Impact of Oral Anticoagulation in Atrial Fibrillation Patients at Very Low Thromboembolic Risk

Section Head – Arrhythmias and sudden death

Frederik H. Verbrugge M.D. Ph.D.1, Anne-Céline Martin M.D. Ph.D.2,3, Deborah Siegal M.D. M.Sc.4, Karen Pieper M.Sc.5,6, Laura Illingworth M.Sc.6, A. John Camm M.D.7, Keith A. A. Fox M.B. Ch.B. F.R.C.P.8

1. Department of Cardiovascular Medicine, UZ Leuven, Leuven, Belgium
2. Hôpital d’Instruction des Armées Percy, Service de Cardiologie, Service de Santé des Armées, Clamart, France
3. Inserm UMR-S1140, Faculté de Pharmacie, Université Paris Descartes, Paris, France
4. Department of Medicine, Population Health Research Institute, McMaster University, Hamilton, Canada
5. Duke Clinical Research Institute, Duke University Medical Center, Durham, NC, United States of America
6. Thrombosis Research Institute, London, United Kingdom
7. Institute of Clinical and Molecular Sciences, Department of Cardiology, St. George’s University of London, London, United Kingdom
8. Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, United Kingdom

Word Count: 2,818 (not including title page, abstract, tables, acknowledgements, contributions, and references)

Corresponding author:

Frederik H. Verbrugge M.D. Ph.D.

Department of Cardiovascular Medicine, UZ Leuven

Herestraat 49, 3000 Leuven, BELGIUM

Phone: +32 473 924199 | E-mail: frederik.verbrugge@zol.be

**Abstract**

Objective: To investigate reasons for and impact of oral anticoagulation (OAC) in atrial fibrillation (AF) patients at very low thromboembolic risk.

Methods: Individuals with CHA2DS2-VASc score 0 (men) or 1 (women) from the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) were studied. Baseline characteristics according to OAC use were evaluated by logistic regression analysis. Non-haemorrhagic stroke or systemic embolism, major bleeding, cardiovascular and all-cause mortality were compared.

Results: From 2,224 low CHA2DS2-VASc patients in GARFIELD-AF, 44% received OAC. In an adjusted model, increasing age up to 65 years [OR (95%CI) = 1.31 (1.19-1.44)] and persistent AF [OR (95%CI) = 3.25 (2.44-4.34)] or permanent AF [OR (95%CI) = 2.29 (1.59-3.30)] versus paroxysmal/unclassified AF were associated with OAC use. Concomitant antiplatelet therapy [OR (95%CI) = 0.21 (0.17-0.27)] was inversely associated. Crude incidence rates per 100 person‑years over 2 years in patients on versus not on OAC were 0.32 (0.14-0.71) versus 0.30 (0.14-0.63) for non-haemorrhagic stroke or systemic embolism, 0.21 (0.08-0.57) versus 0.17 (0.06-0.46) for major bleeding, 0.26 (0.11-0.64) versus 0.26 (0.12-0.57) for cardiovascular mortality, and 0.74 (0.44-1.25) versus 0.99 (0.66-1.49) for all-cause mortality, respectively.

Conclusions: In contrast to guideline recommendations, almost half of real-world AF patients at a very low thromboembolic risk according to the CHA2DS2-VASc score receive oral anticoagulation. Persistent or permanent AF and increasing age up to 65 years are associated with OAC use, while concomitant antiplatelet therapy shows an inverse association. Regardless whether patients received OAC therapy, few thromboembolic and bleeding events occur, highlighting the low risk of this population.

**Key questions**

What is already known about this subject?

Guidelines recommend using the CHA2DS2‑VASc score to predict thromboembolic risk in patients with atrial fibrillation and identify individuals at very low risk who do not benefit from oral anticoagulation.

What does this study add?

Physicians’ perceptions of stroke risk rather than a very low CHA2DS2‑VASc score influence the prescription of anticoagulants. Forty-four percent of patients at very low thromboembolic risk (CHA2DS2‑VASc score 0 for men or 1 for women) received oral anticoagulation, in contrast to guideline recommendations.

