BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Do stroke risk characteristics account for geographical disparities in the outcomes of patients with newly diagnosed atrial fibrillation? The GARFIELD-AF registry

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-049933
Article Type:	Original research
Date Submitted by the Author:	11-Feb-2021
Complete List of Authors:	Fox, Keith; University of Edinburgh Division of Clinical and Surgical Sciences, Centre for Cardiovascular Science Virdone, Saverio; Thrombosis Research Institute Bassand, Jean-Pierre; Thrombosis Research Institute; University Hospital Centre Besancon, Department of Cardiology Camm, John; St George's University of London, Cardiology Clinical Academic Group Molecular & Clinical Sciences Research Institute, Goto, Shinya; Tokai University School of Medicine Graduate School of Medicine, Department of Medicine (Cardiology) Goldhaber, Samuel; Brigham and Women's Hospital Department of Medicine, Department of Medicine Haas, Sylvia ; Technical University of Munich, Department of Medicine Kayani, Gloria; Thrombosis Research Institute Koretsune, Yukihiro; National Hospital Organization Osaka National Hospital Misselwitz, Frank; Bayer Healthcare Pharmaceuticals Research and Development Berlin Oh, Seil; Seoul National University Hospital Piccini, Jonathan; Duke University Medical Center Parkhomenko, Alex; National Scientific Center Academician M D Strazhesko Institute of Cardiology of the National Academy of Medical Sciences of Ukraine Sawhney, J P S; Sir Ganga Ram Hospital Stepinska, Janina; Intensive Cardiac therapy clinic Turpie, Alexander G. G.; McMaster University, Department of Medicine Verheugt, Freek; OLVG, Cardiology Kakkar, Ajay ; Thrombosis Research Institute; University College London
Keywords:	CARDIOLOGY, Anticoagulation < HAEMATOLOGY, Thromboembolism < CARDIOLOGY

SCHOLARONE™
Manuscripts

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

Title Page

Do stroke risk characteristics account for geographical disparities in the outcomes of patients with newly diagnosed atrial fibrillation? The GARFIELD-AF registry

Keith A.A. Fox MBChB[1], Saverio Virdone M. Sc[2], Jean-Pierre Bassand MD[2,3], A. John Camm MD[4], Shinya Goto MD, PhD[5], Samuel Z. Goldhaber MD[6], Sylvia Haas MD[7], Gloria Kayani B. Sc[2], Yukihiro Koretsune MD, PhD[8], Frank Misselwitz MD, PhD[9], Seil Oh MD, PhD[10], Jonathan P. Piccini MD[11], Alex Parkhomenko MD, PhD[12], Jitendra Pal Singh Sawhney MD[13], Janina Stepinska MD, PhD[14], Alexander G.G. Turpie MD[15], Freek W.A. Verheugt MD, PhD[16], Ajay K. Kakkar MBBS, PhD[2,17] for the GARFIELD-AF investigators*

1. Centre for Cardiovascular Science, University of Edinburgh, United Kingdom
2. Thrombosis Research Institute, London, United Kingdom
3. Department of Cardiology, University of Besançon, Besançon, France
4. Cardiology Clinical Academic Group Molecular & Clinical Sciences Research Institute, St. George's University of London, London, UK
5. Department of Medicine (Cardiology), Tokai school of medicine, Kanagawa, Japan
6. Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
7. Department of Medicine, Formerly Technical University of Munich, Munich, Germany
8. National Hospital Organization Osaka National Hospital, Osaka, Japan
9. Bayer AG, Berlin, Germany
10. Seoul National University Hospital, Seoul, Korea

For peer review only

11. Duke University Medical Center and the Duke Clinical Research Institute, Durham, NC, USA
12. National Scientific Centre "MD Strazhesko Institute of Cardiology", Kiev, Ukraine
13. Department of Cardiology, Ganga Ram Hospital, New Delhi, India
14. Institute of Cardiology, Intensive cardiac therapy clinic, Warsaw, Poland
15. Department of Medicine, McMaster University, Hamilton, ON, Canada
16. Department of Cardiology, Onze Lieve Vrouwe Gasthuis (OLVG), Amsterdam, The Netherlands
17. University College London, London, UK

Corresponding author

Keith A.A. Fox, FRCP, FESC, FMedSci,

Professor of Cardiology,

BHF Centre for Cardiovascular Science,

University of Edinburgh,

47 Little France Crescent,

Edinburgh EH16 4TJ.

Email: k.a.a.fox@ed.ac.uk;

Tel: +44 131 242 6378

*A complete list of investigators is given in the supplementary

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

Word count:

Abstract: 299 (Max: 300)

Text: 3430

Reference: 32

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Abstract

Objective To determine whether geographical variations in outcomes are accounted for by baseline clinical risk factors and stroke prevention strategies.

Design GARFIELD-AF is a prospective non-interventional registry of patients with newly diagnosed AF. A total of 52,018 patients were enrolled (2010- 2016).

Setting Investigator sites (n=1317) are representative of the care settings/locations in each of the 35 participating countries.

Participants A total of 52,018 patients 18 years and older with newly diagnosed AF and at least 1 investigator-determined stroke risk factor were included.

Main outcomes and measures Observed 1-year Kaplan-Meier event rates and national risk-standardised rates derived.

Results Despite similar conventional measures of stroke risk (CHA_2DS_2-VASc 3.0 in each region), anticoagulant treatment varied three-fold and rates of non-haemorrhagic stroke/SE and mortality differed substantially, even after adjustment for baseline factors and treatments. High observed mortality rates in Canada, France and Germany were largely accounted for by clinical case mix, but countries with some of the lowest Healthcare Access and Quality (HAQ) indices (India, Ukraine, Argentina and Brazil) had the highest mortality, even after risk adjustment. The lowest observed rates of mortality in Japan and South Korea persisted after risk adjustment. The lowest risk-standardised rates of non-haemorrhagic stroke/SE were seen in Germany, Czech Republic and Canada and the highest risk-standardized rates of major bleeding in the Netherlands and USA. Patients from countries with the highest rates of cardiovascular mortality and stroke were among the least likely to receive oral anticoagulants. However, differences in antithrombotic regimens account for only part of the substantial geographic variations in outcomes.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Conclusion Only part of the variability in outcomes among countries is accounted for by baseline demographics, modifiable cardiovascular risk factors, comorbidities and antithrombotic regimens. The potential exists to improve outcomes by addressing modifiable risk factors and the gap between evidence based guidelines and clinical practice among patients with AF.

Clinical Trial Registration—URL http://www.clinicaltrials.gov, unique identifier: NCT01090362.

Key words Geographical variations; Atrial Fibrillation; All-cause mortality; Stroke/systemic embolism; major bleeding

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Strengths and limitations of this study

- Marked geographic variations in outcomes (up to two-fold differences in mortality, and in bleeding) are attenuated, but persist after accounting for demographic and clinical characteristics of patients with incident AF.
- The potential exists to improve outcomes among patients with newly diagnosed AF, and to diminish geographic disparities, not only through guideline appropriate stroke prevention, but also by addressing potentially modifiable risk factors.
- The mortality data from GARFIELD-AF reflect the life expectancy in countries with highest and lowest mortality rates, and there is a significant ($p<0.001$) inverse association with the choice of antithrombotic regimen, multinationality, and the Healthcare Access and Quality Indices derived from national data
- Ascertainment bias may have been responsible for the apparently high rates of bleeding in some countries but rates of anticoagulation and combined treatment with antiplatelets may also have contributed to the observed rates of bleeding.

eer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

INTRODUCTION

The 2015 Global Burden of Disease (GDB) report of 195 countries and territories suggests that AF prevalence is highest in Northern and Central Europe, and the United States [1], and is projected to rise globally because of aging and population growth worldwide [2].

The gains in cardiovascular health in high-income countries are related, at least in part, to modification of cardiovascular risk factors as well as improved disease management. In the context of atrial fibrillation, the changes include the availability of treatment strategies for stroke prophylaxis, and/or rhythm or rate control [3-7]. However, the extent to which baseline characteristics and treatment strategies account for geographic variations in outcomes is unclear.

The Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) aimed to define geographical variations in all-cause mortality, stroke/systemic embolism (SE) and major bleeding in patients with newly diagnosed AF. The primary aim of this report was to determine whether variations in outcomes of AF are accounted for by baseline clinical risk characteristics. A secondary aim was to consider the impact of other factors including national differences in life expectancy, access to quality healthcare, and stroke prevention strategies.

MATERIALS AND METHODS

Design

GARFIELD-AF is the largest multinational prospective registry in AF [8]. The study recruited patients from >1,000 investigational sites (identified nationally as representative) in 35 countries. Patients were recruited from: Europe (Finland, Norway, Sweden, Denmark, United Kingdom, Netherlands, Belgium, Germany, Switzerland, France, Spain, Italy, Austria, Hungary, Russia, Poland, Czech Republic, Ukraine and Turkey), Asia (Singapore, China, Japan, South Korea, Thailand and India), North America (USA and Canada), Latin America

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

(Mexico, Brazil, Argentina and Chile) and other countries including Egypt, United Arab Emirates, South Africa and Australia.

Adults ≥18 years were eligible for inclusion if they were diagnosed with non-valvular AF within 6 weeks of study entry. Patients with AF were required to have at least one risk factor for stroke, as judged by the investigator (entry to GARFIELD-AF did not require performance of a stroke risk predictor, nor a specific threshold if such a score was performed). Patients were enrolled prospectively and consecutively at sites that aimed to reflect diverse care settings (including office/outpatient practice; hospital departments including neurology, cardiology, geriatrics, internal medicine and emergency; anticoagulation clinics; and general practice) [8,9].

Independent ethics committee and hospital-based institutional review board approvals were obtained. The registry was conducted in accordance with the principles of the Declaration of Helsinki, local regulatory requirements, and the International Conference on Harmonisation–Good Pharmacoepidemiological and Clinical Practice guidelines. Written informed consent was obtained from all study participants.

GARFIELD-AF data were captured using an electronic case report form (eCRF). Submitted data were examined for completeness and accuracy by the coordinating centre (Thrombosis Research Institute, London, UK), and data queries were sent to study sites. An audit and quality control programme was implemented, and this included source documentation (20% of all eCRFs were monitored against source records) [10]. This paper adheres to the guidelines from STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) [11].

Patient and Public Involvement

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Procedures and outcome measures

Baseline characteristics collected at study entry included: medical history, care setting, type of AF, date and method of diagnosis of AF, symptoms, antithrombotic treatment (vitamin K antagonists [VKAs], non-vitamin K antagonist oral anticoagulants [NOACs] and antiplatelet [AP] treatment), as well as all cardiovascular drugs. Race was classified by the investigator in agreement with the patient [8]. Vascular disease included coronary artery disease (CAD) with a history of acute coronary syndromes (ACS) and/or peripheral artery disease. Chronic kidney disease (CKD) was classified according to National Kidney Foundation guidelines into moderate-to-severe (stages 3–5), mild (stages 1 and 2) or none. Data on components of the CHA_2DS_2-VASc and HAS-BLED risk stratification schemes were collected and calculated retrospectively. HAS-BLED scores were calculated excluding fluctuations in international normalised ratio. In addition, the risk of death, non-haemorrhagic stroke/SE and major bleeding was evaluated with the GARFIELD-AF risk calculator [12].

Patients were followed over a minimum of 24 months or until death or loss to follow-up, whichever occurred first. As reported previously, standardised definitions for clinical events, death (cardiovascular and non-cardiovascular), non-hemorrhagic stroke/SE and major bleeding) were used [8,9]. Data for this report were extracted from the study database on 30th June 2019.

Statistical analysis

Univariate data are presented as medians (1st and 3rd quartile) for continuous variables and as absolute frequencies with percentages for categorical variables.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

"Time at risk" for each event was calculated over the first year after enrolment up to the first occurrence of an event or last follow-up or at 365 days, which ever occurred earlier. All-cause mortality, non-haemorrhagic stroke/SE and major bleeding were described as the number of events and the Kaplan-Meier event rate with 95% confidence intervals.

In this study, national risk-standardised measures of event rates were calculated to compare the observed event rates based on case mix (i.e. the clinical characteristics of patients) in each country, with the expected rates for a similar case mix. The risk-standardised event rates were calculated using the following equation:

$$\frac{Observed\ event\ rate}{Expected\ event\ rate} \times Global\ event\ rate = Risk\ standardized\ rate$$

Where the **Observed event rate** was the crude rate calculated for each country using the Kaplan-Meier estimator (1 *minus* event-free survival probability at 1 year after enrolment).

Expected event rate was calculated (using multivariable Cox regression with a series of demographic and clinical characteristics as covariates) for every patient and the national average computed.

Global (and regional) event rates were the crude rate calculated with the Kaplan-Meier rate across all countries in GARFIELD-AF without exclusion.

When the observed and expected rates were the same, the risk-standardised rate equalled the global event rates. However, when the observed event rate was greater or less than the expected rate, then the country had more or less events than expected, based on its case mix. Hence, the observed to expected ratio was greater or less than 1.0, making the risk-standardised rate higher or lower than the global rate.

Patients' characteristics included in the initial Cox model were: age, gender, type of AF, history of hypertension, blood pressure (systolic and diastolic) and pulse rate (at enrolment),

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

hypercholesterolemia, smoking status (never/ex/current) and heavy alcohol consumption, diabetes mellitus (type 1 or 2), ACS, coronary artery bypass graft (CABG), vascular disease, carotid occlusive disease, venous thromboembolism (VTE), history of stroke/transient ischaemic attack (TIA)/SE, history of bleeding, heart failure, moderate-to-severe CKD and cirrhosis. Confidence intervals for the risk-standardized measures were computed using estimates extracted from 1000 bootstrap samples. Patients with missing values were not removed from the study; single imputation was applied.

Both baseline risk factors and antithrombotic regimens (with oral AC and/or AP) at the time of diagnosis of AF (baseline) were included in the Cox model.

The observed rates in a contemporary US registry, the ORBIT-AF II, were derived to assess the representability of the US patients in GARFIELD-AF.

All analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline demographics and clinical characteristics

Baseline characteristics were analysed for the 52,018 patients with newly diagnosed AF, enrolled consecutively into GARFIELD-AF between March 2010 and August 2016, in 35 countries. The largest cohort was recruited from Europe (57.4%), followed by Asia (26.6%), Latin America (8.2%), "Other" countries (4.7%) (including South Africa, Egypt, United Arab Emirates and Australia) and North America (3.1%).

The observed variability in patients' baseline characteristics among regions in GARFIELD-AF is reported in **table 1.** Patients from Asia compared with Europe tended to be younger, had a lower body mass index, a lower prevalence of hypertension, hypercholesterolemia, vascular disease and CKD. By contrast, patients from North America in GARFIELD-AF had the highest

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

proportion of patients aged ≥75, together with the highest prevalence of diabetes, hypercholesterolemia and prior/current smokers from any region (except "Other Region" where the highest prevalence of diabetes was observed). The prevalence of heart failure was consistent and approximately one in five of patients in every region. Approximately 70% of patients overall (and 91.6% of patients in North America) were categorised at having paroxysmal or unclassified AF at enrolment in this study **(Table 1).**

Standard risk assessment scores (including the GARFIELD-AF risk score) found that the calculated risks of stroke or major bleeding were similar across regions (median CHA_2DS_2-VASc score 3.0 in all regions). The GARFIELD-AF risk model for death revealed regional differences, with a lower expected rate of death in patients from Asia and highest in those from Latin America **(Table 1).**

Treatment setting

In Asia and Latin America, patients were predominantly diagnosed and managed by cardiologists (83.7% and 75.0%, respectively), while in Europe and North America, the role of managing patients with AF was shared between cardiologists (in approximately 60% of cases), internists (~20%) and primary care (~20%). The likelihood of being diagnosed and treated in the emergency care setting was highest in North America (38.0% of patients) followed by Latin America (24.7%), "Other" countries (13.4%), Europe (11.5%) and Asia (2.5%).

Observed global and regional outcomes

In GARFIELD-AF, the lowest observed rate of death at one year was recorded in Asia (2.8; 95% CI: 2.6-3.1) with rates less than half those observed in "Other" countries (6.0; 95% CI: 5.1-7.0) (namely, South Africa, Egypt, United Arab Emirates and Australia). Non-

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

haemorrhagic stroke/SE rates showed less regional variability, but once again, the lowest observed rates were reported in Asia (1.0; 95% CI: 0.9-1.2). For major bleeding, the highest observed rates were recorded in North America (2.9; 95% CI: 2.2-3.8) and the lowest in Asia (0.9; 95% CI: 0.7-1.0). Reflecting the high proportion of patients from Europe, the global rates across all countries in GARFIELD-AF were similar to European event rates for mortality, non-haemorrhagic stroke/SE and major bleeding **(Table 2).**

Observed and risk-standardised outcomes by country

Figures 1 to 3 depict the observed and risk-standardised rates of mortality, non-haemorrhagic stroke/SE and major bleeding for countries that enrolled more than 90% of the patients into GARFIELD-AF, i.e. omitting countries with potentially unrepresentative findings due to low enrolment. Full details of the observed rates from all countries, including those omitted from the figures, i.e. South Africa (n=639), Denmark (n=532), Egypt (n=527), Austria (n=460), United Arab Emirates (n=397), Finland (n=359), Singapore (n=306), Norway (n=270), and Switzerland (n=89), are reported in **Supplement Tables S1-S3.**

Figures 1-3 show the marked variations in observed event rates by country. This variability persisted even after adjusting for all 22 baseline factors (demographics, modifiable cardiovascular risk factors and comorbidities).

India and Ukraine experienced the highest risk-standardised mortality rates, primarily driven by cardiovascular events. Marked differences were also observed for the USA, where the rate of non-cardiovascular mortality was more than 3-fold higher compared to cardiovascular mortality. Within most other countries the rates of cardiovascular and non-cardiovascular mortality were similar (**Supplementary Table S1**).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

To display the relation between healthcare access and outcomes in more detail, we colour-coded each country according to the Healthcare Access and Quality (HAQ) Index (overall score on a scale of 0–100) from the Global Burden of Disease Study 2016 [14]. The results show that some of the countries with highest risk-standardised mortality rates (i.e. India, Mexico, Argentina and Brazil) had some of the lowest HAQ indices (HAQ: <70); only Thailand had a similarly low HAQ and a mortality rate. Conversely, the three countries with the lowest risk-standardised mortality rate (South Korea, Japan, and Sweden) all obtained a high HAQ score (HAQ: ≥90).

The observed mortality rate from the US study, ORBIT-AF II, was similar to the GARFIELD-AF global rate (4.3 [95% CI: 3.7-4.9] vs 4.2 [95% CI: 4.0-4.4] respectively) and below the global rate for non-haemorrhagic stroke/SE (ORBIT-AF-II 0.8 [95% CI: 0.6-1.1] vs GARFIELD-AF 1.2 [95% CI: 1.1-1.3]). Nevertheless, both GARFIELD-AF and ORBIT-AF II reported high rates of major bleeding in the US: 3.4 (95% CI: 2.3-5.0) [GARFIELD-AF] and 3.3 (95% CI: 2.8-3.8) [ORBIT-AF II] relative to the global rate of 1.2(95% CI: 1.1-1.3) in GARFIELD-AF.

The rates of each type of outcome differed by country. For instance, the lowest risk-standardised mortality rates were observed for South Korea, Japan and Sweden, while the lowest risk-standardised rates of non-haemorrhagic stroke/SE were observed in Germany, Czech Republic and Canada. The highest risk-standardised rates non-haemorrhagic stroke/SE were reported in Ukraine and Australia, and the highest risk-standardised rates of major bleeding in the Netherlands and the USA.

Antithrombotic regimen for stroke prevention at baseline

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

GARFIELD-AF recorded substantial differences in the overall rate of anticoagulation by region (from 73% in Europe to 56% in Asia, **Supplementary Figure S1a**), as well as large variations within countries (**Supplementary Figure S1b).** At the time of diagnosis of AF, the highest proportion of patients receiving NOACs was in North America (44.8%). This included 14.4% of patients who received NOAC in combination with APs. VKAs were most commonly prescribed in Europe, Latin America and "Other" countries (in 44.4%, 39.8% and 41.1% of patients, respectively) (**Figure S1a**).

Even though CHA_2DS_2-VASc scores were similar across countries (**Supplementary Table S2**), anticoagulant treatment varied three-fold among countries (30% to 90%) (**Figure S1b**). The highest rate of anticoagulation was in the Netherlands and Switzerland (90%) and lowest in China (30%), India (35%) and Ukraine (48%) (Figure 4b). More than 40% of newly diagnosed patients with AF in China and India received anti-platelet therapy only and a further 20%, approximately, received no anti-thrombotic therapy. Across all countries, we found a significant ($p<0.001$) association with the choice of antithrombotic regimen and HAQ index, i.e. with a greater likelihood of AC and NOAC prescribing (and lower likelihood of AP therapy alone) with increasing HAQ score **(Figure 4)**.

ACs (with or without AP therapy) were prescribed to more than 70% of patients in 18 of 35 countries.

The choice of stroke prevention strategy by region and country was analysed and included in the Cox model. Even after adjustment for baseline risk factors and antithrombotic regimen (AC and/or AP treatment), substantial inter-country differences remained in the rate of non-haemorrhagic stroke/SE (**Supplementary table S4**).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

DISCUSSION

Analysis of the 52,018 prospectively enrolled patients from the GARFIELD-AF registry shows that after adjusting for the baseline demographics and clinical characteristics (including modifiable cardiovascular risk factors and comorbidities) variability in outcomes among countries is attenuated, but persists. This finding highlights the importance of identifying factors beyond those collected in conventional risk prediction tools to estimate outcomes in patients with AF. Such factors may include practice patterns, access to quality health care, and numerous environmental and epigenetic characteristics to account for the substantial differences in risk-standardised event rates among countries [15].

The findings show that the apparently high observed rates of mortality (relative to the global average) in countries such as Canada, USA, France and Germany could be largely accounted for by clinical patient characteristics at enrolment. By contrast, countries with some of the lowest Healthcare Access and Quality (HAQ) indices in GARFIELD-AF (India, Ukraine, Argentina and Brazil) had the highest risk-standardised mortality rates. Conversely, the lowest observed rates of mortality in Japan and South Korea persisted even after risk adjustment.

The risk-standardised mortality rates in GARFIELD-AF appear to be a reflection of average national life expectancy, with the lowest mortality rates in this population with newly diagnosed AF in countries with life-expectancies (in years) of 82.2, 83.8, 82.6, 78.2 and 81.6, whereas countries with the highest mortalities in this AF population have life expectancies (in years) of 68.3, 71.2, 76.3, 78.7 and 74.7 [16].

Patients from participating centres with the highest rates of mortality and non-haemorrhagic stroke/SE and were among the least likely to receive oral ACs for stroke prevention over the 5

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

years of recruitment into GARFIELD-AF **(Figure S1b)**. This is consistent with the observed higher rates of cardiovascular (vs non-cardiovascular) mortality in such countries and where AP therapy or no antithrombotic therapy for AF is most prevalent **(Table 2).**

It is possible that the higher rates of major bleeding at participating centres in the Netherlands (GARFIELD-AF) and the USA (GARFIELD-AF and ORBIT-AF II) are a reflection of prescribing practice (e.g. high use of anticoagulation in the Netherlands [90%]; and the frequent use of combined NOAC+ AP therapy in the USA [20.7%]) as well as possible ascertainment bias.

It is notable that further analyses of stroke rates revealed that differences in OAC and AP treatment regimens account for only some of the differences among countries, and substantial differences remain (**Supplementary Figure S1).**

Achieving population-wide control of modifiable risk factors (including tobacco use, diet, physical inactivity, plasma glucose and hypertension) could abrogate a substantial part of the global stroke burden, irrespective of age, gender or ethnicity [17,18]. Even small changes in the distribution of these risk factors could lead to clinically relevant reductions in the risks of cardiovascular disease, stroke, and mortality [19-21]. The findings from GARFIELD-AF and other recently published global and regional studies [7,22-26] suggest that high rates of potentially modifiable metabolic disorders and smoking persist. Thus there remains considerable scope to improve the outcomes of patients with newly diagnosed AF, even in high- and middle-income countries.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Substantially higher than global rates of antiplatelet therapy (without anticoagulation), are prescribed in China and India than in Thailand, South Korea, Singapore and Japan (Figure 1b). Fewer older patients were recruited from India, (26% vs 37% of patients were ≥75 years) but there were more diabetics (36% vs 22%) and CAD patients (28% vs 22%) compared with global average [27]. By contrast, patients from Japan were older than the global average (42% vs 37% of patients were ≥75 years) with a lower prevalence of hypercholesterolemia (29.2% and 42.9%) and CAD (10.3% and 22.8%) at the time of diagnosis of AF [28].

GARFIELD-AF has demonstrated major disparities in the rate of anticoagulation for AF (Figure 1b) and these are not accounted for by conventional measures of stroke risk [29]. Such findings are consistent with other observational studies, including: PINNACLE (Practice Innovation and Clinical Excellence) [30], EORP-AF (EUR Observational Research Programme-Atrial Fibrillation) [31] and GLORIA-AF (Global Registry on Long-Term Antithrombotic Treatments in Patients with Atrial Fibrillation) [32]. However, in GARFIELD-AF there were geographic disparities, not only in antithrombotic regimens for AF, but also in other cardiovascular and lifestyle management measures. These may account to a substantial part of the remaining geographic differences in outcomes. The clear relation of outcomes with indices of healthcare access (HAQ indices) supports this concept.

Strengths and limitations

GARFIELD-AF is a non-interventional registry, and it provided a record of consecutively enrolled patients with newly diagnosed AF who were treated, according to local standards of care, in each participating centre without exclusion of participants by age, risk profile or concomitant disease. GARFIELD-AF mitigated some of the limitations inherent to observational studies through the standardisation of clinical definitions and the rigorous audit

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

(using both remote and onsite monitoring) to ensure the completeness and accuracy of the data collected. However, reported rates will be influenced by the characteristics of recruiting centres and treatment settings. Nevertheless, the mortality data from GARFIELD-AF reflect the life expectancy in countries with highest and lowest mortality rates, and there is a significant ($p<0.001$) inverse association with the choice of antithrombotic regimen in GARFIELD-AF and average HAQ index (derived from national data). Ascertainment bias may have been responsible for the apparently high rates of bleeding in some countries (e.g. Netherlands and USA) but rates of anticoagulation and combined treatment with antiplatelets may also have contributed to the observed rates of bleeding. It is also possible that there was lower ascertainment of outcomes in some countries.

CONCLUSIONS

Despite similar conventional measures of stroke risk (CHA_2DS_2-VASc equalled 3.0 in each region), anticoagulant treatment varied three-fold across countries and the observed rates of stroke/SE and mortality differed substantially by region, even after adjustment for baseline factors and antithrombotic treatments. The new diagnosis of AF signals an increased risk of diverse adverse cardiovascular outcomes, but with striking geographic variations. The variations persisted after adjusting for CHA_2DS_2-VASc risk factors and other baseline and risk characteristics (e.g., smoking, type of AF and moderate-to-severe CKD). Other factors, including variations in clinical practice, organization and access to quality healthcare (as measured by HAQ) as well as patient-related factors may be responsible for the substantial differences in the rates of mortality, stroke/SE and major bleeding across countries. Conventional stroke and cardiovascular risk factors and antithrombotic treatments do not explain the substantial national and regional disparities in outcomes for patients with newly diagnosed AF.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Acknowledgements We thank the physicians, nurses, and patients involved in the GARFIELD-AF registry. Programming support was provided by Madhusudana Rao (TRI, London, UK). Editorial support was provided by Rae Hobbs and Dr Surekha Damineni (TRI, London, UK).

Contributor KAAF, JPB, AJC, SG, SZG, SH, GK, FM, JPP, AGGT, FWAV and AKK contributed to the study design. YK, SO, AP, JPSS, JS contributed to the data collection. SV analysed the data. All authors supervised the data analysis, provided the interpretation of results and contributed to the drafting and critical review of the manuscript. All authors approved the final draft.

Funding This study was supported by an unrestricted research grant from Bayer AG, Berlin, Germany, to TRI, London, UK, which sponsors the GARFIELD-AF registry. The work is supported by KANTOR CHARITABLE FOUNDATION for the Kantor-Kakkar Global Centre for Thrombosis Science. The funding sources had no involvement in the data collection, data analysis, or data interpretation.

Competing Interests KAA Fox has received grants and personal fees from Bayer/Janssen and AstraZeneca and personal fees from Sanofi/Regeneron and Verseon. AJ Camm: Institutional grants and personal fees from Bayer, Boehringer Ingelheim, BMS/Pfizer and Daichi Sankyo; S Goto has received Personal fees from Thrombosis Research Institute and the American Heart Association, grants from Sanofi, Pfizer, Ono, Bristol Myer Squibb, the Vehicle Racing Commemorative Foundation and Nakatani Foundation for Advancement of Measuring Technologies in Biomedical Engineering. SZ Goldhaber has received research support from Boehringer-Ingelheim, BMS, BTG EKOS, Daiichi, Janssen, NHLBI, and the Thrombosis Research Institute; has served as a consultant for Agile, Bayer, Boehringer-Ingelheim, BMS, Daiichi, Janssen and Zafgen. S Haas has received personal fees from Aspen, Bayer Healthcare,

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMS/Pfizer, Daiichi-Sankyo, and Sanofi. Y Koretsune: Research grant from Daiichi Sankyo and Boeringer Ingelheim. Personal fees from: Daiichi Sankyo, Boehringer Ingelheim, Bayer, Bristol Meyers and Pfizer; F Misselwitz is an employee of Bayer AG. S Oh: consultant/advisory board payments from Bayer Pharma AG, Bristol-Myers Squibb Korea, Boehringer-Ingelheim Korea, Pfizer Korea, Sanofi-Aventis, and St Jude Medical. J PS Sawhney: Personal fee from Pfizer, Astra Zeneca, Novartis, Sanofi & BMS; J. P. Piccini: Reported grants for clinical research from Abbott, American Heart Association, Boston Scientific, Gilead, Janssen Pharmaceuticals, NHLBI, and Philips and serves as a consultant to Abbott, Allergan, ARCA Biopharma, Biotronik, Boston Scientific, Johnson & Johnson, LivaNova, Medtronic, Milestone, Oliver Wyman Health, Sanofi, Philips, and Up-to-Date. J Stepinska: Research grants from Bayer; personal fees from Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, BMS/Pfizer, Novartis, Sanofi, Servier; Expert witness for Boehringer Ingelheim; AGG Turpie has received personal fees from Bayer Healthcare, Janssen Pharmaceutical Research & Development LLC, and Portola. FWA Verheugt has received grants from Bayer Healthcare; personal fees from Bayer Healthcare, BMS/Pfizer, Daiichi-Sankyo, and Boehringer-Ingelheim. AK Kakkar has received research support from Bayer AG and Sanofi; personal fees from Bayer AG, Pfizer, Janssen, Sanofi, Verseon and Anthos Therapeutics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Patient consent for publication Obtained.

