GARFIELD-AF: Risk profiles, treatment patterns and two-year outcomes in patients with atrial fibrillation in Germany, Austria and Switzerland (DACH) compared to 32 countries in other regions worldwide

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Abstract *(250/250)*

Background: The *G*lobal *A*nticoagulant *R*egistry in the *FIELD–A*trial *F*ibrillation (GARFIELD-AF) is a worldwide non-interventional study of stroke prevention in patients with non-valvular AF.
Methods and results: 52,080 patients with newly diagnosed AF were prospectively enrolled from 2010 to 2016. 4121 (7.9%) of these patients were recruited in DACH (Germany (n=3,567), Austria (n=465) and Switzerland (n=89) combined), and 47,959 patients were from 32 countries in other regions worldwide (ORW*)*. Hypertension was most prevalent in DACH and ORW (85.3% and 75.6 %, respectively). Diabetes, hypercholesterolemia, carotid occlusive disease and vascular disease were more prevalent in DACH patients vs ORW (27.6%, 49.4%, 5.8% and 29.0% vs 21.7%, 40.9%, 2.8 % and 24.5%). The use of non-vitamin K antagonist oral anticoagulants (NOACs) increased more in DACH over time. Management of vitamin K antagonists was suboptimal in DACH and ORW (time in therapeutic range of INR ≥65% in 44.6% and 44.4% of patients or ≥70% in 36.9% and 36.0% of patients, respectively). Adjusted rates of cardiovascular mortality and MI/ACS were higher in DACH while non-haemorrhagic stroke/systemic embolism was lower after 2-year follow-up.
Conclusion: Similarities and dissimilarities in AF management and clinical outcomes are seen in DACH and ORW. The increased use of NOAC was associated with a mismatch of risk-adapted anticoagulation (over-and-undertreatment) in DACH. Suboptimal control of INR requires educational activities in both regional groups. Higher rates of cardiovascular death in DACH may reflect the higher risk profile of these patients and lower rates of non-haemorrhagic stroke could be associated with increased NOAC use.

Keywords: Atrial fibrillation, GARFIELD-AF, Oral anticoagulation, Non-vitamin K antagonist oral anticoagulants, Vitamin K antagonists, Phenprocoumon

Introduction

Atrial Fibrillation (AF) is the most common arrhythmia in the general population and it is associated with an increased risk of ischaemic stroke (1) and other comorbidities. Schnabel et al. reported an AF prevalence of 2.5% for people aged between 35 and 74 in a population-based German cohort study, with a significant rise in the number of cases with increasing age (2). Recent projections estimate that between 2010 and 2060, the number of elderly population with AF in the European Union will have more than doubled (3). The increasing prevalence, association of AF with significant morbidity, mortality and advances in the treatment of acute cardiac treatment has major public health implications (4). For many decades, chronic anticoagulation with vitamin K antagonists (VKA) was the only option for stroke prophylaxis in patients with atrial fibrillation. However, this changed after four non-vitamin K antagonist oral anticoagulants (NOAC) proved their efficacy and tolerability as

well as significantly simplified handling in randomised controlled trials (RCTs) (5-8). RCTs need to be complemented by non-interventional observational studies to verify that the results of studies conducted under stringent inclusion and exclusion criteria can also be applied to routine clinical care and to much broader patient populations.

GARFIELD-AF (ClinicalTrials.gov identifier: NCT01090362) is a prospective, non-interventional, observational, global registry of newly diagnosed non valvular AF (9). The aim of this study is to observe strategies of stroke prevention over time and to analyse the burden of disease and outcomes associated with AF. In this manuscript, we compare the patient characteristics and treatment patterns in all patients prospectively enrolled in GARFIELD-AF in Germany, Austria and Switzerland (DACH) with those enrolled in 32 countries in other regions worldwide (ORW). We also describe the differences of clinical outcomes after 2 years of follow-up in DACH and ORW.

Methods

Study design and participants

Patients were enrolled in 5 cohorts from over 1,000 centres in 35 countries worldwide, including from America, Europe, Africa and Asia. Eligible patients included men and women aged ≥ 18 years with non-valvular AF diagnosed according to standard local procedures within the previous 6 weeks and with at least one investigator defined risk factor(s) for stroke. Risk factors were neither pre-specified in the protocol nor were they limited to the components of existing risk stratification schemes. The registry excluded patients with a transient reversible cause of AF and those for whom follow-up was not envisaged or possible. In order to reflect the clinical care situations worldwide investigator sites were selected randomly from the different care settings in each participating country (office-based practice; hospital departments – neurology, cardiology, geriatrics, internal and emergency medicine; anticoagulation clinics; and general or family practice).

Data collection

GARFIELD-AF data were collected using an electronic case report form (eCRF) and captured by trained personnel. The eCRF was designed by Dendrite Clinical Systems Ltd, Henley-on-Thames, UK, the group which is also responsible for the ongoing database program management. Oversight of operations and data management are managed by the sponsor and coordinating centre (Thrombosis Research Institute [TRI], London, UK), with support from Quintiles (Durham, NC, USA), The University of Birmingham Department of Primary Care Clinical Sciences (Birmingham, UK), Thrombosis Research Group-Brigham and Women's Hospital (Boston, MA, USA), and AIXIAL (Paris, France).

The GARFIELD-AF protocol requires that 20% of all eCRFs are monitored against source documentation, that there is an electronic audit trail for all data modifications, and that critical variables are subjected to additional audit (9). This study reports data from prospective patients enrolled between the periods March 2010 - August 2016. The data was extracted from the study database on November 19, 2018.

Definitions

The following terms have been defined previously (10). The term AC (anticoagulants) includes vitamin K antagonists (VKAs) and non-vitamin K antagonist oral anticoagulants (NOACs). The term NOAC includes oral direct factor Xa inhibitors and oral direct thrombin inhibitors. Vascular disease was defined as peripheral artery disease and/or coronary artery disease with or without a history of acute coronary syndrome (ACS) but did not include carotid arterial disease. Hypertension was defined as a documented history of hypertension or systolic blood pressure > 140/90 mmHg at rest. Moderate-to-severe chronic kidney disease (CKD) includes stage III to stage V according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines (11).

Ethics statement

All patients had provided written informed consent to participate in the registry. Independent ethics committee and hospital-based institutional review board approvals were obtained, as necessary, for the registry protocol. 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. Confidentiality and anonymity of all patients recruited into this registry are maintained at all times.

