specialty	Nordic (n = 2396)	Non-Nordic European (n = 27,512)	Sweden (n = 1233)	Denmark (n = 532)	Finland (n = 359)	Norway (n = 272)
Internal Medicine, n (%)	559 (23.3)	5754 (20.9)	296 (24.0)	38 (7.1)	189 (52.6)	36 (13.2)
Cardiology, n (%)	1089 (45.4)	15,757 (57.3)	485 (39.3)	410 (77.1)	33 (9.2)	161 (59.2)
Neurology, n (%)	73 (3.0)	550 (2.0)	15 (1.2)	6 (1.1)	51 (14.2)	1 (0.4)
Geriatrics, n (%)	6 (0.3)	142 (0.5)	2 (0.2)	4 (0.8)	0 (0.0)	0 (0.0)
Primary Care/General Practice, n (%)	669 (27.9)	5306 (19.3)	435 (35.3)	74 (13.9)	86 (24.0)	74 (27.2)

Table 2. Clinical characteristics for Nordic and Non-Nordic European patients.

Baseline characteristics	Nordic (n = 2396)	Non-Nordic European (n = 27,512)	p Value
Male, n (%)	1389 (58.0)	14,944 (54.3)	<.001
Age at diagnosis, mean (SD)	71.7 (9.7)	70.6 (11.1)	<.001
Age group, n (%)			<.001
<65	476 (19.9)	7549 (27.4)	
65–69	413 (17.2)	4171 (15.2)	
70–74	491 (20.5)	4693 (17.1)	
≥75	1016 (42.4)	11,099 (40.3)	
BMI (kg/m ²), mean (SD)	28.2 (5.8)	28.9 (5.5)	<.001
Pulse (bpm), mean (SD)	100.2 (30.7)	90.3 (26.8)	<.001
Systolic BP (mmHg), mean (SD)	139.1 (21.4)	135.6 (19.2)	<.001
Hypertension, n (%)	1659 (69.4)	22,104 (80.5)	<.001
Hypercholesterolaemia, n (%)	845 (36.1)	12540 (47.2)	<.001
Diabetes, n (%)	387 (16.2)	5981 (21.7)	<.001
Heart failure, n (%)	348 (14.5)	6497 (23.6)	<.001
Vascular disease ^a , n (%)	379 (15.9)	7845 (28.7)	<.001
History of stroke/TIA/SE, n (%)	323 (13.5)	3125 (11.4)	.002
History of bleeding, n(%)	46 (1.9)	719 (2.6)	.039
Moderate to Severe CKD, n(%)	185 (7.9)	3424 (12.8)	<.001
Type of AF, n (%)			<.001
Permanent	222 (9.3)	4367 (15.9)	
Persistent	160 (6.7)	4160 (15.1)	
Paroxysmal	529 (22.1)	6853 (24.9)	
Unclassified	1485 (62.0)	12,129 (44.1)	
Alcohol consumption light to heavy, n (%)	1095 (80.3)	11,883 (50.3)	<.001
Ex-/Current smoker, n (%)	707 (40.1)	8861 (34.8)	<.001
CHA ₂ DS ₂ Score, mean (SD)	1.8 (1.1)	1.9 (1.1)	<.001
CHA ₂ DS ₂ -VASc Score, mean (SD)	3.2 (1.5)	3.4 (1.6)	<.001
CHA ₂ DS ₂ -VASc score ≥ 2, n (%)	2086 (87.6)	23,960 (88.2)	.408
HAS-BLED score, mean (SD)	1.4 (0.9)	1.4 (0.9)	.002
GARFIELD-AF Score for death ^b , mean (SD)	6.6 (6.5)	7.7 (5.4)	<.001
GARFIELD-AF Score for stroke ^b , mean (SD)	1.9 (1.4)	2.0 (1.5)	.002
GARFIELD-AF Score for major bleeding ^d , mean (SD)	2.0 (1.3)	2.1 (1.5)	.050

^aDefined as peripheral vascular disease and/or coronary artery disease.

^bIndicates the probability of death occurrence within 2 years of follow-up.

^cIndicates the probability of non-haemorrhagic stroke occurrence within 2 years of follow-up.