Persistent or permanent atrial fibrillation and increasing age up to 65 years were associated with oral anticoagulation use, while concomitant antiplatelet therapy showed an inverse association.

Irrespective of the oral anticoagulation use, few thromboembolic and bleeding events occurred in this very low risk population.

How might this impact on clinical practice?

More efforts should be made to reduce the substantial number of patients with atrial fibrillation who are treated with oral anticoagulation despite very low thromboembolic risk and without evidence of a clinically meaningful benefit.

**Introduction**

Atrial fibrillation (AF) is associated with a 5-fold increased risk of non-haemorrhagic stroke and contemporary studies show that 20‑30% of patients with an ischaemic stroke have AF diagnosed before, during, or after the initial event.1 2 Oral anticoagulation (OAC) reduces the risk of ischaemic stroke in AF, but is associated with an increased risk of bleeding.3-7 Current guidelines therefore, recommend using the CHA2DS2‑VASc score [heart failure, hypertension, age ≥65 years (doubled ≥75 years), diabetes, previous stroke (doubled), vascular disease, and female sex] to predict thromboembolic risk and guide OAC therapy in individual patients, with the aim of enhancing net clinical benefit.8 9 OAC is indicated for patients at high thromboembolic risk [CHA2DS2‑VASc score ≥2 (men) or ≥3 in (women)]. Conversely, guidelines recommend against OAC use in patients at very low thromboembolic risk [CHA2DS2‑VASc score 0 (men) or 1 (women)], as the bleeding risk is considered to outweigh potential benefits of thromboembolic risk reduction.8 9 Nevertheless, OAC use has been reported in up to 25-40% of AF patients in recent cohorts.10 Reasons for this observation and its impact on clinical outcomes remain unclear. This analysis of the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD‑AF) describes characteristics and outcomes associated with OAC use or non-use in patients with newly diagnosed AF at very low thromboembolic risk.

**Methods**

Study design

This study is an analysis of the GARFIELD-AF, a large, prospective, observational, worldwide cohort of newly diagnosed AF patients recruited from 1,215 sites in 35 countries. The GARFIELD‑AF study design has been described previously in detail.11 Briefly, all consecutive men and women aged ≥18 years with non‑valvular AF diagnosed no more than 6 weeks before enrolment and with at least 1 additional risk factor for stroke as judged by the investigator, were eligible for inclusion. Risk factors for stroke were not pre‑specified in the study protocol, nor limited to components of existing risk stratification scores such as the CHA2DS2-VASc score. Patients with a transient, reversible cause of AF, as well as those for whom follow‑up was not envisaged or possible, were excluded. Investigator sites were selected randomly with the aim of obtaining a representative sample of different care settings in each participating country. Consecutive patients were enrolled prospectively into 5 sequential cohorts from March 2010 to August 2016. For the current study, patients with very low thromboembolic risk were defined as having a CHA2DS2-VASc score equal to 0 (men) or 1 (women). Independent ethics committee and hospital‑based institutional review board approvals were obtained, as necessary, for the registry protocol. A list of central ethics committees and regulatory authorities that provided approval can be found in the Supplementary Table. Additional approvals were obtained from individual study sites. The registry is being conducted in accordance with the principles of the Declaration of Helsinki, local regulatory requirements, and the International Conference on Harmonization, Good Pharmaco‑epidemiological and Clinical Practice Guidelines. Written informed consent was obtained from all study participants. Confidentiality and anonymity of all enrolled patients are maintained.

Patient and public involvement statement

We did not directly include patient and public involvement in this study, but the database used in the study was developed with patient and public involvement and is updated by a committee that includes patient representatives.

Data collection

The GARFIELD-AF data were captured using an electronic case report form. The GARFIELD‑AF protocol requires that 20% of all electronic case report forms were monitored against source documentation, that there was an electronic audit trail for all data modifications, and that critical variables were subjected to additional audit. Endpoints of interest were non‑haemorrhagic stroke or systemic embolism, major bleeding defined according to the ISTH criteria11, cardiovascular mortality and all-cause mortality. Follow-up time for all patients included in this analysis was 2 years.