Ethics approval Independent ethics committee and hospital-based institutional review board approvals were obtained, as necessary, for the registry protocol.

Provenance and peer review Not commissioned; externally peer reviewed.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Data sharing statement The data underlying this article will be shared on reasonable request from Karen S Pieper (KPieper@tri-london.ac.uk).

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

REFERENCES

1. Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation.* 2018;137(12):e67-e492.
2. Patel NJ, Atti V, Mitrani RD, Viles-Gonzalez JF, Goldberger JJ. Global rising trends of atrial fibrillation: a major public health concern. *Heart.* 2018.
3. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N. Engl. J. Med.* 2007;356(23):2388-2398.
4. Koopman C, Vaartjes I, van Dis I, et al. Explaining the Decline in Coronary Heart Disease Mortality in the Netherlands between 1997 and 2007. *PLoS One.* 2016;11(12):e0166139.
5. Bandosz P, O'Flaherty M, Drygas W, et al. Decline in mortality from coronary heart disease in Poland after socioeconomic transformation: modelling study. *BMJ.* 2012;344:d8136.
6. Palmieri L, Bennett K, Giampaoli S, Capewell S. Explaining the decrease in coronary heart disease mortality in Italy between 1980 and 2000. *Am. J. Public Health.* 2010;100(4):684-692.
7. Ng M, Freeman MK, Fleming TD, et al. Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. *JAMA.* 2014;311(2):183-192.
8. Kakkar AK, Mueller I, Bassand JP, et al. International longitudinal registry of patients with atrial fibrillation at risk of stroke: Global Anticoagulant Registry in the FIELD (GARFIELD). *Am Heart J.* 2012;163(1):13-19 e11.
9. Kakkar AK, Mueller I, Bassand JP, et al. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

international, observational, prospective GARFIELD registry. *PLoS One.* 2013;8(5):e63479.

10. Fox KAA, Gersh BJ, Traore S, et al. Evolving quality standards for large-scale registries: the GARFIELD-AF experience. *Eur Heart J Qual Care Clin Outcomes.* 2017;3(2):114-122.

11. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS medicine.* 2007;4(10):e297.

12. Fox KAA, Lucas JE, Pieper KS, et al. 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(12):e017157.

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):160-167.

14. Measuring performance on the Healthcare Access and Quality Index for 195 countries and territories and selected subnational locations: a systematic analysis from the Global Burden of Disease Study 2016. *Lancet (London, England).* 2018;391(10136):2236-2271.

15. Khambhati J, Allard-Ratick M, Dhindsa D, et al. The art of cardiovascular risk assessment. *Clin. Cardiol.* 2018;41(5):677-684.

16. World Economic Forum. Life Expectancy. . *Available at: http://reports.weforum.org/global-competitiveness-index-2017-2018/competitiveness-rankings/#series=LIFEEXPECT.* (Last accessed Decmber 2018).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

17. O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet (London, England).* 2016;388(10046):761-775.

18. Feigin VL, Norrving B, George MG, Foltz JL, Roth GA, Mensah GA. Prevention of stroke: a strategic global imperative. *Nature Reviews Neurology.* 2016;12:501.

19. Fang N, Jiang M, Fan Y. Ideal cardiovascular health metrics and risk of cardiovascular disease or mortality: A meta-analysis. *Int. J. Cardiol.* 2016;214:279-283.

20. Guo L, Zhang S. Association between ideal cardiovascular health metrics and risk of cardiovascular events or mortality: A meta-analysis of prospective studies. *Clin. Cardiol.* 2017;40(12):1339-1346.

21. Colpani V, Baena CP, Jaspers L, et al. Lifestyle factors, cardiovascular disease and all-cause mortality in middle-aged and elderly women: a systematic review and meta-analysis. *Eur. J. Epidemiol.* 2018;33(9):831-845.

22. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet (London, England).* 2016;387(10026):1377-1396.

23. Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1.9 million participants. *The Lancet. Global health.* 2018;6(10):e1077-e1086.

24. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet (London, England).* 2017;389(10064):37-55.

25. Danaei G, Finucane MM, Lu Y, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet (London, England)*. 2011;378(9785):31-40.

26. Kotseva K, De Bacquer D, De Backer G, et al. Lifestyle and risk factor management in people at high risk of cardiovascular disease. A report from the European Society of Cardiology European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) IV cross-sectional survey in 14 European regions. *European journal of preventive cardiology*. 2016;23(18):2007-2018.

27. Sawhney JPS, Kothiwale VA, Bisne V, et al. Risk profiles and one-year outcomes of patients with newly diagnosed atrial fibrillation in India: Insights into the GARFIELD-AF Registry. *Ind Heart J (in presss)*. 2018;https://doi.org/10.1016/j.ihj.2018.09.001.

28. Koretsune Y, Etoh T, Katsuda Y, et al. Risk profiles and one-year outcomes of patients with newly diagnosed atrial fibrillation in Japan: Insights from the GARFIELD-AF Registry. *Circ J. (In press)*. 2018.

29. Camm AJ, Accetta G, Ambrosio G, et al. Evolving antithrombotic treatment patterns for patients with newly diagnosed atrial fibrillation. *Heart*. 2017;103(4):307-314.

30. Chan PS, Maddox TM, Tang F, Spinler S, Spertus JA. Practice-level variation in warfarin use among outpatients with atrial fibrillation (from the NCDR PINNACLE program). *Am J Cardiol*. 2011;108(8):1136-1140.

31. Lip GY, Laroche C, Boriani G, et al. Regional differences in presentation and treatment of patients with atrial fibrillation in Europe: a report from the EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. *Europace*. 2015;17(2):194-206.

32. McIntyre WF, Conen D, Olshansky B, et al. Stroke-prevention strategies in North American patients with atrial fibrillation: The GLORIA-AF registry program. *Clinical cardiology*. 2018;41(6):744-751.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Figure Legends:

Figure 1. Observed (a) and risk-standardized (b) one-year mortality rates with 95% confidence intervals by country. *

*Showing only countries with more than 700 patients enrolled. Horizontal dashed line represents overall observed global rate calculated from all 35 countries. Measures of performance are based on the Healthcare Access and Quality Index for 195 countries and territories from the Global Burden of Disease Study [reference 20].

Figure 2. Observed (a) and risk-standardized (b) one-year non-haemorrhagic stroke/systemic embolism (SE) rates with 95% confidence intervals by country. *

*Showing only countries with more than 700 patients enrolled. Horizontal dashed line represents overall observed global rate calculated from all 35 countries. Measures of performance are based on the Healthcare Access and Quality Index for 195 countries and territories from the Global Burden of Disease Study [reference 20].

Figure 3. Observed (a) and risk-standardized (b) one-year major bleeding rates with 95% confidence intervals by country

*Showing only countries with more than 700 patients enrolled. Horizontal dashed line represents overall observed global rate calculated from all 35 countries. Measures of performance are based on the Healthcare Access and Quality Index for 195 countries and territories from the Global Burden of Disease Study [reference 20].

Figure 4. Baseline antithrombotic treatment distribution by Healthcare Access and Quality (HAQ) index[1]

[1]As HAQ index is a country measure, all patients enrolled within a specific country are assigned the same HAQ index

HAQ index of OAC+AP or AP only: <70=46.7%; 70-79=52.5%; 80-89=30.1%; ≥90=28.6%

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1. Baseline demographics and clinical characteristics of patients stratified by region

Baseline characteristics	Region				
	Europe (N = 29,876)	Asia (N = 13,821)	Latin America (N = 4247)	North America (N = 1619)	Other countries (N = 2455)
Gender female, n (%)	13,563 (45.4)	5622 (40.7)	2016 (47.5)	734 (45.3)	1051 (42.8)
Age, median (Q1; Q3), years	72.0 (64.0; 79.0)	69.0 (60.0; 76.0)	71.0 (63.0; 79.0)	72.0 (64.0; 80.0)	67.0 (59.0; 75.0)
Age group, n (%)					
<65 years	8016 (26.8)	4980 (36.0)	1258 (29.6)	441 (27.2)	996 (40.6)
65-74 years	9761(32.7)	4564 (33.0)	1336 (31.5)	494 (30.5)	791 (32.2)
≥75 years	12,099 (40.5)	4277 (30.9)	1653 (38.9)	684 (42.2)	668 (27.2)
Race/Ethnicity, n (%)					
Caucasian	27934 (96.9)	13 (0.1)	957 (23.1)	1421 (90.5)	1672 (70.3)
Hispanic/Latino	344 (1.2)	0 (0.0)	3000 (72.5)	35 (2.2)	14 (0.6)
Asian	160 (0.6)	13789 (99.8)	11 (0.3)	11 (0.7)	305 (12.8)
Black/Mixed/Other	394 (1.4)	16 (0.1)	172 (4.2)	103 (6.6)	386 (16.2)
Prior/current smoker, n (%)	9558 (35.2)	3833 (31.2)	1348 (32.9)	709 (47.6)	949 (40.4)
Heavy alcohol use, n (%)	486 (1.9)	365 (3.2)	72 (1.8)	36 (2.7)	69 (3.1)
Body mass index, median (Q1; Q3), kg/m²	28.0 (25.1;31.8)	24.2 (22.0;26.6)	27.9 (24.8;31.6)	29.4 (25.4;34.0)	29.8 (26.0;34.3)
Pulse, median (Q1; Q3), bpm	85.0 (70.0; 108.0)	82.0 (70.0; 98.0)	80.0 (70.0; 102.0)	89.0 (72.0; 117.0)	98.0 (80.0; 122.0)
SBP, median (Q1; Q3), mm Hg	135 (120.0;147.0)	130 (118.0;140.0)	130(120.0;141.0)	130 (118.0;143.0)	133 (120.0;148.0)
DBP, median (Q1; Q3), mm Hg	80.0 (71.0;90.0)	78.0 (70.0;86.0)	80.0 (70.0;86.0)	78.0 (68.0;86.0)	80.0 (70.0;90.0)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Type of atrial fibrillation, n (%)					
Permanent	4587 (15.4)	1108 (8.0)	666 (15.7)	35 (2.2)	234 (9.5)
Persistent	4313 (14.4)	2505 (18.1)	625 (14.7)	100 (6.2)	210 (8.6)
Paroxysmal	7375 (24.7)	5165 (37.4)	1086 (25.6)	345 (21.3)	333 (13.6)
Unclassified	13598 (45.5)	5042 (36.5)	1870 (44.0)	1137 (70.3)	1678 (68.4)
Medical history, n (%)					
Hypertension	23740 (79.7)	9353 (67.9)	3420 (80.8)	1229 (76.4)	1862 (76.2)
Hypercholesterolemia	13368 (46.3)	3743 (27.7)	1550 (38.6)	940 (59.3)	1354 (56.8)
Diabetes mellitus	6359 (21.3)	2976 (21.5)	1041 (24.5)	422 (26.1)	744 (30.3)
Heart failure	6841 (22.9)	3072 (22.2)	951 (22.4)	312 (19.3)	563 (22.9)
Acute coronary syndromes	3262 (11.0)	1160 (8.4)	433 (10.2)	209 (13.0)	469 (19.2)
Moderate to severe chronic renal disease	3606 (12.4)	1052 (7.8)	282 (7.2)	142 (9.5)	272 (11.3)
History of stroke/TIA/SE	3445 (11.6)	1400 (10.2)	492 (11.7)	165 (10.4)	337 (13.9)
History of bleeding	764 (2.6)	222 (1.6)	173 (4.1)	76 (4.7)	80 (3.3)
Carotid occlusive disease	1071 (3.6)	251 (1.8)	109 (2.6)	56 (3.5)	51 (2.1)
Venous thromboembolism	995 (3.3)	81 (0.6)	102 (2.4)	73 (4.6)	104 (4.3)
Cirrhosis	148 (0.5)	96 (0.7)	15 (0.4)	14 (0.9)	20 (0.8)
Dementia	381 (1.3)	246 (1.8)	47 (1.1)	34 (2.1)	56 (2.3)
Care setting specialty at diagnosis, n (%)					
Internal medicine/Neurology/Geriatrics	7077 (23.7)	1807 (13.1)	654 (15.4)	345 (21.3)	560 (22.8)
Cardiology	16824 (56.3)	11571 (83.7)	3184 (75.0)	968 (59.9)	1626 (66.2)
Primary care/general practice	5972 (20.0)	442 (3.2)	409 (9.6)	304 (18.8)	269 (11.0)
Care setting location at diagnosis, n (%)					
Hospital	16647 (55.7)	10112 (73.2)	1792 (42.2)	615 (38.1)	1169 (47.6)
Office/Anticoagulation clinic/Thrombosis centre	9804 (32.8)	3366 (24.4)	1404 (33.1)	387 (23.9)	957 (39.0)
Emergency room	3422 (11.5)	342 (2.5)	1051 (24.7)	614 (38.0)	329 (13.4)
Risk scores					
CHA_2DS_2-VASc score, median (Q1; Q3)	3.0 (2.0; 4.0)	3.0 (2.0; 4.0)	3.0 (2.0; 4.0)	3.0 (2.0; 4.0)	3.0 (2.0; 4.0)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

HAS-BLED score, median (Q1; Q3)*	1.0 (1.0; 2.0)	1.0 (1.0; 2.0)	1.0 (1.0; 2.0)	2.0 (1.0; 2.0)	1.0 (1.0; 2.0)
GARFIELD-AF risk score, median (IQR)					
All-cause mortality	5.3 (3.1;9.4)	3.1 (1.8;6.0)	6.0 (3.5;10.9)	5.8 (3.1;10.9)	4.3 (2.5;8.5)
Non-haemorrhagic stroke/SE	1.6 (1.1;2.4)	1.5 (1.0;2.3)	1.6 (1.1;2.4)	1.6 (1.1;2.4)	1.4 (0.9;2.3)
Major bleeding	1.7 (1.1;2.6)	1.3 (0.9;2.0)	1.6 (1.0;2.4)	1.6 (1.0;2.6)	1.6 (1.0;2.4)

*The risk factor 'Labile INRs' is not included in the HAS-BLED score as it is not collected at baseline. As a result, the maximum HAS-BLED score at baseline is 8 points (not 9).

BPM, beats per minute; DBP, diastolic blood pressure; SBP, systolic blood pressure, Q1, 1st quartile, Q3, 3rd quartile, SE, systemic embolism

Countries in each region are as follows: Europe (Finland, Norway, Sweden, Denmark, United Kingdom, Netherlands, Belgium, Germany, Switzerland, France, Spain, Italy, Austria, Hungary, Russia, Poland, Czech Republic, Ukraine and Turkey), Asia (Singapore, China, Japan, South Korea, Thailand and India), North America (USA and Canada), Latin America (Mexico, Brazil, Argentina and Chile) and Other countries (Egypt, United Arab Emirates, South Africa and Australia)

For peer review only

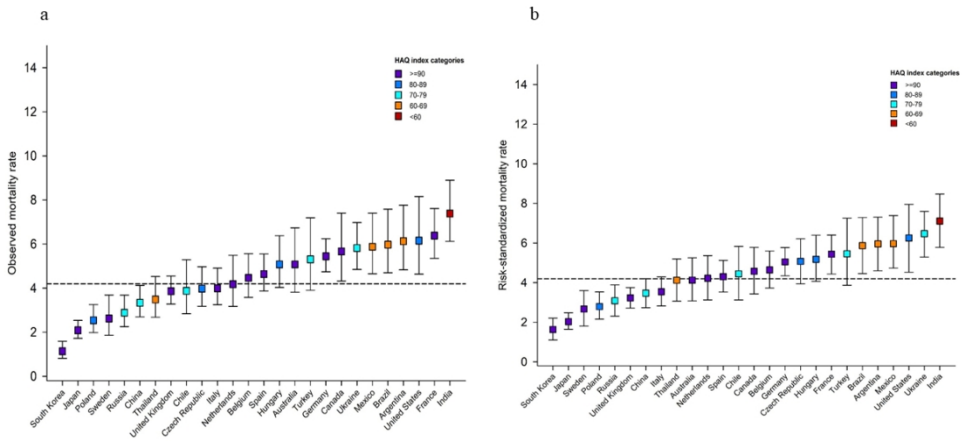
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 2. Observed rate and corresponding 95% confidence interval for all-cause mortality, non-haemorrhagic stroke/SE and major bleeding by region and in all 35 countries in GARFIELD-AF

	Outcome		
Region	**Mortality**	**Non-haemorrhagic Stroke/SE**	**Major bleeding**
Europe	4.4 (4.2-4.6)	1.2 (1.1-1.3)	1.3 (1.2-1.4)
Asia	2.8 (2.6-3.1)	1.0 (0.9-1.2)	0.9 (0.7-1.0)
Latin America	5.5 (4.8-6.2)	1.4 (1.1-1.8)	1.3 (1.0-1.7)
North America	5.9 (4.8-7.2)	1.0 (0.6-1.6)	2.9 (2.2-3.8)
Other countries	6.0 (5.1-7.0)	1.8 (1.3-2.4)	1.3 (0.9-1.9)
All countries	4.2 (4.0-4.4)	1.2 (1.1-1.3)	1.2 (1.1-1.3)

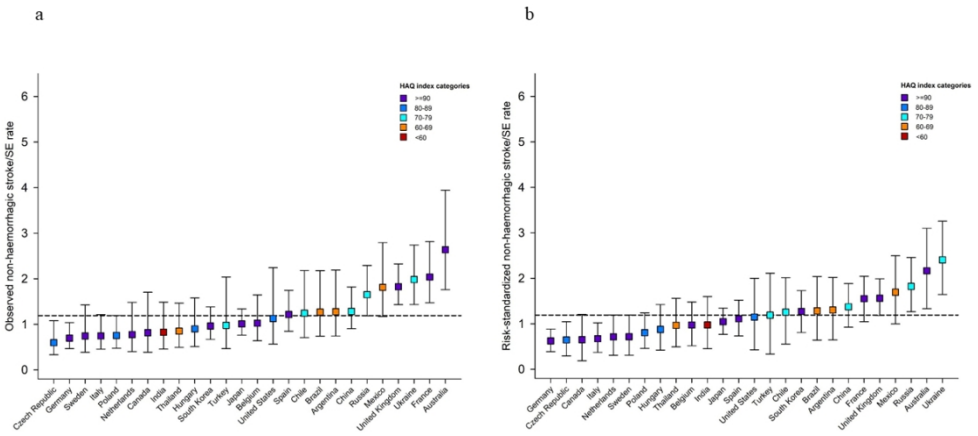
SE: Systemic embolism

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml



Observed (a) and risk-standardized (b) one-year mortality rates with 95% confidence intervals by country. * *Showing only countries with more than 700 patients enrolled. Horizontal dashed line represents overall observed global rate calculated from all 35 countries. Measures of performance are based on the Healthcare Access and Quality Index for 195 countries and territories from the Global Burden of Disease Study [reference 20].

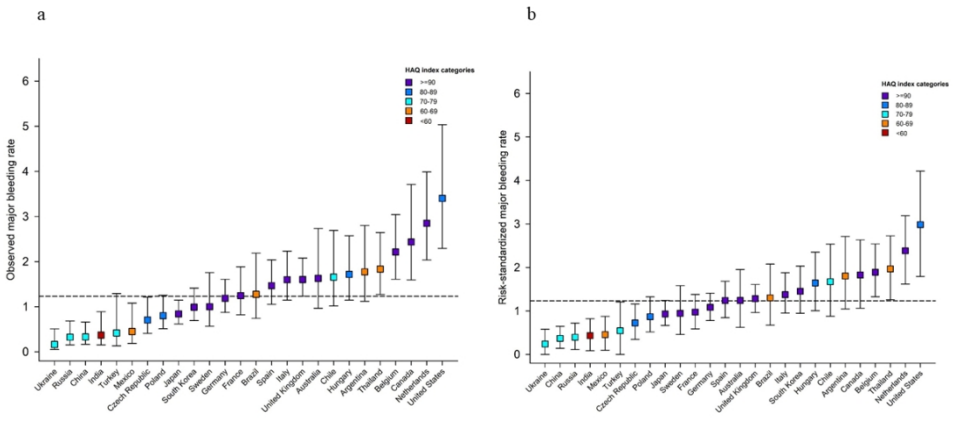
108x60mm (300 x 300 DPI)



Observed (a) and risk-standardized (b) one-year non-haemorrhagic stroke/systemic embolism (SE) rates with 95% confidence intervals by country. *

*Showing only countries with more than 700 patients enrolled. Horizontal dashed line represents overall observed global rate calculated from all 35 countries. Measures of performance are based on the Healthcare Access and Quality Index for 195 countries and territories from the Global Burden of Disease Study [reference 20].

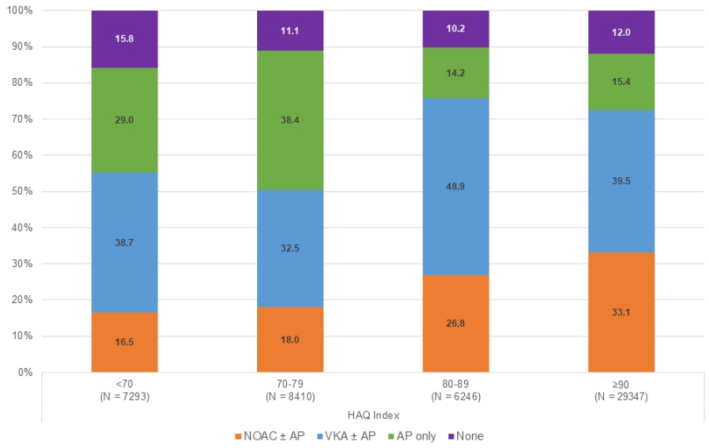
108x60mm (300 x 300 DPI)



Observed (a) and risk-standardized (b) one-year major bleeding rates with 95% confidence intervals by country

*Showing only countries with more than 700 patients enrolled. Horizontal dashed line represents overall observed global rate calculated from all 35 countries. Measures of performance are based on the Healthcare Access and Quality Index for 195 countries and territories from the Global Burden of Disease Study [reference 20].

108x60mm (300 x 300 DPI)



[1]As HAQ index is a country measure, all patients enrolled within a specific country are assigned the same HAQ index
HAQ index of OAC+AP or AP only: <70=46.7%; 70-79=52.5%; 80-89=30.1%; ≥90=28.6%

108x60mm (300 x 300 DPI)

Supplementary Tables and Figures

Table S1. Observed and risk-standardized all-cause mortality rates by country in GARFIELD-AF

Country by region	Events	Observed mortality rate (95% CI)			Risk standardized mortality rate (95% CI)
		All-cause mortality	Cardiovascular mortality*	Non-cardiovascular mortality*	
Global (all GARFIELD-AF)	2140	4.2 (4.0-4.4)	1.6 (1.5 - 1.7)	1.6 (1.5 - 1.7)	-
Latin America					
Argentina	64	6.1 (4.8-7.8)	2.7 (1.9-3.9)	2.6 (1.8-3.8)	6.0 (4.6-7.3)
Brazil	63	6.0 (4.7-7.6)	2.5 (1.7-3.7)	2.5 (1.7-3.7)	5.9 (4.5-7.3)
Chile	38	3.9 (2.8-5.3)	2.3 (1.5-3.4)	1.3 (0.8-2.3)	4.4 (3.1-5.8)
Mexico	67	5.9 (4.7-7.4)	3.2 (2.3-4.4)	1.4 (0.9-2.3)	6.0 (4.7-7.4)
North America					
Canada	50	5.7 (4.3-7.4)	1.7 (1.1-2.9)	2.2 (1.4-3.4)	4.6 (3.4-5.8)
United States (GARFIELD-AF)	45	6.2 (4.6-8.2)	0.8 (0.4-1.9)	2.9 (1.9-4.4)	6.3 (4.5-7.9)
United States (ORBIT-AF II)	202	4.3 (3.7-4.9)			-
Other					
Australia	45	5.1 (3.8-6.7)	1.8 (1.1-3.0)	2.2 (1.4-3.4)	4.1 (3.1-5.3)
Egypt	6	1.1 (0.5-2.5)	0.2 (0.0-1.3)	0.2 (0.0-1.3)	1.7 (0.5-3.1)
South Africa	70	11.0 (8.8-13.7)	5.1 (3.7-7.2)	2.9 (1.9-4.6)	10.5 (8.2-13)
United Arab Emirates	26	6.5 (4.5-9.5)	2.3 (1.2-4.4)	3.6 (2.1-6.0)	5.4 (3.6-7.5)
Europe					
Austria	23	5.1 (3.4-7.5)	1.8 (0.9-3.5)	1.8 (0.9-3.5)	4.4 (2.8-6.2)
Belgium	76	4.5 (3.6-5.6)	1.3 (0.9-2.0)	2.5 (1.8-3.4)	4.6 (3.7-5.6)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Czech Republic	74	4.0 (3.2-5.0)	1.3 (0.9-1.9)	1.6 (1.1-2.3)	5.1 (3.9-6.2)
Denmark	41	7.8 (5.8-10.4)	2.1 (1.2-3.8)	3.9 (2.5-5.9)	6.5 (4.8-8.4)
Finland	12	3.3 (1.9-5.8)	1.1 (0.4-3.0)	0.8 (0.3 - 2.6)	3.6 (1.8-5.4)
France	116	6.4 (5.4-7.6)	2.0 (1.4-2.7)	2.8 (2.1-3.7)	5.4 (4.4-6.4)
Germany	192	5.4 (4.7-6.2)	2.3 (1.8-2.8)	2.2 (1.7-2.7)	5.0 (4.3-5.8)
Hungary	69	5.1 (4-6.4.0)	2.5 (1.7 - 3.4)	2.2 (1.5-3.1)	5.2 (4.1-6.4)
Italy	87	4.0 (3.2-4.9)	1.4 (1.0-2.0)	1.7 (1.2 - 2.3)	3.5 (2.8-4.3)
Netherlands	49	4.2 (3.2-5.5)	1.6 (1.0 - 2.5)	1.8 (1.2-2.8)	4.2 (3.1-5.4)
Norway	3	1.1 (0.4-3.4)	0.0 (0.0 - 0.0)	0.7 (0.2-2.9)	1.5 (0.0-3.4)
Poland	61	1.5 (0.0-3.4)	1.2 (0.8-1.7)	0.6 (0.3-1.0)	2.8 (2.2-3.5)
Russia	62	2.9 (2.3-3.7)	1.6 (1.1 - 2.2)	0.8 (0.5 - 1.2)	3.1 (2.3-3.9)
Spain	113	4.6 (3.9-5.6)	1.6 (1.2 - 2.2)	2.2 (1.7-2.9)	4.3 (3.5-5.1)
Sweden	32	2.6 (1.9-3.7)	1.2 (0.7-1.9)	1.0 (0.6-1.7)	2.7 (1.8-3.6)
Switzerland	5	5.6 (2.4-13.0)	1.2 (0.2 - 8.1)	3.4 (1.1 - 10.1)	4.8 (1.4-9.1)
Turkey	39	5.3 (3.9-7.2)	3.4 (2.3 - 5.0)	1.7 (1.0-2.9)	5.5 (3.9-7.3)
Ukraine	109	5.8 (4.8-7.0)	3.0 (2.3-3.9)	0.2 (0.1 - 0.6)	6.5 (5.3-7.6)
United Kingdom	137	3.9 (3.3-4.5)	1.1 (0.8 - 1.5)	2.0 (1.6-2.5)	3.2 (2.7-3.7)
Asia					
China	82	3.3 (2.7-4.1)	1.4 (1.0-1.9)	0.7 (0.4 - 1.1)	3.5 (2.7-4.2)
India	102	7.4 (6.1-8.9)	3.5 (2.6-4.6)	1.4 (0.9-2.2)	7.1 (5.8-8.5)
Japan	100	2.1 (1.7-2.5)	0.6 (0.4 - 0.9)	0.9 (0.6 - 1.2)	2.0 (1.6-2.5)
Singapore	12	3.9 (2.3-6.8)	0.0 (0.0 - 0.0)	2.6 (1.3-5.2)	3.8 (1.9-6.0)
South Korea	34	1.1 (0.8-1.6)	0.3 (0.2 - 0.6)	0.6 (0.4-1.0)	1.6 (1.1-2.2)
Thailand	54	3.5 (2.7-4.6)	0.3 (0.1-0.8)	2.5 (1.9-3.4)	4.1 (3.1-5.2)

CI: Confidence interval

*Note the rate of cardiovascular and non-cardiovascular mortality do not add up to the total because the cause of death is not known is some cases.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table S2. Observed and risk-standardized non-haemorrhagic stroke/systemic embolism (SE) rates by country in GARFIELD-AF