^dIndicates the probability of major bleeding occurrence within 2 years of follow-up.

patients had a $\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$ (87.6% and 88.2%). The mean HAS-BLED score was 1.4 for both Nordic and Non-Nordic-European patients. The GARFIELD-AF score showed that Nordic patients had a lower expected rate of all-cause mortality and stroke, while the expected rate of bleeding was comparable to Non-Nordic Europeans.

A high frequency of smoking was observed in both Nordic and Non-Nordic European patients (40.1% and 34.8%, respectively). The proportion of patients drinking alcohol (light to heavy consumption), was higher in Nordic patients (80.3%) than Non-Nordic European patients (50.3%).

Clinical characteristics for patients from the four Nordic countries are shown in Table 3.

Antithrombotic therapy

Figure 2 depicts the distribution of antithrombotic therapies. Over 90% of the European patients (Nordic and Non-Nordic) received antithrombotic therapy. A total of 11.4% and 9.8% of patients respectively in Nordic and Non-Nordic European countries did not receive any antithrombotic therapy. Nordic countries had a higher use of OAC, alone or in combination with AP, in all $\text{CHA}_2\text{DS}_2\text{-VASc}$ categories; 0–1 (72.8% vs 60.3%), 2–3 (78.7% vs 72.9%) and ≥ 4 (79.2% vs 74.1%), and lower use of AP monotherapy than Non-Nordic European countries in all $\text{CHA}_2\text{DS}_2\text{-VASc}$ categories; 0–1 (7.6% vs 19.8%), 2–3 (8.8% vs 17.0%), ≥ 4 (13.4% vs 19.0%). In both Nordic and Non-Nordic European patient populations, more than four in five

Table 3. Selected clinical characteristics for patients in the four Nordic countries Sweden, Denmark, Finland and Norway.

Baseline characteristics	Sweden (n = 1233)	Denmark (n = 532)	Finland (n = 359)	Norway (n = 272)
Age at Diagnosis, mean (SD)	72.9 (8.7)	71.5 (10.8)	69.8 (10.3)	69.6 (10.0)
BMI (kg/m^2), mean (SD)	27.9 (5.4)	27.9 (5.6)	30.5 (7.4)	28.5 (5.8)
Systolic BP (mmHg), mean (SD)	138.1 (19.4)	138.4 (21.4)	143.7 (26.5)	137.8 (20.6)
Hypercholesterolaemia, n (%)	341 (28.6)	233 (44.7)	137 (38.4)	134 (49.4)
Diabetes, n (%)	199 (16.1)	74 (13.9)	80 (22.3)	34 (12.5)
Stroke/TIA/SE, n (%)	147 (11.9)	64 (12.1)	88 (24.5)	24 (8.9)
Heart failure, n (%)	136 (11.0)	113 (21.2)	69 (19.2)	30 (11.0)
$\text{CHA}_2\text{DS}_2\text{-VASc}$ Score, mean (SD)	3.1 (1.4)	3.2 (1.5)	3.5 (1.6)	2.8 (1.4)

