

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Do stroke risk characteristics account for geographical disparities in the outcomes of patients with newly diagnosed atrial fibrillation? The GARFIELD-AF registry
AUTHORS	Fox, Keith; Virdone, Saverio; Bassand, Jean-Pierre; Camm, John; Goto, Shinya; Goldhaber, Samuel; Haas, Sylvia; Kayani, Gloria; Koretsune, Yukihiro; Misselwitz, Frank; Oh, Seil; Piccini, Jonathan; Parkhomenko, Alex; Sawhney, J P S; Stepinska, Janina; Turpie, Alexander G. G.; Verheugt, Freek; Kakkar, Ajay

VERSION 1 – REVIEW

REVIEWER	Pastori, Daniele Sapienza University of Rome, Internal Medicine and Medical Specialties
REVIEW RETURNED	31-Mar-2021

GENERAL COMMENTS	<p>This is an analysis from the GARFIELD registry on geographical differences in stroke risk. The Authors conclude that stroke incidence may be only partially explained by stroke risk factor distribution among countries. I am not sure about the conclusions and the message of this manuscript. In detail:</p> <ul style="list-style-type: none">- Honestly, I had to read twice the title to understand the meaning. I think it would be better changed into: "Does the distribution of stroke risk factors account for..." Stroke characteristics refers to stroke location and severity.- P values should be added to table 1 to appreciate differences among study groups- If the observed difference in the stroke rate is not explained by the distribution of risk factors, how could an intervention on modifiable risk factors improve outcomes in AF? I would rather say that there are some unexplored factors not considered (anticoagulation quality, adherence to treatment, statin use, LDL cholesterol target, diabetes control, and so on)- The discussion is too simplistic and does not provide a possible explanation for the observed results.- Results of the abstract are not informative at all. Please improve.- Please avoid citing figures in the Discussion.
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REVIEWER	Tai, Ying-Hsuan Taipei Medical University Shuang Ho Hospital Ministry of Health and Welfare, Anesthesiology
REVIEW RETURNED	01-Apr-2021

GENERAL COMMENTS	<p>Thank you for the opportunity of reviewing this article. This study aimed to examine the geographical variation in the outcome of newly-diagnosed atrial fibrillation (Af) using an international registry. This study has the strengths of a large patient sample, a comprehensive collection of covariates, and a wide coverage of various countries and races. The study provides some valuable descriptive statistics about the clinical outcome of Af patients across different countries. However, there are several issues needed to be addressed.</p> <ol style="list-style-type: none"> 1. I suggest presenting the data of the initial treatment regimen for Af at the time of diagnosis in the Table 1. 2. Have you conducted any regression analyses about the influential factors of the outcome of interest (i.e., mortality, stroke, etc)? This will better clarify the cause of geographical variation in Af outcome. 3. It is important to elucidate the relationship between treatment regimens for Af and adverse events. Multivariable analyses using regression models would be helpful. 4. The analyses of stroke, embolism, and bleeding should consider the competing risk from mortality. 5. What is the clinical implication of the study results? This should be further discussed in the article.
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REVIEWER	Seiffge, David Inselspital University Hospital Bern, Department of Neurology
REVIEW RETURNED	12-May-2021

GENERAL COMMENTS	<p>The authors performed a subanalysis of the GARFIELD registry, a prospective, global registry of patients with atrial fibrillation. They assessed regional differences in anticoagulation use and outcome events (stroke/systemic embolism; major bleeding; mortality). They found pronounced regional differences, most importantly a higher rates of mortality – even after adjustment – in countries with low health economical standards but also lower use of anticoagulants in countries with high cardiovascular morbidity.</p> <p>This paper has many strengths and merits: a) prospective, high-quality large dataset, b) global recruitment and c) robust statistical methods.</p> <p>I apologize to the editors and authors about my slow reply due to unscheduled clinical duties.</p> <p>I have the following comments for the authors:</p> <ul style="list-style-type: none"> - Where outcome events centrally adjudicated or where they investigator-reported only? - Some countries/regions may still be underrepresented (see page 13, lines 22ff)
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	<ul style="list-style-type: none"> - Do the authors have information on DOAC dosing (e.g. use of on-/off-label dosages, underdosing)? - Please provide information on missing data and lost-to follow-up
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Daniele Pastori, Sapienza University of Rome