Procedures and outcomes measures

Baseline data included patient characteristics, medical history, care setting, type of AF, date and method of diagnosis, symptoms and anticoagulant (AC) treatment (VKAs and NOACs), as well as antiplatelet (AP) treatment). Ethnicity was classified by the investigator in agreement with the patient (12).

Data on all components of the CHA_2DS_2-VASc score [congestive heart failure (CHF), hypertension, diabetes, vascular disease, age 65–74 years and female gender, age ≥75 years and previous stroke or systemic embolism (SE)] (13) and the HAS-BLED score (uncontrolled hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, elderly (> 65 years), drugs/alcohol concomitantly) (14) were collected to assess the risks of stroke and bleeding retrospectively. The GARFIELD-AF risk scores were developed to predict risk of death, stroke or systemic embolism,

and/or major bleeding. The components across the three models include age, heart failure, heart rate, OAC use, chronic kidney disease, vascular disease, systolic blood pressure, history of bleeding, history of stroke, world region and race (15).

Collection of follow-up data occurred at 4-month intervals up to 24 months for the analyses of this manuscript. The main clinical outcome measures include mortality, stroke/systemic embolism (SE) and major bleeding. Submitted data were examined for completeness and accuracy by the coordinating centre (TRI), and data queries were sent to study sites.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) or median with 25^{th} and 75^{th} percentiles, and categorical variables as frequency and percentage. Use of antithrombotic therapy at baseline was stratified by CHA_2DS_2-VASc and 'modified' HAS-BLED (excluding fluctuations in the international normalised ratio) scores, calculated retrospectively from the data collected. All data presented in the baseline table are complete case with the exception of the GARFIELD-AF scores in which multiple imputation was applied.

Prothrombin time international normalized ratio (PT-INR) readings during the first year of follow-up with VKA as baseline treatment were described. Implausible INR values of less than 0.8 or greater than 20 were excluded. Patients with fewer than three readings during the follow-up, were excluded from the analysis. Time in therapeutic range (TTR) was estimated between two consecutive INR readings only if the interval did not exceed 90 days. Patient-level TTR was estimated by linear interpolation according to Rosendaal et al (16) using 2.0–3.0 as the target INR range for all countries. TTR was estimated using INR readings until discontinuation or interruption of VKA, an outcome event, or the end of follow-up. The distribution of INR and TTR values are described by counts and percentages below, within, and above the therapeutic range (above or below 65% or 70%, respectively for TTR), and by the mean, standard deviation (SD), and median (Q1;Q3).

Occurrence of major clinical events (primarily stroke/SE, major bleeding, and all-cause mortality) is described using the number of events and person-time event rate (per 100 person-years) with 95% confidence interval (CI). We estimated person-year rates using a Poisson model. Only the first

occurrence of each event was taken into account. Data analysis was performed at the TRI with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline patient characteristics

A total of 52,080 patients with a newly diagnosed AF were prospectively enrolled in GARFIELD-AF registry. Of these, 4121 (7.9%) of patients were from DACH, recruited between March 2010 and August 2016 from 82 centres. The patients were enrolled in five sequential cohorts: C1 (2010-2011; n=1062), C2 (2011-2012; n=1039), C3 (2013-2014; n=696), C4 (2014-2015; n=624), C5 (2015-2016; n=700). The proportion of patients recruited by cohort is reported in Supplementary Table S1. 42% of DACH patients with AF were diagnosed and managed by either internal medicine, neurology, or geriatrics, followed by cardiology (30.1%), and primary care physicians (27.8%). The patients from DACH were more frequently treated by office based physicians (56.3%) than the patients from ORW (29.9%), whereas the opposite was seen for treatment by hospital based doctors (43.7% for DACH and 71.6% for ORW) as listed in table 1.

The baseline clinical characteristics of patients recruited in DACH and ORW are summarised in Table 1. In DACH, the majority (53.3%) of patients were men and the median (Q1;Q3) age at diagnosis of AF was 73 years (62.0;78.0). A higher median body mass index (BMI) of 28.3 kg/m^2 was observed in patients from DACH compared to ORWwith a median BMI of 26.8 kg/m^2. Hypertension was the most prevalent risk factor for AF in 85.3% of patients from DACH and in 75.6% of patients in ORW. Diabetes and hypercholesterolemia were higher for patients from DACH than ORW (27.6% vs 21.7%; 49.4% vs 40.9%). Approximately 12% of the patients had a history of transient ischaemic attack (TIA) or prior systemic embolism (SE) stroke in DACH and ORW. The median (Q1;Q2) CHA_2DS_2-VASc and HAS-BLED scores in DACH and ORW were 4.0 (2.0;5.0) vs 3.0 (2.0;4.0) and 1.0 (1.0;2.0) vs 1.0 (1.0;2.0), respectively (Table 1). The median (Q1;Q2) GARFIELD-AF score for death and major bleed in DACH and ORWwere 5.6 (3.3;9.7) vs 4.6 (2.5;8.6) and 1.7(1.1;2.5) vs 1.6(1.0;2.4), respectively (Table 1).

The majority of patients in DACH and ORW had newly detected AF (47.3% and 44.6%) which therefore, could not be further classified by the investigators. Among the classified patients, the most prevalent form of AF was paroxysmal in 23.8% of patients in DACH and 27.8% in ORW followed by 17.5% permanent AF in DACH and 12.3% in ORW. Persistent AF was recorded for 11.4% and 15.2% of the patients in DACH and ORW, respectively.

Antithrombotic treatments

Figure 1 shows the patterns of antithrombotic treatment in each cohort (C1 to C5) for DACH and ORW. In C1, 5.8% of DACH patients and 3.8% of patients globally were on non-VKA oral anticoagulant therapies (NOACs). From C2 onwards, however, there was a rapid increase of NOAC uptake, especially in DACH compared with the average of ORW in GARFIELD-AF over the same time period. By the last year of enrolment (2015-16; cohort 5), 70.0% of patients in DACH and 41.4% of patients in ORW were on NOAC ± antiplatelet therapy (AP). Overall, use of vitamin K antagonists VKA ± AP tended to be lower in patients from DACH in GARFIELD-AF (30.8% vs. 40.1%). The use of AP therapy in DACH patients either alone (18.7% vs 21.2%) or combined with AC (38.5% vs 26.6%) was similar to ORW. Between the first (2010) and last year of recruitment (2016), the proportion of patients on AP alone in DACH fell from 33.0% to 9.5% whereas this was much less pronounced in ORW (29.5% to 17.4%).

Overall, 38.5% and 26.6% of patients in DACH and ORW, received AC with or without AP therapy and 12.0% and 12.2% of patients, respectively, did not receive stroke prevention treatment. However, the percentage of patients without any antithrombotic therapy generally decreased in DACH over time.