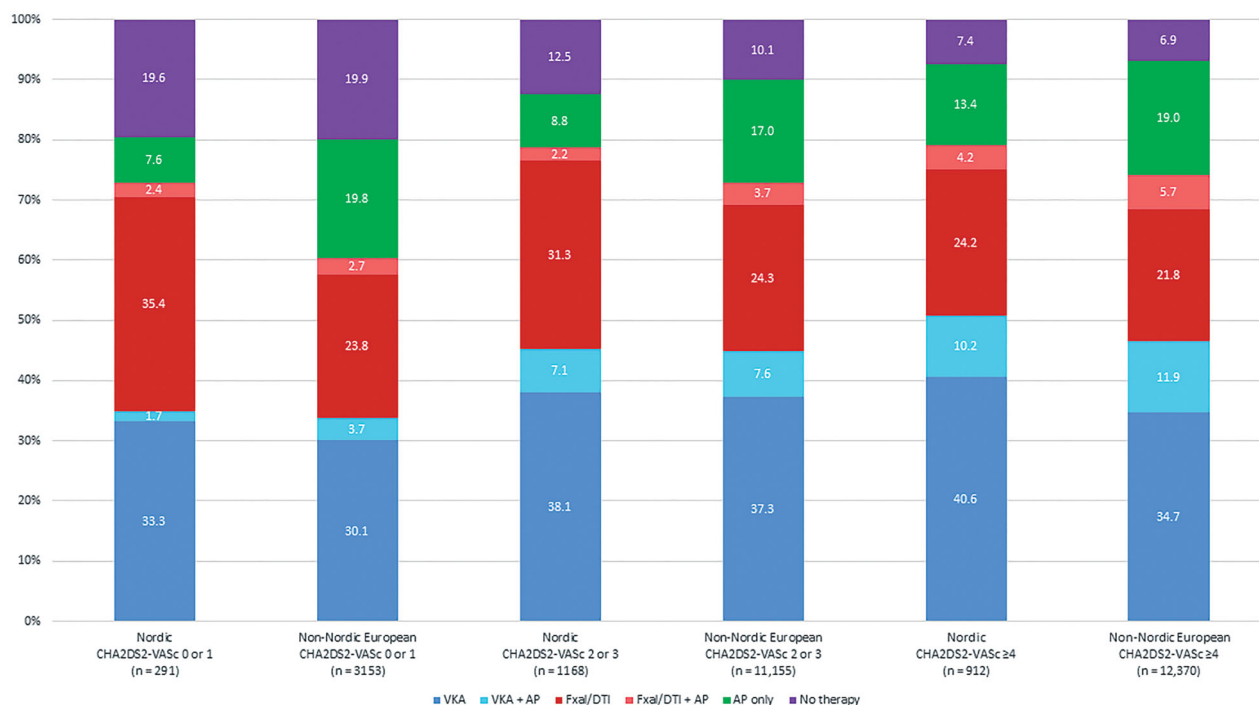


Figure 2. Antithrombotic treatment in $\text{CHA}_2\text{DS}_2\text{-VASc}$ categories 0–1, 2–3, ≥ 4 in Nordic and Non-Nordic European countries. AP: antiplatelet; DTI: direct thrombin inhibitors; Fxal: factor Xa inhibitors; VKA: vitamin K antagonists.