Comments to the Author:

This is an analysis from the GARFIELD registry on geographical differences in stroke risk. The Authors conclude that stroke incidence may be only partially explained by stroke risk factor distribution among countries. I am not sure about the conclusions and the message of this manuscript. In detail:

- Honestly, I had to read twice the title to understand the meaning. I think it would be better changed into: “Does the distribution of stroke risk factors account for...” Stroke characteristics refers to stroke location and severity.

Response: We have revised the title, as indicated above:

“Do baseline characteristics and treatments account for geographical disparities in the outcomes of patients with newly diagnosed atrial fibrillation? The prospective GARFIELD-AF registry”

- P values should be added to table 1 to appreciate differences among study groups

Response: P-values have been calculated and added to TABLE 1.

- If the observed difference in the stroke rate is not explained by the distribution of risk factors, how could an intervention on modifiable risk factors improve outcomes in AF? I would rather say that there are some unexplored factors not considered (anticoagulation quality, adherence to treatment, statin use, LDL cholesterol target, diabetes control, and so on)

Response: We have included the following sentence in page no 17:

The observed differences in stroke rates, by country and by region, are not explained by the risk predictors within commonly used stroke prediction tools.
(e.g. anticoagulation quality and adherence to treatment, statin use, LDL cholesterol management, diabetes control)

- The discussion is too simplistic and does not provide a possible explanation for the observed results.

Response: We have revised the discussion section as per your suggestion.

The following were included in the discussion section:

Page no 16: “ In some regions more comprehensive treatment of comorbidities in patients with AF may have influenced cardiovascular and non-cardiovascular outcomes and may have accounted, at least in part, for the residual geographic variation in outcomes. The demonstrated clear relation of outcomes with indices of healthcare access (HAQ indices) supports this concept.”

Page no 18: “However, higher rates of major bleeding were observed in the Netherlands (GARFIELD-AF) and the USA (GARFIELD-AF and ORBIT-AF II). These findings may reflect prescribing practice

as in the US where combination therapy, OAC+ AP was more often used (28%) than in other countries. In the Netherlands the rate of OAC prescription is very high, in the range of 90%, chiefly with VKA (78%) and far less with NOAC (28%). These factors may account for the higher-than-expected rates of major bleeding in these two countries.”

- Results of the abstract are not informative at all. Please improve.

Response: We have revised and clarified the abstract.

Abstract

Objective In patients with newly diagnosed AF, do baseline risk factors and stroke prevention strategies account for the geographically diverse outcomes.

Design GARFIELD-AF is a prospective multinational non-interventional registry of patients with newly diagnosed AF (n=52,018 patients).

Setting Investigator sites (n=1317) were representative of the care settings/locations in each of the 35 participating countries. Treatment decisions were all determined by the local responsible clinicians. Participants The patients (18 years and over) with newly diagnosed AF had at least 1 investigator-determined stroke risk factor and patients were not required to meet specific thresholds of risk score for anticoagulant treatment.

Main outcomes and measures Observed 1-year event rates and risk-standardised rates were derived. Results Rates of death, non-haemorrhagic stroke/SE and major bleeding varied more than three-to-four fold across countries even after adjustment for baseline factors and antithrombotic treatments. Rates of anticoagulation and antithrombotic treatment varied widely. Patients from countries with the highest rates of cardiovascular mortality and stroke were among the least likely to receive oral anticoagulants. Beyond anticoagulant treatment, variations in the treatment of comorbidities and lifestyle factors may have contributed to the variations in outcomes. Countries with the lowest healthcare Access and Quality indices (India, Ukraine, Argentina, Brazil) had the highest risk-standardized mortality.