Country by region	CHA_2DS_2-VASC		Events	Observed stroke/SE rate (95% CI)	Risk standardized stroke/SE rate (95% CI)
	Median (Q1; Q3)	Mean (SD)			
Global (all GARFIELD-AF)			**602**	**1.2 (1.1-1.3)**	**-**
Latin America					
Argentina	3.0 (2.0; 4.0)	3.1 (1.5)	13	1.3 (0.7-2.2)	1.3 (0.6-2.0)
Brazil	3.0 (2.0; 4.0)	3.2 (1.7)	13	1.3 (0.7-2.2)	1.3 (0.6-2.0)
Chile	3.0 (2.0; 4.0)	3.4 (1.6)	12	1.2 (0.7-2.2)	1.3 (0.6-2.0)
Mexico	4.0 (2.0; 4.0)	3.5 (1.6)	20	1.8 (1.2-2.8)	1.7 (1.0-2.5)
North America					
Canada	3.0 (2.0; 5.0)	3.5 (1.6)	7	0.8 (0.4-1.7)	0.7 (0.2-1.2)
United States (GARFIELD-AF)	3.0 (2.0; 4.0)	3.1 (1.6)	8	1.1 (0.6-2.2)	1.1 (0.4-2.0)
United States (ORBIT-AF II)			41	0.8 (0.6-1.1)	-
Other					
Australia	3.0 (2.0; 4.0)	3.3 (1.6)	23	2.6 (1.8-3.9)	2.2 (1.3-3.1)
Egypt	3.0 (2.0; 4.0)	3.2 (1.7)	0	0.0 (0.0-0.0)	0.0 (0.0-0.0)
South Africa	3.0 (2.0; 4.0)	3.2 (1.7)	16	2.6 (1.6-4.3)	2.4 (1.3-3.6)
United Arab Emirates	3.0 (2.0; 4.0)	3.0 (1.8)	3	0.8 (0.3-2.4)	0.8 (0.0-1.8)
Europe					
Austria	3.0 (2.0; 4.0)	3.5 (1.5)	8	1.8 (0.9-3.6)	1.6 (0.6-2.7)
Belgium	3.0 (2.0; 4.0)	3.1 (1.6)	17	1.0 (0.6-1.6)	1.0 (0.5-1.5)
Czech Republic	3.0 (2.0; 4.0)	3.3 (1.6)	11	0.6 (0.3-1.1)	0.6 (0.3-1.0)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Denmark	3.0 (2.0; 4.0)	3.2 (1.5)	10	1.9 (1.0-3.6)	1.6 (0.7-2.7)
Finland	3.0 (2.0; 5.0)	3.5 (1.6)	2	0.6 (0.1-2.2)	0.5 (0.0-1.3)
France	4.0 (3.0; 5.0)	3.6 (1.6)	36	2.0 (1.5-2.8)	1.6 (1.0-2.0)
Germany	4.0 (2.0; 5.0)	3.6 (1.7)	24	0.7 (0.5-1.0)	0.6 (0.4-0.9)
Hungary	3.0 (2.0; 5.0)	3.4 (1.6)	12	0.9 (0.5-1.6)	0.9 (0.4-1.4)
Italy	4.0 (3.0; 4.0)	3.6 (1.5)	16	0.7 (0.5-1.2)	0.7 (0.4-1.0)
Netherlands	3.0 (2.0; 4.0)	3.1 (1.5)	9	0.8 (0.4-1.5)	0.7 (0.3-1.2)
Norway	3.0 (2.0; 4.0)	2.8 (1.4)	4	1.5 (0.6-3.9)	1.7 (0.4-3.5)
Poland	3.0 (2.0; 4.0)	3.2 (1.7)	18	0.8 (0.5-1.2)	0.8 (0.5-1.2)
Russia	3.0 (2.0; 5.0)	3.5 (1.7)	35	1.7 (1.2-2.3)	1.8 (1.3-2.5)
Spain	3.0 (2.0; 4.0)	3.1 (1.4)	29	1.2 (0.8-1.7)	1.1 (0.7-1.5)
Sweden	3.0 (2.0; 4.0)	3.1 (1.4)	9	0.7 (0.4-1.4)	0.7 (0.3-1.2)
Switzerland	4.0 (2.0; 4.0)	3.4 (1.6)	1	2.3 (0.6-8.9)	2.0 (0.0-5.1)
Turkey	3.0 (2.0; 4.0)	3.0 (1.8)	7	1.0 (0.5-2.0)	1.2 (0.3-2.1)
Ukraine	3.0 (2.0; 5.0)	3.6 (1.6)	36	2.0 (1.4-2.7)	2.4 (1.6-3.3)
United Kingdom	3.0 (2.0; 4.0)	3.3 (1.5)	64	1.8 (1.4-2.3)	1.6 (1.2-2.0)
Asia					
China	3.0 (2.0; 4.0)	3.2 (1.7)	31	1.3 (0.9-1.8)	1.4 (0.9-1.9)
India	3.0 (2.0; 4.0)	3.0 (1.5)	11	0.8 (0.5-1.5)	1.0 (0.5-1.6)
Japan	3.0 (2.0; 4.0)	3.0 (1.6)	48	1.0 (0.8-1.3)	1.0 (0.8-1.3)
Singapore	3.0 (2.0; 4.0)	3.1 (1.8)	7	2.3 (1.1-4.8)	2.2 (0.6-3.9)
South Korea	2.0 (1.0; 3.0)	2.5 (1.5)	29	1.0 (0.7-1.4)	1.3 (0.8-1.7)
Thailand	3.0 (2.0; 4.0)	2.9 (1.5)	13	0.9 (0.5-1.5)	1.0 (0.5-1.6)

CI: Confidence interval

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table S3. Observed and risk-standardized major bleeding rates by country in GARFIELD-AF

Country by region	Events	Observed major bleeding rate (95% CI)	Risk standardized major bleeding rate (95% CI)
Global (all GARFIELD-AF)	**411**	**1.2 (1.1-1.3)**	-
Latin America			
Argentina	18	1.8 (1.1-2.8)	1.8 (1-2.7.0)
Brazil	13	1.3 (0.7-2.2)	1.3 (0.7-2.1)
Chile	16	1.7 (1.0-2.7)	1.7 (0.9-2.5)
Mexico	5	0.5 (0.2-1.1)	0.5 (0.1-0.9)
North America			
Canada	21	2.4 (1.6-3.7)	1.8 (1.1-2.6)
United States (GARFIELD-AF)	24	3.4 (2.3-5.0)	3.0 (1.8-4.2)
United States (ORBIT-AF II)	158	3.3 (2.8-3.8)	-
Other			
Australia	14	1.6 (1.0-2.7)	1.2 (0.6-2.0)
Egypt	4	0.8 (0.3-2.0)	1.0 (0.2-2.0)
South Africa	9	1.5 (0.8-2.8)	1.5 (0.6-2.5)
United Arab Emirates	4	1.1 (0.4-2.8)	1.0 (0.2-2.1)
Europe			
Austria	11	2.5 (1.4-4.4)	1.9 (0.8-3.0)
Belgium	37	2.2 (1.6-3.0)	1.9 (1.3-2.5)
Czech Republic	13	0.7 (0.4-1.2)	0.7 (0.3-1.2)
Denmark	13	2.5 (1.5-4.3)	2.1 (1.1-3.2)
Finland	9	2.5 (1.3-4.8)	2.4 (1.1-4.1)
France	22	1.2 (0.8-1.9)	1.0 (0.6-1.4)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Germany	41	1.2 (0.9-1.6)	1.1 (0.8-1.4)
Hungary	23	1.7 (1.1-2.6)	1.6 (1.0-2.4)
Italy	34	1.6 (1.1-2.2)	1.4 (1.0-1.9)
Netherlands	33	2.9 (2.0-4.0)	2.4 (1.6-3.2)
Norway	7	2.6 (1.3-5.4)	2.9 (0.9-5.4)
Poland	19	0.8 (0.5-1.3)	0.9 (0.5-1.3)
Russia	7	0.3 (0.2-0.7)	0.4 (0.1-0.7)
Spain	35	1.5 (1.1-2.0)	1.2 (0.8-1.7)
Sweden	12	1.0 (0.6-1.8)	0.9 (0.5-1.6)
Switzerland	1	1.1 (0.2-7.8)	0.8 (0.0-3.0)
Turkey	3	0.4 (0.1-1.3)	0.5 (0.0-1.2)
Ukraine	3	0.2 (0.1-0.5)	0.2 (0.0-0.6)
United Kingdom	56	1.6 (1.2-2.1)	1.3 (1.0-1.6)
Asia			
China	8	0.3 (0.2-0.7)	0.4 (0.1-0.6)
India	5	0.4 (0.2-0.9)	0.4 (0.1-0.8)
Japan	40	0.8 (0.6-1.1)	0.9 (0.7-1.2)
Singapore	6	2.0 (0.9-4.4)	1.9 (0.6-3.6)
South Korea	30	1.0 (0.7-1.4)	1.5 (0.9-2.0)
Thailand	28	1.8 (1.3-2.6)	2.0 (1.3-2.7)

CI: Confidence intervals

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table S4. Risk-standardized1 event rates within one year by country

Country	Risk-standardized mortality rate (95% CI)	Risk-standardized non-haemorrhagic stroke/SE rate (95% CI)	Risk-standardized major bleeding rate (95% CI)
Argentina	5.7 (4.4-7.0)	1.2 (0.6-1.9)	1.9 (1.1-2.9)
Australia	4.0 (3.0-5.1)	2.1 (1.3-3.0)	1.3 (0.6-2.0)
Austria	4.4 (2.9-6.3)	1.6 (0.6-2.8)	1.9 (0.8-3.1)
Belgium	4.9 (3.9-5.9)	1.1 (0.6-1.6)	1.8 (1.3-2.4)
Brazil	5.7 (4.3-7.1)	1.2 (0.6-1.9)	1.4 (0.7-2.2)
Canada	4.6 (3.4-5.8)	0.6 (0.2-1.2)	1.8 (1.1-2.6)
Chile	4.6 (3.3-6.1)	1.4 (0.6-2.2)	1.6 (0.8-2.4)
China	3.1 (2.5-3.8)	1.1 (0.8-1.5)	0.4 (0.2-0.7)
Czech Republic	5.1 (4.0-6.3)	0.7 (0.3-1.1)	0.7 (0.3-1.2)
Denmark	6.7 (4.9-8.6)	1.7 (0.8-2.8)	2.0 (1-3.1.0)
Egypt	1.8 (0.6-3.3)	0.0 (0.0-0.0)	0.9 (0.2-1.8)
Finland	3.7 (1.9-5.6)	0.5 (0.0-1.3)	2.4 (1.1-4.0)
France	5.6 (4.6-6.6)	1.6 (1.1-2.2)	0.9 (0.6-1.3)
Germany	5.0 (4.3-5.8)	0.6 (0.4-0.9)	1.1 (0.8-1.4)
Hungary	5.4 (4.3-6.7)	0.9 (0.5-1.5)	1.6 (1.0-2.2)
India	6.5 (5.3-7.8)	0.8 (0.4-1.3)	0.5 (0.1-0.9)
Italy	3.8 (3.0-4.6)	0.8 (0.4-1.2)	1.3 (0.9-1.8)
Japan	2.1 (1.7-2.6)	1.1 (0.8-1.5)	0.9 (0.6-1.2)
Mexico	5.7 (4.5-7.1)	1.5 (0.9-2.2)	0.5 (0.1-0.9)
Netherlands	4.6 (3.4-5.8)	0.8 (0.4-1.4)	2.2 (1.5-2.9)
Norway	1.7 (0.0-3.7)	1.9 (0.4-4.1)	2.7 (0.8-5.0)
Poland	2.8 (2.2-3.6)	0.8 (0.5-1.3)	0.9 (0.5-1.3)
Russia	3.0 (2.2-3.8)	1.7 (1.2-2.3)	0.4 (0.1-0.8)
Singapore	3.7 (1.8-5.8)	2.0 (0.6-3.6)	1.9 (0.6-3.7)
South Africa	10.5 (8.3-13)	2.4 (1.3-3.7)	1.5 (0.6-2.5)
South Korea	1.6 (1.1-2.1)	1.2 (0.8-1.6)	1.5 (1.0-2.1)
Spain	4.4 (3.6-5.2)	1.1 (0.8-1.6)	1.2 (0.8-1.7)
Sweden	2.8 (1.9-3.7)	0.8 (0.3-1.3)	0.9 (0.5-1.6)
Switzerland	5.3 (1.5-10.0)	1.2 (0.0-3.9)	0.8 (0.0-2.8)
Thailand	3.9 (2.9-5.0)	0.9 (0.5-1.5)	2.1 (1.3-2.9)
Turkey	5.5 (3.9-7.4)	1.2 (0.3-2.2)	0.5 (0.0-1.2)
Ukraine	6.2 (5.0-7.3)	2.1 (1.5-2.9)	0.3 (0.0-0.6)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

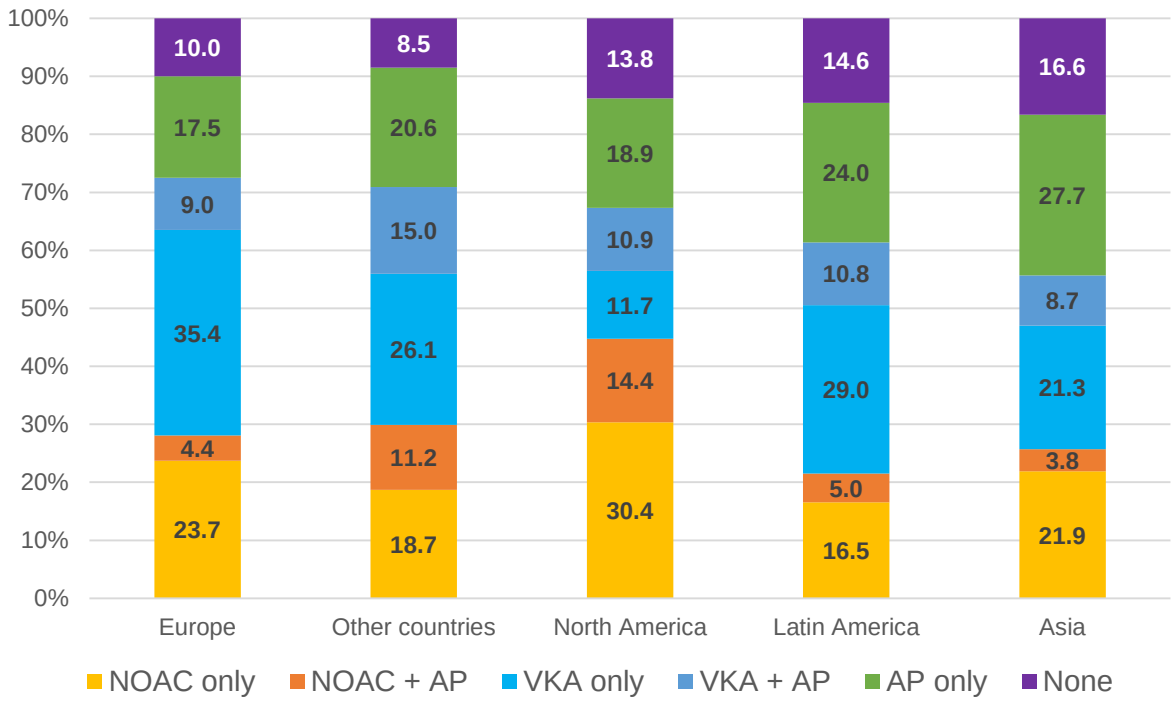
United Arab Emirates	5.2 (3.5-7.1)	0.8 (0.0-1.7)	1.1 (0.2-2.1)
United Kingdom	3.2 (2.7-3.7)	1.5 (1.1-1.9)	1.3 (1.0-1.6)
United States	6.3 (4.5-8.0)	1.2 (0.4-2.0)	2.9 (1.7-4.1)

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

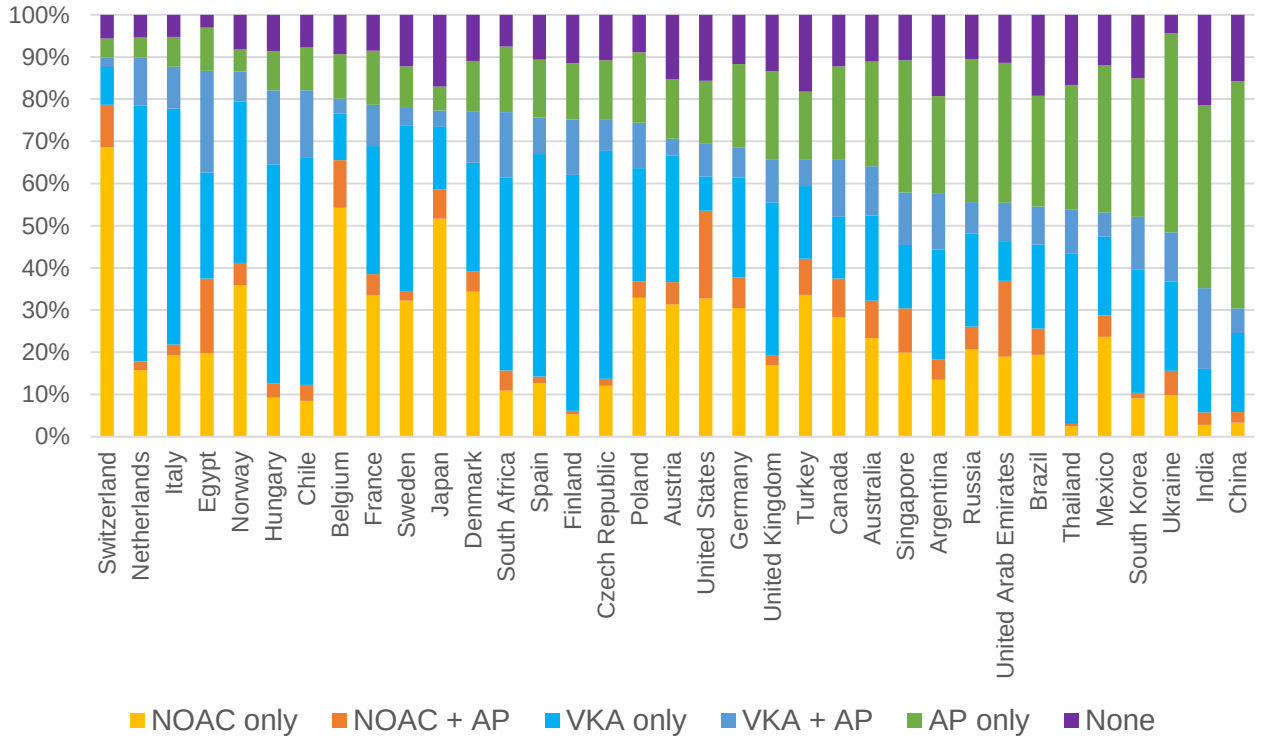
Figure S1. Initial choice of antithrombotic treatment following diagnosis of AF by a. region and b. country.

(a) Region



For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

(b) Country



For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

GARFIELD-AF Registry Investigators

Global Steering Committee

Ajay K. Kakkar (UK) (Chair), Jean-Pierre Bassand (France), A. John Camm (UK), David A. Fitzmaurice (UK), Keith A.A. Fox (UK), Bernard J. Gersh (USA), Samuel Z. Goldhaber (USA), Shinya Goto (Japan), Sylvia Haas (Germany), Werner Hacke (Germany), Lorenzo G. Mantovani (Italy), Frank Misselwitz (Germany), Karen S. Pieper (USA), Alexander G.G. Turpie (Canada), Martin van Eickels (Germany), Freek W.A. Verheugt (the Netherlands).

Audit Committee

Keith A.A. Fox (UK), Bernard J. Gersh (USA).

GARFIELD-AF National Coordinators

Hector Lucas Luciardi (Argentina), Harry Gibbs (Australia), Marianne Brodmann (Austria), Frank Cools (Belgium), Antonio Carlos Pereira Barretto (Brazil), Stuart J. Connolly, John Eikelboom (Canada), Ramon Corbalan (Chile), Zhi-Cheng Jing (China), Petr Jansky (Czech Republic), Jørn Dalsgaard Nielsen (Denmark), Hany Ragy (Egypt), Pekka Raatikainen (Finland), Jean-Yves Le Heuzey (France), Harald Darius (Germany), Matyas Keltai (Hungary), Jitendra Pal Singh Sawhney (India), Giancarlo Agnelli and Giuseppe Ambrosio (Italy), Yukihiro Koretsune (Japan), Carlos Jerjes Sánchez Díaz (Mexico), Hugo Ten Cate (the Netherlands), Dan Atar (Norway), Janina Stepinska (Poland), Elizaveta Panchenko (Russia), Toon Wei Lim (Singapore), Barry Jacobson (South Africa), Seil Oh (South Korea), Xavier Viñolas (Spain), Marten Rosenqvist (Sweden), Jan Steffel (Switzerland), Pantep Angchaisuksiri (Thailand), Ali Oto (Turkey), Alex Parkhomenko (Ukraine), Wael Al Mahmeed (United Arab Emirates), David Fitzmaurice (UK), Samuel Z. Goldhaber (USA).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

GARFIELD-AF National Investigators

China

Dayi Hu, Kangning Chen, Yusheng Zhao, Huaiqin Zhang, Jiyan Chen, Shiping Cao, Daowen Wang, Yuejin Yang, Weihua Li, Hui Li, Yuehui Yin, Guizhou Tao, Ping Yang, Yingmin Chen, Shenghu He, Yong Wang, Guosheng Fu, Xin Li, Tongguo Wu, Xiaoshu Cheng, Xiaowei Yan, Ruiping Zhao, Moshui Chen, Longgen Xiong, Ping Chen, Yang Jiao, Ying Guo, Li Xue, Zhiming Yang.

India

Praveen Jadhavm, Raghava Sarma, Govind Kulkarni, Prakash Chandwani, Rasesh Atulbhai Pothiwala, Mohanan Padinhare Purayil, Kamaldeep Chawla, Veerappa Annasaheb Kothiwale, Bagirath Raghuraman, Vinod Madan Vijan, Jitendra Sawhney, Ganapathi Bantwal, Aziz Khan, Ramdhan Meena, Manojkumar Chopada, Sunitha Abraham, Vikas Bisne, Govindan Vijayaraghavan, Debabrata Roy, Rajashekhar Durgaprasad, A.G. Ravi Shankar, Sunil Kumar, Dinesh Jain, Kartikeya Bhargava, Vinay Kumar, Udigala Madappa Nagamalesh, Rajeeve Kumar Rajput.

Japan

Yukihiro Koretsune, Seishu Kanamori, Kenichi Yamamoto, Koichiro Kumagai, Yosuke Katsuda, Keiki Yoshida, Fumitoshi Toyota, Yuji Mizuno, Ikuo Misumi, Hiroo Noguchi, Shinichi Ando, Tetsuro Suetsugu, Masahiro Minamoto, Hiroyuki Oda, Susumu Adachi, Kei Chiba, Hiroaki Norita, Makoto Tsuruta, Takeshi Koyanagi, Kunihiko Yamamoto, Hiroshi Ando, Takayuki Higashi, Megumi Okada, Shiro Azakami, Shinichiro Komaki, Kenshi Kumeda, Takashi Murayama, Jun Matsumura, Yurika Oba, Ryuji Sonoda, Kazuo Goto, Kotaro Minoda, Yoshikuni Haraguchi, Hisakazu Suefuji, Hiroo Miyagi, Hitoshi Kato, Tsugihiro Nakamura, Tadashi Nakamura, Hidekazu Nandate, Ryuji Zaitsu, Yoshihisa Fujiura, Akira Yoshimura, Hiroyuki Numata, Jun Ogawa, Yasuyuki Kamogawa, Kinshiro Murakami, Yutaka Wakasa, Masanori Yamasawa, Hiromitsu Maekawa, Sumihisa Abe, Hajime Kihara, Satoru Tsunoda, Katsumi Saito, Hiroki Tachibana, Ichiro Oba, Takashi Kuwahata, Satoshi Higa, Masamichi Gushiken, Takuma Eto, Hidetoshi Chibana, Kazuaki Fujisawa, Yuhei Shiga, Hirokuni Sumi, Toshihisa Nagatomo, Yoshihiko Atsuchi, Toshiro Nagoshi, Kazuhisa Sanno, Fumihiro Hoshino, Naoto Yokota, Masahiro Kameko, Toshifumi Tabuchi, Munesumi Ishizawa, Yoshitake Fujiura, Daisuke Ikeda,Taku Seto, Tetsu Iwao, Norio Ishioka, Koichi Oshiro, Keizo Tsuchida, Yutaka Hatori, Motoshi Takeuchi, Hiroto Takezawa, Shinjiro Nagano, Masaaki Iwaki, Yuichiro Nakamura, Naomasa Miyamoto, Toshifumi Taguchi, Ko Ashida, Naoto Yoshizawa, Jun Agata, Seishiro

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Matsukawa, Osamu Arasaki, Shuji Fukuoka, Hirofumi Murakami, Kazuya Mishima, Yoshiki Hata, Ichiro Sakuma, Kotaro Obunai, Ichiro Takamura, Mitsuyuki Akutsu, Toshihide Unoki, Yoshinori Go, Makoto Ikemura, Shoji Morii, Shigeru Marusaki, Hideo Doi, Mitsuru Tanaka, Takaaki Kusumoto, Shigeo Kakinoki, Chiga Ogurusu, Kazuya Murata, Masaki Shimoyama, Masami Nakatsuka, Yutaka Kitami, Yoichi Nakamura, Hiroshi Oda, Rikimaru Oyama, Masato Ageta, Teruaki Mita, Kazuhiko Nagao, Takafumi Mito, Junichi Minami, Mitsunori Abe, Masako Fujii, Makoto Okawa, Tsuneo Fujito, Toshiya Taniguchi, Tenei Ko, Hiroshi Kubo, Mizuho Imamaki, Masahiro Akiyama, Takashi Ueda, Hironori Odakura, Masahiko Inagaki, Yoshiki Katsube, Atsuyuki Nakata, Shinobu Tomimoto, Mitsuhiro Shibuya, Masayuki Nakano, Kenichiro Ito, Masahiro Matsuta, Motoyuki Ishiguro, Taro Minagawa, Masamichi Wada, Hiroaki Mukawa, Masato Mizuguchi, Fumio Okuda, Teruaki Kimura, Kuniaki Taga, Masaaki Techigawara, Morio Igarashi, Hiroshi Watanabe, Toshihiko Seo, Shinya Hiramitsu, Hiroaki Hosokawa, Mitsumoto Hoshiai, Michitaka Hibino, Koichi Miyagawa, Hideki Horie, Nobuyoshi Sugishita, Yukio Shiga, Akira Soma, Kazuo Neya, Tetsuro Yoshida, Kunio Akahane, Sen Adachi, Chiei Takanaka, Takashi Ueda, Saori Matsui, Hirofumi Kanda, Masanori Kaneko, Shiro Nagasaka, Atsushi Taguchi, Shuta Toru, Kazuyuki Saito, Akiko Miyashita, Hiroki Sasaguri, Jin Nariyama, Taketo Hatsuno, Takash Iwase, Kazuki Sato, Kazuya Kawai, Tomobumi Kotani, Tsuyoshi Tsuji, Hirosumi Sakai, Kiyoshi Nishino, Kenichi Ikeda, Kazuo Maeda, Tomohiro Shinozuka, Takeshi Inoue, Koichi Kawakami, Hiromichi Kitazumi, Tsutomu Takagi, Mamoru Hamaoka, Jisho Kojima, Akitoshi Sasaki, Yoshihiro Tsuchiya, Tetsuo Betsuyaku, Koji Higuchi, Masaaki Honda, Koichi Hasegawa, Takao Baba, Kazuaki Mineoi, Toshihiko Koeda, Kunihiko Hirasawa, Toshihide Kumazaki, Akira Nakagomi, Eiji Otaki, Takashi Shindo, Hiroyoshi Hirayama, Chikako Sugimoto, Takashi Yamagishi, Ichiro Mizuguchi, Kazunori Sezaki, Isamu Niwa, Ken Takenaka, Osamu Iiji, Koichi Taya, Hitoshi Kitazawa, samu Ueda, Hirokazu Kakuda, Takuya Ono, Seizo Oriso, Junya Kamata, Toshihiko Nanke, Itaru Maeda, Yoshifusa Matsuura, Hiroki Teragawa, Yasuyuki Maruyama, Kazuo Takei, Hajime Horie, Tetsutaro Kito, Hiroshi Asano, Koji Matsushita, Masaichi Nakamura, Takashi Washizuka, Tomoki Yoshida, Masato Sawano, Shinichi Arima, Hidekazu Arai, Hisanori Shinohara, Hiroyuki Takai, Nobufusa Furukawa, Akira Ota, Kentaro Yamamoto, Kenji Aoki, Taku Yamamoto, Takeaki Kasai, Shunji Suzuki, Shu Suzuki, Nitaro Shibata, Masayuki Watanabe, Yosuke Nishihata, Toru Arino, Masaki Okuyama, Tetsushi Wakiyama, Tomoko Kato, Yasuo Sasagawa, Takeshi Tana, Yoshihito Hayashi, Shinichi Hirota, Yukihiko Abe, Yoshihiro Saito, Hirohide Uchiyama, Hiroshi Takeda, Hiroshi Ono, Shuichi Tohyo, Naoto Hanazono, Seiichi Miyajima, Hisashi Shimono, Takuma Aoyama, Yasunobu Shozawa, Yawara Niijima, Osamu Murai, Osamu Murai, Hideko Inaba, Katsumasa Nomura, Masatsugu Nozoe, Kazuo Suzuki, Toshiyuki Furukawa, Toshihiko Shiraiwa, Nobuhisa Ito, Shunichi Nagai, Kiyoharu Sato, Shiro Nakahara, Yujin Shimoyama, Naoko Ohara, Teruhiko Kozuka, Hideaki Okita, Masato Endo, Tsutomu Goto, Makoto Hirose, Emiko Nagata, Noriyuki Nakanishi, Toshizumi Mori, Shuichi Seki, Katsuhiro Okamoto, Osamu Moriai, Yoko Emura, Tsuyoshi Fukuda, Haruhiko Date, Shuichi Kawakami, Sho Nagai, Yuya Ueyama, Tetsuro Fudo, Mitsuru Imaizumi, Takuo Ogawa, Shunsuke Take, Hideo Ikeda, Hiroaki Nishioka, Norihiko Sakamoto, Kiyomitsu Ikeoka, Nobuo Wakaki, Masatake Abe, Junji Doiuchi, Tetsuya Kira, Masato Tada, Ken Tsuzaki, Naoya Miura, Yasuaki Fujisawa, Wataru Furumoto, Susumu Suzuki, Akinori Fujisawa, Ryosai Nakamura, Hiroyasu Komatsu, Rei Fujiki, Shuichi Kawano, Keijiro Nishizawa, Yoji Kato, Junya Azuma, Kiyoshi Yasui,Toshio Amano, Yasuhiro Sekine, Tatsuo Honzawa, Yuichiro Koshibu, Yasuhide Sakamoto, Yukihiro Seta, Shingo Miyaguchi, Kojuro Morishita, Yasuko Samejima, Toyoshi Sasaki, Fumiko Iseki, Toshiyuki

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Kobayashi, Hiroshi Kano, Jaeyoung Kim, Hiroshi Yamaguchi, Yoichi Takagi, Yoko Onuki Pearce, Yasuyuki Suzuki, Takayuki Fukui, Toru Nakayama, Hideaki Kanai, Yoshiyuki Kawano, Tetsuji Ino, Hironori Miyoshi, Yasufumi Miyamoto, Masahito Shigekiyo, Shimato Ono, Yoshiyuki Kawano, Yutaka Okamoto, Satoshi Ubukata, Kojiro Kodera, Tatsuo Oriuchi, Naoki Matsumoto, Koichi Inagaki, Atsushi Iseki, Tomohiro Yoshida, Toshihiro Goda, Tsukasa Katsuki, Atsushi Sato, Etsuo Mori, Toshio Tsubokura, Hiroshi Shudo, Shunichi Fujimoto, Tomohiro Katsuya, Yoshiyuki Furukawa, Hiroshi Hosokawa, Jun Narumi, Kiichiro Yamamoto, Masaki Owari, Takuya Inakura, Takafumi Anno, Kazuyuki Shirakawa.