Statistical analysis

Continuous variables are expressed as median (interquartile range). Categorical data are expressed as absolute numbers (percentages). The Wilcoxon rank-sum test and Pearson’s *χ²*-test were used to compare baseline characteristics according to OAC status. Multivariable logistic regression analysis was performed, on an multiple imputed dataset, using a pre-specified set of covariates to determine the factors associated with OAC use. Since the patient cohort is defined as patients with none of the CHA2DS2‑VASc criteria other than gender, the modelling process necessitated excluding these characteristics. The factors considered were antiplatelet treatment, type of AF, age, body mass index, sex, alcohol use, smoking status, hypercholesterolemia, world region, use of direct current cardioversion, and cohort. Occurrences of non‑haemorrhagic stroke or systemic embolism, major bleeding, cardiovascular and all‑cause mortality are described per 100 person-years with 95% confidence intervals. Person-year rates were estimated using a Poisson model with the number of events as the dependent variable and the log of person-time as an offset. Only the first occurrence of each event was used. Statistical significance was assumed for a 2‑tailed probability level of <0.05, recognizing that all analyses are hypothesis‑generating. Statistics were performed using SAS® Enterprise Guide 7.15. The manuscript was drafted according to the STROBE guidelines for observational studies.

**Results**

Study population

A flowchart of the study is provided as Figure 1. From the entire prospective GARFIELD‑AF population (n=52,080), 2,224 patients had a very low thromboembolic risk, including 1,461 men with CHA2DS2-VASc score 0 and 763 women with CHA2DS2‑VASc score 1. In this group, 985 patients (44%) received OAC including 497 on vitamin K antagonists and 488 on direct oral anticoagulant therapy. Baseline characteristics according to OAC status are presented in Table 1. Compared to patients without OAC, unadjusted, OAC users were slightly older, more frequently Caucasian men, past or current smokers, with moderate or heavy alcohol consumption and higher body mass index. A history of prior pulmonary embolism or deep venous thrombosis was more frequent in OAC users. Patients with persistent or permanent AF received OAC more frequently when compared to patients with paroxysmal AF. Direct cardioversion and ablation were more frequently performed in patients receiving OAC. Finally, OAC users versus non-users used antiplatelet therapy less frequently and had a lower HAS‑BLED score. In the majority of patients with data available on prior antiplatelet use, results indicated that antiplatelet therapy was started at the moment of enrolment in GARFIELD-AF (OAC users: 53/81 or 65% versus OAC non‑users: 232/307 or 76%).

Characteristics associated with oral anticoagulation use

Table 2 and Figure 2 demonstrate characteristics significantly associated with OAC use in the multivariable model. Increasing age in patients up to 65 years and persistent or permanent versus paroxysmal or undetermined AF were significantly associated with OAC use. Concomitant antiplatelet therapy was inversely associated with OAC use. Hypercholesterolemia, body mass index, and smoking behaviour were not significantly associated with OAC use. Borderline results were observed for gender and alcohol use. When including presence of baseline cardioversion use in the model, it was not significantly associated with OAC use.