Conclusion The variability in outcomes across countries for patients with newly diagnosed AF is not accounted for by baseline characteristics and antithrombotic treatments. Residual mortality rates were correlated with Healthcare Access and Quality indices. The findings suggest the management of patients with AF needs to not only address guideline indicated and sustained anticoagulation, but also the treatment of comorbidities and lifestyle factors.

- Please avoid citing figures in the Discussion.

Response: We have removed the figure citations from the discussion section.

Reviewer: 2

Dr. Ying-Hsuan Tai, Taipei Medical University Shuang Ho Hospital Ministry of Health and Welfare, Taipei Medical University Shuang Ho Hospital

Comments to the Author:

Thank you for the opportunity of reviewing this article. This study aimed to examine the geographical variation in the outcome of newly-diagnosed atrial fibrillation (Af) using an international registry. This study has the strengths of a large patient sample, a comprehensive collection of covariates, and a wide coverage of various countries and races. The study provides some valuable descriptive statistics about the clinical outcome of Af patients across different countries. However, there are several issues needed to be addressed.

1. I suggest presenting the data of the initial treatment regimen for Af at the time of diagnosis in the Table 1.

Response: We have added this information in TABLE 1.

2. Have you conducted any regression analyses about the influential factors of the outcome of interest (i.e., mortality, stroke, etc)? This will better clarify the cause of geographical variation in Af outcome.

Response: We have calculated regression analyses of the outcomes of interest in our other papers. Below are two examples where such analyses have performed.

Based on these papers and clinical input, we used regression analyses to determine risk standardization which provided the data for Figures 1-3.

Fox KAA, Virdone S, Pieper KS, Bassand J-P, Camm AJ, Fitzmaurice DA, Goldhaber SZ, Goto S, Haas S, Kayani G, Oto A, Misselwitz F, Piccini JP, Dalgaard F, Turpie AGG13, Verheugt FWA and Kakkar AK for the GARFIELD-AF Investigators. GARFIELD-AF risk score for mortality, stroke and bleeding within 2 years in patients with atrial fibrillation. *Eur Heart J Qual Care Clin Outcomes*. 2021 Apr 21:qcab028. doi: 10.1093/ehjqcco/qcab028.

Bassand J.P., Accetta G., Al Mahmeed W., Corbalan R., Eikelboom J., Fitzmaurice D.A., Fox K.A.A., Gao H., Goldhaber S.Z., Goto S., Haas S., Kayani G., Pieper K., Turpie A.G.G, van Eickels M., Verheugt F.W.A., Kakkar A.K., GARFIELD-AF Investigators. 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; 25:13(1):e0191592.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5784935/pdf/pone.0191592.pdf>

3. It is important to elucidate the relationship between treatment regimens for Af and adverse events. Multivariable analyses using regression models would be helpful.

Response: We agree that this is an important topic for GARFIELD-AF. The analyses were published in the below manuscript.

Camm AJ, Fox KAA, Virdone S, Bassand J-P, Fitzmaurice DA, Berchuck SI, Gersh BJ, Goldhaber SZ, Goto S, Haas S, Misselwitz F, Pieper KS, Turpie AGG, Verheugt FWA, Cappato R, Kakkar AJ, for the GARFIELD-AF investigators. Comparative effectiveness of oral anticoagulants in everyday practice. *Heart* 2021;107:962–970
. doi:10.1136/heartjnl-2020-318420. <https://heart.bmj.com/content/early/2021/02/15/heartjnl-2020-318420>

4. The analyses of stroke, embolism, and bleeding should consider the competing risk from mortality.

Response: We agree. Non-haemorrhagic stroke/SE and major bleeding outcomes now account for death as competing risk according to Fine-Gray proportional sub-distribution hazards model. Results in FIGURES 3,4 and supplementary table S1 –S4 have been updated accordingly.