Singapore

Chi Keong Ching, Toon Wei Lim, David Foo, Kelvin Wong, Tan Yuyang.

South Korea

Seil Oh, Hui Nam Park, Woo-Shik Kim, HyeYoung Lee, Sung-Won Jang, Dae Hyeok Kim, Jun Kim, DongRyeol Ryu, Jaemin Shim, Dae-Kyeong Kim, Dong Ju Choi, Yong Seog Oh, Myeong-Chan Cho, Hack-Lyoung Kim, Hui-Kyung Jeon, Dong-Gu Shin, Sang Weon Park, Hoon Ki Park, Sang-Jin Han, Jung Hoon Sung, Hyung-Wook Park, Gi-Byoung Nam, Young Keun On, Hong Euy Lim, JaeJin Kwak, Tae-Joon Cha, Taek Jong Hong, Seong Hoon Park, Jung Han Yoon, Nam-Ho Kim, Kee-Sik Kim, Byung Chun Jung, Gyo-Seung Hwang, Chong-Jin Kim.

Thailand

Sakda Rungaramsin, Peerapat Katekangplu, Porames Khunrong, Thanita Bunyapipat, Wanwarang Wongcharoen, Pinij Kaewsuwanna, Khanchai Siriwattana, Waraporn Tiyanon, Supalerk Pattanaprichakul, Khanchit Likittanasombat, Doungrat Cholsaringkarl, Warangkana Boonyapisit, Sirichai Cheewatanakornkul, Songkwan Silaruks, Pisit Hutayanon, Seksan Chawanadelert, Pairoj Chattranukulchai, Boonsert Chatlaong, Yingsak Santanakorn, Khompiya Kanokphatcharakun, Piya Mongkolwongroj, Sasivimon Jai-Aue, Ongkarn Komson.

Turkey

Armagan Altun, Ali Aydinlar, Ramazan Topsakal, Zeki Ongen, Sadik Acikel, Durmus Yildiray Sahin, Ozcan Yilmaz, Mehmet Birhan Yilmaz, Hasan Pekdemir, Mesut Demir, Murat Sucu, Levent Sahiner, Ali Oto, Murat Ersanli, Ertugrul Okuyan, Dursun Aras.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Argentina

Florencia Rolandi, Adrian Cesar Ingaramo, Gustavo Alberto Sambadaro, Vanina Fernandez Caputi, Hector Luciardi, Sofia Graciela Berman, Pablo Dragotto, Andres Javier Kleiban, Nestor Centurion, Rodolfo Andres Ahuad Guerrero, Leonel Adalberto Di Paola, Ricardo Dario Dran, Javier Egido, Matias Jose Fosco, Victor Alfredo Sinisi, Luis Rodolfo Cartasegna, Oscar Gomez Vilamajo, Jose Luis Ramos, Sonia Sassone, Gerardo Zapata, Diego Conde, Guillermo Giacomi, Alberto Alfredo Fernandez, Mario Alberto Berli, Fabian Ferroni.

Brazil

Dário Celestino Sobral Filho, Jefferson Jaber, Luciana Vidal Armaganijan, Costantino Roberto Frack Costantini, André Steffens, Weimar Kunz Sebba Barroso de Souzaem, João David de Souza Neto, José Márcio Ribeiro, Marcelo Silveira Teixeira, Paulo Rossi, Leonardo Pires, Daniel Moreira, José Carlos Moura Jorge, Adalberto Menezes Lorga Filho, Luiz Bodanese, Marcelo Westerlund Montera, Carlos Henrique Del Carlo, Jamil Abdalla Saad, Fernando Augusto Alves da Costa, Renato Lopes, Gilson Roberto de Araújo, Euler Roberto Manenti, Jose Francisco Kerr Saraiva, João Carlos Ferreira Braga, Alexandre Negri, Carlos Moncada, Dalton Precoma, Fernando Roquette, Gilmar Reis, Roberto Álvaro Ramos Filho,: Estêvão Lanna Figueiredo, Roberto Vieira Botelho, Cláudio Munhoz da Fontoura Tavares, Helius Carlos Finimundi, Adriano Kochi, César Cássio Broilo França, Fábio Alban, Guido Bernardo Aranha Rosito, João Batista de Moura Xavier Moraes Junior, Rogério Tadeu Tumelero, Lilia Maia,: Roberto Simões de Almeida, Ney Carter do Carmo Borges, Luís Gustavo Gomes Ferreira.

Chile

Ramón Corbalán, Benjamin Aleck Joseh Stockins Fernandez, Humberto Montecinos, Fernando Lanas, Martín Larico Gómez, Carlos Astudillo, Carlos Conejeros, Patricio Marin Cuevas, Alejandro Forero, Claudio Bugueño Gutiérrez, Juan Aguilar, Sergio Potthoff Cardenas, German Eggers, Cesar Houzvic, Carlos Rey, Germán Arriagada, Gustavo Charme Vilches.

Mexico

Carlos Jerjes Sanchez Diaz, Jesus Jaime Illescas Diaz, Raul Leal Cantu, Maria Guadalupe Ramos Zavala, Ricardo Cabrera Jardines, Nilda Espinola Zavaleta, Enrique Lopez Rosas, Guillermo Antonio Llamas Esperón, Gerardo Pozas, Ernesto Cardona Muñoz, Norberto Matadamas Hernandez, Adolfo Leyva Rendon, Norberto Garcia Hernandez, Manuel de los Rios Ibarra, Luis Ramon Virgen Carrillo, David Lopez Villezca, Carlos

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Hernandez Herrera, Juan Jose Lopez Prieto, Rodolfo Gaona Rodriguez, Efrain Villeda Espinosa, David Flores Martinez, Jose Velasco Barcena, Omar Fierro Fierro, Ignacio Rodriguez Briones, Jose Luis Leiva Pons, Humberto Alvarez Lopez, Rafael Olvera Ruiz, Carlos Gerardo Cantu Brito, Eduardo Julian Jose Roberto Chuquiure Valenzuela, Roxana Reyes Sanchez, Alberto Esteban Bazzoni Ruiz, Oscar Martin Lopez Ruiz, Roberto Arriaga Nava, Jesus David Morales Cerda, Pedro Fajardo Campos, Mario Benavides Gonzalez.

Austria

Marianne Brodmann, Kurt Lenz, Claus Hagn, Johannes Foechterle, Heinz Drexel, Kurt Huber, Andrea Podczeck-Schweighofer, Michael Winkler, Bruno Schneeweiss, Alfons Gegenhuber, Wilfried Lang, Sabine Eichinger-Hasenauer, Peter Kaserer, Josef Sykora, Heribert Rasch, Bernhard Strohmer.

Belgium

Luc Capiau, Geert Vervoort, Bart Wollaert, Frank Cools, Geert Hollanders, Jan Vercammen, Dirk Faes, Yohan Balthazar, Marc Delforge, Olivier Xhaet, Harry Striekwold, John Thoeng, Kurt Hermans, Georges Mairesse, Wim Anné, Ivan Blankoff, Michel Beutels, Stefan Verstraete, Peter Vandergoten, Philippe Purnode, Pascal Godart, Tim Boussy, Philippe Desfontaines, Alex Heyse, Joeri Voet, Axel De Wolf.

Czech Republic

Eva Zidkova, Petr Jansky, Rudolf Spacek, Vilma Machova, Ondrej Ludka, Josef Olsr, Lubos Kotik, Blazej Racz, Richard Ferkl, Jan Hubac, Ilja Kotik, Zdenek Monhart, Hana Burianova, Ondrej Jerabek, Jana Pisova, Iveta Petrova, Vratislav Dedek, Michaela Honkova, Petr Podrazil, Petr Reichert, Jindrich Spinar, Miroslav Novak, Vaclav Durdil, Katarina Plocova, Jiri Lastuvka.

Denmark

Jørn Nielsen, Steen Husted, Helena Dominguez, Ulrik Hintze, Søren Rasmussen, Næstved Sygehus, Arne Bremmelgaard, John Markenvard, Jan Børger, Jorgen Solgaard, Ebbe Eriksen, Thomas Løkkegaard, Michael Bruun, Jacob Mertz, Morten Schou, Helena Dominguez, Michael Olsen.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Finland

Pekka Raatikainen, K.E. Juhani Airaksinen.

France

Franck Paganelli, Joël Ohayon, Frédéric Casassus, Jean-Yves Le Heuzey, Michel Galinier, Yannick Gottwalles, Philippe Loiselet, Jean-Joseph Muller, Mohamed Bassel Koujan, André Marquand, Sylvain Destrac, Olivier Piot, Nicolas Delarche, Jean-Pierre Cebron, Maxime Guenoun, Dominique Guedj-Meynier, Lokesh A G, Mathieu Zuber, Pierre Amarenco, Emmanuel Ellie, James Kadouch, Pierre-Yves Fournier, Jean-Pierre Huberman, Nestor Lemaire, Gilles Rodier, Xavier Vandamme, Igor Sibon, Jean-Philippe Neau, Marie Hélène Mahagne, Antoine Mielot, Marc Bonnefoy, Jean-Baptiste Churet, Vincent Navarre, Frederic Sellem, Gilles Monniot, Jean-Paul Boyes, Bernard Doucet, Michel Martelet, Désiré Obadia, Bernard Crousillat, Joseph Mouallem, Etienne Bearez, Jean Philippe Brugnaux, Alain Fedorowsky, Pierre Nazeyrollas, Jean-Baptiste Berneau, Frédéric Chemin.

Germany

Sebastien Schellong, Harald Darius, Georg Koeniger, Andreas Kopf, Uwe Gerbaulet, Bernd-Thomas Kellner, Thomas Schaefer, Jan Purr, Enno Eißfeller, Heinz-Dieter Zauzig, Peter Riegel, Christoph Axthelm, Gerd-Ulrich Heinz, Holger Menke, Andreas Pustelnik, Stefan Zutz, Wolfgang Eder, Guenter Rehling, Dirk Glatzel, Norbert Ludwig, Petra Sandow, Henning Wiswedel, Cosmas Wildenauer, Steffen Schoen, Toralf Schwarz, Adyeri Babyesiza, Maximilian Kropp, Hans-Hermann Zimny, Friedhelm Kahl, Andreas Caspar, Sabine Omankowsky, Torsten Laessig, Hermann-Josef Hartmann, Gunter Lehmann, Hans-Walter Bindig, Gunter Hergdt, Dietrich Reimer, Joachim Hauk, Holger Michel, Praxis Dres. Werner Erdle, Wilfried Dorsch, Janna Dshabrailov, Karl-Albrecht Rapp, Reinhold Vormann, Thomas Mueller, Peter Mayer, Uwe Horstmeier, Volker Eissing, Heinz Hey, Heinz Leuchtgens, Volker Lilienweiss, Heiner Mueller, Christian Schubert, Herrmann Lauer, Thomas Buchner, Gunter Brauer, Susanne Kamin, Karsten Mueller, Sylvia Baumbach, Muwafeg Abdel-Qader, Hans-Holger Ebert, Carsten Schwencke, Peter Bernhardt, Laszlo Karolyi, Britta Sievers, Wilhelm Haverkamp, Jens-Uwe Roehnisch.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Hungary

Andras Vertes, Gabor Szantai, Andras Matoltsy, Nikosz Kanakaridisz, Zoltan Boda, Erno Kis, Balazs Gaszner, Ferenc Juhasz, Gizella Juhasz, Sandor Kancz, Zoltan Laszlo, Zsolt May, Bela Merkely, Ebrahim Noori, Tamas Habon, Peter Polgar, Gabriella Szalai, Sandor Vangel, Andras Nagy, Gabriella Engelthaler, Judit Ferenczi, Mihaly Egyutt.

Italy

Giuliana Martini, Leone Maria Cristina, Eros Tiraferri, Rita Santoro, Sophie Testa, Giovanni Di Minno, Marco Moia, Teresa Maria Caimi, Maria Tessitori, Giancarlo Agnelli, Roberto Cappelli, Daniela Poli, Roberto Quintavalla, Franco Cosmi, Raffaele Fanelli, Vincenzo Oriana, Raffaele Reggio, Roberto Santi, Leonardo Pancaldi, Raimondo De Cristofaro, Giuliana Guazzaloca, Angelo De Blasio, Jorge Salerno Uriate, Flavia Lillo, Enrico Maria Pogliani, Grzegorz Bilo, Michele Accogli, Antonio Mariani, Mauro Feola, Arturo Raisaro, Luciano Fattore, Andrea Mauric, Fabrizio Germini, Luca Tedeschi, Maria Settimi, Sergio Nicoli, Paolo Ricciarini, Antonio Argena, Paolo Ronchini, Claudio Bulla, Filippo Tradati, Massimo Volpe, Maria D'Avino, Maria Grazia Bongiorni, Silva Severi, Alessandro Capucci, Corrado Lodigiani, Enrico Salomone, Gaetano Serviddio, Claudio Tondo, Giuseppe Ambrosio, Paolo Golino, Carmine Mazzone, Saverio Iacopino.

The Netherlands

Hugo ten Cate, J.H. Ruiter, Andreas Lucassen, Henk Adriaansen, Maarten Bongaerts, Mathijs Pieterse, Coen van Guldener, Johannes Herrman, S.H.K. P.R. Nierop, Pieter Hoogslag, Walter Hermans, B.E. Groenemeijer, W. Terpstra, Cees Buiks, L.V.A. Boersma.

Norway

Eivind Berge, Per Anton Sirnes, Erik Gjertsen, Torstein Hole, Knut Erga, Arne Hallaråker, Gunnar Skjelvan, Anders Østrem, Beraki Ghezai, Arne Svilaas, Peter Christersson, Torbjørn Øien, Svein Høegh Henrichsen, Jan Erik Otterstad, Jan Berg-Johansen.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Poland

Janina Stepinska, Andrzej Gieroba, Malgorzata Biedrzycka, Michal Ogorek, Beata Wozakowska-Kaplon, Krystyna Loboz-Grudzien, Jaroslaw, Wieslaw Supinski, Jerzy Kuzniar, Roman Zaluska, Jaroslaw Hiczkiewicz, Lucyna Swiatkowska-Byczynska, Lech Kucharski, Marcin Gruchala, Piotr Minc, Maciej Olszewski, Grzegorz Kania, Malgorzata Krzciuk, Zbigniew Lajkowski, Bozenna Ostrowska-Pomian, Jerzy Lewczuk, Elzbieta Zinka, Agnieszka Karczmarczyk, Malgorzata Chmielnicka-Pruszczynska, Iwona Wozniak-Skowerska, Grzegorz Opolski, Marek Bronisz, Marcin Ogorek, Grazyna Glanowska, Piotr Ruszkowski, Grzegorz Skonieczny, Ryszard Sciborski, Boguslaw Okopien, Piotr Kukla, Krzysztof Galbas, Krzysztof Cymerman, Jaroslaw Jurowiecki, Pawel Miekus, Waldemar Myszka, Stanislaw Mazur, Roman Lysek, Jacek Baszak, Teresa Rusicka-Piekarz, Grzegorz Raczak, Ewa Domanska, Jadwiga Nessler, Jozef Lesnik.

Russia

Vera Eltishcheva, Roman Libis, Gadel Kamalov, Dmitry Belenky, Liudmila Egorova, Alexander Khokhlov, Eduard Yakupov, Dmitry Zateyshchikov, Olga Barbarash, Olga Miller, Evgeniy Mazur, Konstantin Zrazhevskiy, Tatyana Novikova, Yulia Moiseeva, Elena Polkanova, Konstantin Sobolev, Maria Rossovskaya, Yulia Shapovalova, Alla Kolesnikova, Konstantin Nikolaev, Oksana Zemlianskaia, Anna Zateyshchikova, Victor Kostenko, Sergey Popov, Maria Poltavskaya, Anton Edin,Elena Aleksandrova, Oksana Drapkina, Alexander Vishnevsky, Oleg Nagibovich, Petr Chizhov, Svetlana Rachkova, Mikhail Sergeev, Borys Kurylo, Alexey Ushakov.

Spain

Xavier Vinolas, Pere Alvarez Garcia, Maria Fernanda Lopez Fernandez, Luis Tercedor Sanchez, Salvador Tranche Iparraguirre, Pere Toran Monserrat, Emilio Marquez Contreras, Jordi Isart Rafecas, Juan Motero Carrasco, Pablo Garcia Pavia, Casimiro Gomez Pajuelo, Luis Miguel Rincon Diaz, Luis Fernando Iglesias Alonso, Angel Grande Ruiz, Jordi Merce Klein, Jose Ramon Gonzalez Juanatey, Ines Monte Collado, Herminia Palacin Piquero, Carles Brotons Cuixart, Esther Fernandez Escobar, Joan Bayo i Llibre, Cecilia Corros Vicente, Manuel Vida Gutierrez, Francisco Epelde Gonzalo, Carlos Alexandre Almeida Fernandez, Encarnacion Martinez Navarro, Jordi Isart Rafecas, Juan Jose Montero Alia, Maria Barreda Gonzalez, Maria Angels Moleiro Oliva, Jose Iglesias Sanmartin, Mercedes Jimenez Gonzalez, Maria del Mar Rodriguez Alvarez, Juan Herreros Melenchon, Tomas Ripoll Vera, Manuel Jimenez Navarro, Maria Vazquez Caamano, Maria Fe Arcocha Torres, Gonzalo Marcos Gomez, Andres Iniguez Romo, Miguel Angel Prieto Diaz.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Sweden

Mårten Rosenqvist, Alexander Wirdby, Centrumkliniken, Jan Lindén, Kerstin Henriksson, Micael Elmersson, Arnor Egilsson, Ulf Börjesson, Gunnar Svärd, Bo Liu, Anders Lindh, Lars-Bertil Olsson, Mikael Gustavsson, Lars Andersson, Lars Benson, Claes Bothin, Ali Hajimirsadeghi, Björn Martinsson, Marianne Ericsson, Åke Ohlsson, Håkan Lindvall, Peter Svensson, Katarina Thörne, Hans Händel, Pyotr Platonov, Fredrik Bernsten, Ingar Timberg, Milita Crisby, Jan-Erik Karlsson, Agneta Andersson, Lennart Malmqvist, Johan Engdahl, Jörgen Thulin, Aida Hot-Bjelak, Steen Jensen, Per Stalby.

Switzerland

Jan Steffel, Johann Debrunner, Juerg H. Beer, Dipen Shah.

Ukraine

Iurii Rudyk, Vira Tseluyko, Oleksandr Karpenko, Svitlana Zhurba, Igor Kraiz, Oleksandr Parkhomenko, Iryna Kupnovytska, Nestor Seredyuk, Yuriy Mostovoy, Oleksiy Ushakov, Olena Koval, Igor Kovalskiy, Yevgeniya Svyshchenko, Oleg Sychov, Mykola Stanislavchuk, Andriy Yagensky, Susanna Tykhonova, Ivan Fushtey.

United Kingdom

Will Murdoch, Naresh Chauhan, Daryl Goodwin, Louise Lumley, Ramila Patel, Philip Saunders, Bennett Wong, Alex Cameron, Philip Saunders, Niranjan Patel, P Jhittay, Andrew Ross, M S Kainth, Karim Ladha, Kevin Douglas, Gill Pickavance, Joanna McDonnell, Laura Handscombe, Trevor Gooding, Helga Wagner, Cumberlidge, Colin Bradshaw, Catherine Bromham, Kevin Jones, Shoeb Suryani, Richard Coates, Bhupinder Sarai, W Willcock, S Sircar, John Cairns, A Gilliand, Roman Bilas, E Strieder, Peter Hutchinson, Anne Wakeman, Michael Stokes, Graham Kirby, Bhaskhar Vishwanathan, Nigel Bird, Paul Evans, M Clark, John Bisatt, Jennifer Litchfield, E Fisher, Tim Fooks, Richard Kelsall, Neil Paul, Elizabeth Alborough, Michael Aziz, C Ramesh, Pete Wilson, Simon Franklin, Sue Fairhead, Julian Thompson, Hasan Chowan, Gary Taylor, Dawn Tragen, Matt Parfitt, Claire Seamark, Carolyn Paul, Mark Richardson, Angus Jefferies, Helen Sharp, Hywel Jones, Claire Giles, Matthew Bramley, Philip Williams, Jehad Aldegather, Simon Wetherell, William Lumb, Phil Evans, Frances Scouller, Neil Macey, Stephen Rogers, Yvette Stipp, Richard West, Philip Pinney, Paul Wadeson, John Matthews, Preeti Pandya, Andrew Gallagher, T Railton, Emyr Davies, Jonathan McClure, Marc

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Jacobs, Claire Hutton, R Thompson, Bijoy Sinha, Keith Butter, Susan Barrow, Helen Little, David Russell, Ulka Choudhary, Ikram Haq, Paul Ainsworth, Claire Jones, Phil Weeks, Jane Eden, Lisa Gibbons, Janet Glencross, Alison MacLeod, K Poland, Conor Mulolland, A Warke, Paul Conn, D Burns, R Smith, R Kamath, Jonathan Webster, Ian Hodgins, Stephen Vercoe, Paul Roome, Hilary Pinnock, Jayesh Patel, Amar Ali, Nigel Hart, Richard Davies, Nigel De-Sousa, Catherine Neden, Mark Danielsen, Purnima Sharma, Sophia Galloway, Charlotte Hawkins, Raife Oliver, Martin Aylward, Mira Pattni, Gordon Irvine, Shahid Ahmad, Catherine Rothwell, Fiaz Choudhary, Sabrina Khalaque, Stephanie Short, Sharon Peters, Warwick Coulson, Neil Roberts, Amy Butler, Steven Coates, Ben Ward, Daniel Jackson, Steve Walton, Diane Shepherd, Toh Wong, Mark Boon, Melanie Deacon, David Cornelius, Sarah Davies, Ben Frankel, Nick Hargreaves, Henry Choi, Jon Sumner, Tim Myhill, Salah Estifanos, Diane Geatch, Justin Wilkinson, Richard Veale, Karen Forshaw, Rob Hirst, Kashif Zaman, Catherine Liley, Rebecca Wastling, Paul McEleny, Andre Beattie, Philip Cooke, Mike Wong, Mark Pugsley, Chaminda Dooldeniya, Greg Rogers, James Bennett, Polly Jacobs, Rajesh Muvva, Matthew Adam, Robin Fox, Nicolas Thomas, Simon Cartwright, Rory Reed, Simon Randfield, Christine A'Court, Ann Flynn, Andrew Halpin, Shoeb Suryani, Simon Dobson, Louise Lomax, Minnal Nadaph, Iain Munro, Jane Goram, Helen Stoddart, Phil Simmons, John Shewring, Emma Bowen-Simpkins, Mark Rickenbach, Polly Jacobs.

Australia

Adam Blenkhorn, Bhuwanendu Singh, Penny Astridge, William van Gaal, Walter Abhayaratna, Philip Thomson, Ron Lehman, Jens Kilian, David Coulshed, Andrei Catanchin, David Colquhoun, Hosen Kiat, David Eccleston, John French, Bronte Ayres, Peter Blombery, Thanh Phan, James Rogers, David O'Donnell, Sang Cheol Bae, Harry Gibbs, Patrick Carroll, Greg Starmer, Margaret Arstall, Maurits Binnekamp, Astin Lee.

Canada

John Eikelboom, Robert Luton, Milan Gupta, Amritanshu Shekhar Pandey, Stephen Cheung, Rolland Leader, Philippe Beaudry, Félix Ayala-Paredes, Joseph Berlingieri, John Heath, Germain Poirier, Miranda du Preez, Bradley Schweitzer, Reginald Nadeau, Ripple Dhillon, Tomasz Hruczkowski, Andrea Lavoie, Ratika Parkash, James Cha, Benoit Coutu, Paul MacDonald, Brian Ramjattan, Jorge Bonet, Saul Vizel, Paul Angaran, Sameh Fikry.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Egypt

Ahmed Mowafy, Azza Katta, Mazen Tawfik, Moustafa Nawar, Mohamed Sobhy, Seif Kamal Abou Seif, Tarek Khairy, Ahmed Abd El-Aziz, Nasser Taha, Ashraf Reda, Atef Elbahry, Mohamed Setiha, Mohamed Gamal El Din, Magdi Elkhadem, Adel El-Etreby.

South Africa

David Kettles, Junaid Bayat, Heidi Siebert, Adrian Horak, Ynez Kelfkens, Riaz Garda, Barry Jacobson, Thayabran Pillay, Michele Guerra, Louis van Zyl, Hendrik Theron, Andrew Murray, Rikus Louw, Deon Greyling, Pindile Mntla, Siddique Ismail, Fayzal Ahmed, Johannes Engelbrecht, Shambu Maharajh, Wessel Oosthuysen, Rehana Loghdey, Veronica Ueckermann.

United Arab Emirates

Wael Al Mahmeed, Abdullah Al Naeemi, Ghazi Yousef, Nooshin Bazargani, Munther AlOmairi, Rajan Maruthanayagam, Rupesh Singh, Ahmed Naguib, Mohamed Ibrahim, Amrish Agrawal, Mukesh Nathani, Ehab M. Esheiba, Adel Wassef, Rajeev Gupta.

United States

Michael Cox, Scott Beach, Peter Duffy, Stephen Falkowski, Kevin Ferrick, Miguel Franco, W. Michael Kutayli, Annette Quick, Niraj Sharma, Vance Wilson, Stephen Miller, Mark Alberts, Edwin Blumberg, Roddy Canosa, Ted Gutowski, Rodney Ison, Jorge Garcia, Paul Mullen, Howard Noveck, Pamela Rama, Rajneesh Reddy, Marcus Williams, Daniel Nishijima, Keith Ferdinand, Ihsan Haque, Robert Mendelson, Sridevi Pitta, Daniel Theodoro, Charles Treasure, Moustafa Moustafa, Cas Cader, Walter Pharr, Alisha Oropallo, George Platt, Jaspal Gujral, James Welker, Firas Koura.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract- **title page 1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found- **page 4 &5**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported- **page 6**
Objectives	3	State specific objectives, including any prespecified hypotheses- **page 6**
Methods		
Study design	4	Present key elements of study design early in the paper- **Page 6-7**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection –**pages 6-8**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up-**page 6-7** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable- **page 7**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group- **page 8-10**
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding- **page 8-10**
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **page 10**
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **page 10-11**
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **page 11-13**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **page 9-10**
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **page 13-14**
Discussion		
Key results	18	Summarise key results with reference to study objectives- **page 14-15**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias-**page 17-18**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence- **page 14-18**
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based- **page 19**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-049933.R1
Article Type:	Original research
Date Submitted by the Author:	24-Aug-2021
Complete List of Authors:	Fox, Keith; University of Edinburgh Division of Clinical and Surgical Sciences, Centre for Cardiovascular Science Virdone, Saverio; Thrombosis Research Institute Bassand, Jean-Pierre; Thrombosis Research Institute; University of Besançon, Department of Cardiology Camm, John; St George's University of London, Cardiology Clinical Academic Group Molecular & Clinical Sciences Research Institute, Goto, Shinya; Tokai University School of Medicine Graduate School of Medicine, Department of Medicine (Cardiology) Goldhaber, Samuel; Brigham and Women's Hospital Department of Medicine, Department of Medicine Haas, Sylvia ; Technical University of Munich, Department of Medicine Kayani, Gloria; Thrombosis Research Institute Koretsune, Yukihiro; National Hospital Organization Osaka National Hospital Misselwitz, Frank; Formerly Bayer AG Oh, Seil; Seoul National University Hospital Piccini, Jonathan; Duke University Medical Center Parkhomenko, Alex; National Scientific Center Academician M D Strazhesko Institute of Cardiology of the National Academy of Medical Sciences of Ukraine Sawhney, J P S; Sir Ganga Ram Hospital Stepinska, Janina; Intensive Cardiac therapy clinic Turpie, Alexander G. G.; McMaster University, Department of Medicine Verheugt, Freek; Onze Lieve Vrouwe Gasthuis (OLVG), Cardiology Kakkar, Ajay ; Thrombosis Research Institute
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	CARDIOLOGY, Anticoagulation < HAEMATOLOGY, Thromboembolism < CARDIOLOGY

SCHOLARONE™
Manuscripts

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

Title Page

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

Keith A.A. Fox MBChB[1], Saverio Virdone M. Sc[2], Jean-Pierre Bassand MD[2,3], A. John Camm MD[4], Shinya Goto MD, PhD[5], Samuel Z. Goldhaber MD[6], Sylvia Haas MD[7], Gloria Kayani B. Sc[2], Yukihiro Koretsune MD, PhD[8], Frank Misselwitz MD, PhD[9], Seil Oh MD, PhD[10], Jonathan P. Piccini MD[11], Alex Parkhomenko MD, PhD[12], Jitendra Pal Singh Sawhney MD[13], Janina Stepinska MD, PhD[14], Alexander G.G. Turpie MD[15], Freek W.A. Verheugt MD, PhD[16], Ajay K. Kakkar MBBS, PhD[2] for the GARFIELD-AF investigators*

1. Centre for Cardiovascular Science, University of Edinburgh, United Kingdom
2. Thrombosis Research Institute, London, United Kingdom
3. Department of Cardiology, University of Besançon, Besançon, France
4. Cardiology Clinical Academic Group Molecular & Clinical Sciences Research Institute, St. George's University of London, London, UK
5. Department of Medicine (Cardiology), Tokai school of medicine, Kanagawa, Japan
6. Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
7. Department of Medicine, Formerly Technical University of Munich, Munich, Germany
8. National Hospital Organization Osaka National Hospital, Osaka, Japan
9. Formerly Bayer AG, Berlin, Germany

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

10. Seoul National University Hospital, Seoul, Korea

11. Duke University Medical Center and the Duke Clinical Research Institute, Durham, NC, USA

12. National Scientific Centre "MD Strazhesko Institute of Cardiology", Kiev, Ukraine

13. Department of Cardiology, Ganga Ram Hospital, New Delhi, India

14. Institute of Cardiology, Intensive cardiac therapy clinic, Warsaw, Poland

15. Department of Medicine, McMaster University, Hamilton, ON, Canada

16. Department of Cardiology, Onze Lieve Vrouwe Gasthuis (OLVG), Amsterdam, The Netherlands

For peer review only

Corresponding author

Keith A.A. Fox, FRCP, FESC, FMedSci,

Professor of Cardiology,

BHF Centre for Cardiovascular Science,

University of Edinburgh,

47 Little France Crescent,

Edinburgh EH16 4TJ.