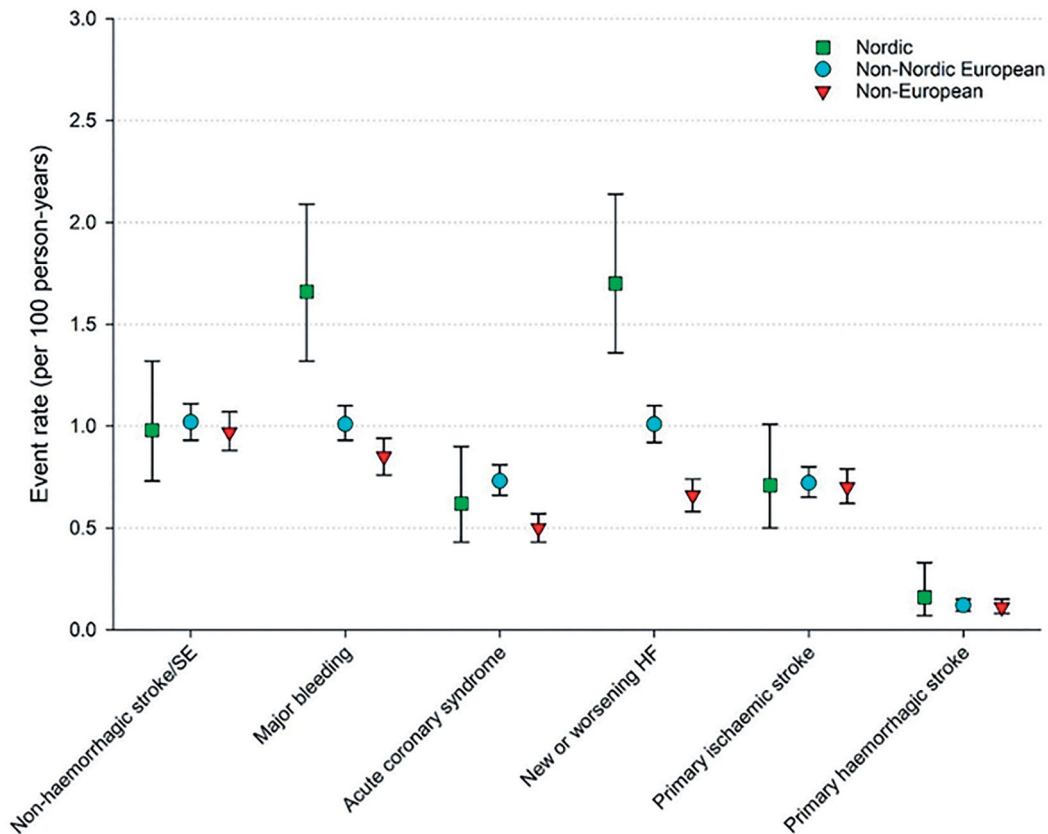


Figure 3. Clinical event rate (event per 100 person-years) through 2-year follow-up in Nordic, Non-Nordic European and Non-European countries.

patients in CHA₂DS₂-VASc category 0–1 received antithrombotic treatment (80.4% vs 80.1%). The percentage of patients on antithrombotic therapy increased with higher CHA₂DS₂-VASc score (Figure 2).

For patients treated with VKA, the mean INR value was 2.41 (SD: 0.80) in Nordic and 2.46 (SD: 0.87) in Non-Nordic-European countries. The percentage of patients with a mean Time in Therapeutic Range [29] ≥ 65 was 65.1% in Nordic patients and 47.7% for Non-Nordic-European patients.

Patients from Finland differed from those from other Nordic countries by more frequently receiving VKA \pm AP (69%), and less frequently NOACs \pm AP (6.2%). Finland was also the Nordic country with the highest use of AP monotherapy (13.4%), while Norway was the country with the lowest prescription of AP monotherapy (5.2%). Norway had the highest use of OAC treatment (86.6%); the overall proportion for Nordic countries was 78.3%.

Event rate

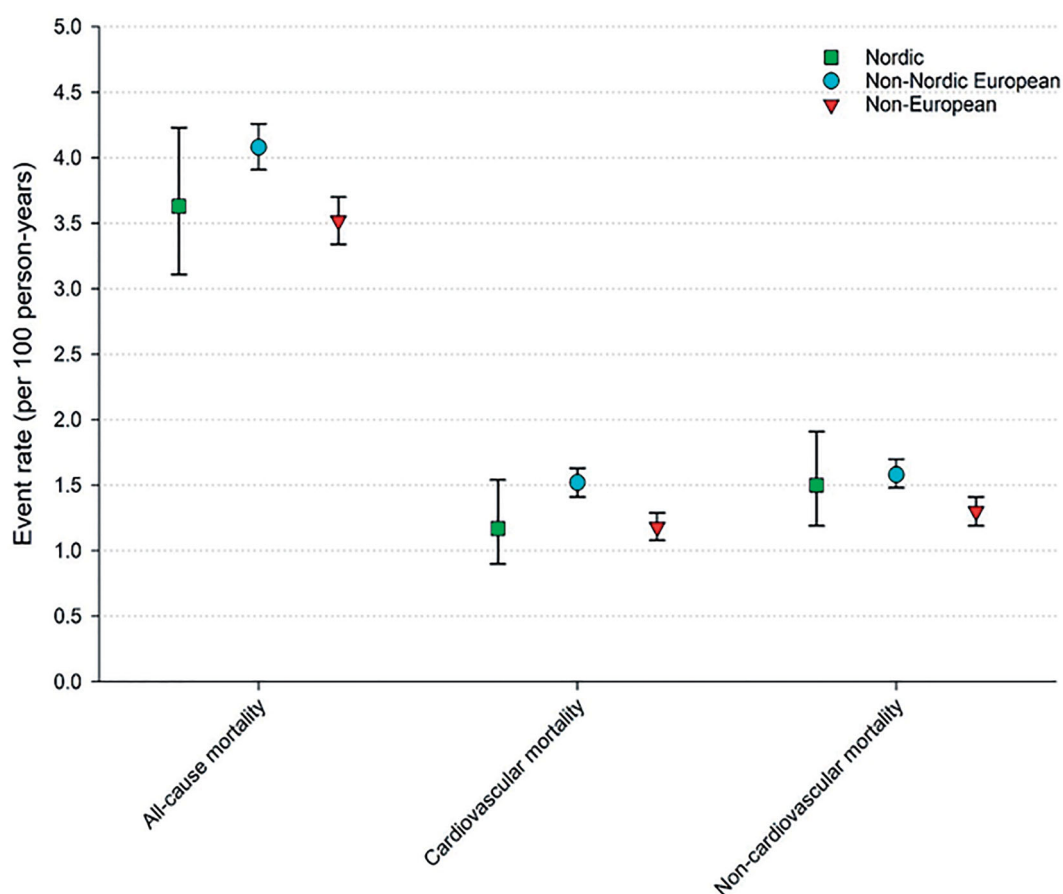
Figure 3 shows the clinical event rates per 100 person-years to 2 years of follow-up (95% confidence intervals), stratified according to the populations