Risk of stroke and antithrombotic treatments

Figure 2 shows the distribution of treatment therapies according to the CHA_2DS_2-VASc scores in DACH and ORW. In DACH, 51.4 % of patients with a CHA_2DS_2-VASc score of '0' received oral AC ± AP and this was the case for 46.3 % in ORW. The percentages of oral AC ± AP rose in both groups with an increase of the stroke risk. The prescription of AP only therapy also rose with an increased CHA_2DS_2-VASc score in the DACH group whereas AP only was frequently prescribed in patients in ORW, irrespective of stroke risk (Figure 2).

Risk of bleeding and antithrombotic treatments

Figure 3 shows the distribution of antithrombotic treatment by HAS-BLED score. In general, a decrease in anticoagulation and an increase in the use of antiplatelets is seen with an increase in the HAS-BLED score in both geographical groups, albeit much more pronounced in DACH than in ORW. In the group with the highest HAS-BLED score of 4-6, 62.8% of patients in DACH were treated with AP only and 35.2% with an anticoagulant, compared with 19.6% AP only and 71.0% OAC in ORW.

International normalised ratio (INR readings) and TTR:

A total of 15,945 INR readings were analysed from 1,251 DACH patients receiving VKA, retaining those who had at least three INR readings. 237,035 ORW INR readings were analysed from a total of

18,951 patients receiving VKA, with the same inclusion. Overall, the median INR (Q1;Q3) value was 2.2 (1.9; 2.7) in DACH and 2.3 (1.9; 2.8), ORW. Approximately one-third of INR readings (31.5%) were <2.0, 54.6% between 2.0-3.0 and 13.9% >3.0 in DACH. Median patient-level TTR was comparable in DACH and ORW (61.1% vs 61.2%). Only 44.6% of the patients in DACH and 44.4% in ORW achieved a TTR of 65% or greater. Using the cut off ≥70%, only 36.9% of patients in DACH and 36.0 % in ORW reached this value. (Table 2).

Event rates at 2 year follow-up

The unadjusted event rates per 100 person-years as well as the adjusted and unadjusted hazard ratios during the first two years after diagnosis of AF in GARFIELD-AF as well as the comparisons of DACH and ORW are presented in Figure 4. Patients from DACH had higher rates per 100 person-years of all-cause mortality compared with ORW (4.8 [4.4 to 5.4] vs 3.7 [3.6 to 3.9] adjusted HR:1.08) and also cardiovascular mortality was higher in DACH compared to ORW (2.1 [1.8-2.4] vs 1.3 [1.2-1.4] adjusted HR:1.31). Rates per 100 person-years of stroke/systemic embolism and major bleeding were lower in DACH compared with ORW (0.8 [0.6 to 1.0] vs. 1.0 [1.0 to 1.1]) adjusted HR:0.64) and (1.1 [0.9 to 1.4] vs 1.0 [0.9 to 1.0] adjusted HR:1.00), respectively. The incidence of other cardiovascular events such as acute coronary syndrome and congestive heart failure tended to be higher in the DACH (Table 3).

Discussion

Atrial fibrillation is a global burden on healthcare systems, but there are differences in patient risk profiles and management, particularly the modalities of stroke prevention worldwide. Identifying those differences may have an impact on improving AF care. There are some AF observational studies and registry data for Germany, Switzerland and Austria as well as other European countries, but direct comparisons with other countries worldwide are missing (2-4, 17, 18).

The global GARFIELD-AF registry provides important insights of AF epidemiology, management and outcomes in the three DACH countries Germany, Austria and Switzerland and offers the opportunity to compare the outcomes in DACH to 32 countries in other regions worldwide (ORW). There were considerable differences between DACH and ORW countries regarding care setting specialties and locations. While the DACH patients with AF were more often treated by internists and general practitioners in primary care, the ORW patients were most often treated by cardiologists in hospital.

When compared to ORW, the profiles of the 4121 DACH patients showed that many patients were at higher stroke risk, with a median age of 73 years and median CHA_2DS_2-VASc score of 4. The GARFIELD scores for stroke, bleeding and death were also higher in the DACH group than in the

ORW patients. The DACH patients also had more often concomitant diseases such as vascular disease, carotid occlusive disease, hypertension, hypercholesterolaemia and diabetes. Thus, the patients enrolled in DACH were definitely sicker than those in ORW. Whether there may be a relationship between the care structures and the patient populations can only be discussed speculatively. It is at least conceivable that more complex patient populations are treated by internists and general practitioners in the outpatient setting as observed in DACH than by specialised cardiologists in hospital as seen in ORW.

GARFIELD-AF started patient enrolment after NOACs had recently become available. As NOACs were then also recommended as preferred substances compared to VKAs (19), it is of interest to see how these substances have become established worldwide for stroke prevention. As shown in fig.1 the prescribing of VKA±AP as an initial treatment after diagnosis of AF in GARFIELD-AF was lower in DACH than all other countries (48.5% vs 54.4%) and declined gradually over time (from 48.5 to 12.8%). A remarkable rise in NOAC use has been observed from cohort to cohort however and the increase was more pronounced in DACH than in ORW. In DACH, the use of NOACs rose from cohort 3-5 (2013-2016) from 53.8% over 63.3% to 70.0% whereas an increase from 24.4% over 35.7% to 41.4% was seen in ORW during the same period of time. The different uptake of NOACs in real-world probably reflects the different availabilities and reimbursement in different regions around the world. The prescription of VKAs was inversely proportional to that. This means that over time, VKAs in DACH had been replaced by NOACs faster than in ORW. However, it is also worth noting that there has been a general increase in the prescription of oral anticoagulants over time, which is much more evident in DACH than in ORW. This occurred through displacement of AP-only, with a decrease from 33% (cohort 1) to 9.5% (cohort 5) in DACH compared with 29.5% to 17.4% in ORW. An increased prescription rate of OAC over the same period of time has also been reported by Hohnloser et al. for Germany as well as the decrease of VKA and increase NOACs (17).