Email: k.a.a.fox@ed.ac.uk;

Tel: +44 131 242 6378

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

Word count:

Abstract:266 (Max: 300)

Text: 3722

Reference: 33

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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.

Key words Geographical variations; Atrial Fibrillation; All-cause mortality; Stroke/systemic embolism; major bleeding

For peer review only

Strengths and limitations of this study

- This is a prospective observational study where patients with newly diagnosed AF were identified and followed and outcomes evaluated.
- All patients were managed according to local standards of care.
- Remote and onsite monitoring and robust quality control methods were used.
- As in any observational study the findings may have been influenced by unmeasured confounders.
- Ascertainment of bleeding outcomes was according to local standards of care and thus ascertainment criteria, locally, may have influenced observed rates of bleeding.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

INTRODUCTION

The 2015 Global Burden of Disease (GDB) report of 195 countries and territories suggests that AF prevalence is highest in Northern and Central Europe, and the United States [1], and is projected to rise globally because of aging and population growth worldwide [2]. However, whether the diverse outcomes of patients with newly diagnosed AF are accounted for by baseline risk characteristics and antithrombotic therapies is uncertain.

The gains in cardiovascular health in high-income countries are related, at least in part, to modification of cardiovascular risk factors as well as improved disease management. In the context of atrial fibrillation, the changes include the availability of treatment strategies for stroke prophylaxis, and/or rhythm or rate control [3-7]. However, the extent to which baseline characteristics and treatment strategies account for geographic variations in outcomes is unclear.

The Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) aimed to define geographical variations in all-cause mortality, stroke/systemic embolism (SE) and major bleeding in patients with newly diagnosed AF. The primary aim of this report was to determine whether variations in outcomes of AF are accounted for by baseline clinical risk characteristics. A secondary aim was to consider the impact of other factors including national differences in life expectancy, access to quality healthcare, and stroke prevention strategies.

METHODS

Design

GARFIELD-AF is the largest multinational prospective registry in AF [8]. The study recruited patients from >1,000 investigational sites (identified nationally as representative) in 35 countries. Patients were recruited from: Europe (Finland, Norway, Sweden, Denmark, United Kingdom, Netherlands, Belgium, Germany, Switzerland, France, Spain, Italy, Austria,

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Hungary, Russia, Poland, Czech Republic, Ukraine and Turkey), Asia (Singapore, China, Japan, South Korea, Thailand and India), North America (USA and Canada), Latin America (Mexico, Brazil, Argentina and Chile) and other countries including Egypt, United Arab Emirates, South Africa and Australia.

Adults ≥18 years were eligible for inclusion if they were diagnosed with non-valvular AF within 6 weeks of study entry. Patients with AF were required to have at least one risk factor for stroke, as judged by the investigator (entry to GARFIELD-AF did not require performance of a stroke risk predictor, nor a specific threshold if such a score was performed). Patients were enrolled prospectively and consecutively at sites that aimed to reflect diverse care settings (including office/outpatient practice; hospital departments including neurology, cardiology, geriatrics, internal medicine and emergency; anticoagulation clinics; and general practice) [8,9].

Ethics statement

Independent ethics committee and hospital-based institutional review board approvals were obtained, as necessary, for the registry protocol. 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 Harmonisation Good Pharmacoepidemiological and Clinical Practice Guidelines. Written informed consent was obtained from all study participants. Confidentiality and anonymity of all enrolled patients was maintained.

GARFIELD-AF data were captured using an electronic case report form (eCRF). Submitted data were examined for completeness and accuracy by the coordinating centre (Thrombosis Research Institute, London, UK), and data queries were sent to study sites. An audit and quality control programme was implemented, and this included source documentation (20% of all

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

eCRFs were monitored against source records) [10]. This paper adheres to the guidelines from STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) [11].

Patient and Public Involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Procedures and outcome measures

Baseline characteristics collected at study entry included: medical history, care setting, type of AF, date and method of diagnosis of AF, symptoms, antithrombotic treatment (vitamin K antagonists [VKAs], non-vitamin K antagonist oral anticoagulants [NOACs] and antiplatelet [AP] treatment), as well as all cardiovascular drugs. Race was classified by the investigator in agreement with the patient [8]. Vascular disease included coronary artery disease (CAD) with a history of acute coronary syndromes (ACS) and/or peripheral artery disease. Chronic kidney disease (CKD) was classified according to National Kidney Foundation guidelines into moderate-to-severe (stages 3–5), mild (stages 1 and 2) or none. Data on components of the CHA_2DS_2-VASc and HAS-BLED risk stratification schemes were collected and calculated retrospectively. HAS-BLED scores were calculated excluding fluctuations in international normalised ratio. In addition, the risk of death, non-haemorrhagic stroke/SE and major bleeding was evaluated with the GARFIELD-AF risk calculator [12].

Patients were followed over a minimum of 24 months or until death or loss to follow-up, whichever occurred first. As reported previously, standardised definitions for clinical events, death (cardiovascular and non-cardiovascular), non-hemorrhagic stroke/SE and major bleeding) were used [8,9]. Outcome events were not centrally adjudicated.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Data for this report were extracted from the study database on 30th June 2019.

Statistical analysis

Univariate data are presented as medians (1st and 3rd quartile) for continuous variables and as absolute frequencies with percentages for categorical variables.

"Time at risk" for each event was calculated over the first year after enrolment up to the first occurrence of an event or last follow-up or at 365 days, which ever occurred earlier. All-cause mortality, non-haemorrhagic stroke/SE and major bleeding were described as the number of events and the Kaplan-Meier event rate with 95% confidence intervals.

In this study, national risk-standardised measures of event rates were calculated to compare the observed event rates based on case mix (i.e. the clinical characteristics of patients) in each country, with the expected rates for a similar case mix. The risk-standardised event rates were calculated using the following equation:

$$\frac{Observed\ event\ rate}{Expected\ event\ rate} \times Global\ event\ rate = Risk\ standardized\ rate$$

Where the **Observed event rate** was the crude rate calculated for each country using the Kaplan-Meier estimator (1 *minus* event-free survival probability at 1 year after enrolment).

Expected event rate was calculated (using multivariable Cox regression with a series of demographic and clinical characteristics as covariates) for every patient and the national average computed.

Global (and regional) event rates were the crude rate calculated with the Kaplan-Meier rate across all countries in GARFIELD-AF without exclusion.

When the observed and expected rates were the same, the risk-standardised rate equalled the global event rates. However, when the observed event rate was greater or less than the expected rate, then the country had more or less events than expected, based on its case mix. Hence, the

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

observed to expected ratio was greater or less than 1.0, making the risk-standardised rate higher or lower than the global rate.

Patients' characteristics included in the initial Cox model were: age, gender, type of AF, history of hypertension, blood pressure (systolic and diastolic) and pulse rate (at enrolment), hypercholesterolemia, smoking status (never/ex/current) and heavy alcohol consumption, diabetes mellitus (type 1 or 2), ACS, coronary artery bypass graft (CABG), vascular disease, carotid occlusive disease, venous thromboembolism (VTE), history of stroke/transient ischaemic attack (TIA)/SE, history of bleeding, heart failure, moderate-to-severe CKD and cirrhosis. Fine-Gray modelling was applied to the outcomes of non-haemorrhagic stroke/SE and major bleeding with death as the competing risk. Confidence intervals for the risk-standardized measures were computed using estimates extracted from 1000 bootstrap samples. Patients with missing values were not removed from the study; single imputation was applied.

Both baseline risk factors and antithrombotic regimens (with oral AC and/or AP) at the time of diagnosis of AF (baseline) were included in the Cox model.

The observed rates in a contemporary US registry, the ORBIT-AF II, were derived to assess the representability of the US patients in GARFIELD-AF.

All analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline demographics and clinical characteristics

Baseline characteristics were analysed for the 52,018 patients with newly diagnosed AF, enrolled consecutively into GARFIELD-AF between March 2010 and August 2016, in 35 countries. The largest cohort was recruited from Europe (57.4%), followed by Asia (26.6%), Latin America (8.2%), "Other" countries (4.7%) (including South Africa, Egypt, United Arab Emirates and Australia) and North America (3.1%). The rate of missing data was below <3%,

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

with the exception of lifestyle information, BMI and some vital signs. Loss to follow-up was about 1% for all world regions except Asia (4.3%).

The observed variability in patients' baseline characteristics among regions in GARFIELD-AF is reported in **table 1.** Patients from Asia compared with Europe tended to be younger, had a lower body mass index, a lower prevalence of hypertension, hypercholesterolemia, vascular disease and CKD. By contrast, patients from North America in GARFIELD-AF had the highest proportion of patients aged ≥75, together with the highest prevalence of diabetes, hypercholesterolemia and prior/current smokers from any region (except "Other Region" where the highest prevalence of diabetes was observed). The prevalence of heart failure was consistent and approximately one in five of patients in every region. Approximately 70% of patients overall (and 91.6% of patients in North America) were categorised at having paroxysmal or unclassified AF at enrolment in this study **(Table 1).**

Standard risk assessment scores (including the GARFIELD-AF risk score) found that the calculated risks of stroke or major bleeding were similar across regions (median CHA_2DS_2-VASc score 3.0 in all regions). However, the GARFIELD-AF risk model for death revealed regional differences, with a lower expected rate of death in patients from Asia and highest in those from Latin America **(Table 1).**

Treatment setting

In Asia and Latin America, patients were predominantly diagnosed and managed by cardiologists (83.7% and 75.0%, respectively), while in Europe and North America, the role of managing patients with AF was shared between cardiologists (in approximately 60% of cases), internists (~20%) and primary care (~20%). The likelihood of being diagnosed and treated in the emergency care setting was highest in North America (38.0% of patients) followed by Latin America (24.7%), "Other" countries (13.4%), Europe (11.5%) and Asia (2.5%).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Observed global and regional outcomes

In GARFIELD-AF, the lowest observed rate of death at one year was recorded in Asia (2.8; 95% CI: 2.6-3.1) with rates less than half those observed in "Other" countries (6.0; 95% CI: 5.1-7.0) (namely, South Africa, Egypt, United Arab Emirates and Australia). Non-haemorrhagic stroke/SE rates showed less regional variability, but once again, the lowest observed rates were reported in Asia (1.0; 95% CI: 0.9-1.2). For major bleeding, the highest observed rates were recorded in North America (2.9; 95% CI: 2.2-3.8) and the lowest in Asia (0.9; 95% CI: 0.7-1.0). Reflecting the high proportion of patients from Europe, the global rates across all countries in GARFIELD-AF were similar to European event rates for mortality, non-haemorrhagic stroke/SE and major bleeding **(Table 2).**

Observed and risk-standardised outcomes by country

Figures 1 to 3 depict the observed and risk-standardised rates of mortality, non-haemorrhagic stroke/SE and major bleeding for countries that enrolled more than 90% of the patients into GARFIELD-AF, i.e. omitting countries with potentially unrepresentative findings due to low enrolment. Full details of the observed rates from all countries, including those omitted from the figures, i.e. South Africa (n=639), Denmark (n=532), Egypt (n=527), Austria (n=460), United Arab Emirates (n=397), Finland (n=359), Singapore (n=306), Norway (n=270), and Switzerland (n=89), are reported in **Supplement Tables S1-S3.**

Figures 1-3 show the marked variations in observed event rates by country. This variability persisted even after adjusting for all 22 baseline factors (demographics, modifiable cardiovascular risk factors and comorbidities).

India and Ukraine experienced the highest risk-standardised mortality rates, primarily driven by cardiovascular events. Marked differences were also observed for the USA, where the rate of non-cardiovascular mortality was more than 3-fold higher compared to cardiovascular

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

mortality. Within most other countries the rates of cardiovascular and non-cardiovascular mortality were similar (**Supplementary Table S1**).

To display the relation between healthcare access and outcomes in more detail, we colour-coded each country according to the Healthcare Access and Quality (HAQ) Index (overall score on a scale of 0–100) from the Global Burden of Disease Study 2016 [13]. The results show that some of the countries with highest risk-standardised mortality rates (i.e. India, Mexico, Argentina and Brazil) had some of the lowest HAQ indices (HAQ: <70); only Thailand had a similarly low HAQ and a mortality rate. Conversely, the three countries with the lowest risk-standardised mortality rate (South Korea, Japan, and Sweden) all obtained a high HAQ score (HAQ: ≥90).

The observed mortality rate from the US study, ORBIT-AF II, was similar to the GARFIELD-AF global rate (4.3 [95% CI: 3.7-4.9] vs 4.2 [95% CI: 4.0-4.4] respectively) and below the global rate for non-haemorrhagic stroke/SE (ORBIT-AF-II 0.8 [95% CI: 0.6-1.1] vs GARFIELD-AF 1.2 [95% CI: 1.1-1.3]). Nevertheless, both GARFIELD-AF and ORBIT-AF II reported high rates of major bleeding in the US: 3.4 (95% CI: 2.3-5.0) [GARFIELD-AF] and 3.3 (95% CI: 2.8-3.8) [ORBIT-AF II] relative to the global rate of 1.2 (95% CI: 1.1-1.3) in GARFIELD-AF.

The rates of each type of outcome differed by country. For instance, the lowest risk-standardised mortality rates were observed for South Korea, Japan and Sweden, while the lowest risk-standardised rates of non-haemorrhagic stroke/SE were observed in Germany, Czech Republic and Canada. The highest risk-standardised rates non-haemorrhagic stroke/SE were reported in Ukraine and Australia, and the highest risk-standardised rates of major bleeding in the Netherlands and the USA.

Antithrombotic regimen for stroke prevention at baseline

GARFIELD-AF recorded substantial differences in the overall rate of anticoagulation by region (from 73% in Europe to 56% in Asia, **Supplementary Figure S1a**), as well as large variations

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

within countries (**Supplementary Figure S1b).** At the time of diagnosis of AF, the highest proportion of patients receiving NOACs was in North America (44.8%). This included 14.4% of patients who received NOAC in combination with APs. VKAs were most commonly prescribed in Europe, Latin America and "Other" countries (in 44.4%, 39.8% and 41.1% of patients, respectively) (**Figure S1a**).

Even though CHA_2DS_2-VASc scores were similar across countries (**Supplementary Table S2**), anticoagulant treatment varied three-fold among countries (30% to 90%) (**Figure S1b**). The highest rate of anticoagulation was in the Netherlands and Switzerland (90%) and lowest in China (30%), India (35%) and Ukraine (48%) **(Figure S1b).** More than 40% of newly diagnosed patients with AF in China and India received anti-platelet therapy only and a further 20%, approximately, received no anti-thrombotic therapy. Across all countries, we found a significant ($p<0.001$) association with the choice of antithrombotic regimen and HAQ index, i.e. with a greater likelihood of AC and NOAC prescribing (and lower likelihood of AP therapy alone) with increasing HAQ score **(Figure 4)**.

ACs (with or without AP therapy) were prescribed to more than 70% of patients in 18 of 35 countries.

The choice of stroke prevention strategy by region and country was analysed and included in the Cox model. Even after adjustment for baseline risk factors and antithrombotic regimen (AC and/or AP treatment), substantial inter-country differences remained in the rate of non-haemorrhagic stroke/SE (**Supplementary table S4**).

DISCUSSION

Our analysis revealed a wide variability in standardized rates of all-cause mortality, non-haemorrhagic stroke/SE and major bleeding across regions and countries. It also showed a wide variability in baseline characteristics and treatment patterns across regions and countries. Asians had a lower risk profile than patients of any other regions, with lower mean age, BMI,

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

systolic and diastolic blood pressure, and pulse rate. They had lower rates of comorbidities, particularly history of ACS, vascular disease, stroke/SE, hypertension, high blood cholesterol, moderate to severe chronic kidney disease, and much lower risk of death according to the GARFIELD-AF risk score. With few exceptions, patients of non-Asian regions had substantially higher rates of any of these variables and higher risk of death according to GARFIELD-AF mortality risk score, though median CHA_2DS_2-VASc score and GARFIELD-AF stroke risk score were similar across regions.

In addition, there was a wide variability in treatment patterns as regards stroke prevention that was not accounted for by conventional measures of stroke risk, namely CHA_2DS_2-VASc score [14]. Such findings are consistent with other observational studies, including PINNACLE (Practice Innovation and Clinical Excellence) [15], EORP-AF (EUR Observational Research Programme-Atrial Fibrillation) [16] and GLORIA-AF (Global Registry on Long-Term Antithrombotic Treatments in Patients with Atrial Fibrillation) [17]. In our population, there were also wide variations across countries in antithrombotic therapy prescription. The rate of prescription of OAC w/wo antiplatelet agent was in the range of 70% in Europe, North America and Other Countries but approximately 60% in Latin America, and 56% in Asia. In China, India, South Korea, Singapore, Russia, United Arab Emirates, Mexico, Ukraine patients had substantially higher than global rates of antiplatelet therapy (without anticoagulation) (over 30%), and substantially lower than global average rates of OAC prescription (range 22% to 58%), and a higher proportion of patients with no antithrombotic at all.

After adjusting for the baseline demographics and clinical characteristics (including modifiable cardiovascular risk factors and comorbidities), the variability in all three major outcomes among countries persisted, though attenuated. Even after including antithrombotic regimen as a model covariate, substantial differences in the expected rates of events across countries remained. OAC treatment was shown to be associated with 30% and 28% lower risks of death

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

and stroke/SE in a previous report[18]. However, type and quality of OAC matter. NOAC instead of VKA, appropriateness of NOAC dosing and quality of VKA monitoring had significant impact on outcomes [19,20], as well as adherence to treatment [21]. This was not accounted for in this analysis and may explain that the differences in outcomes were only partly attenuated after adjustment.

In GARFIELD-AF there were geographic disparities, not only in antithrombotic regimens for AF, but also in other cardiovascular management measures. Indeed, AF is no longer considered as an isolated arrhythmia as it is associated with comorbidities that all need a specific therapeutic approach in other words a comprehensive management is now recommended. There may be wide geographic variations in the management of comorbidities such as CHF, diabetes, hypertension, high total and LDL cholesterol, as well as other non-cardiovascular comorbidities such as respiratory failure, sepsis and malignancy. Non-cardiovascular death accounts for at least 50% of all cause death. 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.

The observed differences in stroke rates, by country and by region, are not explained by the risk predictors within commonly used stroke prediction tools. These findings highlight the importance of identifying factors beyond those collected in conventional risk prediction tools to estimate outcomes in patients with AF. Such factors may include practice patterns (e.g. anticoagulation quality and adherence to treatment, statin use, LDL cholesterol management, diabetes control), access to quality health care, and environmental, lifestyle and epigenetic characteristics. The sum impact may account for the substantial differences in risk-standardised event rates among countries [22]. Achieving population-wide control of modifiable risk factors

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

(including tobacco use, diet, physical inactivity, plasma glucose and hypertension) could abrogate a substantial part of the global stroke burden, irrespective of age, gender or ethnicity [23,24]. Even small changes in the distribution of these risk factors could lead to clinically relevant reductions in the risks of cardiovascular disease, stroke, and mortality [25-27]. The findings from GARFIELD-AF and other recently published global and regional studies [7,28-32] suggest that high rates of potentially modifiable metabolic disorders and smoking persist. Thus, there remains considerable scope to improve the outcomes of patients with newly diagnosed AF, even in high- and middle-income countries.

Across countries huge variations in outcomes may also be influenced by factors beyond baseline characteristics, stroke prevention and management. Outcomes may depend on access to good quality care and may reflect standardized mortality rates per country. In GARFIELD-AF, the proportion of anticoagulated patients was highly correlated with the average HAQ index (derived from national data). And it was not surprising to observe that both these measures were found to be high in most countries with low risk-standardized mortality rates. Countries with some of the lowest Healthcare Access and Quality (HAQ) indices in GARFIELD-AF (India, Ukraine, Argentina and Brazil) had the highest risk-standardised mortality rates. Conversely, the lowest observed rates of mortality in Japan and South Korea persisted even after risk adjustment. Not all countries fit in this frame though. High observed mortality rates (relative to the global average) were found in countries with high Healthcare Access and Quality (HAQ) indices such as USA, France, and Germany, which remained greater than average even after risk adjustment.

The risk-standardised mortality rates in GARFIELD-AF appeared to be a reflection of average national life expectancy, with the lowest mortality rates in this population with newly diagnosed AF in countries with life-expectancies (in years) of 82.2, 83.8, 82.6, 78.2 and 81.6, whereas

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

countries with the highest mortalities in this AF population have life expectancies (in years) of 68.3, 71.2, 76.3, 78.7 and 74.7 [33].

Patients from participating centres with the highest rates of mortality and non-haemorrhagic stroke/SE were among the least likely to receive OAC for stroke prevention over the 5 years of recruitment into GARFIELD-AF**.** This is consistent with the observed higher rates of cardiovascular (vs non-cardiovascular) mortality in such countries and where AP therapy or no antithrombotic therapy for AF is most prevalent**.** 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.

CLINICAL IMPLICATIONS

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

CONCLUSIONS

Antithrombotic regimens varied substantially across countries as well as the observed rates of death, stroke/SE and bleeding. Differences in the event rates persisted even after adjustment for

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

baseline characteristics and antithrombotic treatments. Other factors, including variations in clinical practice and access to quality healthcare, as well as unobserved patient-related factors, may be responsible for the substantial differences in the rates of mortality, stroke/SE and major bleeding across countries. The comprehensive management of patients with AF extends beyond anticoagulation.

Acknowledgements We thank the physicians, nurses, and patients involved in the GARFIELD-AF registry. Programming support was provided by Madhusudana Rao (TRI, London, UK). Editorial support was provided by Rae Hobbs and Dr Surekha Damineni (TRI, London, UK).

Contributor KAAF, JPB, AJC, SG, SZG, SH, GK, FM, JPP, AGGT, FWAV and AKK contributed to the study design. YK, SO, AP, JPSS, JS contributed to the data collection. SV analysed the data. All authors supervised the data analysis, provided the interpretation of results and contributed to the drafting and critical review of the manuscript. All authors approved the final draft.

Funding The work is supported by KANTOR CHARITABLE FOUNDATION for the Kantor-Kakkar Global Centre for Thrombosis Science. The funding sources had no involvement in the data collection, data analysis, or data interpretation.

Competing Interests KAA Fox has received grants and personal fees from Bayer/Janssen and AstraZeneca and personal fees from Sanofi/Regeneron and Verseon. AJ Camm: Institutional grants and personal fees from Bayer, Boehringer Ingelheim, BMS/Pfizer and Daichi Sankyo; S Goto has received Personal fees from Thrombosis Research Institute and the American Heart Association, grants from Sanofi, Pfizer, Ono, Bristol Myer Squibb, the Vehicle Racing Commemorative Foundation and Nakatani Foundation for Advancement of Measuring Technologies in Biomedical Engineering. SZ Goldhaber has received research support from

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Boehringer-Ingelheim, BMS, BTG EKOS, Daiichi, Janssen, NHLBI, and the Thrombosis Research Institute; has served as a consultant for Agile, Bayer, Boehringer-Ingelheim, BMS, Daiichi, Janssen and Zafgen. S Haas has received personal fees from Aspen, Bayer Healthcare, BMS/Pfizer, Daiichi-Sankyo, and Sanofi. Y Koretsune: Research grant from Daiichi Sankyo and Boeringer Ingelheim. Personal fees from: Daiichi Sankyo, Boehringer Ingelheim, Bayer, Bristol Meyers and Pfizer; F Misselwitz is a former employee of Bayer AG. S Oh: consultant/advisory board payments from Bayer Pharma AG, Bristol-Myers Squibb Korea, Boehringer-Ingelheim Korea, Pfizer Korea, Sanofi-Aventis, and St Jude Medical. J PS Sawhney: Personal fee from Pfizer, Astra Zeneca, Novartis, Sanofi & BMS; J. P. Piccini: Reported grants for clinical research from Abbott, American Heart Association, Boston Scientific, Gilead, Janssen Pharmaceuticals, NHLBI, and Philips and serves as a consultant to Abbott, Allergan, ARCA Biopharma, Biotronik, Boston Scientific, Johnson & Johnson, LivaNova, Medtronic, Milestone, Oliver Wyman Health, Sanofi, Philips, and Up-to-Date. J Stepinska: Research grants from Bayer; personal fees from Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, BMS/Pfizer, Novartis, Sanofi, Servier; Expert witness for Boehringer Ingelheim; AGG Turpie has received personal fees from Bayer Healthcare, Janssen Pharmaceutical Research & Development LLC, and Portola. FWA Verheugt has received grants from Bayer Healthcare; personal fees from Bayer Healthcare, BMS/Pfizer, Daiichi-Sankyo, and Boehringer-Ingelheim. AK Kakkar has received research support from Bayer AG and Sanofi; personal fees from Bayer AG, Pfizer, Janssen, Sanofi, Verseon and Anthos Therapeutics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Data sharing statement The data underlying this article will be shared on reasonable request from Karen S Pieper (KPieper@tri-london.ac.uk).

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial.

*A complete list of investigators is given in the supplementary

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

REFERENCES

1. Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation.* 2018;137(12):e67-e492.
2. Patel NJ, Atti V, Mitrani RD, Viles-Gonzalez JF, Goldberger JJ. Global rising trends of atrial fibrillation: a major public health concern. *Heart.* 2018.
3. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med.* 2007;356(23):2388-2398.
4. Koopman C, Vaartjes I, van Dis I, et al. Explaining the Decline in Coronary Heart Disease Mortality in the Netherlands between 1997 and 2007. *PLoS One.* 2016;11(12):e0166139.
5. Bandosz P, O'Flaherty M, Drygas W, et al. Decline in mortality from coronary heart disease in Poland after socioeconomic transformation: modelling study. *BMJ.* 2012;344:d8136.
6. Palmieri L, Bennett K, Giampaoli S, Capewell S. Explaining the decrease in coronary heart disease mortality in Italy between 1980 and 2000. *Am J Public Health.* 2010;100(4):684-692.
7. Ng M, Freeman MK, Fleming TD, et al. Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. *JAMA.* 2014;311(2):183-192.
8. Kakkar AK, Mueller I, Bassand JP, et al. International longitudinal registry of patients with atrial fibrillation at risk of stroke: Global Anticoagulant Registry in the FIELD (GARFIELD). *American heart journal.* 2012;163(1):13-19 e11.
9. Kakkar AK, Mueller I, Bassand JP, et al. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

international, observational, prospective GARFIELD registry. *PLoS One.* 2013;8(5):e63479.

10. Fox KAA, Gersh BJ, Traore S, et al. Evolving quality standards for large-scale registries: the GARFIELD-AF experience. *European heart journal Quality of care & clinical outcomes.* 2017;3(2):114-122.

11. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS medicine.* 2007;4(10):e297.

12. Fox KAA, Lucas JE, Pieper KS, et al. 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(12):e017157.

13. Measuring performance on the Healthcare Access and Quality Index for 195 countries and territories and selected subnational locations: a systematic analysis from the Global Burden of Disease Study 2016. *Lancet (London, England).* 2018;391(10136):2236-2271.

14. Camm AJ, Accetta G, Ambrosio G, et al. Evolving antithrombotic treatment patterns for patients with newly diagnosed atrial fibrillation. *Heart (British Cardiac Society).* 2017;103(4):307-314.

15. Chan PS, Maddox TM, Tang F, Spinler S, Spertus JA. Practice-level variation in warfarin use among outpatients with atrial fibrillation (from the NCDR PINNACLE program). *Am J Cardiol.* 2011;108(8):1136-1140.