5. What is the clinical implication of the study results? This should be further discussed in the article.

Response: We have included the clinical implications in page 20:

CLINICAL IMPLICATIONS

Implications are twofold: firstly, that cardiovascular secondary prevention measures, including lifestyle measures need to be systematically adhered to and anticoagulation measures adhered to. Secondly,

that additional factors, beyond those in commonly used risk prediction tools (like CHADS2VASc) need to be evaluated, including renal dysfunction, smoking status and the extent of vascular disease. Such comorbidities require additional management.

Reviewer: 3

Dr. David Seiffge, Inselspital University Hospital Bern

Comments to the Author:

The authors performed a subanalysis of the GARFIELD registry, a prospective, global registry of patients with atrial fibrillation. They assessed regional differences in anticoagulation use and outcome events (stroke/systemic embolism; major bleeding; mortality). They found pronounced regional differences, most importantly a higher rates of mortality – even after adjustment – in countries with low health economical standards but also lower use of anticoagulants in countries with high cardiovascular morbidity.

This paper has many strengths and merits: a) prospective, high-quality large dataset, b) global recruitment and c) robust statistical methods.

We thank the reviewers for their supportive comments

I apologize to the editors and authors about my slow reply due to unscheduled clinical duties.

I have the following comments for the authors:

- Where outcome events centrally adjudicated or where they investigator-reported only?

Response: They are investigator reported but a comprehensive audit and quality control system was enacted in GARFIELD-AF and this includes onsite audits and remote quality control measures.

- Some countries/regions may still be underrepresented (see page 13, lines 22ff)

Response: This is true. Although our study design insures patients are enrolled by centers that represent AF diagnosis practices within each country, the percent of patients enrolled within a country does not reflect the population size of the country relative to the other enrolling countries.

- Do the authors have information on DOAC dosing (e.g. use of on-/off-label dosages, underdosing)?

Response: In general, we observed that patients enrolled in Asia were prescribed lower NOAC dosages than expected in the anticoagulation guidelines for AF patients.

However, the issue of on-/off- label dosage requires multiple assumptions, as creatinine information was not recorded for GARFIELD-AF patients. Additional selection criteria also need to be applied (only patients with CKD information). NOAC dosing information is provided for each NOAC, by region and overall, but without crossing with country guideline recommendations. The below article that deals extensively with the issue of non-recommended NOAC dosing in GARFIELD-AF.

Mortality in Patients With Atrial Fibrillation Receiving Nonrecommended Doses of Direct Oral Anticoagulants:

Alan John Camm, MD Frank Cools, MD Saverio Virdone, MSc Jean-Pierre Bassand, MD David Andrew Fitzmaurice, MD Keith Alexander Arthur Fox, MBChB Samuel Zachary Goldhaber, MD Shinya Goto, MD, PhD Sylvia Haas, MD, PhD Lorenzo Giovanni Mantovani, MSc Gloria Kayani, BSc Alexander Graham Grierson Turpie, MD Freek Willem Antoon Verheugt, MD, PhD Ajay Kumar

Kakkar, MBBS, PhD for the GARFIELD-AF Investigators.
<https://www.jacc.org/doi/full/10.1016/j.jacc.2020.07.045>

- Please provide information on missing data and lost-to follow-up

Response: We have included the following missing data and lost to follow-up information in page no: 11

The rate of missing data was below <3%, with the exception of lifestyle information variables like BMI and vital signs. Loss to follow-up was about 1% for all world regions except Asia (4.3%).

VERSION 2 – REVIEW

REVIEWER	Tai, Ying-Hsuan Taipei Medical University Shuang Ho Hospital Ministry of Health and Welfare, Anesthesiology
REVIEW RETURNED	25-Aug-2021
GENERAL COMMENTS	The manuscript has been greatly improved after revision. I have no more comments.
REVIEWER	Seiffge, David Inselspital University Hospital Bern, Department of Neurology
REVIEW RETURNED	31-Aug-2021
GENERAL COMMENTS	Many thanks for revising your manuscript. I have no further comments.