studied. In this section, we also included data from the Non-European countries in the GARFIELD-AF database for comparison. The incidence of non-haemorrhagic stroke/systemic embolism (SE) was lower [0.98 (0.73–1.32) vs 1.02 (0.93–1.11), *p* value .819] and major bleeding was significantly higher [1.66 (1.32–2.09) vs 1.01 (0.93–1.10), *p* value <.001] in the Nordic patient population compared to the Non-Nordic-European patient population (Table 4). New or worsening CHF was significantly higher in the Nordic patients [1.70 (1.36–2.14) vs 1.01 (0.92–1.10), *p* value <.001]. For Non-European patients the event rate per 100 person-years were 0.97 (0.88–1.07) for non-haemorrhagic stroke/SE, 0.85 (0.76–0.94) for major bleeding and 0.66 (0.58–0.74) for new or worsening CHF.

Figure 4 depicts the mortality event rates per 100 person-years. Patients in Nordic countries had numerically lower event rates than patients in Non-Nordic European countries of all-cause mortality [3.63 (3.11–4.23) vs 4.08 (3.91–4.26), *p* value 0.147], cardiovascular mortality [1.17 (0.90–1.54) vs 1.52 (1.41–1.63), *p* value .070] and non-cardiovascular mortality [1.50 (1.19–1.91) vs 1.58 (1.48–1.70), *p* value .681] (Table 4). For Non-European patients the rates were 3.52 (3.34–3.70), 1.18 (1.08–1.29) and 1.30 (1.19–1.41), respectively.

Table 4. Clinical outcomes through 2-year follow-up in Nordic, Non-Nordic European and Non-European countries.

Outcome	Nordic		Non-Nordic European		Non-European	
	Events	Rate (95% CI)	Events	Rate (95% CI)	Events	Rate (95% CI)
Non-haemorrhagic stroke/SE	44	0.98 (0.73–1.32)	520	1.02 (0.93–1.11)	393	0.97 (0.88–1.07)
Major bleeding	74	1.66 (1.32–2.09)	517	1.01 (0.93–1.10)	344	0.85 (0.76–0.94)
Acute coronary syndrome	28	0.62 (0.43–0.90)	372	0.73 (0.66–0.81)	202	0.50 (0.43–0.57)
New or worsening HF	75	1.70 (1.36–2.14)	511	1.01 (0.92–1.10)	265	0.66 (0.58–0.74)
Primary ischaemic stroke	32	0.71 (0.50–1.01)	369	0.72 (0.65–0.80)	284	0.70 (0.62–0.79)
Primary haemorrhagic stroke	7	0.16 (0.07–0.33)	61	0.12 (0.09–0.15)	46	0.11 (0.08–0.15)
All-cause mortality	164	3.63 (3.11–4.23)	2102	4.08 (3.91–4.26)	1436	3.52 (3.34–3.70)
Cardiovascular mortality	53	1.17 (0.90–1.54)	781	1.52 (1.41–1.63)	480	1.18 (1.08–1.29)
Non-cardiovascular mortality	68	1.50 (1.19–1.91)	816	1.58 (1.48–1.70)	530	1.30 (1.19–1.41)

**Figure 4.** Mortality event rate (event per 100 person-years) through 2-year follow-up in Nordic, Non-Nordic European and Non-European countries.

Within the Nordic countries, the rates of all-cause mortality were relatively high in Denmark [6.37 (4.97–8.17)], and low in Norway [1.89 (1.01–3.51)]. For Finland and Sweden, the rates were 2.47 (1.54–3.98) and 3.22 (2.57–4.04). In Finland and Denmark, the occurrence of new or worsening CHF was higher, 5.22 (3.71–7.35) and 2.89 (1.98–4.21) respectively. The event rate of non-haemorrhagic stroke/SE was 0.65 (0.39–1.07) in Sweden, 1.17 (0.59–2.34) in Finland, 1.34 (0.64–2.80) in Norway and 1.46 (0.87–2.47) in Denmark, and for major bleed, it was 1.17 (0.80–1.71)

in Sweden, 1.93 (1.12–3.32) in Finland, 1.93 (1.04–3.58) in Norway and 2.51 (1.69–3.75) in Denmark.

Discussion

Prior to the present study, several articles from different Nordic countries have been published [8,13,24], while data on the Nordic patient population as a whole, with information on risk factors, treatment practices and clinical outcomes, has not been published to our knowledge.

Intra-Nordic differences

The data from the Nordic countries: Sweden ($n = 1233$), Denmark ($n = 532$), Finland ($n = 359$) and Norway ($n = 272$) showed some interesting observations. Patients from Finland had higher comorbidity at baseline, with more diabetes, history of stroke/TIA and CHF. In addition, Finland had a more frequent use of VKA than the other Nordic countries, which might be due to lack of reimbursement to NOACs prescriptions. All-cause mortality rate was considerably higher in Denmark than in the other Nordic countries. Even though these findings might reflect actual dissimilarities between the countries, these might be due to the different care settings in which the patients were diagnosed. For instance, a higher percentage of patients from Denmark were recruited by cardiologists and patients from Finland by internists than their counterparts in Sweden and Norway, which might explain their increased morbidity and mortality.

Nordic versus Non-Nordic European comparisons

Based on our findings, Nordic patients were older than Non-Nordic European patients, but the latter had a higher risk profile and morbidity at baseline.

Nine in ten European patients received antithrombotic treatment, and almost the same percentage of patients had a CHA₂DS₂-VASc score ≥ 2 , with an estimated annual adjusted stroke rate ranging from 2.2% to 15.2% [30]. Stroke prevention therapy, therefore, seems to be extensively employed. At the same time, the use of AP monotherapy is quite high in Non-Nordic European countries, where it was prescribed to almost one in five patients. In contrast, the Nordic countries, only one in ten patients received the AP monotherapy. There may be many reasonable factors influencing the therapeutic choices, but this might also reflect a potential for improvement on the choice of antithrombotic drug for stroke prevention in AF, especially in Non-Nordic European countries. One possible explanation for the difference in treatment might be the cost for the individual patient for doctor appointments (e.g. INR controls when treatment with warfarin) and for the medicine, as acetylsalicylic acid is far cheaper than AC treatment. In Nordic countries the healthcare is tax financed with universal coverage and minimal direct patient cost, and prescription medicine is financed by the government [31].

In Nordic and Non-Nordic European patients with a CHA₂DS₂-VASc score of 0–1, regarded to be at very low risk of stroke [32], more than four in five patients received antithrombotic therapy. Over 70% of Nordic

and almost 60% of Non-Nordic European patients in this CHA₂DS₂-VASc category received OAC. Although this may represent overtreatment, one of the inclusion criteria for patients in this study was AF with at least one additional risk factor for stroke. This additional risk factor might have been modified and thus not have been present over time, and could conceivably be the reason why so many patients received OAC. In the future, GARFIELD-AF score might help to identify the patients who are at low risk of stroke who would reasonably not need to receive AC therapy.

Nordic versus Non-Nordic european versus global comparisons

For the particular analysis of clinical endpoints, our analysis encompassed a global (non-European) comparison cohort, in addition to the Nordic and non-Nordic European cohorts. The event rate of stroke was lower in Nordic and Non-European countries compared to Non-Nordic European countries. This could partly be explained by the difference in baseline risk of stroke, as Nordic patients had lower proportion of patients with CKD, vascular disease, CHF and diabetes than Non-Nordic European patients, which are all known risk factors for stroke [33]. Another contributing factor could be that Nordic patients received more guideline-recommended antithrombotic treatment.

The event rate of major bleeding was higher in Nordic patients than Non-Nordic European and Non-European patients. Nordic patients were older, a higher percentage had a history of stroke at baseline and the proportion of the population consuming alcohol was higher than in the Non-Nordic European population. They also had less CKD and vascular disease, other known risk factors for bleeding [33]. Despite a lower risk profile for bleeding in Nordic versus Non-Nordic European patients, there was an increased event rate of major bleeding, which could partly be caused by a higher percentage of Nordic patients receiving OAC treatment. In particular, a higher proportion of VKA \pm AP prescription among patients with CHA₂DS₂-VASc ≥ 4 in Nordic vs non-Nordic was observed; 50.6% vs 46.6% respectively. The difference in major bleeding rates was mostly evident in this high-risk group [2.91 (2.19–3.86) in Nordic patients vs 1.36 (1.22–1.52) in Non-Nordic European patients].

All-cause mortality and cardiovascular mortality were lower in Nordic and non-European countries than in Non-Nordic European countries, which might be explained by a combination of lower comorbidity and baseline risk for death, and different antithrombotic treatment.

Limitations

The GARFIELD-AF is an observational study and the data collection is non-randomized. As with all registry data, this must be taken into careful consideration when interpreting these data. Countries varied in care settings where patients were enrolled, which may have influenced patient characteristics, disease severity, as well as treatment decisions. Further, the registry was limited to patients with newly diagnosed AF. Results can therefore not *a priori* be extrapolated to a general cohort of chronic AF.

Conclusion

The use of antithrombotic treatment in patients with AF in Europe is high. There is a need for management of patients according to the guidelines, especially in Non-Nordic-European countries. Nordic countries had significantly higher major bleeding than Non-Nordic-European countries. In contrast, rates of mortality and non-haemorrhagic stroke/SE were similar with a non-significant lower trend.

Acknowledgments

The authors thank the physicians, nurses, and patients involved in the GARFIELD-AF registry. The authors thank Dr Surekha Damineni for editorial support and Madhusudana Rao for SAS programming support (Thrombosis Research Institute, London, UK).

Disclosure statement

DA: Personal fees from Bayer Healthcare, BMS/Pfizer, Boehringer-Ingelheim, MSD; KSP reports personal fees from Thrombosis Research Institute, during the conduct of the study; J-YLH: Personal fees from Boehringer-Ingelheim, Bayer, BMS/Pfizer, Daiichi Sankyo, Servier, Meda; Dr. Steffel has received consultant and/or speaker fees from Abbott, Amgen, Astra-Zeneca, Bayer, Berlin Chemie/Menarini, Biosense Webster, Biotronik, Boehringer-Ingelheim, Boston Scientific, Bristol-Myers Squibb, Daiichi Sankyo, Medscape, Medtronic, Merck/MSD, Novartis, Pfizer, Sanofi-Aventis, WebMD, and Zoll. He reports ownership of CorXL. Dr. Steffel has received grant support through his institution from Abbott, Bayer Healthcare, Biosense Webster, Biotronik, Boston Scientific, Daiichi Sankyo, and Medtronic. JS: Grants from Bayer, personal fees from Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, BMS/Pfizer, Novartis, Sanofi, Servier, expert witness for Boehringer Ingelheim; AJC: Institutional grants and personal fees from Bayer, Boehringer Ingelheim, Pfizer/BristolMyers Squibb, and Daiichi-Sankyo, outside the submitted work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Funding

This work was supported by an unrestricted research grant from Bayer AG, Berlin, Germany, to TRI, London, UK, which sponsors the GARFIELD-AF registry. This work is supported by KANTOR CHARITABLE FOUNDATION for the Kantor-Kakkar Global Centre for Thrombosis Science. The funding sources were not involved in data collection, analysis or interpretation.

ORCID

Dan Atar  <http://orcid.org/0000-0003-1513-8793>
K. E. Juhani Airaksinen  <http://orcid.org/0000-0002-0193-568X>

Data availability statement

Requests for patient level data can be made to the head of statistics at TRI (kpieper@tri-london.ac.uk). These requests should include a protocol summary and a summary of the statistical analysis plan. The request will be reviewed by the data sharing committee for approval and next steps will be discussed with the requestor.

References

- [1] Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Rev Esp Cardiol (Engl Ed)*. 2017;70:50.
- [2] Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation*. 2004;110:1042–1046.
- [3] Heeringa J, van der Kuip DA, Hofman A, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J*. 2006;27:949–953.
- [4] Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation*. 2014;129:837–847.
- [5] Krijthe BP, Kunst A, Benjamin EJ, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J*. 2013;34:2746–2751.
- [6] Lane DA, Skjoth F, Lip GYH, et al. Temporal trends in incidence, prevalence, and mortality of atrial fibrillation in primary care. *JAMA*. 2017;6:e005155.
- [7] Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98:946–952.
- [8] Andersson T, Magnuson A, Bryngelsson IL, et al. All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995-2008: a Swedish nationwide long-term case-control study. *Eur Heart J*. 2013;34:1061–1067.

- [9] Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22:983–988.
- [10] Stewart S, Hart CL, Hole DJ, et al. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med*. 2002;113:359–364.
- [11] Kannel WB, Wolf PA, Benjamin EJ, et al. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol*. 1998;82:2n–9n.
- [12] January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014; 64:e1–e76.
- [13] Jorgensen HS, Nakayama H, Reith J, et al. Acute stroke with atrial fibrillation. The Copenhagen Stroke Study. *Stroke*. 1996;27:1765–1769.
- [14] Patel MR, Mahaffey KW, Garg J, et al., the ROCKET AF Steering Committee. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365: 883–891.
- [15] Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992.
- [16] Dentali F, Riva N, Crowther M, et al. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. *Circulation*. 2012;126:2381–2391.
- [17] Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151.
- [18] Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011; 364:806–817.
- [19] Connolly S, Pogue J, Hart R, et al., ACTIVE Writing Group of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet*. 2006;367: 1903–1912.
- [20] Lansberg MG, O'Donnell MJ, Khatri P, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e601S–e636S.
- [21] Verma A, Cairns JA, Mitchell LB, et al., CCS Atrial Fibrillation Guidelines Committee. 2014 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. *Can J Cardiol*. 2014;30:1114–1130.
- [22] Kakkar AK, Mueller I, Bassand JP, et al. GARFIELD-AF Investigators. International longitudinal registry of patients with atrial fibrillation at risk of stroke: Global Anticoagulant Registry in the FIELD (GARFIELD). *Am Heart J*. 2012;163:13–19.e1.
- [23] Kakkar AK, Mueller I, Bassand JP, et al., GARFIELD-AF Registry Investigators. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. *PLoS One*. 2013;8:e63479.
- [24] Friberg L, Rosenqvist M, Lip GY. Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study. *Circulation*. 2012;125:2298–2307.
- [25] Christiansen T, Lauridsen JT, Kifmann M, et al. Healthcare, health and inequality in health in the Nordic countries. *Nordic J Health Eco*. 2018; 6:10–28.
- [26] Fox KAA, Lucas JE, Pieper KS, et al., GARFIELD-AF Investigators. Improved risk stratification of patients with atrial fibrillation: an integrated GARFIELD-AF tool for the prediction of mortality, stroke and bleed in patients with and without anticoagulation. *BMJ Open*. 2017;7:e017157.
- [27] Fox KAA, Gersh BJ, Traore S, GARFIELD-AF Investigators, et al. Evolving quality standards for large-scale registries: the GARFIELD-AF experience. *Eur Heart J Qual Care Clin Outcomes*. 2017;3:114–122.
- [28] National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39: S1–S266.
- [29] Gitt AK, Smolka W, Michailov G, et al. Types and outcomes of cardioversion in patients admitted to hospital for atrial fibrillation: results of the German RHYTHM-AF Study. *Clin Res Cardiol*. 2013;102: 713–723.
- [30] Lip GY, Nieuwlaet R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137:263–272.
- [31] Jan Poulsen IM, Mørkøre H, Voipio T, et al. Medicines Consumption in the Nordic Countries 2004–2008. Nowbase; 2009. Available from: <http://norden.diva-portal.org/smash/get/diva2:968736/FULLTEXT01.pdf>
- [32] Olesen JB, Torp-Pedersen C, Hansen ML, et al. The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0-1: a nationwide cohort study. *Thromb Haemost*. 2012;107:1172–1179.
- [33] Bassand JP, Accetta G, Al Mahmeed W, GARFIELD-AF Investigators, et al. Risk factors for death, stroke, and bleeding in 28,628 patients from the GARFIELD-AF registry: Rationale for comprehensive management of atrial fibrillation. *PLoS One*. 2018;13:e0191592.