16. Lip GY, Laroche C, Boriani G, et al. Regional differences in presentation and treatment of patients with atrial fibrillation in Europe: a report from the

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. *Europace.* 2015;17(2):194-206.

17. McIntyre WF, Conen D, Olshansky B, et al. Stroke-prevention strategies in North American patients with atrial fibrillation: The GLORIA-AF registry program. *Clinical cardiology.* 2018;41(6):744-751.

18. Bassand JP, Accetta G, Al Mahmeed W, 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(1):e0191592.

19. Camm AJ, Fox KAA, Virdone S, et al. Comparative effectiveness of oral anticoagulants in everyday practice. *Heart (British Cardiac Society).* 2021.

20. Haas S, Ten Cate H, Accetta G, et al. Quality of Vitamin K Antagonist Control and 1-Year Outcomes in Patients with Atrial Fibrillation: A Global Perspective from the GARFIELD-AF Registry. *PLoS One.* 2016;11(10):e0164076.

21. Cools F, Johnson D, Camm AJ, et al. Risks associated with discontinuation of oral anticoagulation in newly diagnosed patients with atrial fibrillation: Results from the GARFIELD-AF Registry. *Journal of thrombosis and haemostasis : JTH.* 2021.

22. Khambhati J, Allard-Ratick M, Dhindsa D, et al. The art of cardiovascular risk assessment. *Clin Cardiol.* 2018;41(5):677-684.

23. O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet (London, England).* 2016;388(10046):761-775.

24. Feigin VL, Norrving B, George MG, Foltz JL, Roth GA, Mensah GA. Prevention of stroke: a strategic global imperative. *Nature Reviews Neurology.* 2016;12:501.

25. Fang N, Jiang M, Fan Y. Ideal cardiovascular health metrics and risk of cardiovascular disease or mortality: A meta-analysis. *Int J Cardiol.* 2016;214:279-283.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

26. Guo L, Zhang S. Association between ideal cardiovascular health metrics and risk of cardiovascular events or mortality: A meta-analysis of prospective studies. *Clin Cardiol.* 2017;40(12):1339-1346.

27. Colpani V, Baena CP, Jaspers L, et al. Lifestyle factors, cardiovascular disease and all-cause mortality in middle-aged and elderly women: a systematic review and meta-analysis. *Eur J Epidemiol.* 2018;33(9):831-845.

28. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet (London, England).* 2016;387(10026):1377-1396.

29. Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1.9 million participants. *The Lancet Global health.* 2018;6(10):e1077-e1086.

30. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet (London, England).* 2017;389(10064):37-55.

31. Danaei G, Finucane MM, Lu Y, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet (London, England).* 2011;378(9785):31-40.

32. Kotseva K, De Bacquer D, De Backer G, et al. Lifestyle and risk factor management in people at high risk of cardiovascular disease. A report from the European Society of Cardiology European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) IV cross-sectional survey in 14 European regions. *European journal of preventive cardiology.* 2016;23(18):2007-2018.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

33. World Economic Forum. Life Expectancy. . *Available at: http://reportsweforumorg/global-competitiveness-index-2017-2018/competitiveness-rankings/#series=LIFEEXPECT*. (Last accessed Decmber 2018).

For peer review only

Figure Legends:

Figure 1. Observed (a) and risk-standardized1 (b) mortality rates by country.

[1]Computed as the ratio of observed and predicted rate for each country, multiplied by the global observed rate. The predicted rate estimated from a Cox model with the following covariates: age, sex, type of AF, systolic and diastolic blood pressure, pulse, BMI, hypertension, diabetes, heart failure, history of stroke/TIA/SE, history of bleeding, vascular disease, acute coronary syndromes, moderate to severe CKD, hypercholesterolemia, cirrhosis, carotid occlusive disease, VTE, dementia, smoking status, heavy alcohol consumption. Confidence intervals for risk-standardized rates are calculated through bootstrap sampling with 1000 replications. Showing only countries with more than 700 patients enrolled. Horizontal dashed line represents overall observed global rate.

Figure 2. Observed (a) and risk-standardized[1] (b) non-haemorrhagic stroke/SE rates by country.

[1]Computed as the ratio of observed and predicted rate for each country, multiplied by the global observed rate. The predicted rate estimated from a Fine-Gray model with the following covariates: age, sex, type of AF, systolic and diastolic blood pressure, pulse, BMI, hypertension, diabetes, heart failure, history of stroke/TIA/SE, history of bleeding, vascular disease, acute coronary syndromes, moderate to severe CKD, hypercholesterolemia, cirrhosis, carotid occlusive disease, VTE, dementia, smoking status, heavy alcohol consumption. Confidence intervals for risk-standardized rates are calculated through bootstrap sampling with 1000 replications. Showing only countries with more than 700 patients enrolled. Horizontal dashed line represents overall observed global rate.

Figure 3. Observed (a) and risk-standardized[1] (b) major bleeding rates by country.

[1]Computed as the ratio of observed and predicted rate for each country, multiplied by the global observed rate. The predicted rate estimated from a Fine-Gray model with the following covariates: age, sex, type of AF, systolic and diastolic blood pressure, pulse, BMI, hypertension, diabetes, heart failure, history of stroke/TIA/SE, history of bleeding, vascular disease, acute coronary syndromes, moderate to severe CKD, hypercholesterolemia, cirrhosis, carotid occlusive disease, VTE, dementia, smoking status, heavy alcohol consumption. Confidence intervals for risk-standardized rates are calculated through bootstrap sampling with 1000 replications. Showing only countries with more than 700 patients enrolled. Horizontal dashed line represents overall observed global rate.

Figure 4. Baseline antithrombotic treatment distribution by Healthcare Access and Quality (HAQ) index[1]

[1]As HAQ index is a country measure, all patients enrolled within a specific country are assigned the same HAQ index

HAQ index of OAC+AP or AP only: <70=46.7%; 70-79=52.5%; 80-89=30.1%; ≥90=28.6%

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1. Baseline characteristics distribution by region of enrolment

Variable	Region					P-value[1]
	Europe (N = 29876)	Asia (N = 13821)	Latin America (N = 4247)	North America (N = 1619)	Other countries (N = 2455)	
Sex, n (%)						
Male	16313 (54.6)	8199 (59.3)	2231 (52.5)	885 (54.7)	1403 (57.2)	<0.001
Female	13563 (45.4)	5622 (40.7)	2016 (47.5)	734 (45.3)	1051 (42.8)	
Age, median (Q1; Q3), years	72.0 (64.0;79.0)	69.0 (60.0;76.0)	71.0 (63.0;79.0)	72.0 (64.0;80.0)	67.0 (59.0;75.0)	<0.001
Age, n (%), years						
<65	8016 (26.8)	4980 (36.0)	1258 (29.6)	441 (27.2)	996 (40.6)	<0.001
65-69	4578 (15.3)	2165 (15.7)	628 (14.8)	237 (14.6)	407 (16.6)	
70-74	5183 (17.3)	2399 (17.4)	708 (16.7)	257 (15.9)	384 (15.6)	
≥75	12099 (40.5)	4277 (30.9)	1653 (38.9)	684 (42.2)	668 (27.2)	
Race/Ethnicity,n (%)						
Caucasian	27934 (96.9)	13 (0.1)	957 (23.1)	1421 (90.5)	1672 (70.3)	<0.001
Hispanic/Latino	344 (1.2)	0 (0.0)	3000 (72.5)	35 (2.2)	14 (0.6)	
Asian	160 (0.6)	13789 (99.8)	11 (0.3)	11 (0.7)	305 (12.8)	
Black/Mixed/Other	394 (1.4)	16 (0.1)	172 (4.2)	103 (6.6)	386 (16.2)	
BMI, median (Q1; Q3), kg/m²	28.0 (25.1;31.8)	24.2 (22.0;26.6)	27.9 (24.8;31.6)	29.4 (25.4;34.0)	29.8 (26.0;34.3)	<0.001
Systolic blood pressure, median (Q1; Q3), mmHg	135.0 (120.0;147.0)	130.0 (118.0;140.0)	130.0 (120.0;141.0)	130.0 (118.0;143.0)	132.5 (120.0;148.0)	<0.001
Diastolic blood pressure, median (Q1; Q3), mmHg	80.0 (71.0;90.0)	78.0 (70.0;86.0)	80.0 (70.0;86.0)	78.0 (68.0;86.0)	80.0 (70.0;90.0)	<0.001
Pulse, median (Q1; Q3), bpm	85.0 (70.0;108.0)	82.0 (70.0;98.0)	80.0 (70.0;102.0)	89.0 (72.0;117.0)	98.0 (80.0;122.0)	<0.001
Type of atrial fibrillation,n (%)						
Permanent	4587 (15.4)	1108 (8.0)	666 (15.7)	35 (2.2)	234 (9.5)	<0.001
Persistent	4313 (14.4)	2505 (18.1)	625 (14.7)	100 (6.2)	210 (8.6)	
Paroxysmal	7375 (24.7)	5165 (37.4)	1086 (25.6)	345 (21.3)	333 (13.6)	
New onset (unclassified)	13598 (45.5)	5042 (36.5)	1870 (44.0)	1137 (70.3)	1678 (68.4)	
Care setting specialty at diagnosis,n (%)						
Internal medicine/Neurology/Geriatrics	7077 (23.7)	1807 (13.1)	654 (15.4)	345 (21.3)	560 (22.8)	<0.001
Cardiology	16824 (56.3)	11571 (83.7)	3184 (75.0)	968 (59.9)	1626 (66.2)	
Primary care/general practice	5972 (20.0)	442 (3.2)	409 (9.6)	304 (18.8)	269 (11.0)	
Care setting location at diagnosis, n (%)						
Hospital	16647 (55.7)	10112 (73.2)	1792 (42.2)	615 (38.1)	1169 (47.6)	<0.001

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Office/Anticoagulation clinic/Thrombosis centre	9804 (32.8)	3366 (24.4)	1404 (33.1)	387 (23.9)	957 (39.0)	
Emergency room	3422 (11.5)	342 (2.5)	1051 (24.7)	614 (38.0)	329 (13.4)	
Medical history, n (%)						
Heart failure	6841 (22.9)	3072 (22.2)	951 (22.4)	312 (19.3)	563 (22.9)	0.012
Acute coronary syndromes	3262 (11.0)	1160 (8.4)	433 (10.2)	209 (13.0)	469 (19.2)	<0.001
Vascular disease	8220 (27.7)	2629 (19.2)	791 (18.8)	438 (27.4)	737 (30.2)	<0.001
Carotid occlusive disease	1071 (3.6)	251 (1.8)	109 (2.6)	56 (3.5)	51 (2.1)	<0.001
VTE	995 (3.3)	81 (0.6)	102 (2.4)	73 (4.6)	104 (4.3)	<0.001
Prior stroke/TIA/SE	3445 (11.6)	1400 (10.2)	492 (11.7)	165 (10.4)	337 (13.9)	<0.001
History of bleeding	764 (2.6)	222 (1.6)	173 (4.1)	76 (4.7)	80 (3.3)	<0.001
Hypertension	23740 (79.7)	9353 (67.9)	3420 (80.8)	1229 (76.4)	1862 (76.2)	<0.001
Hypercholesterolaemia	13368 (46.3)	3743 (27.7)	1550 (38.6)	940 (59.3)	1354 (56.8)	<0.001
Diabetes	6359 (21.3)	2976 (21.5)	1041 (24.5)	422 (26.1)	744 (30.3)	<0.001
Cirrhosis	148 (0.5)	96 (0.7)	15 (0.4)	14 (0.9)	20 (0.8)	0.003
Moderate to severe CKD	3606 (12.4)	1052 (7.8)	282 (7.2)	142 (9.5)	272 (11.3)	<0.001
Dementia	381 (1.3)	246 (1.8)	47 (1.1)	34 (2.1)	56 (2.3)	<0.001
Heavy alcohol use, n (%)	486 (1.9)	365 (3.2)	72 (1.8)	36 (2.7)	69 (3.1)	<0.001
Current smoker, n (%)	2786 (10.2)	1595 (13.0)	348 (8.5)	180 (12.1)	293 (12.5)	<0.001
Treatment, n (%)						
NOAC ± AP	8240 (28.1)	3532 (25.7)	900 (21.5)	715 (44.7)	725 (29.9)	<0.001
VKA ± AP	13042 (44.4)	4119 (30.0)	1666 (39.9)	361 (22.6)	995 (41.0)	
AP only	5148 (17.5)	3807 (27.7)	1004 (24.0)	302 (18.9)	500 (20.6)	
None	2922 (10.0)	2282 (16.6)	610 (14.6)	220 (13.8)	206 (8.5)	
AP treatment, n (%)	9074 (30.9)	5522 (40.2)	1666 (39.9)	706 (44.2)	1135 (46.8)	<0.001
CHA_2DS_2-VASc score, median (Q1; Q3)	3.0 (2.0;4.0)	3.0 (2.0;4.0)	3.0 (2.0;4.0)	3.0 (2.0;4.0)	3.0 (2.0;4.0)	<0.001
HAS-BLED score, median (Q1; Q3)[2]	1.0 (1.0;2.0)	1.0 (1.0;2.0)	1.0 (1.0;2.0)	2.0 (1.0;2.0)	1.0 (1.0;2.0)	<0.001
GARFIELD death score, median (Q1; Q3)[3]	5.3 (3.1;9.4)	3.1 (1.8;6.0)	6.0 (3.5;10.9)	5.8 (3.1;10.9)	4.3 (2.5;8.5)	<0.001
GARFIELD stroke score, median (Q1; Q3)[4]	1.6 (1.1;2.4)	1.5 (1.0;2.3)	1.6 (1.1;2.4)	1.6 (1.1;2.4)	1.4 (0.9;2.3)	<0.001
GARFIELD bleeding score, median (Q1; Q3)[5]	1.7 (1.1;2.6)	1.3 (0.9;2.0)	1.6 (1.0;2.4)	1.6 (1.0;2.6)	1.6 (1.0;2.4)	<0.001

[1]P-values for categorical variables obtained from Chi-square or Fisher's exact test, as appropriate. P-value for continuous variables obtained from one-way ANOVA or Kruskal-Wallis test, as appropriate;
[2]The risk factor 'Labile INRs' is not included in the HAS-BLED score as it is not collected at baseline. As a result, the maximum HAS-BLED score at baseline is 8 points (not 9);
[3]Represent the risk of mortality within 2 years;
[4]Represent the risk of non-haemorrhagic stroke/SE within 2 years;
[5]Represent the risk of major bleeding within 2 years.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 2. Observed 1-year rates and corresponding 95% confidence intervals for all-cause mortality, non-haemorrhagic stroke/SE and major bleeding by region and in all 35 countries in GARFIELD-AF

	Outcome		
Region	**Mortality**	**Non-haemorrhagic Stroke/SE**	**Major bleeding**
Europe	4.4 (4.2-4.6)	1.2 (1.1-1.3)	1.3 (1.2-1.4)
Asia	2.8 (2.6-3.1)	1.0 (0.9-1.2)	0.9 (0.7-1.0)
Latin America	5.5 (4.8-6.2)	1.4 (1.1-1.8)	1.3 (1.0-1.7)
North America	5.9 (4.8-7.2)	1.0 (0.6-1.6)	2.9 (2.2-3.8)
Other countries	6.0 (5.1-7.0)	1.8 (1.3-2.4)	1.3 (0.9-1.9)
All countries	4.2 (4.0-4.4)	1.2 (1.1-1.3)	1.2 (1.1-1.3)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

SE: Systemic embolism

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

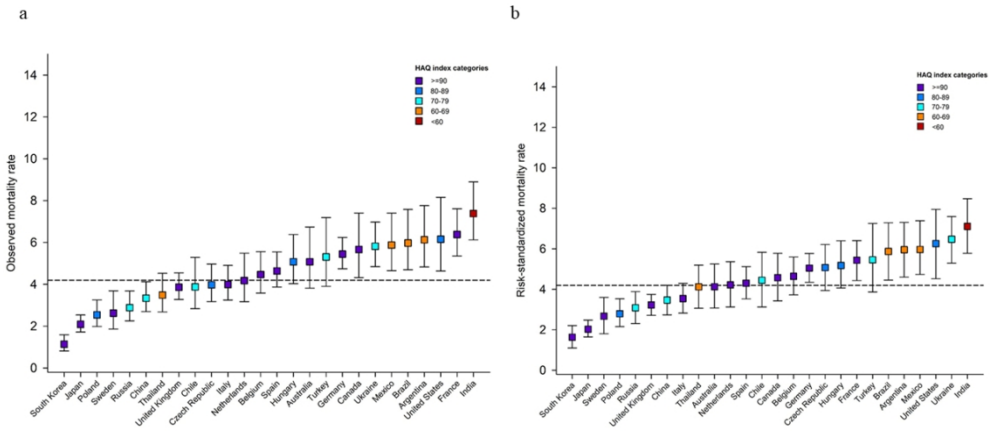


Figure 1. Observed (a) and risk-standardized[1] (b) mortality rates by country.

[1]Computed as the ratio of observed and predicted rate for each country, multiplied by the global observed rate. The predicted rate estimated from a Cox model with the following covariates: age, sex, type of AF, systolic and diastolic blood pressure, pulse, BMI, hypertension, diabetes, heart failure, history of stroke/TIA/SE, history of bleeding, vascular disease, acute coronary syndromes, moderate to severe CKD, hypercholesterolemia, cirrhosis, carotid occlusive disease, VTE, dementia, smoking status, heavy alcohol consumption. Confidence intervals for risk-standardized rates are calculated through bootstrap sampling with 1000 replications. Showing only countries with more than 700 patients enrolled. Horizontal dashed line represents overall observed global rate.

108x60mm (300 x 300 DPI)

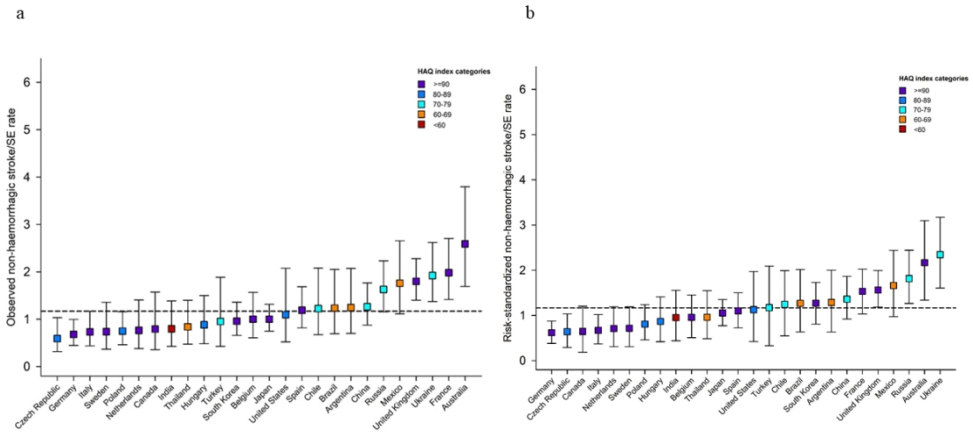


Figure 2. Observed (a) and risk-standardized[1] (b) non-haemorrhagic stroke/SE rates by country.
[1]Computed as the ratio of observed and predicted rate for each country, multiplied by the global observed rate. The predicted rate estimated from a Fine-Gray model with the following covariates: age, sex, type of AF, systolic and diastolic blood pressure, pulse, BMI, hypertension, diabetes, heart failure, history of stroke/TIA/SE, history of bleeding, vascular disease, acute coronary syndromes, moderate to severe CKD, hypercholesterolemia, cirrhosis, carotid occlusive disease, VTE, dementia, smoking status, heavy alcohol consumption. Confidence intervals for risk-standardized rates are calculated through bootstrap sampling with 1000 replications. Showing only countries with more than 700 patients enrolled. Horizontal dashed line represents overall observed global rate.

108x60mm (300 x 300 DPI)

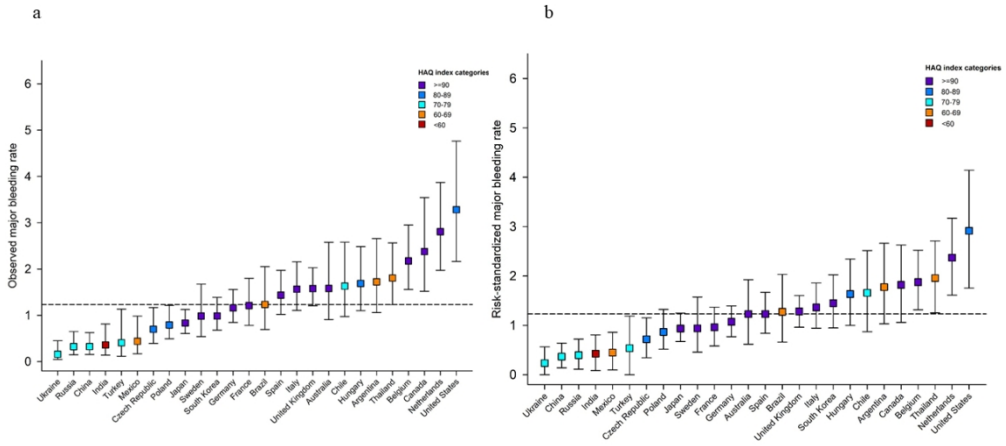
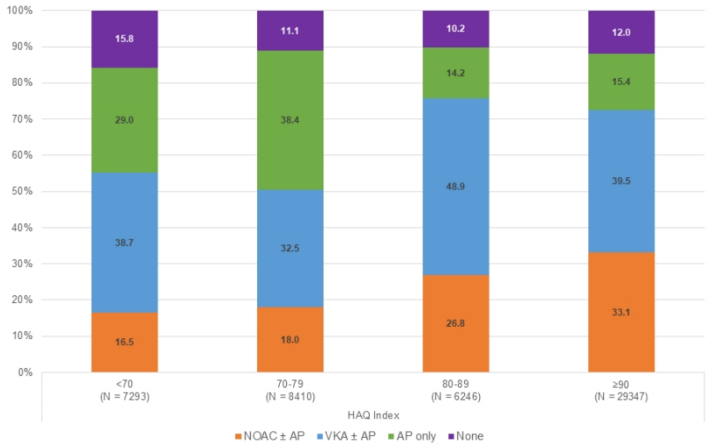


Figure 3. Observed (a) and risk-standardized[1] (b) major bleeding rates by country.
[1]Computed as the ratio of observed and predicted rate for each country, multiplied by the global observed rate. The predicted rate estimated from a Fine-Gray model with the following covariates: age, sex, type of AF, systolic and diastolic blood pressure, pulse, BMI, hypertension, diabetes, heart failure, history of stroke/TIA/SE, history of bleeding, vascular disease, acute coronary syndromes, moderate to severe CKD, hypercholesterolemia, cirrhosis, carotid occlusive disease, VTE, dementia, smoking status, heavy alcohol consumption. Confidence intervals for risk-standardized rates are calculated through bootstrap sampling with 1000 replications. Showing only countries with more than 700 patients enrolled. Horizontal dashed line represents overall observed global rate.

108x60mm (300 x 300 DPI)



Baseline antithrombotic treatment distribution by Healthcare Access and Quality (HAQ) index1
1As HAQ index is a country measure, all patients enrolled within a specific country are assigned the same HAQ index
HAQ index of OAC+AP or AP only: <70=46.7%; 70-79=52.5%; 80-89=30.1%; ≥90=28.6%

108x60mm (300 x 300 DPI)

Supplementary Tables and Figures

Table S1. Observed and risk-standardized[1] all-cause mortality rates by country in GARFIELD-AF

Country	Observed mortality rate (95% CI)			Risk standardized mortality rate (95% CI)
	All-cause mortality	Cardiovascular mortality*	Non-cardiovascular mortality*	
Global (all GARFIELD-AF)	4.2 (4.0-4.4)			-
Argentina	6.1 (4.8-7.8)	2.7 (1.9-3.9)	2.6 (1.8-3.8)	6.0 (4.6-7.3)
Australia	5.1 (3.8-6.7)	1.8 (1.1-3.0)	2.2 (1.4-3.4)	4.1 (3.1-5.3)
Austria	5.1 (3.4-7.5)	1.8 (0.9-3.5)	1.8 (0.9-3.5)	4.4 (2.8-6.2)
Belgium	4.5 (3.6-5.6)	1.3 (0.9-2.0)	2.5 (1.8-3.4)	4.6 (3.7-5.6)
Brazil	6.0 (4.7-7.6)	2.5 (1.7-3.7)	2.5 (1.7-3.7)	5.9 (4.5-7.3)
Canada	5.7 (4.3-7.4)	1.7 (1.1-2.9)	2.2 (1.4-3.4)	4.6 (3.4-5.8)
Chile	3.9 (2.8-5.3)	2.3 (1.5-3.4)	1.3 (0.8-2.3)	4.4 (3.1-5.8)
China	3.3 (2.7-4.1)	1.4 (1.0-1.9)	0.7 (0.4 - 1.1)	3.5 (2.7-4.2)
Czech Republic	4.0 (3.2-5.0)	1.3 (0.9-1.9)	1.6 (1.1-2.3)	5.1 (3.9-6.2)
Denmark	7.8 (5.8-10.4)	2.1 (1.2-3.8)	3.9 (2.5-5.9)	6.5 (4.8-8.4)
Egypt	1.1 (0.5-2.5)	0.2 (0.0-1.3)	0.2 (0.0-1.3)	1.7 (0.5-3.1)
Finland	3.3 (1.9-5.8)	1.1 (0.4-3.0)	0.8 (0.3 - 2.6)	3.6 (1.8-5.4)
France	6.4 (5.4-7.6)	2.0 (1.4-2.7)	2.8 (2.1-3.7)	5.4 (4.4-6.4)
Germany	5.4 (4.7-6.2)	2.3 (1.8-2.8)	2.2 (1.7-2.7)	5.0 (4.3-5.8)
Hungary	5.1 (4-6.4.0)	2.5 (1.7 - 3.4)	2.2 (1.5-3.1)	5.2 (4.1-6.4)
India	7.4 (6.1-8.9)	3.5 (2.6-4.6)	1.4 (0.9-2.2)	7.1 (5.8-8.5)
Italy	4.0 (3.2-4.9)	1.4 (1.0-2.0)	1.7 (1.2 - 2.3)	3.5 (2.8-4.3)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Japan	2.1 (1.7-2.5)	0.6 (0.4 - 0.9)	0.9 (0.6 - 1.2)	2.0 (1.6-2.5)
Mexico	5.9 (4.7-7.4)	3.2 (2.3-4.4)	1.4 (0.9-2.3)	6.0 (4.7-7.4)
Netherlands	4.2 (3.2-5.5)	1.6 (1.0 - 2.5)	1.8 (1.2-2.8)	4.2 (3.1-5.4)
Norway	1.1 (0.4-3.4)	0.0 (0.0 - 0.0)	0.7 (0.2-2.9)	1.5 (0.0-3.4)
Poland	2.5 (2.0-3.3)	1.2 (0.8-1.7)	0.6 (0.3-1.0)	2.8 (2.2-3.5)
Russia	2.9 (2.3-3.7)	1.6 (1.1 - 2.2)	0.8 (0.5 - 1.2)	3.1 (2.3-3.9)
Singapore	3.9 (2.3-6.8)	0.0 (0.0 - 0.0)	2.6 (1.3-5.2)	3.8 (1.9-6.0)
South Africa	11.0 (8.8-13.7)	5.1 (3.7-7.2)	2.9 (1.9-4.6)	10.5 (8.2-13)
South Korea	1.1 (0.8-1.6)	0.3 (0.2 - 0.6)	0.6 (0.4-1.0)	1.6 (1.1-2.2)
Spain	4.6 (3.9-5.6)	1.6 (1.2 - 2.2)	2.2 (1.7-2.9)	4.3 (3.5-5.1)
Sweden	2.6 (1.9-3.7)	1.2 (0.7-1.9)	1.0 (0.6-1.7)	2.7 (1.8-3.6)
Switzerland	5.6 (2.4-13.0)	1.2 (0.2 - 8.1)	3.4 (1.1 - 10.1)	4.8 (1.4-9.1)
Thailand	3.5 (2.7-4.5)	0.3 (0.1-0.8)	2.5 (1.9-3.4)	4.1 (3.1-5.2)
Turkey	5.3 (3.9-7.2)	3.4 (2.3 - 5.0)	1.7 (1.0-2.9)	5.5 (3.9-7.3)
Ukraine	5.8 (4.8-7.0)	3.0 (2.3-3.9)	0.2 (0.1 - 0.6)	6.5 (5.3-7.6)
United Arab Emirates	6.5 (4.5-9.5)	2.3 (1.2-4.4)	3.6 (2.1-6.0)	5.4 (3.6-7.5)
United Kingdom	3.9 (3.3-4.5)	1.1 (0.8 - 1.5)	2.0 (1.6-2.5)	3.2 (2.7-3.7)
United States	6.2 (4.6-8.2)	0.8 (0.4-1.9)	2.9 (1.9-4.4)	6.3 (4.5-7.9)

[1]Computed as the ratio of observed and predicted rate for each country, multiplied by the global observed rate. The predicted rate estimated from a Cox model with the following covariates: age, sex, type of AF, systolic and diastolic blood pressure, pulse, BMI, hypertension, diabetes, heart failure, history of stroke/TIA/SE, history of bleeding, vascular disease, acute coronary syndromes, moderate to severe CKD, hypercholesterolemia, cirrhosis, carotid occlusive disease, VTE, dementia, smoking status, heavy alcohol consumption. Confidence intervals for risk-standardized rates are calculated through bootstrap sampling with 1000 replications.