Clinical outcomes according to oral anticoagulant use

Major adverse events were rare during the study period and irrespective of OAC status (Table 3 and Figure 3). Thirteen patients experienced a non‑haemorrhagic stroke or systemic embolism during 2 years of follow‑up. Six of them were prescribed OAC therapy, while seven were not. Calculated rates per 100 person‑years were 0.32 (0.14‑0.71) in OAC users versus 0.30 (0.14‑0.63) in non‑users (P‑value=0.92). Major bleeding was reported in eight patients, four of them on versus four not on OAC therapy. Calculated crude event rates were 0.21 (0.08‑0.57) versus 0.17 (0.06‑0.46) per 100‑person‑years, respectively (P‑value=0.77). Event rates for haemorrhagic stroke were 0.05 (0.01‑0.38) versus 0.04 (0.01-0.30) per 100 person‑years], respectively. Event rates for cardiovascular mortality [0.26 (0.11‑0.64) versus 0.26 (0.12‑0.57) per 100 person‑years] and all‑cause mortality [0.74 (0.44‑1.25) versus 0.99 (0.66‑1.49) per 100 person‑years], were not significantly different in patients on versus not on OAC therapy (P‑value=0.96 and 0.39, respectively). In patients not on OAC therapy and neither receiving antiplatelet therapy (n=751), 5 patients experienced a non-haemorrhagic stroke or systemic embolism [0.36 (0.15 to 0.86)] and 3 major bleeding episodes occurred [0.21 (0.07‑0.66) per 100 person‑years].

**Discussion**

In this analysis of GARFIELD-AF, it was found that almost half of the patients with a CHA2DS2‑VASc score equal to 0 (men) or 1 (women) received OAC. This contrasts with current guidelines recommending against treating AF patients at very low thromboembolic risk with OAC, as the benefit of thromboembolic risk reduction is insufficient to outweigh the increased bleeding risk.12 Inappropriate OAC was more commonly prescribed by cardiologists when compared to other specialties, and more frequent in an outpatient context. Outcomes in this study showed that such patients both have a very low thromboembolic and very low bleeding risk, regardless of OAC prescription. The frequency of major bleeding approximately balances that of stroke/systemic embolism irrespective of whether patients were prescribed OAC or not. Although AF is an important risk factor for stroke/systemic embolism on itself, it may also reflect a potential clustering of risk factors (not necessarily embedded in the CHA2DS2-VASc score). This should be differentiated further to select patients that would benefit from OAC treatment, especially in those who have a low risk for stroke. Such risk stratification should be based on rigorous evidence rather than *perceived* risk by the treating clinician.

To explain the frequent use of OAC in AF patients at very low thromboembolic risk, one might consider limitations of the CHA2DS2‑VASc score to assess thromboembolic risk. Although it was specifically designed and validated for this purpose, it only captures part of this risk. Notably, to be included in GARFIELD‑AF, patients were considered by their treating physicians to have at least one perceived risk factor for stroke. Therefore, the study population of patients with a CHA2DS2‑VASc score equal to 0 (men) or 1 (women) was potentially enriched with emerging risk factors: chronic kidney disease (less than 1.5% in this cohort), overweight (nearly half the population had a body mass index 25‑30), and alcohol consumption among others. This might explain why so many patients at low thromboembolic risk according to their CHA2DS2‑VASc score did receive OAC. Importantly, physicians’ perceptions of benefit versus harm regarding OAC in AF may be partly subjective and do not necessarily reflect actual risks, potentially leading to different treatment choices for a similar patient, depending on the treating physician.13 This highlights the need for a better understanding of key factors that influence physicians’ decisions to prescribe OAC in patients at very low thromboembolic risk and assessment of its clinical impact.

Another limitation of the CHA2DS2‑VASc score is that it defines an arbitrary cut-off for continuous variables. It was observed that OAC use was more likely as the age in patients increased (below the cut‑off from 65 years). Any age cut‑off would be somewhat arbitrary because an individual’s thromboembolic risk is continuous with age. For this reason, it is possible that clinicians may consider OAC therapy in the group of patients approaching 65 years. Moreover, recommendations to prescribe OAC according to age have different cut-offs in some parts of the world (E.g. Hong Kong). On the contrary, OAC treatment was also more frequent in patients with persistent or permanent AF, while recommendations are irrespective of the type of AF.14 Consequently, physicians seemed to attribute a different thromboembolic risk according to the type of AF, while available data suggested no differences in stroke risk between paroxysmal and non-paroxysmal AF after adjustment to the CHA2DS2‑VASc score.