The most commonly prescribed VKA in DACH was phenprocoumon (91.7%), which is known to differ from warfarin in terms of pharmacodynamic characteristics. Because of the longer functional half-life of phenprocoumon compared to other VKAs, it has been postulated that more stable anticoagulation with less INR fluctuations can be achieved with phenprocoumon (20). According to international guidelines the percentage of time the patients INR were within the target range of 2.0 to 3.0 (TTR) was determined. Separate analyses were performed using cut offs ≥65% and ≥70%, respectively. Using the 65% cut off we followed the recommendations of NICE (National Institute for Health and Care Excellence) stating: "Poor anticoagulation control can be shown by any of the

following: 2 INR values higher than 5 or 1 INR value higher than 8 within the past 6 months, 2 INR values less than 1.5 within the past 6 months, or TTR less than 65%" (21).
That approach has also been used a few years ago for our publication on “Quality of Vitamin K Antagonist Control and 1-Year Outcomes in Patients with Atrial Fibrillation: A Global Perspective from the GARFIELD-AF Registry”. This publication highlighted already a large proportion of AF patients having poor VKA control and that these patients had significantly higher risks of stroke/SE, major bleeding, and all-cause mortality (23).

In both DACH and ORW, the recommended minimum values of 65% TTR could only be achieved for approximately 44% of the VKA patients, i.e. 55.4% in DACH and 55.6% of the ORW patients had TTR values of <65%. Even more surprisingly, more DACH patients tended to be underanticoagulated (INR < 2.0 in DACH 31.5% vs 28.6% in ORW) and fewer were overanticoagulated (13.9% vs 16.7%). Thus, guideline supported management of VKA remains suboptimal in DACH.
Applying the ESC (European Society of Cardiology) definition of "good TTR at >70%" the impression of insufficient anticoagulation with VKA was even more pronounced (22). With the use of this cut off, only 36.9% of patients in DACH and 36.0 % in ORW had a TTR 70% or more.
Therefore, the idea that better values could be achieved with phenprocoumon than with warfarin and other VKAs was not fulfilled and further educational activities are required to improve the quality of VKA control. Attempts to explain the poor control of anticoagulation with VKA in DACH are speculative, but there might be an association between the different care structures for AF patients in DACH or ORW and VKA management. Significantly more patients were treated by cardiologists in ORW than in DACH (68.8% vs 31.1%) and the opposite is seen for primary care/general practice with 13.0% vs 27.8% respectively. This would imply that the recommendations of the ESC guidelines should be more widely adopted in primary care and general practice.
It is noteworthy that some Asian countries are included in ORW, where an INR target range of 1.5 to 2.5 is recommended instead of 2.0 to 3.0 which may explain the low median TTR values in ORW. The issue of VKA control in Asia compared with other regions of the world has already been addressed in a separate GARFIELD-AF publication (24).

In principle, GARFIELD-AF reflects the change of stroke prevention with AC therapy over time. Whereas Schnabel et al. reported in 2012 that 42.7% of persons with AF in Germany were not taking either anticoagulants or platelet inhibitor (2) this was the case in DACH for only 12% of the patients. The PREFER-in-AF registry which started some time before GARFIELD-AF showed that 11.6% of patients with AF were treated with NOAC and 79.1% were on VKAs (25). The EORP-AF registry

(from February 2012 to March 2013), which included nine European countries showed that 8.4% of patients were on NOAC and 71.6% were on VKAs (4).

The distribution of antithrombotic treatment at baseline by region and CHA_2-DS_2-VASc score at enrolment (fig. 2) shows a clear over-prescription for patients with a truly low CHA_2-DS_2-VASc score, especially in DACH, where over 50% of patients with CHA_2-DS_2-VASc 0 received an anticoagulant, of which again the vast majority received a NOAC. This type of overuse shows that there is still a need for further medical education in view of the unfavourable benefit/risk ratio in patients with a very low risk of stroke due to the risk of bleeding. The overanticoagulation of the truly low risk patients was much more pronounced in DACH than previously reported by Hohnloser et al. In that study using German claims data only about 30% of patients with CHA2-DS2-VASc 0 received an OAC. This could be related to the different care structures that were analysed in GARFIELD-AF and by Hohnloser et al. who only examined the statutory health-insured population in Germany whereas GARFIELD-AF also included all patients with private health insurance. It is noteworthy that 6.6% of patients with the highest CHA_2-DS_2-VASc scores of 6-9 in both regional groups received no antithrombotic therapy at all in GARFIELD-AF. This is a much lower percentage than reported by Hohnloser for patients with CHA2-DS2-VASc scores >2 (17).

A special feature of the prospective GARFIELD-AF registry are the analyses of the distribution of antithrombotic treatment at baseline by region and HAS-BLED score at enrolment. As shown in fig. 3, there was a marked increase in AP only and displacement of OAC therapy with an increase in HAS-BLED score. The rise of AP only was much more pronounced in DACH from 0% to 62.8% than in ORW from 0% to 38.6% in the groups with HAS-BLED scores 0 and 4-6 respectively, while the use of OAC in DACH decreased from 71.6% to 35.2% and in ORW only from 74.3% to 71.0%. This suggests again that DACH physicians are "disregarding" ESC guideline recommendations, which explicitly state that HAS-BLED scores should not deter anticoagulation (22).

There is a clear reduction of AP-only therapy in both groups over time which decreased to much greater extent in DACH than in ORW. Fig. 1 shows the decreases from 33.0% to 9.5% and from 29.5% to 17.4%, respectively. This suggests good concordance with the ESC guidelines, which no longer recommend AP therapy for stroke prevention. The majority of the remaining antiplatelet prescription rates may be triggered by concomitant diseases as many patients, particularly in DACH, had higher proportions of carotid occlusive disease, vascular disease, hypercholesterolaemia and diabetes.

Unadjusted analyses showed that the rate of all-cause mortality was numerically higher in DACH when compared to ORW but this could not be confirmed after adjustment. Cardiovascular mortality

was significantly higher in DACH than in ORW and this was separately confirmed for MI/ACS. However, the rates of non-haemorrhagic stroke/SE were significantly lower in the patients treated in the DACH countries which is in agreement with the retrospective German data claim analyses of Hohnloser et al (17).

Strengths and limitations

As a particular strength of GARFIELD-AF, it should be emphasised that it is a global registry observing the care of patients with non-valvular atrial fibrillation under prospective and non-interventional conditions. In contrast to randomised controlled trials patients with concomitant diseases of any kind could be included and risk assessment and treatment decisions were made exclusively by the investigator. In difference to retrospective claim database analyses, informations on BMI and laboratory data, such as INR values and analyses of renal function, could also be recorded in GARFIELD-AF. A limitation is that the causes of death are based on clinical data and no independent central adjudication could be performed.

Conclusions

In contrast to other German database analyses, these results from the global GARFIELD-AF registry provide important information on the management of stroke prevention in AF in the three German-speaking countries (DACH) compared with 32 other countries worldwide. The results of anticoagulation control with VKA provide large room for improvement in both groups. Even though the use of NOACs increased in DACH to a greater extent than in other parts of the world, a non-negligible proportion of patients with increased stroke risk did not receive any AC treatment. The increased use of NOACs was associated with a mismatch of stroke-risk adapted anticoagulation (over-and-undertreatment) in DACH. In relation to the HAS-BLED score, a disproportionate number of patients at higher risk of bleeding were treated with AP instead of OAC in DACH. Higher rates of cardiovascular death in DACH may reflect the higher risk profile of these patients and illustrate the remaining challenges for AF patients including the need of holistic treatment approach. Compared to ORW the lower rates of non-haemorrhagic stroke/systemic embolism in DACH could be associated with the increased NOAC use.

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Competing Interests

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Figure legends

Figure 1. Distribution of antithrombotic treatment at baseline by region and cohort of enrolment a) overall and b) among patients with CHA_2DS_2-VASc ≥2 (excl. sex)

Figure 2. Distribution of antithrombotic treatment at baseline by region and CHA_2DS_2-VASc score at enrolment

Figure 3. Distribution of antithrombotic treatment at baseline by region and HAS-BLED score at enrolment

Table 1. Baseline patient characteristics by region of enrolment

Baseline characteristics	Region of enrolment		p-value
	DACH (N=4121)	**ORW (N=47936)**	
Sex, n (%)			
Male	2197 (53.3)	26855 (56.0)	
Female	1924 (46.7)	21080 (44.0)	<.001
Age, median (Q1; Q3), years	73.0 (65.0;79.0)	71.0 (62.0;78.0)	<.001
Ethnicity, n (%)			
White	3963 (97.4)	28048 (60.1)	
Hispanic/Latino	6 (0.1)	3391 (7.3)	
Asian	5 (0.1)	14291 (30.6)	<.001
Black/Mixed/Other	95 (2.3)	977 (2.1)	
BMI, median (Q1; Q3), kg/m^2	28.3 (25.2;31.8)	26.8 (23.8;30.5)	<.001
Systolic blood pressure, median (Q1; Q3), mmHg	136.0 (125.0;150.0)	130.0 (120.0;144.0)	<.001
Diastolic blood pressure, median (Q1; Q3), mmHg	80.0 (75.0;90.0)	80.0 (70.0;88.0)	<.001
Pulse, median (Q1; Q3), bpm	83.0 (71.0;102.0)	84.0 (70.0;105.0)	<.001
Type of atrial fibrillation, n (%)			
Permanent	721 (17.5)	5915 (12.3)	
Persistent	469 (11.4)	7291 (15.2)	<.001
Paroxysmal	980 (23.8)	13327 (27.8)	
New onset (unclassified)	1949 (47.3)	21399 (44.6)	
Care setting specialty at diagnosis, n (%)			
Internal medicine/Neurology/Geriatrics	1732 (42.0)	8717 (18.2)	
Cardiology	1240 (30.1)	32960 (68.8)	<.001
Primary care/General practice	1147 (27.8)	6255 (13.0)	
Care setting location at diagnosis, n (%)			
Hospital	1800 (43.7)	34324 (71.6)	
Office/Anticoagulation clinic/thrombosis centre	2319 (56.3)	13607 (28.4)	<.001
Medical history, n (%)			
Heart failure	912 (22.1)	10844 (22.6)	0.482
Acute coronary syndromes	439 (10.7)	5102 (10.7)	0.973
Vascular disease[b]	1183 (29.0)	11645 (24.5)	<.001
Carotid occlusive disease	237 (5.8)	1302 (2.8)	<.001
VTE	172 (4.2)	1183 (2.5)	<.001

Prior stroke/TIA/SE	500 (12.3)	5342 (11.2)	0.046
Prior bleeding	105 (2.6)	1211 (2.5)	0.942
Hypertension	3504 (85.3)	36126 (75.6)	<.001
Hypercholesterolaemia	1974 (49.4)	18995 (40.9)	<.001
Diabetes	1138 (27.6)	10412 (21.7)	<.001
Cirrhosis	29 (0.7)	265 (0.6)	0.200
Moderate to severe CKD	444 (11.1)	4913 (10.6)	0.316
Dementia	113 (2.8)	651 (1.4)	<.001
Heavy alcohol consumption, n (%)	62 (1.8)	968 (2.4)	0.043
Current smoker, n (%)	338 (9.4)	4866 (11.1)	0.002
Treatment, n (%)			
NOAC ± AP	1561 (38.5)	12556 (26.6)	
VKA ± AP	1251 (30.8)	18951 (40.1)	
AP only	760 (18.7)	10007 (21.2)	<.001
None	485 (12.0)	5763 (12.2)	
Antiplatelet treatment[c]	1319 (32.5)	16795 (35.5)	<.001
CHA_2DS_2-VASc score, median (Q1; Q3)	4.0 (2.0;5.0)	3.0 (2.0;4.0)	<.001
HAS-BLED score, median (Q1; Q3)[d]	1.0 (1.0;2.0)	1.0 (1.0;2.0)	<.001
GARFIELD death score, median (Q1; Q3)[e]	5.6 (3.3;9.7)	4.6 (2.5;8.6)	<.001
GARFIELD stroke score, median (Q1; Q3)[f]	1.7 (1.2;2.5)	1.6 (1.1;2.3)	<.001
GARFIELD bleeding score, median (Q1; Q3)[g]	1.7 (1.1;2.5)	1.6 (1.0;2.4)	<.001

AP antiplatelet, DACH Germany Austria and Switzerland, ORW other regions worldwide, NOAC non-vitamin K oral anticoagulant, TIA transient ischemic attack, SE systemic embolism, VKA vitamin K antagonist

[a]P-values calculated using T-test or Wilcoxon-Mann-Whitney test for continuous variables, as appropriate, and Chi-square or Fisher's exact test for categorical variables, as appropriate;

[b]Defined as peripheral artery disease and/or coronary artery disease;

[c]This includes patients who received antiplatelet therapy with or without anticoagulants. It consists patients who took AP only, as well as NOAC+AP and VKA+AP.

[d]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);

[e]Represent the expected risk of mortality within 2 years;

[f]Represent the expected risk of non-haemorrhagic stroke within 2 years;

[g]Represent the expected risk of major bleeding within 2 years.

Table 2. Distribution of INR and TTR values among patients treated with VKA at baseline by region of enrolment

VKA monitoring variables	**Region of enrolment**	
	DACH (N=1251)	**ORW (N=18951)**
INR readings, n	15945	237035
INR, n (%)		
<2.0	5029 (31.5)	67723 (28.6)
2.0-3.0	8699 (54.6)	129654 (54.7)
>3.0	2217 (13.9)	39658 (16.7)
INR, mean (SD)	2.4 (0.8)	2.4 (0.9)
INR, median (Q1; Q3)	2.2 (1.9; 2.7)	2.3 (1.9; 2.8)
TTR readings, n	796	11386
TTR, n (%)		
<65	441 (55.4)	6332 (55.6)
≥65	355 (44.6)	5054 (44.4)
<70	502 (63.1)	7292 (64.0)
≥70	294 (36.9)	4094 (36.0)
TTR, mean (SD)	58.9 (25.2)	56.7 (26.5)
TTR, median (Q1; Q3)	61.1 (42.3; 76.9)	61.2 (39.7; 76.7)

DACH Germany Austria and Switzerland, ORW other regions worldwide, INR International Normalised Ratio, Q, quartile; SD, standard deviation, TTR Time in Theraputic range.

Table 3. Event rates (per 100 person-years), adjusted[a] and unadjusted hazard ratios for selected outcomes through two-years of follow-up by region of enrolment[b]

Outcome Region of enrolment	**Events**	**Rate (95% CI)**	**Unadjusted HR (95% CI)**	**P-value**	**Adjusted HR (95% CI)**	**P-value**
All-cause mortality						
ORW	3344	3.7 (3.6-3.9)	1 (ref.)		1 (ref.)	
DACH	364	4.8 (4.4-5.4)	1.29 (1.09-1.53)	0.004	1.08 (0.95-1.21)	0.235
Cardiovascular mortality						
ORW	1165	1.3 (1.2-1.4)	1 (ref.)		1 (ref.)	
DACH	155	2.1 (1.8-2.4)	1.57 (1.22-2.03)	0.001	1.31 (1.10-1.56)	0.003
Non-cardiovascular mortality						
ORW	1298	1.4 (1.4-1.5)	1 (ref.)		1 (ref.)	
DACH	130	1.7 (1.5-2.1)	1.19 (0.96-1.47)	0.116	0.97 (0.83-1.14)	0.708
Unknown cause of death						
ORW	881	1.0 (0.9-1.1)	1 (ref.)		1 (ref.)	
DACH	79	1.1 (0.8-1.3)	1.06 (0.86-1.31)	0.568	0.94 (0.79-1.13)	0.529
Non-haemorrhagic stroke/SE						
ORW	910	1.0 (1.0-1.1)	1 (ref.)		1 (ref.)	
DACH	56	0.8 (0.6-1.0)	0.73 (0.50-1.05)	0.086	0.64 (0.44-0.94)	0.024
Major bleeding						
ORW	857	1.0 (0.9-1.0)	1 (ref.)		1 (ref.)	
DACH	85	1.1 (0.9-1.4)	1.17 (0.89-1.55)	0.263	1.00 (0.79-1.27)	0.999
MI/ACS						
ORW	541	0.6 (0.6-0.7)	1 (ref.)		1 (ref.)	
DACH	71	1.0 (0.8-1.2)	1.55 (1.27-1.90)	<.001	1.24 (1.11-1.40)	<.001
New/worsening heart failure						

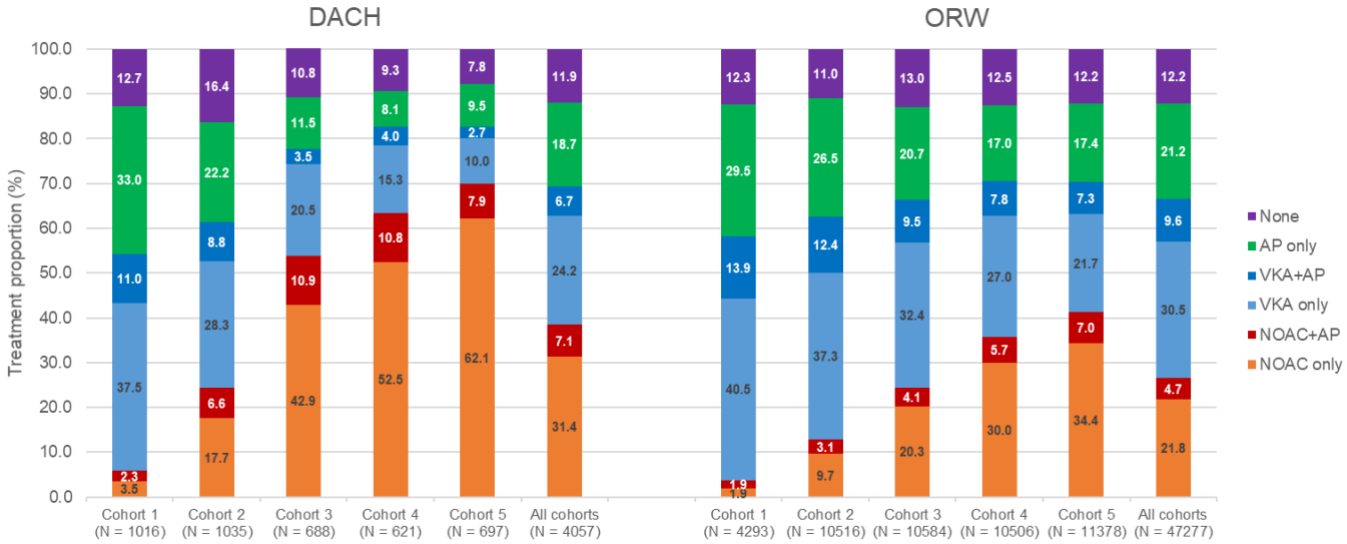
ORW	746	0.8 (0.8-0.9)	1 (ref.)		1 (ref.)	
DACH	79	1.1 (0.9-1.3)	1.25 (0.93-1.68)	0.135	0.97 (0.71-1.32)	0.831

ACS acute coronary syndrome, DACH Germany Austria and Switzerland, CI, confidence interval, HR, hazard ratio, ORW other regions worldwide, MI myocardial infarction, SE systemic embolism

[a] Hazard ratio adjusted by age, sex, ethnicity, type of AF, heart failure, vascular disease, hypertension, prior stroke/TIA/SE, prior bleeding, diabetes, moderate-to-severe CKD, baseline anticoagulation and antiplatelet therapy;

[b] A total of 39 patients had unavailable follow-up information (34 among ORWand 5 among DACH); the sample size for this analysis thus consists of 47902 for ORW and 4116 for DACH.

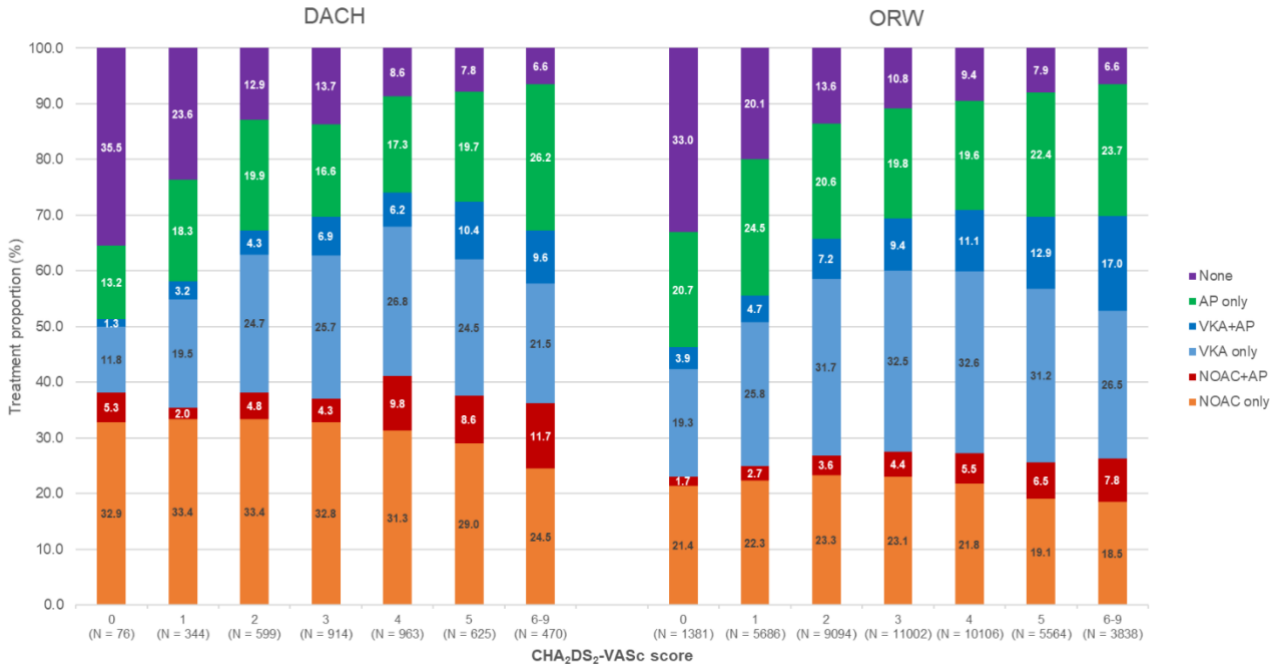
Figure 1: Distribution[a] of antithrombotic treatment at baseline by region and cohort of enrolment overall



AP antiplatelet, DACH Germany Austria and Switzerland, ORW other regions worldwide, NOAC non-vitamin K oral anticoagulant, VKA Vitamin-K antagonist.

[a]A total of 723 patients had unavailable baseline treatment information (659 among ORW and 64 among DACH). These patients were excluded from this analysis.

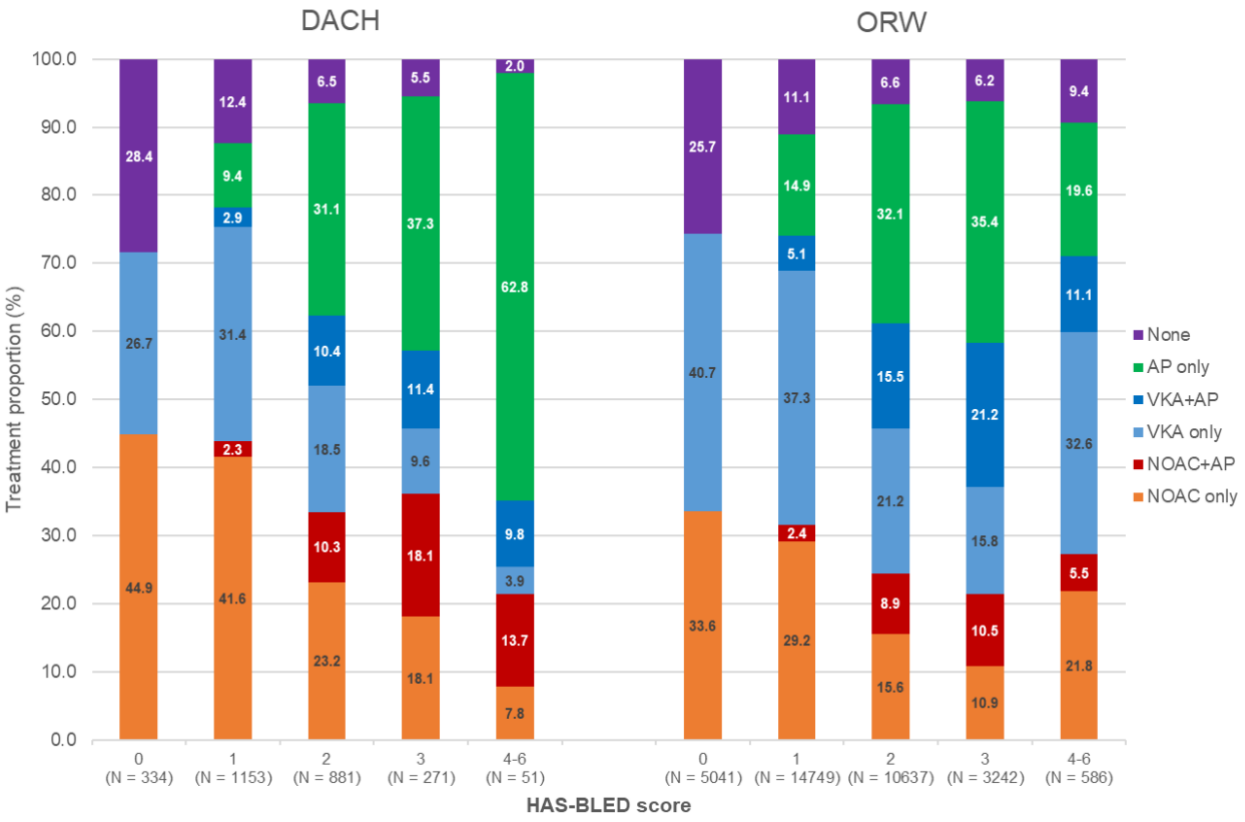
Figure 2: Distribution[a] of antithrombotic treatment at baseline by region and CHA_2-DS_2-VASc score at enrolment



AP antiplatelet, DACH Germany Austria and Switzerland, ORW other regions worldwide, NOAC non-vitamin K oral anticoagulant, VKA vitamin-K antagonist.