*Note the rate of cardiovascular and non-cardiovascular mortality do not add up to the total because the cause of death is not known is some cases.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table S2. Observed and risk-standardized non-haemorrhagic stroke/systemic embolism (SE) rates by country in GARFIELD-AF

Country	CHA_2DS_2-VASC		Observed stroke/SE rate (95% CI)	Risk standardized stroke/SE rate (95% CI)
	Median (Q1; Q3)	Mean (SD)		
Global (all GARFIELD-AF)			**1.2 (1.1-1.3)**	-
Argentina	3.0 (2.0; 4.0)	3.1 (1.5)	1.2 (0.7-2.1)	1.3 (0.6-2.0)
Australia	3.0 (2.0; 4.0)	3.3 (1.6)	2.6 (1.7-3.8)	2.2 (1.3-3.1)
Austria	3.0 (2.0; 4.0)	3.5 (1.5)	1.8 (0.8-3.3)	1.6 (0.6-2.7)
Belgium	3.0 (2.0; 4.0)	3.1 (1.6)	1.0 (0.6-1.6)	1.0 (0.5-1.5)
Brazil	3.0 (2.0; 4.0)	3.2 (1.7)	1.2 (0.7-2.1)	1.3 (0.6-2.0)
Canada	3.0 (2.0; 5.0)	3.5 (1.6)	0.8 (0.4-1.6)	0.6 (0.2-1.2)
Chile	3.0 (2.0; 4.0)	3.4 (1.6)	1.2 (0.7-2.1)	1.2 (0.5-2.0)
China	3.0 (2.0; 4.0)	3.2 (1.7)	1.3 (0.9-1.8)	1.4 (0.9-1.9)
Czech Republic	3.0 (2.0; 4.0)	3.3 (1.6)	0.6 (0.3-1.0)	0.6 (0.3-1.0)
Denmark	3.0 (2.0; 4.0)	3.2 (1.5)	1.9 (1.0-3.3)	1.6 (0.7-2.7)
Egypt	3.0 (2.0; 4.0)	3.2 (1.7)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Finland	3.0 (2.0; 5.0)	3.5 (1.6)	0.6 (0.1-1.9)	0.5 (0.0-1.3)
France	4.0 (3.0; 5.0)	3.6 (1.6)	2.0 (1.4-2.7)	1.5 (1.0-2.0)
Germany	4.0 (2.0; 5.0)	3.6 (1.7)	0.7 (0.4-1.0)	0.6 (0.4-0.9)
Hungary	3.0 (2.0; 5.0)	3.4 (1.6)	0.9 (0.5-1.5)	0.9 (0.4-1.4)
India	3.0 (2.0; 4.0)	3.0 (1.5)	0.8 (0.4-1.4)	1.0 (0.4-1.6)
Italy	4.0 (3.0; 4.0)	3.6 (1.5)	0.7 (0.4-1.2)	0.7 (0.4-1.0)
Japan	3.0 (2.0; 4.0)	3.0 (1.6)	1.0 (0.7-1.3)	1.1 (0.8-1.4)
Mexico	4.0 (2.0; 4.0)	3.5 (1.6)	1.8 (1.1-2.7)	1.7 (1.0-2.4)
Netherlands	3.0 (2.0; 4.0)	3.1 (1.5)	0.8 (0.4-1.4)	0.7 (0.3-1.2)
Norway	3.0 (2.0; 4.0)	2.8 (1.4)	1.5 (0.5-3.5)	1.7 (0.4-3.5)
Poland	3.0 (2.0; 4.0)	3.2 (1.7)	0.7 (0.5-1.2)	0.8 (0.5-1.2)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Russia	3.0 (2.0; 5.0)	3.5 (1.7)	1.6 (1.2-2.2)	1.8 (1.3-2.4)
Singapore	3.0 (2.0; 4.0)	3.1 (1.8)	2.3 (1-4.5.0)	2.2 (0.6-4.0)
South Africa	3.0 (2.0; 4.0)	3.2 (1.7)	2.5 (1.5-3.9)	2.3 (1.3-3.5)
South Korea	2.0 (1.0; 3.0)	2.5 (1.5)	1.0 (0.7-1.4)	1.3 (0.8-1.7)
Spain	3.0 (2.0; 4.0)	3.1 (1.4)	1.2 (0.8-1.7)	1.1 (0.7-1.5)
Sweden	3.0 (2.0; 4.0)	3.1 (1.4)	0.7 (0.4-1.4)	0.7 (0.3-1.2)
Switzerland	4.0 (2.0; 4.0)	3.4 (1.6)	1.1 (0.1-5.5)	0.9 (0.0-3.1)
Thailand	3.0 (2.0; 4.0)	2.9 (1.5)	0.8 (0.5-1.4)	1.0 (0.5-1.5)
Turkey	3.0 (2.0; 4.0)	3.0 (1.8)	1.0 (0.4-1.9)	1.2 (0.3-2.1)
Ukraine	3.0 (2.0; 5.0)	3.6 (1.6)	1.9 (1.4-2.6)	2.3 (1.6-3.2)
United Arab Emirates	3.0 (2.0; 4.0)	3.0 (1.8)	0.8 (0.2-2.1)	0.8 (0.0-1.8)
United Kingdom	3.0 (2.0; 4.0)	3.3 (1.5)	1.8 (1.4-2.3)	1.6 (1.2-2.0)
United States	3.0 (2.0; 4.0)	3.1 (1.6)	1.1 (0.5-2.1)	1.1 (0.4-2.0)

[1]Computed as the ratio of observed and predicted rate for each country, multiplied by the global observed rate. The predicted rate estimated from a Fine-Gray model with the following covariates: age, sex, type of AF, systolic and diastolic blood pressure, pulse, BMI, hypertension, diabetes, heart failure, history of stroke/TIA/SE, history of bleeding, vascular disease, acute coronary syndromes, moderate to severe CKD, hypercholesterolemia, cirrhosis, carotid occlusive disease, VTE, dementia, smoking status, heavy alcohol consumption. Confidence intervals for risk-standardized rates are calculated through bootstrap sampling with 1000 replications.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table S3. Observed and risk-standardized[1] major bleeding rates by country in GARFIELD-AF

Country	Observed major bleeding rate (95% CI)	Risk standardized major bleeding rate (95% CI)
Global (all GARFIELD-AF)	**1.2 (1.1-1.3)**	**-**
Argentina	1.7 (1.1-2.7)	1.8 (1.0-2.7)
Australia	1.6 (0.9-2.6)	1.2 (0.6-1.9)
Austria	2.4 (1.3-4.1)	1.9 (0.8-3.0)
Belgium	2.2 (1.6-3.0)	1.9 (1.3-2.5)
Brazil	1.2 (0.7-2.1)	1.3 (0.7-2.0)
Canada	2.4 (1.5-3.5)	1.8 (1.1-2.6)
Chile	1.6 (1.0-2.6)	1.7 (0.9-2.5)
China	0.3 (0.2-0.6)	0.4 (0.1-0.6)
Czech Republic	0.7 (0.4-1.2)	0.7 (0.3-1.2)
Denmark	2.5 (1.4-4.1)	2.0 (1.0-3.1)
Egypt	0.8 (0.3-1.8)	1.0 (0.2-2.0)
Finland	2.5 (1.2-4.5)	2.4 (1.1-4.1)
France	1.2 (0.8-1.8)	1.0 (0.6-1.4)
Germany	1.2 (0.8-1.6)	1.1 (0.8-1.4)
Hungary	1.7 (1.1-2.5)	1.6 (1.0-2.3)
India	0.4 (0.1-0.8)	0.4 (0.1-0.8)
Italy	1.6 (1.1-2.2)	1.4 (0.9-1.9)
Japan	0.8 (0.6-1.1)	0.9 (0.7-1.2)
Mexico	0.4 (0.2-1.0)	0.4 (0.1-0.9)
Netherlands	2.8 (2.0-3.9)	2.4 (1.6-3.2)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Norway	2.6 (1.2-5.0)	2.9 (0.9-5.3)
Poland	0.8 (0.5-1.2)	0.9 (0.5-1.3)
Russia	0.3 (0.1-0.7)	0.4 (0.1-0.7)
Singapore	2.0 (0.8-4.0)	1.9 (0.6-3.6)
South Africa	1.4 (0.7-2.6)	1.4 (0.6-2.5)
South Korea	1.0 (0.7-1.4)	1.4 (0.9-2.0)
Spain	1.4 (1.0-2.0)	1.2 (0.8-1.7)
Sweden	1.0 (0.5-1.7)	0.9 (0.5-1.6)
Switzerland	1.1 (0.1-5.5)	0.9 (0.0-3.0)
Thailand	1.8 (1.2-2.6)	2.0 (1.3-2.7)
Turkey	0.4 (0.1-1.1)	0.5 (0.0-1.2)
Ukraine	0.2 (0.0-0.5)	0.2 (0.0-0.6)
United Arab Emirates	1.0 (0.3-2.4)	1.0 (0.2-2.1)
United Kingdom	1.6 (1.2-2.0)	1.3 (1.0-1.6)
United States	3.3 (2.2-4.8)	2.9 (1.8-4.1)

[1]Computed as the ratio of observed and predicted rate for each country, multiplied by the global observed rate. The predicted rate estimated from a Fine-Gray model with the following covariates: age, sex, type of AF, systolic and diastolic blood pressure, pulse, BMI, hypertension, diabetes, heart failure, history of stroke/TIA/SE, history of bleeding, vascular disease, acute coronary syndromes, moderate to severe CKD, hypercholesterolemia, cirrhosis, carotid occlusive disease, VTE, dementia, smoking status, heavy alcohol consumption. Confidence intervals for risk-standardized rates are calculated through bootstrap sampling with 1000 replications.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table S4. Risk-standardized[1] event rates within one year by country

Country	Risk-standardized mortality rate (95% CI)	Risk-standardized non-haemorrhagic stroke/SE rate (95% CI)	Risk-standardized major bleeding rate (95% CI)
Argentina	5.7 (4.4-7.0)	1.2 (0.6-1.9)	1.9 (1.1-2.8)
Australia	4.0 (3.0-5.1)	2.1 (1.3-3.0)	1.2 (0.6-2.0)
Austria	4.4 (2.9-6.3)	1.6 (0.6-2.8)	1.9 (0.8-3.1)
Belgium	4.9 (3.9-5.9)	1.0 (0.6-1.6)	1.8 (1.3-2.4)
Brazil	5.7 (4.3-7.1)	1.2 (0.6-1.9)	1.3 (0.7-2.1)
Canada	4.6 (3.4-5.8)	0.6 (0.2-1.2)	1.8 (1.0-2.6)
Chile	4.6 (3.3-6.1)	1.3 (0.6-2.2)	1.6 (0.8-2.4)
China	3.1 (2.5-3.8)	1.1 (0.8-1.5)	0.4 (0.2-0.7)
Czech Republic	5.1 (4.0-6.3)	0.7 (0.3-1.1)	0.7 (0.3-1.2)
Denmark	6.7 (4.9-8.6)	1.6 (0.8-2.8)	2.0 (1.0-3.0)
Egypt	1.8 (0.6-3.3)	0.0 (0.0-0.0)	0.9 (0.2-1.8)
Finland	3.7 (1.9-5.6)	0.5 (0.0-1.3)	2.4 (1.0-4.0)
France	5.6 (4.6-6.6)	1.6 (1.1-2.1)	0.9 (0.6-1.3)
Germany	5.0 (4.3-5.8)	0.6 (0.4-0.9)	1.1 (0.8-1.4)
Hungary	5.4 (4.3-6.7)	0.9 (0.4-1.5)	1.5 (0.9-2.2)
India	6.5 (5.3-7.8)	0.8 (0.4-1.3)	0.5 (0.1-0.9)
Italy	3.8 (3.0-4.6)	0.8 (0.4-1.1)	1.3 (0.9-1.8)
Japan	2.1 (1.7-2.6)	1.1 (0.8-1.5)	0.9 (0.7-1.2)
Mexico	5.7 (4.5-7.1)	1.5 (0.9-2.2)	0.5 (0.1-0.9)
Netherlands	4.6 (3.4-5.8)	0.8 (0.4-1.4)	2.2 (1.5-2.9)
Norway	1.7 (0.0-3.7)	1.9 (0.4-4.1)	2.7 (0.8-4.9)
Poland	2.8 (2.2-3.6)	0.8 (0.5-1.3)	0.9 (0.5-1.3)
Russia	3.0 (2.2-3.8)	1.7 (1.2-2.3)	0.4 (0.1-0.8)
Singapore	3.7 (1.8-5.8)	2.0 (0.6-3.6)	1.9 (0.6-3.7)
South Africa	10.5 (8.3-13)	2.3 (1.3-3.6)	1.4 (0.6-2.4)
South Korea	1.6 (1.1-2.1)	1.2 (0.8-1.6)	1.5 (1.0-2.1)
Spain	4.4 (3.6-5.2)	1.1 (0.7-1.6)	1.2 (0.8-1.7)
Sweden	2.8 (1.9-3.7)	0.8 (0.3-1.3)	0.9 (0.5-1.5)
Switzerland	5.3 (1.5-10.0)	1.1 (0.0-3.8)	0.8 (0.0-2.8)
Thailand	3.9 (2.9-5.0)	0.9 (0.5-1.5)	2.1 (1.3-2.9)
Turkey	5.5 (3.9-7.4)	1.2 (0.3-2.1)	0.5 (0.0-1.2)
Ukraine	6.2 (5.0-7.3)	2.1 (1.4-2.8)	0.3 (0.0-0.6)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

United Arab Emirates	5.2 (3.5-7.1)	0.7 (0.0-1.7)	1.0 (0.2-2.1)
United Kingdom	3.2 (2.7-3.7)	1.5 (1.1-1.9)	1.3 (1.0-1.6)
United States	6.3 (4.5-8.0)	1.1 (0.4-2.0)	2.8 (1.7-4.0)

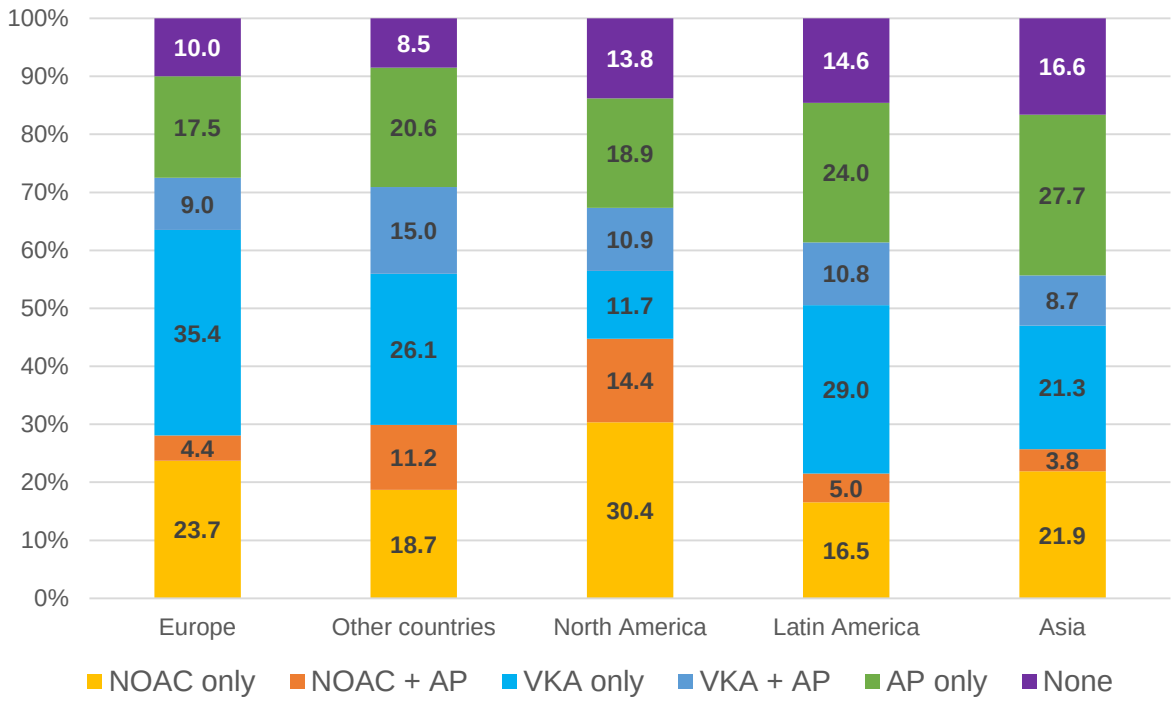
[1]Computed as the ratio of observed and predicted rate for each country, multiplied by the global observed rate. The predicted rate estimated from a Cox model for all-cause mortality or Fine-Gray model for non-haemorrhagic stroke/SE and major bleeding with the following covariates: age, sex, type of AF, systolic and diastolic blood pressure, pulse, BMI, hypertension, diabetes, heart failure, history of stroke/TIA/SE, history of bleeding, vascular disease, acute coronary syndromes, moderate to severe CKD, hypercholesterolemia, cirrhosis, carotid occlusive disease, VTE, dementia, smoking status, heavy alcohol consumption, OAC treatment and AP treatment. Confidence intervals for risk-standardized rates are calculated through bootstrap sampling with 1000 replications.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

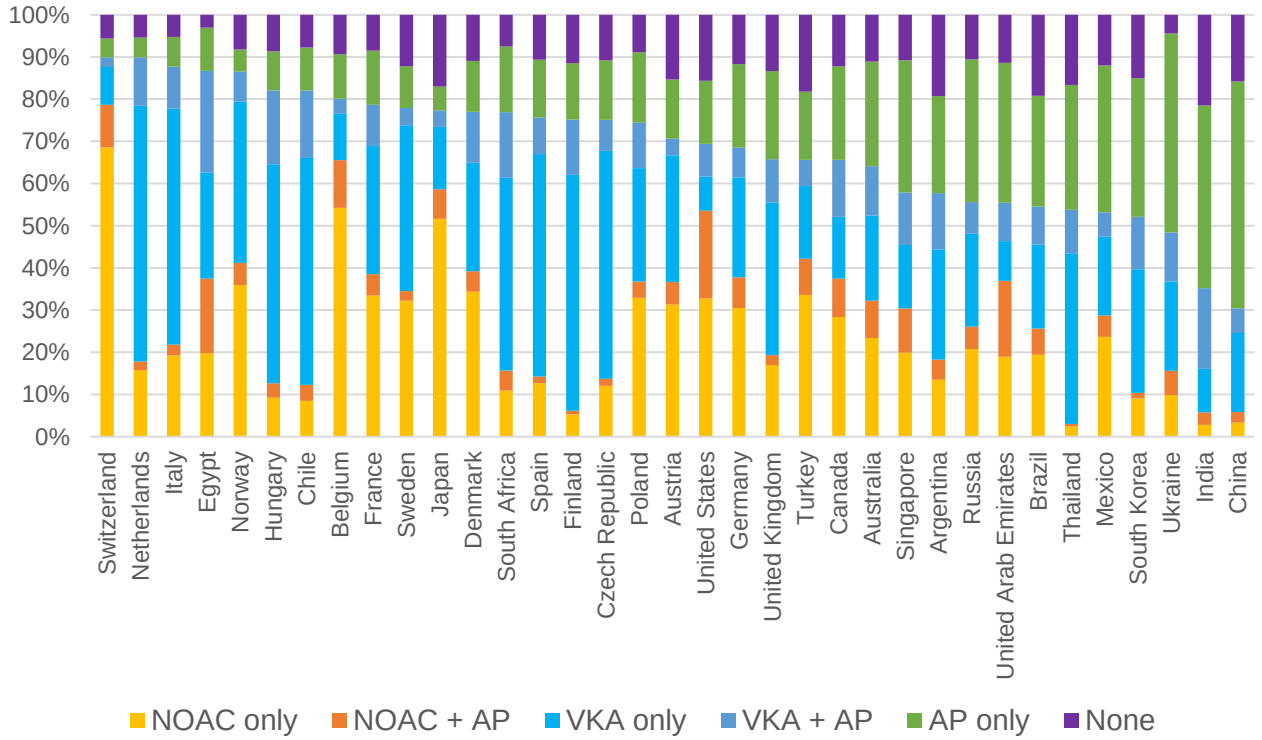
Figure S1. Initial choice of antithrombotic treatment following diagnosis of AF by a. region and b. country.

(a) Region



For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

(b) Country



For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

GARFIELD-AF Registry Investigators

Global Steering Committee

Ajay K. Kakkar (UK) (Chair), Jean-Pierre Bassand (France), A. John Camm (UK), David A. Fitzmaurice (UK), Keith A.A. Fox (UK), Bernard J. Gersh (USA), Samuel Z. Goldhaber (USA), Shinya Goto (Japan), Sylvia Haas (Germany), Werner Hacke (Germany), Lorenzo G. Mantovani (Italy), Frank Misselwitz (Germany), Karen S. Pieper (USA), Alexander G.G. Turpie (Canada), Martin van Eickels (Germany), Freek W.A. Verheugt (the Netherlands).

Audit Committee

Keith A.A. Fox (UK), Bernard J. Gersh (USA).

GARFIELD-AF National Coordinators

Hector Lucas Luciardi (Argentina), Harry Gibbs (Australia), Marianne Brodmann (Austria), Frank Cools (Belgium), Antonio Carlos Pereira Barretto (Brazil), Stuart J. Connolly, John Eikelboom (Canada), Ramon Corbalan (Chile), Zhi-Cheng Jing (China), Petr Jansky (Czech Republic), Jørn Dalsgaard Nielsen (Denmark), Hany Ragy (Egypt), Pekka Raatikainen (Finland), Jean-Yves Le Heuzey (France), Harald Darius (Germany), Matyas Keltai (Hungary), Jitendra Pal Singh Sawhney (India), Giancarlo Agnelli and Giuseppe Ambrosio (Italy), Yukihiro Koretsune (Japan), Carlos Jerjes Sánchez Díaz (Mexico), Hugo Ten Cate (the Netherlands), Dan Atar (Norway), Janina Stepinska (Poland), Elizaveta Panchenko (Russia), Toon Wei Lim (Singapore), Barry Jacobson (South Africa), Seil Oh (South Korea), Xavier Viñolas (Spain), Marten Rosenqvist (Sweden), Jan Steffel (Switzerland), Pantep Angchaisuksiri (Thailand), Ali Oto (Turkey), Alex Parkhomenko (Ukraine), Wael Al Mahmeed (United Arab Emirates), David Fitzmaurice (UK), Samuel Z. Goldhaber (USA).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

GARFIELD-AF National Investigators

China

Dayi Hu, Kangning Chen, Yusheng Zhao, Huaiqin Zhang, Jiyan Chen, Shiping Cao, Daowen Wang, Yuejin Yang, Weihua Li, Hui Li, Yuehui Yin, Guizhou Tao, Ping Yang, Yingmin Chen, Shenghu He, Yong Wang, Guosheng Fu, Xin Li, Tongguo Wu, Xiaoshu Cheng, Xiaowei Yan, Ruiping Zhao, Moshui Chen, Longgen Xiong, Ping Chen, Yang Jiao, Ying Guo, Li Xue, Zhiming Yang.

India

Praveen Jadhavm, Raghava Sarma, Govind Kulkarni, Prakash Chandwani, Rasesh Atulbhai Pothiwala, Mohanan Padinhare Purayil, Kamaldeep Chawla, Veerappa Annasaheb Kothiwale, Bagirath Raghuraman, Vinod Madan Vijan, Jitendra Sawhney, Ganapathi Bantwal, Aziz Khan, Ramdhan Meena, Manojkumar Chopada, Sunitha Abraham, Vikas Bisne, Govindan Vijayaraghavan, Debabrata Roy, Rajashekhar Durgaprasad, A.G. Ravi Shankar, Sunil Kumar, Dinesh Jain, Kartikeya Bhargava, Vinay Kumar, Udigala Madappa Nagamalesh, Rajeeve Kumar Rajput.

Japan

Yukihiro Koretsune, Seishu Kanamori, Kenichi Yamamoto, Koichiro Kumagai, Yosuke Katsuda, Keiki Yoshida, Fumitoshi Toyota, Yuji Mizuno, Ikuo Misumi, Hiroo Noguchi, Shinichi Ando, Tetsuro Suetsugu, Masahiro Minamoto, Hiroyuki Oda, Susumu Adachi, Kei Chiba, Hiroaki Norita, Makoto Tsuruta, Takeshi Koyanagi, Kunihiko Yamamoto, Hiroshi Ando, Takayuki Higashi, Megumi Okada, Shiro Azakami, Shinichiro Komaki, Kenshi Kumeda, Takashi Murayama, Jun Matsumura, Yurika Oba, Ryuji Sonoda, Kazuo Goto, Kotaro Minoda, Yoshikuni Haraguchi, Hisakazu Suefuji, Hiroo Miyagi, Hitoshi Kato, Tsugihiro Nakamura, Tadashi Nakamura, Hidekazu Nandate, Ryuji Zaitsu, Yoshihisa Fujiura, Akira Yoshimura, Hiroyuki Numata, Jun Ogawa, Yasuyuki Kamogawa, Kinshiro Murakami, Yutaka Wakasa, Masanori Yamasawa, Hiromitsu Maekawa, Sumihisa Abe, Hajime Kihara, Satoru Tsunoda, Katsumi Saito, Hiroki Tachibana, Ichiro Oba, Takashi Kuwahata, Satoshi Higa, Masamichi Gushiken, Takuma Eto, Hidetoshi Chibana, Kazuaki Fujisawa, Yuhei Shiga, Hirokuni Sumi, Toshihisa Nagatomo, Yoshihiko Atsuchi, Toshiro Nagoshi, Kazuhisa Sanno, Fumihiro Hoshino, Naoto Yokota, Masahiro Kameko, Toshifumi Tabuchi, Munesumi Ishizawa, Yoshitake Fujiura, Daisuke Ikeda,Taku Seto, Tetsu Iwao, Norio Ishioka, Koichi Oshiro, Keizo Tsuchida, Yutaka Hatori, Motoshi Takeuchi, Hiroto Takezawa, Shinjiro Nagano, Masaaki Iwaki, Yuichiro Nakamura, Naomasa Miyamoto, Toshifumi Taguchi, Ko Ashida, Naoto Yoshizawa, Jun Agata, Seishiro

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Matsukawa, Osamu Arasaki, Shuji Fukuoka, Hirofumi Murakami, Kazuya Mishima, Yoshiki Hata, Ichiro Sakuma, Kotaro Obunai, Ichiro Takamura, Mitsuyuki Akutsu, Toshihide Unoki, Yoshinori Go, Makoto Ikemura, Shoji Morii, Shigeru Marusaki, Hideo Doi, Mitsuru Tanaka, Takaaki Kusumoto, Shigeo Kakinoki, Chiga Ogurusu, Kazuya Murata, Masaki Shimoyama, Masami Nakatsuka, Yutaka Kitami, Yoichi Nakamura, Hiroshi Oda, Rikimaru Oyama, Masato Ageta, Teruaki Mita, Kazuhiko Nagao, Takafumi Mito, Junichi Minami, Mitsunori Abe, Masako Fujii, Makoto Okawa, Tsuneo Fujito, Toshiya Taniguchi, Tenei Ko, Hiroshi Kubo, Mizuho Imamaki, Masahiro Akiyama, Takashi Ueda, Hironori Odakura, Masahiko Inagaki, Yoshiki Katsube, Atsuyuki Nakata, Shinobu Tomimoto, Mitsuhiro Shibuya, Masayuki Nakano, Kenichiro Ito, Masahiro Matsuta, Motoyuki Ishiguro, Taro Minagawa, Masamichi Wada, Hiroaki Mukawa, Masato Mizuguchi, Fumio Okuda, Teruaki Kimura, Kuniaki Taga, Masaaki Techigawara, Morio Igarashi, Hiroshi Watanabe, Toshihiko Seo, Shinya Hiramitsu, Hiroaki Hosokawa, Mitsumoto Hoshiai, Michitaka Hibino, Koichi Miyagawa, Hideki Horie, Nobuyoshi Sugishita, Yukio Shiga, Akira Soma, Kazuo Neya, Tetsuro Yoshida, Kunio Akahane, Sen Adachi, Chiei Takanaka, Takashi Ueda, Saori Matsui, Hirofumi Kanda, Masanori Kaneko, Shiro Nagasaka, Atsushi Taguchi, Shuta Toru, Kazuyuki Saito, Akiko Miyashita, Hiroki Sasaguri, Jin Nariyama, Taketo Hatsuno, Takash Iwase, Kazuki Sato, Kazuya Kawai, Tomobumi Kotani, Tsuyoshi Tsuji, Hirosumi Sakai, Kiyoshi Nishino, Kenichi Ikeda, Kazuo Maeda, Tomohiro Shinozuka, Takeshi Inoue, Koichi Kawakami, Hiromichi Kitazumi, Tsutomu Takagi, Mamoru Hamaoka, Jisho Kojima, Akitoshi Sasaki, Yoshihiro Tsuchiya, Tetsuo Betsuyaku, Koji Higuchi, Masaaki Honda, Koichi Hasegawa, Takao Baba, Kazuaki Mineoi, Toshihiko Koeda, Kunihiko Hirasawa, Toshihide Kumazaki, Akira Nakagomi, Eiji Otaki, Takashi Shindo, Hiroyoshi Hirayama, Chikako Sugimoto, Takashi Yamagishi, Ichiro Mizuguchi, Kazunori Sezaki, Isamu Niwa, Ken Takenaka, Osamu Iiji, Koichi Taya, Hitoshi Kitazawa, samu Ueda, Hirokazu Kakuda, Takuya Ono, Seizo Oriso, Junya Kamata, Toshihiko Nanke, Itaru Maeda, Yoshifusa Matsuura, Hiroki Teragawa, Yasuyuki Maruyama, Kazuo Takei, Hajime Horie, Tetsutaro Kito, Hiroshi Asano, Koji Matsushita, Masaichi Nakamura, Takashi Washizuka, Tomoki Yoshida, Masato Sawano, Shinichi Arima, Hidekazu Arai, Hisanori Shinohara, Hiroyuki Takai, Nobufusa Furukawa, Akira Ota, Kentaro Yamamoto, Kenji Aoki, Taku Yamamoto, Takeaki Kasai, Shunji Suzuki, Shu Suzuki, Nitaro Shibata, Masayuki Watanabe, Yosuke Nishihata, Toru Arino, Masaki Okuyama, Tetsushi Wakiyama, Tomoko Kato, Yasuo Sasagawa, Takeshi Tana, Yoshihito Hayashi, Shinichi Hirota, Yukihiko Abe, Yoshihiro Saito, Hirohide Uchiyama, Hiroshi Takeda, Hiroshi Ono, Shuichi Tohyo, Naoto Hanazono, Seiichi Miyajima, Hisashi Shimono, Takuma Aoyama, Yasunobu Shozawa, Yawara Niijima, Osamu Murai, Osamu Murai, Hideko Inaba, Katsumasa Nomura, Masatsugu Nozoe, Kazuo Suzuki, Toshiyuki Furukawa, Toshihiko Shiraiwa, Nobuhisa Ito, Shunichi Nagai, Kiyoharu Sato, Shiro Nakahara, Yujin Shimoyama, Naoko Ohara, Teruhiko Kozuka, Hideaki Okita, Masato Endo, Tsutomu Goto, Makoto Hirose, Emiko Nagata, Noriyuki Nakanishi, Toshizumi Mori, Shuichi Seki, Katsuhiro Okamoto, Osamu Moriai, Yoko Emura, Tsuyoshi Fukuda, Haruhiko Date, Shuichi Kawakami, Sho Nagai, Yuya Ueyama, Tetsuro Fudo, Mitsuru Imaizumi, Takuo Ogawa, Shunsuke Take, Hideo Ikeda, Hiroaki Nishioka, Norihiko Sakamoto, Kiyomitsu Ikeoka, Nobuo Wakaki, Masatake Abe, Junji Doiuchi, Tetsuya Kira, Masato Tada, Ken Tsuzaki, Naoya Miura, Yasuaki Fujisawa, Wataru Furumoto, Susumu Suzuki, Akinori Fujisawa, Ryosai Nakamura, Hiroyasu Komatsu, Rei Fujiki, Shuichi Kawano, Keijiro Nishizawa, Yoji Kato, Junya Azuma, Kiyoshi Yasui,Toshio Amano, Yasuhiro Sekine, Tatsuo Honzawa, Yuichiro Koshibu, Yasuhide Sakamoto, Yukihiro Seta, Shingo Miyaguchi, Kojuro Morishita, Yasuko Samejima, Toyoshi Sasaki, Fumiko Iseki, Toshiyuki

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Kobayashi, Hiroshi Kano, Jaeyoung Kim, Hiroshi Yamaguchi, Yoichi Takagi, Yoko Onuki Pearce, Yasuyuki Suzuki, Takayuki Fukui, Toru Nakayama, Hideaki Kanai, Yoshiyuki Kawano, Tetsuji Ino, Hironori Miyoshi, Yasufumi Miyamoto, Masahito Shigekiyo, Shimato Ono, Yoshiyuki Kawano, Yutaka Okamoto, Satoshi Ubukata, Kojiro Kodera, Tatsuo Oriuchi, Naoki Matsumoto, Koichi Inagaki, Atsushi Iseki, Tomohiro Yoshida, Toshihiro Goda, Tsukasa Katsuki, Atsushi Sato, Etsuo Mori, Toshio Tsubokura, Hiroshi Shudo, Shunichi Fujimoto, Tomohiro Katsuya, Yoshiyuki Furukawa, Hiroshi Hosokawa, Jun Narumi, Kiichiro Yamamoto, Masaki Owari, Takuya Inakura, Takafumi Anno, Kazuyuki Shirakawa.