Finally, the frequent use of OAC in AF patients at very low thromboembolic risk might be explained by an overestimation of perceived stroke risk and a disproportionate fear of ischaemic stroke over bleeding. A pivotal finding of the current study is that *both* the thromboembolic *and* the bleeding risk are exceedingly low (below approximately 1 per 300 person‑years of follow‑up). In addition, there was no statistically significant difference according to OAC use. The study design, focussing on men with CHA2DS2‑VASc score equal to 0 and women with CHA2DS2‑VASc score equal to 1, explains the very low thromboembolic risk. The fact that this risk was not amenable to treatment with OAC therapy suggests that the cause of the few ischaemic strokes that did happen, was probably not cardioembolic. Alternatively, adherence to OAC therapy in a low risk population may be lower, but this could not be assessed in the current study.

Intriguingly, the fact that OAC use in the population studied, was not associated with more bleeding confirmed that patients with very low thromboembolic risk have also a very low bleeding risk. Indeed, the HAS-BLED score was 0 in more than half of the patients in the current analysis.18 Moreover, it should be noted that this proportion was even higher in the group receiving OAC. This may indicate that clinicians are more likely to prescribe OAC therapy to patients with low inherent bleeding risk. We observed that 39% of the cohort received an antiplatelet agent without OAC, with the agent started at the moment of enrolment in GARFIELD-AF in approximately 3 out of 4 patients. This may reflect the erroneously perceived lower bleeding risk with antiplatelet therapy compared to OAC, but also needs to be interpreted in the light of former guidelines in AF where antiplatelet agents were a treatment option in low risk patients. Such practice is not supported by current guidelines since evidence indicates similar bleeding risk with aspirin and OAC use.3 19 20

More surprisingly, 13% of the cohort received concomitant antiplatelet and OAC therapies, despite a CHA2DS2‑VASc score of 0 [men] or 1 [women], i.e. the absence of patent underlying vascular disease. Further investigations in deciphering the determinants of the decision making are needed to better understand and rationalize the use of antithrombotic therapies in patients with AF.

Study limitations

The results of the current study should be interpreted acknowledging the following study limitations. First, although several characteristics were significantly associated with OAC use despite a very low CHA2DS2-VASc score in AF patients, causality cannot be concluded and confounding by indication cannot be excluded. Secondly, because this was a retrospective analysis, only characteristics reported and obtained through the case record form of the GARFIELD-AF registry could be studied. Thirdly, despite the size of the overall GARFIELD study, the absolute number of adverse outcome events was low in this cohort, limiting the power to show a difference according to OAC use. However, the exceedingly low incidence of both thromboembolic and bleeding events suggests that any real difference would likely be not of clinical relevance. Fourthly, OAC status was determined at the moment of inclusion in the study and in some patients OAC therapy might have been stopped afterwards. Indeed, it is recommended to use OAC therapy irrespective- of the CHA2DS2-VASc thromboembolic risk score after cardioversion and/or AF ablation for at least 4 weeks(cardioversion) and 8 weeks (ablation). It is possible that some of the patients studied might have received short‑term OAC therapy for this reason, potentially overestimating the proportion of patients receiving OAC over the long‑term. Last, patients from GARFIELD-AF were treated according to previous versions of the guidelines and they recommended use OAC therapy in patients with a CHA2DS2-VASc score ≥2, with individual decision-making for patients with a CHA2DS2-VASc score equal to 1. In the current guidelines, female sex is no longer considered in the decision-making for starting OAC. However, in this study, only patients with a CHA2DS2-VASc score equal to 0 [men] or 1 [women] were included who, also according to previous guidelines, had no firm recommendation in favour of OAC therapy. Finally, one might be concerned that the high number of patients taking antiplatelet drugs in this study reflects the presence of vascular disease in some, which would qualify for 1 extra point in the CHA2DS2-VASc score. However, recruiting physicians in GARFIELD-AF were specifically asked for the presence of vascular disease and for the current analysis only patients with a definite statement of absence of vascular disease were included.

Conclusion

Almost half of the patients at very low thromboembolic risk received OAC. In these patients, thromboembolic and major bleeding events were rare, regardless of OAC prescription. The frequency of major bleeding approximately balanced the frequency of stroke/systemic embolism irrespectively of OAC use versus non‑use. Persistent or permanent AF and increasing age <65 years were associated with OAC therapy in AF patients at very low thromboembolic risk, while concomitant antiplatelet therapy showed an inverse correlation. The justification for OAC use in such patients was not well founded and the decision to use OAC was based on factors beyond those in guideline‑recommended risk prediction tools such as the CHA2DS2‑VASc score. These findings prompt additional investigations into clinical decision making for AF patients at very low thromboembolic risk.

**Acknowledgements and affiliations**

We thank the physicians, nurses and patients involved in the GARFIELD-AF registry. Editorial assistance was provided by the Thrombosis Research Institute (London, UK) and SAS programming support by Madhusudana Rao (Thrombosis Research Institute, London, UK).

The GARFIELD-AF registry is funded by an unrestricted research grant from Bayer AG (Berlin, Germany). This study was supported through the Thrombosis Academy for Learning Education and Networking Training (TALENT) programme organised and sponsored by Bayer Healthcare. D.M.S. was supported by Research Early Career Award from the Hamilton Health Sciences Foundation.

F.H.V. has received travel grants from Bayer Healthcare and consultancy fees from Boehringer-Ingelheim. D.M.S has received personal fees from Bayer Healthcare, Servier and BMS-Pfizer. J.C. and K.A.A.F. have received grants and personal fees from Bayer Healthcare.

**Copyright Statement**

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non-exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in HEART editions and any other BMJPGL products to exploit all subsidiary rights

**References**

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22(8):983-8.

2. Kishore A, Vail A, Majid A, et al. Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. *Stroke* 2014;45(2):520-6. doi: 10.1161/STROKEAHA.113.003433

3. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146(12):857-67.

4. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361(12):1139-51. doi: 10.1056/NEJMoa0905561

5. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365(10):883-91. doi: 10.1056/NEJMoa1009638

6. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365(11):981-92. doi: 10.1056/NEJMoa1107039

7. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369(22):2093-104. doi: 10.1056/NEJMoa1310907

8. 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(21):e1-76. doi: 10.1016/j.jacc.2014.03.022

9. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;18(11):1609-78. doi: 10.1093/europace/euw295

10. Bassand JP, Accetta G, Camm AJ, et al. Two-year outcomes of patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF. *Eur Heart J* 2016;37(38):2882-89. doi: 10.1093/eurheartj/ehw233

11. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the S, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3(4):692-4. doi: 10.1111/j.1538-7836.2005.01204.x

12. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;37(38):2893-962. doi: 10.1093/eurheartj/ehw210

13. Steinberg BA, Blanco RG, Ollis D, et al. Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II: rationale and design of the ORBIT-AF II registry. *Am Heart J* 2014;168(2):160-7. doi: 10.1016/j.ahj.2014.04.005

14. Hohnloser SH, Pajitnev D, Pogue J, et al. Incidence of stroke in paroxysmal versus sustained atrial fibrillation in patients taking oral anticoagulation or combined antiplatelet therapy: an ACTIVE W Substudy. *J Am Coll Cardiol* 2007;50(22):2156-61. doi: 10.1016/j.jacc.2007.07.076

15. Fang MC, Singer DE, Chang Y, et al. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. *Circulation* 2005;112(12):1687-91. doi: 10.1161/CIRCULATIONAHA.105.553438

16. Andersson T, Magnuson A, Bryngelsson IL, et al. Gender-related differences in risk of cardiovascular morbidity and all-cause mortality in patients hospitalized with incident atrial fibrillation without concomitant diseases: a nationwide cohort study of 9519 patients. *Int J Cardiol* 2014;177(1):91-9. doi: 10.1016/j.ijcard.2014.09.092

17. Roten L, Rimoldi SF, Schwick N, et al. Gender differences in patients referred for atrial fibrillation management to a tertiary center. *Pacing Clin Electrophysiol* 2009;32(5):622-6. doi: 10.1111/j.1540-8159.2009.02335.x

18. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;138(5):1093-100. doi: 10.1378/chest.10-0134

19. Investigators AWGotA, Connolly S, Pogue J, et al. 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(9526):1903-12. doi: 10.1016/S0140-6736(06)68845-4

20. Sjalander S, Sjalander A, Svensson PJ, et al. Atrial fibrillation patients do not benefit from acetylsalicylic acid. *Europace* 2014;16(5):631-8. doi: 10.1093/europace/eut333

**Figure legends**

**Figure 1.** Study flowchart.

**Figure 2.** Forrest plot of individual odds ratios (ORs) with 95% confidence interval (95% CI) for the association between oral anticoagulation (OAC) use and characteristics in the multivariable logistic regression model.

AF, atrial fibrillation; APT, antiplatelet therapy.

**Figure 3.** Major adverse events according to oral anticoagulation use.

OAC, oral anticoagulation.

**Tables**

|  |  |  |  |
| --- | --- | --- | --- |
| Table 1. Baseline characteristics according to oral anticoagulation use | | | |
|  | **No OAC use** | **OAC use** | **P-value** |
|  | n = 1,239 | n = 985 |  |
| Demographics |  |  |  |
| Age (years) | 54 (45 to 59) | 55 (48 to 60) | <0.001 |
| Men | 780 (63%) | 681 (69%) | 0.002 |
| Race  Caucasian  Asian  Other | 499 (40)  615 (50)  125 (10) | 496 (50)  383 (39)  106 (11) | <0.001 |
| Clinical characteristics |  |  |  |
| Body mass index (kg/m²) | 25 (23 to 28) | 26 (23 to 29) | <0.001 |
| Heart rate (bpm) | 80 (70 to 102) | 84 (72 to 105) | 0.417 |
| Blood pressure (mmHg)  Systolic  Diastolic | 120 (110 to 130)  74 (70 to 80) | 120 (110 to 130)  75 (70 to 80) | 0.563  0.531 |
| Behaviours |  |  |  |
| Smoking habits  No smoking  Past smoker  Current smoker | 676 (59)  194 (17)  272 (24) | 484 (53)  188 (21)  235 (26) | 0.021 |
| Alcohol consumption  None to light  Moderate to heavy | 898 (85%)  164 (15%) | 657 (78%)  182 (22%) | <0.001 |
| Atrial fibrillation diagnosis |  |  |  |
| Specialty to diagnose atrial fibrillation  Cardiology  Primary care  Other | 906 (73%)  115 (9%)  218 (18%) | 754 (77%)  110 (11%)  121 (12%) | 0.002 |
| Care setting  Hospital  Non-hospital | 970 (78%)  269 (22%) | 669 (68%)  316 (32%) | <0.001 |
| Time between atrial fibrillation diagnosis and enrolment (weeks) | 1.2 (0.4 to 3.4) | 1.8 (0.5 to 3.5) | 0.066 |
| Atrial fibrillation type\*  Undetermined  Paroxysmal  Persistent  Permanent | 570 (46%)  513 (41%)  95 (8%)  61 (5%) | 388 (39%)  315 (32%)  186 (19%)  96 (10%) | <0.001 |
| Direct current cardioversion | 192 (16%) | 184 (19%) | 0.06 |
| Ablation\*\* | 2 (0.3%) | 9 (3.5%) | 0.004 |
| Medical history |  |  |  |
| Prior pulmonary embolism or deep venous thrombosis | 12 (1.0%) | 27 (2.7%) | 0.002 |
| History of bleeding | 19 (1.5%) | 7 (0.7%) | 0.138 |
| Cirrhosis | 11 (0.9%) | 5 (0.5%) | 0.294 |
| Chronic kidney disease\*\*\* | 15 (1.2%) | 15 (1.5%) | 0.526 |
| Bleeding risk |  |  |  |
| Use of antiplatelet therapy | 488 (39%) | 123 (13%) | <0.001 |
| HAS-BLED score  0  1  2  3 | 478 (55%)  371 (42%)  26 (3.0%)  1 (0.1%) | 578 (80%)  133 (18%)  13 (1.8%)  1 (0.1%) | <0.001 |

OAC, oral anticoagulation

\*Atrial fibrillation in the GARFIELD-AF registry was characterised as either permanent, persistent (>7 days), paroxysmal (≤7 days) or new (if the patient could not be classified for sure, named here undetermined); \*\* Information only available for cohorts 1&2. \*\*\*Chronic kidney disease defined as an estimated glomerular filtration rate <60 mL/min/1.73m²

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Table 2. Multivariable association between baseline factors and oral anticoagulation use. | | | | | |
| Effect | **DF** | **χ2** | **P-value** | **OR** | **95% CI** |
| Use of antiplatelet therapy | 1 | 169.9 | <0.001 | 0.21 | (0.17 - 0.27) |
| Type of atrial fibrillation | 2 | 76.9 | <0.001 |  |  |
| Permanent versus paroxysmal/undetermined |  |  |  | 2.29 | (1.59 - 3.30) |
| Persistent versus paroxysmal/undetermined |  |  |  | 3.25 | (2.44 - 4.34) |
| Age (per 10 years) | 1 | 29.2 | <0.001 | 1.31 | (1.19 - 1.44) |
| Region of the world | 4 | 26.2 | <0.001 |  |  |
| Asia vs North America |  |  |  | 0.54 | (0.31 - 0.92) |
| Europe vs North America |  |  |  | 0.86 | (0.51 - 1.45) |
| Latin America vs North America |  |  |  | 0.70 | (0.38 - 1.27) |
| Rest of world vs North America |  |  |  | 1.26 | (0.67 - 2.35) |
| Alcohol consumption | 1 | 3.7 | 0.055 |  |  |
| Moderate to heavy vs None to light |  |  |  | 1.30 | (0.99 - 1.70) |
| Female sex | 1 | 3.4 | 0.064 | 0.82 | (0.67 – 1.01) |
| Presence of hypercholesterolaemia | 1 | 0.7 | 0.412 | 1.10 | (0.87 - 1.39) |
| Study cohort | 4 | 2.6 | 0.632 |  |  |
| 2 versus 1 |  |  |  | 1.10 | (0.76 - 1.61) |
| 3 versus 1 |  |  |  | 1.13 | (0.78 - 1.63) |
| 4 versus 1 |  |  |  | 1.28 | (0.89 - 1.84) |
| 5 versus 1 |  |  |  | 1.09 | (0.76 - 1.57) |
| Body mass index (per 5 kg/m²) | 1 | 0.4 | 0.538 | 1.04 | (0.92 - 1.16) |
| Smoking status | 2 | 0.9 | 0.646 |  |  |
| Current smoker versus never smoked |  |  |  | 1.12 | (0.87 - 1.45) |
| Ex-smoker versus never smoked |  |  |  | 1.07 | (0.85 - 1.36) |

CI, confidence interval; DF, degrees of freedom; OR, odds ratio

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Table 3. Event rates according to oral anticoagulation use. | | | | |
| Event | **Events on OAC** | **Rate on OAC (95%CI)** | **Events not on OAC** | **Rate not on OAC (95% CI)** |
| Non-haemorrhagic stroke or SE | 6 | 0.32 (0.14 - 0.71) | 7 | 0.30 (0.14 - 0.63) |
| Major bleeding | 4 | 0.21 (0.08 - 0.57) | 4 | 0.17 (0.06 - 0.46) |
| Haemorrhagic stroke | 1 | 0.05 (0.01 - 0.38) | 1 | 0.04 (0.01 - 0.30) |
| Cardiovascular mortality | 5 | 0.26 (0.11 - 0.64) | 6 | 0.26 (0.12 - 0.57) |
| All-cause mortality | 14 | 0.74 (0.44 - 1.25) | 23 | 0.99 (0.66 - 1.49) |

OAC, oral anticoagulation; CI, confidence interval; SE, systemic embolism