[a]A total of 1395 patients had unavailable baseline treatment or CHA_2DS_2-VASc score information (1265 among ORW and 130 among DACH). These patients were excluded from this analysis.

Figure 3. Distribution[a] of antithrombotic treatment at baseline by region and HAS-BLED[b] score at enrolment

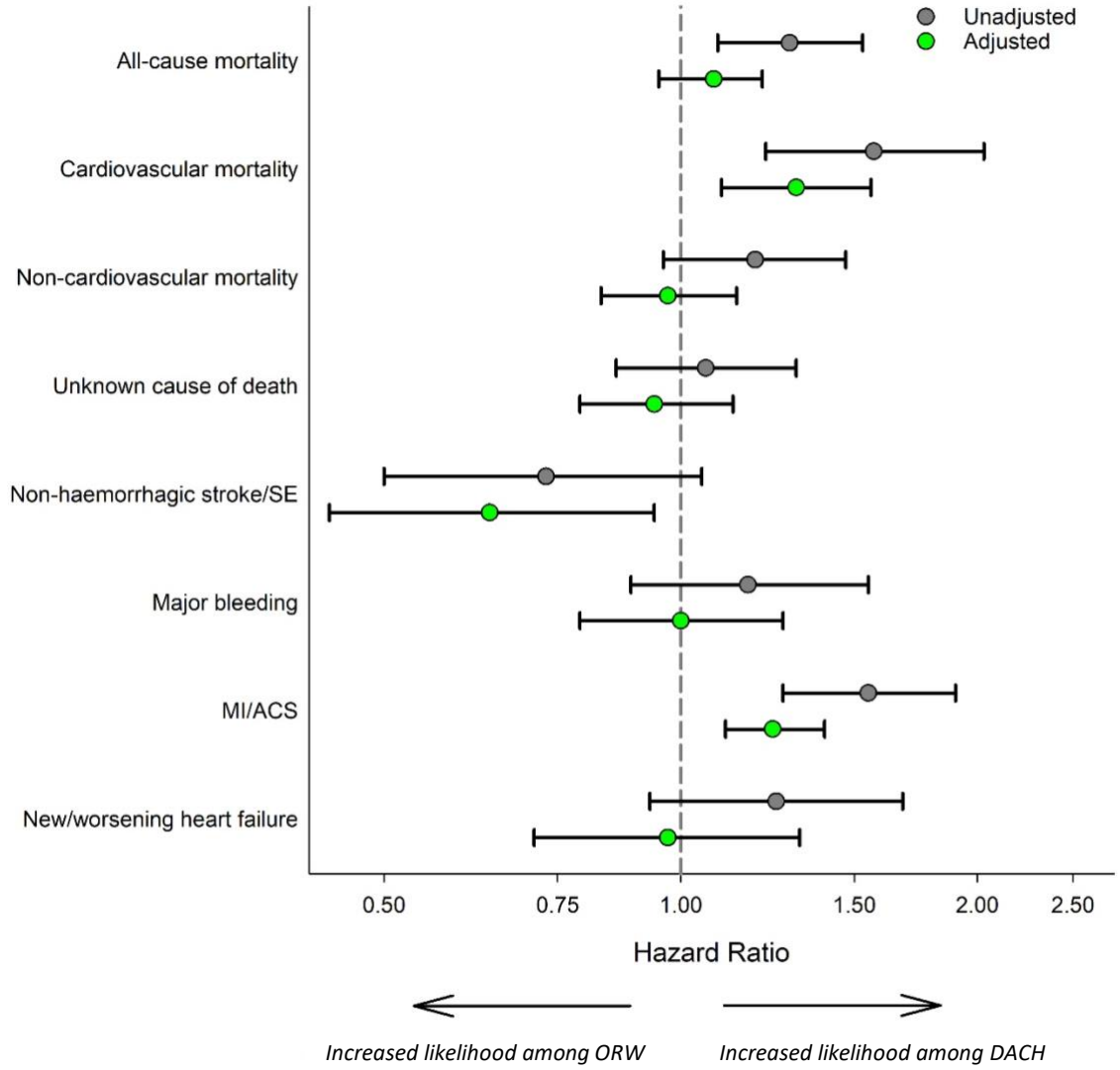


AP antiplatelet, DACH Germany Austria and Switzerland, ORW other regions worldwide, NOAC non-vitamin K oral anticoagulant, VKA vitamin-K antagonist.

[a]A total of 15112 patients had unavailable baseline treatment or HAS-BLED score information (13681 among ORW and 1431 among DACH). These patients were excluded from this analysis;

[b]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 and not 9. However, as no single patient in either region had a score of 7 or 8, the classes with the highest scores were restricted from 4 to 6.

Figure 4: Unadjusted and adjusted[a] event rates (per 100 person-years) within two-years follow-up by region of enrolment[b]



ACS acute coronary syndrome, DACH Germany Austria and Switzerland, MI myocardial infarction, ORW other regions worldwide.

[a]Hazard ratio adjusted by age, sex, ethnicity, type of AF, heart failure, vascular disease, hypertension, prior stroke/TIA/SE, prior bleeding, diabetes, moderate-to-severe CKD, baseline anticoagulation and antiplatelet therapy

[b] A total of 39 patients had unavailable follow-up information (34 among ORW and 5 among DACH); the sample size for this analysis thus consists of 47902 for ORW and 4116 for DACH.

Table S1. Distribution of enrolled patients by cohort and region/country of enrolment

Cohort (enrolment period)	DACH				ORW
	Germany	Austria	Switzerland	All DACH countries	
Cohort 1 (2010-2011)	916 (25.7)	4438 (9.3)	0 (0.0)	1062 (25.8)	4438 (9.3)
Cohort 2 (2011-2013)	917 (25.7)	10615 (22.1)	0 (0.0)	1039 (25.2)	10615 (22.1)
Cohort 3 (2013-2014)	649 (18.2)	10743 (22.4)	0 (0.0)	696 (16.9)	10743 (22.4)
Cohort 4 (2014-2015)	518 (14.5)	10654 (22.2)	27 (30.3)	624 (15.1)	10654 (22.2)
Cohort 5 (2015-2016)	567 (15.9)	11486 (24.0)	62 (69.7)	700 (17.0)	11486 (24.0)
All cohorts (2010-2016)	3567 (100.0)	47936 (100.0)	89 (100.0)	4121 (100.0)	47936 (100.0)

DACH Germany Austria and Switzerland, ORW other regions worldwide.