Singapore

Chi Keong Ching, Toon Wei Lim, David Foo, Kelvin Wong, Tan Yuyang.

South Korea

Seil Oh, Hui Nam Park, Woo-Shik Kim, HyeYoung Lee, Sung-Won Jang, Dae Hyeok Kim, Jun Kim, DongRyeol Ryu, Jaemin Shim, Dae-Kyeong Kim, Dong Ju Choi, Yong Seog Oh, Myeong-Chan Cho, Hack-Lyoung Kim, Hui-Kyung Jeon, Dong-Gu Shin, Sang Weon Park, Hoon Ki Park, Sang-Jin Han, Jung Hoon Sung, Hyung-Wook Park, Gi-Byoung Nam, Young Keun On, Hong Euy Lim, JaeJin Kwak, Tae-Joon Cha, Taek Jong Hong, Seong Hoon Park, Jung Han Yoon, Nam-Ho Kim, Kee-Sik Kim, Byung Chun Jung, Gyo-Seung Hwang, Chong-Jin Kim.

Thailand

Sakda Rungaramsin, Peerapat Katekangplu, Porames Khunrong, Thanita Bunyapipat, Wanwarang Wongcharoen, Pinij Kaewsuwanna, Khanchai Siriwattana, Waraporn Tiyanon, Supalerk Pattanaprichakul, Khanchit Likittanasombat, Doungrat Cholsaringkarl, Warangkana Boonyapisit, Sirichai Cheewatanakornkul, Songkwan Silaruks, Pisit Hutayanon, Seksan Chawanadelert, Pairoj Chattranukulchai, Boonsert Chatlaong, Yingsak Santanakorn, Khompiya Kanokphatcharakun, Piya Mongkolwongroj, Sasivimon Jai-Aue, Ongkarn Komson.

Turkey

Armagan Altun, Ali Aydinlar, Ramazan Topsakal, Zeki Ongen, Sadik Acikel, Durmus Yildiray Sahin, Ozcan Yilmaz, Mehmet Birhan Yilmaz, Hasan Pekdemir, Mesut Demir, Murat Sucu, Levent Sahiner, Ali Oto, Murat Ersanli, Ertugrul Okuyan, Dursun Aras.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Argentina

Florencia Rolandi, Adrian Cesar Ingaramo, Gustavo Alberto Sambadaro, Vanina Fernandez Caputi, Hector Luciardi, Sofia Graciela Berman, Pablo Dragotto, Andres Javier Kleiban, Nestor Centurion, Rodolfo Andres Ahuad Guerrero, Leonel Adalberto Di Paola, Ricardo Dario Dran, Javier Egido, Matias Jose Fosco, Victor Alfredo Sinisi, Luis Rodolfo Cartasegna, Oscar Gomez Vilamajo, Jose Luis Ramos, Sonia Sassone, Gerardo Zapata, Diego Conde, Guillermo Giacomi, Alberto Alfredo Fernandez, Mario Alberto Berli, Fabian Ferroni.

Brazil

Dário Celestino Sobral Filho, Jefferson Jaber, Luciana Vidal Armaganijan, Costantino Roberto Frack Costantini, André Steffens, Weimar Kunz Sebba Barroso de Souzaem, João David de Souza Neto, José Márcio Ribeiro, Marcelo Silveira Teixeira, Paulo Rossi, Leonardo Pires, Daniel Moreira, José Carlos Moura Jorge, Adalberto Menezes Lorga Filho, Luiz Bodanese, Marcelo Westerlund Montera, Carlos Henrique Del Carlo, Jamil Abdalla Saad, Fernando Augusto Alves da Costa, Renato Lopes, Gilson Roberto de Araújo, Euler Roberto Manenti, Jose Francisco Kerr Saraiva, João Carlos Ferreira Braga, Alexandre Negri, Carlos Moncada, Dalton Precoma, Fernando Roquette, Gilmar Reis, Roberto Álvaro Ramos Filho,: Estêvão Lanna Figueiredo, Roberto Vieira Botelho, Cláudio Munhoz da Fontoura Tavares, Helius Carlos Finimundi, Adriano Kochi, César Cássio Broilo França, Fábio Alban, Guido Bernardo Aranha Rosito, João Batista de Moura Xavier Moraes Junior, Rogério Tadeu Tumelero, Lilia Maia,: Roberto Simões de Almeida, Ney Carter do Carmo Borges, Luís Gustavo Gomes Ferreira.

Chile

Ramón Corbalán, Benjamin Aleck Joseh Stockins Fernandez, Humberto Montecinos, Fernando Lanas, Martín Larico Gómez, Carlos Astudillo, Carlos Conejeros, Patricio Marin Cuevas, Alejandro Forero, Claudio Bugueño Gutiérrez, Juan Aguilar, Sergio Potthoff Cardenas, German Eggers, Cesar Houzvic, Carlos Rey, Germán Arriagada, Gustavo Charme Vilches.

Mexico

Carlos Jerjes Sanchez Diaz, Jesus Jaime Illescas Diaz, Raul Leal Cantu, Maria Guadalupe Ramos Zavala, Ricardo Cabrera Jardines, Nilda Espinola Zavaleta, Enrique Lopez Rosas, Guillermo Antonio Llamas Esperón, Gerardo Pozas, Ernesto Cardona Muñoz, Norberto Matadamas Hernandez, Adolfo Leyva Rendon, Norberto Garcia Hernandez, Manuel de los Rios Ibarra, Luis Ramon Virgen Carrillo, David Lopez Villezca, Carlos

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Hernandez Herrera, Juan Jose Lopez Prieto, Rodolfo Gaona Rodriguez, Efrain Villeda Espinosa, David Flores Martinez, Jose Velasco Barcena, Omar Fierro Fierro, Ignacio Rodriguez Briones, Jose Luis Leiva Pons, Humberto Alvarez Lopez, Rafael Olvera Ruiz, Carlos Gerardo Cantu Brito, Eduardo Julian Jose Roberto Chuquiure Valenzuela, Roxana Reyes Sanchez, Alberto Esteban Bazzoni Ruiz, Oscar Martin Lopez Ruiz, Roberto Arriaga Nava, Jesus David Morales Cerda, Pedro Fajardo Campos, Mario Benavides Gonzalez.

Austria

Marianne Brodmann, Kurt Lenz, Claus Hagn, Johannes Foechterle, Heinz Drexel, Kurt Huber, Andrea Podczeck-Schweighofer, Michael Winkler, Bruno Schneeweiss, Alfons Gegenhuber, Wilfried Lang, Sabine Eichinger-Hasenauer, Peter Kaserer, Josef Sykora, Heribert Rasch, Bernhard Strohmer.

Belgium

Luc Capiau, Geert Vervoort, Bart Wollaert, Frank Cools, Geert Hollanders, Jan Vercammen, Dirk Faes, Yohan Balthazar, Marc Delforge, Olivier Xhaet, Harry Striekwold, John Thoeng, Kurt Hermans, Georges Mairesse, Wim Anné, Ivan Blankoff, Michel Beutels, Stefan Verstraete, Peter Vandergoten, Philippe Purnode, Pascal Godart, Tim Boussy, Philippe Desfontaines, Alex Heyse, Joeri Voet, Axel De Wolf.

Czech Republic

Eva Zidkova, Petr Jansky, Rudolf Spacek, Vilma Machova, Ondrej Ludka, Josef Olsr, Lubos Kotik, Blazej Racz, Richard Ferkl, Jan Hubac, Ilja Kotik, Zdenek Monhart, Hana Burianova, Ondrej Jerabek, Jana Pisova, Iveta Petrova, Vratislav Dedek, Michaela Honkova, Petr Podrazil, Petr Reichert, Jindrich Spinar, Miroslav Novak, Vaclav Durdil, Katarina Plocova, Jiri Lastuvka.

Denmark

Jørn Nielsen, Steen Husted, Helena Dominguez, Ulrik Hintze, Søren Rasmussen, Næstved Sygehus, Arne Bremmelgaard, John Markenvard, Jan Børger, Jorgen Solgaard, Ebbe Eriksen, Thomas Løkkegaard, Michael Bruun, Jacob Mertz, Morten Schou, Helena Dominguez, Michael Olsen.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Finland

Pekka Raatikainen, K.E. Juhani Airaksinen.

France

Franck Paganelli, Joël Ohayon, Frédéric Casassus, Jean-Yves Le Heuzey, Michel Galinier, Yannick Gottwalles, Philippe Loiselet, Jean-Joseph Muller, Mohamed Bassel Koujan, André Marquand, Sylvain Destrac, Olivier Piot, Nicolas Delarche, Jean-Pierre Cebron, Maxime Guenoun, Dominique Guedj-Meynier, Lokesh A G, Mathieu Zuber, Pierre Amarenco, Emmanuel Ellie, James Kadouch, Pierre-Yves Fournier, Jean-Pierre Huberman, Nestor Lemaire, Gilles Rodier, Xavier Vandamme, Igor Sibon, Jean-Philippe Neau, Marie Hélène Mahagne, Antoine Mielot, Marc Bonnefoy, Jean-Baptiste Churet, Vincent Navarre, Frederic Sellem, Gilles Monniot, Jean-Paul Boyes, Bernard Doucet, Michel Martelet, Désiré Obadia, Bernard Crousillat, Joseph Mouallem, Etienne Bearez, Jean Philippe Brugnaux, Alain Fedorowsky, Pierre Nazeyrollas, Jean-Baptiste Berneau, Frédéric Chemin.

Germany

Sebastien Schellong, Harald Darius, Georg Koeniger, Andreas Kopf, Uwe Gerbaulet, Bernd-Thomas Kellner, Thomas Schaefer, Jan Purr, Enno Eißfeller, Heinz-Dieter Zauzig, Peter Riegel, Christoph Axthelm, Gerd-Ulrich Heinz, Holger Menke, Andreas Pustelnik, Stefan Zutz, Wolfgang Eder, Guenter Rehling, Dirk Glatzel, Norbert Ludwig, Petra Sandow, Henning Wiswedel, Cosmas Wildenauer, Steffen Schoen, Toralf Schwarz, Adyeri Babyesiza, Maximilian Kropp, Hans-Hermann Zimny, Friedhelm Kahl, Andreas Caspar, Sabine Omankowsky, Torsten Laessig, Hermann-Josef Hartmann, Gunter Lehmann, Hans-Walter Bindig, Gunter Hergdt, Dietrich Reimer, Joachim Hauk, Holger Michel, Praxis Dres. Werner Erdle, Wilfried Dorsch, Janna Dshabrailov, Karl-Albrecht Rapp, Reinhold Vormann, Thomas Mueller, Peter Mayer, Uwe Horstmeier, Volker Eissing, Heinz Hey, Heinz Leuchtgens, Volker Lilienweiss, Heiner Mueller, Christian Schubert, Herrmann Lauer, Thomas Buchner, Gunter Brauer, Susanne Kamin, Karsten Mueller, Sylvia Baumbach, Muwafeg Abdel-Qader, Hans-Holger Ebert, Carsten Schwencke, Peter Bernhardt, Laszlo Karolyi, Britta Sievers, Wilhelm Haverkamp, Jens-Uwe Roehnisch.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Hungary

Andras Vertes, Gabor Szantai, Andras Matoltsy, Nikosz Kanakaridisz, Zoltan Boda, Erno Kis, Balazs Gaszner, Ferenc Juhasz, Gizella Juhasz, Sandor Kancz, Zoltan Laszlo, Zsolt May, Bela Merkely, Ebrahim Noori, Tamas Habon, Peter Polgar, Gabriella Szalai, Sandor Vangel, Andras Nagy, Gabriella Engelthaler, Judit Ferenczi, Mihaly Egyutt.

Italy

Giuliana Martini, Leone Maria Cristina, Eros Tiraferri, Rita Santoro, Sophie Testa, Giovanni Di Minno, Marco Moia, Teresa Maria Caimi, Maria Tessitori, Giancarlo Agnelli, Roberto Cappelli, Daniela Poli, Roberto Quintavalla, Franco Cosmi, Raffaele Fanelli, Vincenzo Oriana, Raffaele Reggio, Roberto Santi, Leonardo Pancaldi, Raimondo De Cristofaro, Giuliana Guazzaloca, Angelo De Blasio, Jorge Salerno Uriate, Flavia Lillo, Enrico Maria Pogliani, Grzegorz Bilo, Michele Accogli, Antonio Mariani, Mauro Feola, Arturo Raisaro, Luciano Fattore, Andrea Mauric, Fabrizio Germini, Luca Tedeschi, Maria Settimi, Sergio Nicoli, Paolo Ricciarini, Antonio Argena, Paolo Ronchini, Claudio Bulla, Filippo Tradati, Massimo Volpe, Maria D'Avino, Maria Grazia Bongiorni, Silva Severi, Alessandro Capucci, Corrado Lodigiani, Enrico Salomone, Gaetano Serviddio, Claudio Tondo, Giuseppe Ambrosio, Paolo Golino, Carmine Mazzone, Saverio Iacopino.

The Netherlands

Hugo ten Cate, J.H. Ruiter, Andreas Lucassen, Henk Adriaansen, Maarten Bongaerts, Mathijs Pieterse, Coen van Guldener, Johannes Herrman, S.H.K. P.R. Nierop, Pieter Hoogslag, Walter Hermans, B.E. Groenemeijer, W. Terpstra, Cees Buiks, L.V.A. Boersma.

Norway

Eivind Berge, Per Anton Sirnes, Erik Gjertsen, Torstein Hole, Knut Erga, Arne Hallaråker, Gunnar Skjelvan, Anders Østrem, Beraki Ghezai, Arne Svilaas, Peter Christersson, Torbjørn Øien, Svein Høegh Henrichsen, Jan Erik Otterstad, Jan Berg-Johansen.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Poland

Janina Stepinska, Andrzej Gieroba, Malgorzata Biedrzycka, Michal Ogorek, Beata Wozakowska-Kaplon, Krystyna Loboz-Grudzien, Jaroslaw, Wieslaw Supinski, Jerzy Kuzniar, Roman Zaluska, Jaroslaw Hiczkiewicz, Lucyna Swiatkowska-Byczynska, Lech Kucharski, Marcin Gruchala, Piotr Minc, Maciej Olszewski, Grzegorz Kania, Malgorzata Krzciuk, Zbigniew Lajkowski, Bozenna Ostrowska-Pomian, Jerzy Lewczuk, Elzbieta Zinka, Agnieszka Karczmarczyk, Malgorzata Chmielnicka-Pruszczynska, Iwona Wozniak-Skowerska, Grzegorz Opolski, Marek Bronisz, Marcin Ogorek, Grazyna Glanowska, Piotr Ruszkowski, Grzegorz Skonieczny, Ryszard Sciborski, Boguslaw Okopien, Piotr Kukla, Krzysztof Galbas, Krzysztof Cymerman, Jaroslaw Jurowiecki, Pawel Miekus, Waldemar Myszka, Stanislaw Mazur, Roman Lysek, Jacek Baszak, Teresa Rusicka-Piekarz, Grzegorz Raczak, Ewa Domanska, Jadwiga Nessler, Jozef Lesnik.

Russia

Vera Eltishcheva, Roman Libis, Gadel Kamalov, Dmitry Belenky, Liudmila Egorova, Alexander Khokhlov, Eduard Yakupov, Dmitry Zateyshchikov, Olga Barbarash, Olga Miller, Evgeniy Mazur, Konstantin Zrazhevskiy, Tatyana Novikova, Yulia Moiseeva, Elena Polkanova, Konstantin Sobolev, Maria Rossovskaya, Yulia Shapovalova, Alla Kolesnikova, Konstantin Nikolaev, Oksana Zemlianskaia, Anna Zateyshchikova, Victor Kostenko, Sergey Popov, Maria Poltavskaya, Anton Edin,Elena Aleksandrova, Oksana Drapkina, Alexander Vishnevsky, Oleg Nagibovich, Petr Chizhov, Svetlana Rachkova, Mikhail Sergeev, Borys Kurylo, Alexey Ushakov.

Spain

Xavier Vinolas, Pere Alvarez Garcia, Maria Fernanda Lopez Fernandez, Luis Tercedor Sanchez, Salvador Tranche Iparraguirre, Pere Toran Monserrat, Emilio Marquez Contreras, Jordi Isart Rafecas, Juan Motero Carrasco, Pablo Garcia Pavia, Casimiro Gomez Pajuelo, Luis Miguel Rincon Diaz, Luis Fernando Iglesias Alonso, Angel Grande Ruiz, Jordi Merce Klein, Jose Ramon Gonzalez Juanatey, Ines Monte Collado, Herminia Palacin Piquero, Carles Brotons Cuixart, Esther Fernandez Escobar, Joan Bayo i Llibre, Cecilia Corros Vicente, Manuel Vida Gutierrez, Francisco Epelde Gonzalo, Carlos Alexandre Almeida Fernandez, Encarnacion Martinez Navarro, Jordi Isart Rafecas, Juan Jose Montero Alia, Maria Barreda Gonzalez, Maria Angels Moleiro Oliva, Jose Iglesias Sanmartin, Mercedes Jimenez Gonzalez, Maria del Mar Rodriguez Alvarez, Juan Herreros Melenchon, Tomas Ripoll Vera, Manuel Jimenez Navarro, Maria Vazquez Caamano, Maria Fe Arcocha Torres, Gonzalo Marcos Gomez, Andres Iniguez Romo, Miguel Angel Prieto Diaz.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Sweden

Mårten Rosenqvist, Alexander Wirdby, Centrumkliniken, Jan Lindén, Kerstin Henriksson, Micael Elmersson, Arnor Egilsson, Ulf Börjesson, Gunnar Svärd, Bo Liu, Anders Lindh, Lars-Bertil Olsson, Mikael Gustavsson, Lars Andersson, Lars Benson, Claes Bothin, Ali Hajimirsadeghi, Björn Martinsson, Marianne Ericsson, Åke Ohlsson, Håkan Lindvall, Peter Svensson, Katarina Thörne, Hans Händel, Pyotr Platonov, Fredrik Bernsten, Ingar Timberg, Milita Crisby, Jan-Erik Karlsson, Agneta Andersson, Lennart Malmqvist, Johan Engdahl, Jörgen Thulin, Aida Hot-Bjelak, Steen Jensen, Per Stalby.

Switzerland

Jan Steffel, Johann Debrunner, Juerg H. Beer, Dipen Shah.

Ukraine

Iurii Rudyk, Vira Tseluyko, Oleksandr Karpenko, Svitlana Zhurba, Igor Kraiz, Oleksandr Parkhomenko, Iryna Kupnovytska, Nestor Seredyuk, Yuriy Mostovoy, Oleksiy Ushakov, Olena Koval, Igor Kovalskiy, Yevgeniya Svyshchenko, Oleg Sychov, Mykola Stanislavchuk, Andriy Yagensky, Susanna Tykhonova, Ivan Fushtey.

United Kingdom

Will Murdoch, Naresh Chauhan, Daryl Goodwin, Louise Lumley, Ramila Patel, Philip Saunders, Bennett Wong, Alex Cameron, Philip Saunders, Niranjan Patel, P Jhittay, Andrew Ross, M S Kainth, Karim Ladha, Kevin Douglas, Gill Pickavance, Joanna McDonnell, Laura Handscombe, Trevor Gooding, Helga Wagner, Cumberlidge, Colin Bradshaw, Catherine Bromham, Kevin Jones, Shoeb Suryani, Richard Coates, Bhupinder Sarai, W Willcock, S Sircar, John Cairns, A Gilliand, Roman Bilas, E Strieder, Peter Hutchinson, Anne Wakeman, Michael Stokes, Graham Kirby, Bhaskhar Vishwanathan, Nigel Bird, Paul Evans, M Clark, John Bisatt, Jennifer Litchfield, E Fisher, Tim Fooks, Richard Kelsall, Neil Paul, Elizabeth Alborough, Michael Aziz, C Ramesh, Pete Wilson, Simon Franklin, Sue Fairhead, Julian Thompson, Hasan Chowan, Gary Taylor, Dawn Tragen, Matt Parfitt, Claire Seamark, Carolyn Paul, Mark Richardson, Angus Jefferies, Helen Sharp, Hywel Jones, Claire Giles, Matthew Bramley, Philip Williams, Jehad Aldegather, Simon Wetherell, William Lumb, Phil Evans, Frances Scouller, Neil Macey, Stephen Rogers, Yvette Stipp, Richard West, Philip Pinney, Paul Wadeson, John Matthews, Preeti Pandya, Andrew Gallagher, T Railton, Emyr Davies, Jonathan McClure, Marc

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Jacobs, Claire Hutton, R Thompson, Bijoy Sinha, Keith Butter, Susan Barrow, Helen Little, David Russell, Ulka Choudhary, Ikram Haq, Paul Ainsworth, Claire Jones, Phil Weeks, Jane Eden, Lisa Gibbons, Janet Glencross, Alison MacLeod, K Poland, Conor Mulolland, A Warke, Paul Conn, D Burns, R Smith, R Kamath, Jonathan Webster, Ian Hodgins, Stephen Vercoe, Paul Roome, Hilary Pinnock, Jayesh Patel, Amar Ali, Nigel Hart, Richard Davies, Nigel De-Sousa, Catherine Neden, Mark Danielsen, Purnima Sharma, Sophia Galloway, Charlotte Hawkins, Raife Oliver, Martin Aylward, Mira Pattni, Gordon Irvine, Shahid Ahmad, Catherine Rothwell, Fiaz Choudhary, Sabrina Khalaque, Stephanie Short, Sharon Peters, Warwick Coulson, Neil Roberts, Amy Butler, Steven Coates, Ben Ward, Daniel Jackson, Steve Walton, Diane Shepherd, Toh Wong, Mark Boon, Melanie Deacon, David Cornelius, Sarah Davies, Ben Frankel, Nick Hargreaves, Henry Choi, Jon Sumner, Tim Myhill, Salah Estifanos, Diane Geatch, Justin Wilkinson, Richard Veale, Karen Forshaw, Rob Hirst, Kashif Zaman, Catherine Liley, Rebecca Wastling, Paul McEleny, Andre Beattie, Philip Cooke, Mike Wong, Mark Pugsley, Chaminda Dooldeniya, Greg Rogers, James Bennett, Polly Jacobs, Rajesh Muvva, Matthew Adam, Robin Fox, Nicolas Thomas, Simon Cartwright, Rory Reed, Simon Randfield, Christine A'Court, Ann Flynn, Andrew Halpin, Shoeb Suryani, Simon Dobson, Louise Lomax, Minnal Nadaph, Iain Munro, Jane Goram, Helen Stoddart, Phil Simmons, John Shewring, Emma Bowen-Simpkins, Mark Rickenbach, Polly Jacobs.

Australia

Adam Blenkhorn, Bhuwanendu Singh, Penny Astridge, William van Gaal, Walter Abhayaratna, Philip Thomson, Ron Lehman, Jens Kilian, David Coulshed, Andrei Catanchin, David Colquhoun, Hosen Kiat, David Eccleston, John French, Bronte Ayres, Peter Blombery, Thanh Phan, James Rogers, David O'Donnell, Sang Cheol Bae, Harry Gibbs, Patrick Carroll, Greg Starmer, Margaret Arstall, Maurits Binnekamp, Astin Lee.

Canada

John Eikelboom, Robert Luton, Milan Gupta, Amritanshu Shekhar Pandey, Stephen Cheung, Rolland Leader, Philippe Beaudry, Félix Ayala-Paredes, Joseph Berlingieri, John Heath, Germain Poirier, Miranda du Preez, Bradley Schweitzer, Reginald Nadeau, Ripple Dhillon, Tomasz Hruczkowski, Andrea Lavoie, Ratika Parkash, James Cha, Benoit Coutu, Paul MacDonald, Brian Ramjattan, Jorge Bonet, Saul Vizel, Paul Angaran, Sameh Fikry.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Egypt

Ahmed Mowafy, Azza Katta, Mazen Tawfik, Moustafa Nawar, Mohamed Sobhy, Seif Kamal Abou Seif, Tarek Khairy, Ahmed Abd El-Aziz, Nasser Taha, Ashraf Reda, Atef Elbahry, Mohamed Setiha, Mohamed Gamal El Din, Magdi Elkhadem, Adel El-Etreby.

South Africa

David Kettles, Junaid Bayat, Heidi Siebert, Adrian Horak, Ynez Kelfkens, Riaz Garda, Barry Jacobson, Thayabran Pillay, Michele Guerra, Louis van Zyl, Hendrik Theron, Andrew Murray, Rikus Louw, Deon Greyling, Pindile Mntla, Siddique Ismail, Fayzal Ahmed, Johannes Engelbrecht, Shambu Maharajh, Wessel Oosthuysen, Rehana Loghdey, Veronica Ueckermann.

United Arab Emirates

Wael Al Mahmeed, Abdullah Al Naeemi, Ghazi Yousef, Nooshin Bazargani, Munther AlOmairi, Rajan Maruthanayagam, Rupesh Singh, Ahmed Naguib, Mohamed Ibrahim, Amrish Agrawal, Mukesh Nathani, Ehab M. Esheiba, Adel Wassef, Rajeev Gupta.

United States

Michael Cox, Scott Beach, Peter Duffy, Stephen Falkowski, Kevin Ferrick, Miguel Franco, W. Michael Kutayli, Annette Quick, Niraj Sharma, Vance Wilson, Stephen Miller, Mark Alberts, Edwin Blumberg, Roddy Canosa, Ted Gutowski, Rodney Ison, Jorge Garcia, Paul Mullen, Howard Noveck, Pamela Rama, Rajneesh Reddy, Marcus Williams, Daniel Nishijima, Keith Ferdinand, Ihsan Haque, Robert Mendelson, Sridevi Pitta, Daniel Theodoro, Charles Treasure, Moustafa Moustafa, Cas Cader, Walter Pharr, Alisha Oropallo, George Platt, Jaspal Gujral, James Welker, Firas Koura.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract- **title page 1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found- **page 4 &5**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported- **page 6**
Objectives	3	State specific objectives, including any prespecified hypotheses- **page 6**
Methods		
Study design	4	Present key elements of study design early in the paper- **Page 6-7**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection –**pages 6-8**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up-**page 6-7** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable- **page 7**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group- **page 8-10**
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding- **page 8-10**
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **page 10**
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **page 10-11**
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **page 11-13**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **page 9-10**
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **page 13-14**
Discussion		
Key results	18	Summarise key results with reference to study objectives- **page 14-15**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias-**page 17-18**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence- **page 14-18**
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based- **page 19**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml