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DOI:
10.1016/j.amjmed.2018.03.024

Accepted Manuscript

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PII: S0002-9343(18)30305-X
DOI: https://doi.org/10.1016/j.amjmed.2018.03.024
Reference: AJM 14608

To appear in: *The American Journal of Medicine*

Please cite this article as: Michał Mazurek, Menno V. Huisman, Kenneth J. Rothman, Miney Paquette, Christine Teutsch, Hans-Christoph Diener, Sergio J. Dubner, Jonathan L. Halperin, Kristina Zint, Lionel Riou França, Shihai Lu, Gregory Y.H. Lip, GLORIA-AF Investigators, Gender Differences in Antithrombotic Treatment for Newly Diagnosed Atrial Fibrillation: the GLORIA-AF Registry Program, *The American Journal of Medicine* (2018), https://doi.org/10.1016/j.amjmed.2018.03.024.

Gender Differences in Antithrombotic Treatment For Newly Diagnosed Atrial Fibrillation: the GLORIA-AF Registry Program

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Running head: Gender-related anticoagulation in atrial fibrillation

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Clinical Trial Registration: http://www.clinicaltrials.gov. Unique identifier: NCT01468701

Authorship: All authors had access to the data and played a role in writing this manuscript.

Highlights:

- Effective stroke prevention in atrial fibrillation requires oral anticoagulation.
- Globally, similar proportions of women and men were prescribed oral anticoagulation.
- The decision to prescribe oral anticoagulation does not seem to be gender-dependant.
- Other non-gender risk factors play a predominant role in anticoagulation decision making.

Abstract

Aims

Data on gender differences in oral anticoagulation for stroke prevention in patients with atrial fibrillation are conflicting, largely limited to regional reports and Vitamin K antagonist (VKA) use. We aimed to analyze gender-specific anticoagulant prescription patterns early following the introduction of non-VKA oral anticoagulants (NOACs) in a large, global registry on atrial fibrillation.

Methods and Results

Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) is an international registry program involving patients with newly diagnosed atrial fibrillation (<3 months from arrhythmia onset). We used data from 15,092 consecutive patients (median age 71.0 years; women 45.5%) enrolled between 2011 and 2014. Globally, 79.7% women and 80.2% men were anticoagulated; the absolute between-gender difference in prevalence of anticoagulant use was −0.5% (95% CI, −1.8%, 0.8%). VKAs

were prescribed to 32.8% and 31.9% (NOACs 46.8% and 48.3%) of women and men, respectively. No confounder for the association between gender and anticoagulant prescription was identified. Between-gender differences in anticoagulant use (lower use in women compared with men by decreasing order of magnitude of the difference) were found for: CHA_2DS_2-VASc score=1; $CHADS_2$ score=0; previous bleeding; age <65 years; no history of hypertension; myocardial infarction; coronary artery disease; North America region; and specialist office setting.

Conclusion

Globally, the prevalence of anticoagulant use is similar in women and men. The decision to prescribe oral anticoagulation seems to depend predominantly upon guideline-related differences in stroke risk stratification rather than on gender.

Keywords: Atrial Fibrillation, Oral Anticoagulation, Gender, GLORIA-AF

Introduction

Atrial fibrillation increases the risk of stroke.[1,2] For reasons not entirely clear, thromboembolic risk is overall higher in women than in men.[3–5] Gender-specific arterial structure, alternations in blood flow and endothelial function, increased inflammatory and thrombogenic status are examples of the potential reasons for this difference.[6,7] Consequently, female gender has been incorporated into the stroke risk stratification scheme, *i.e.,* CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack [TIA], vascular disease, age 65-74 years, sex category [female]).[8] The majority of guidelines for atrial fibrillation recommend that oral anticoagulation should be considered in patients with ≥1 non-gender related risk factors for stroke (*i.e.*, CHA_2DS_2-VASc ≥1 in men and CHA_2DS_2-VASc ≥2 in women).[9–13]

Despite these recommendations, published data indicate variability in anticoagulation by gender, ranging from a 50% lower uptake in women versus men to more prevalent anticoagulation in women.[6,14–17] Patients described in these reports were geographically clustered and the anticoagulant was largely confined to Vitamin K antagonists (VKAs). Here we present findings from Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF), which provides a unique opportunity to assess contemporary anticoagulation uptake worldwide.[18] The Phase II data allow for analyses of early practice patterns following the introduction of non-VKA oral anticoagulants (NOACs). Our goal was to assess baseline antithrombotic treatment strategies in women versus men and identify potential gender-related gaps in treatment for stroke prevention.

Methods

Study Design

The design of GLORIA-AF has been published.[18] In short, GLORIA-AF is a large ongoing, prospective registry program enrolling patients with a diagnosis of new onset, non-valvular atrial fibrillation at risk for stroke. Inclusion criteria are: adult, newly diagnosed non-valvular atrial fibrillation (<3 months prior study enrolment), and ≥1 stroke risk factor in the CHA_2DS_2VASc scale. The main exclusion criteria are mechanical heart valve or valvular disease with the need for surgical intervention, prior VKA therapy for any reason for >60 days, indications other than atrial fibrillation for anticoagulant use, reversible cause of arrhythmia and life expectancy <1 year.

Thromboembolic and bleeding risks were assessed based on CHA_2DS_2-VASc and HAS-BLED (hypertension, abnormal renal and liver function, stroke, bleeding, age ≥65 years, drugs or alcohol) scales, respectively.[8,19] Low-risk of stroke was defined by CHA_2DS_2-VASc=1 in women (men with CHA_2DS_2-VASc=0 were not recruited); moderate-risk were men with CHA_2DS_2-VASc=1; and high-risk were those with CHA_2DS_2-VASc score ≥2, irrespective of gender. Bleeding risk was defined as low (HAS-BLED score<3) or high (score≥3).[19]

Data Collection and Timelines

For collection, storing and assuring safety and confidentiality of data, a validated Electronic Data Capture System was employed. To monitor data quality, multiple edit checks, data quality reviews and on-site monitoring visits were arranged and local investigators were instructed on system functionality and requirements. This analysis is based on cross-sectional, baseline data of patients enrolled from 2011 through 2014 (Phase II of the program, after first NOACs availability).

Statistical Analysis

The continuous variables were expressed as median (Q1, Q3), whereas categorical variables as frequencies and percentages. To investigate the absolute between-gender difference in anticoagulation prescription, both overall and within strata defined by covariates, a binomial regression analysis was employed.[20] Binomial regression allows direct estimation of the difference between proportions of males and females prescribed anticoagulants. The first step of the analysis was to screen out potential confounders for gender. The change−in−estimate method was applied to verify how much adjusting one covariate can change the coefficient (anticoagulant prescription difference) of gender using binomial regression. To be considered potential confounders requiring adjustment in subsequent multivariable analyses, covariates were required to change the gender coefficient by at least 10%.

The second step was to investigate the overall gender difference in anticoagulant prescription by multivariable binomial regression analysis including gender and all potential confounders found, if any, in the first step. The third step was to investigate the gender differences within strata defined by covariates of clinical relevance, as outlined in Table S2. The multivariable binomial regression analyses were performed, each with 2 risk factors (gender and another risk factor) and the interaction term, along with all potential confounders found, if any, in the first step, associated with prescription of anticoagulation against no anticoagulation.

Confidence intervals were based on likelihood ratio. Patients with missing values were excluded from the binomial regression analyses. Analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Overall, 15,092 consecutive patients (45.5% women) were enrolled (Table 1). Women were older, with 45.8% ≥75 years, compared with 33.6% men. The prevalences of hypertension, hyperlipidemia, diabetes, previous stroke/TIA, abnormal kidney function, previous bleeding episode and cancer were similar in both genders. A quarter of men (24.8%) had coronary artery disease and 13.8% prior myocardial infarction, whereas for women the corresponding proportions were approximately 50% lower. Paroxysmal atrial fibrillation was more common in women (57.2%) than in men (50.1%), as was symptomatic arrhythmia (31.4% versus 25.5%, respectively).

Based on the CHA_2DS_2-VASc score, low risk of stroke was observed in 4.8% of women (score=1; female with no additional stroke risk factors), and 95.2% were at high risk (score ≥2). Moderate risk of stroke (score=1) was observed in 21.4% of men and high risk (score ≥2) in 78.6% men (Table 2). Bleeding risk was unknown for 10.3% of women (men: 13.2%), low for 81.3% of women (men: 77.1%) and high for 8.4% of women (men: 9.7%), as assessed by the HAS-BLED score.

Confounders For Gender in the Oral Anticoagulation Prescription

By the change−in−estimate method, because all covariates caused relatively small changes (less than 10%) for the coefficient of gender in the binomial regression, no covariate was

identified as a potential confounder that needed adjustment in subsequent analyses (Table S1).

Antithrombotic Therapy in Women and Men

Overall, 79.7% of women and 80.2% men were prescribed anticoagulants (Table 2), the absolute between-gender difference (women *versus* men) in anticoagulant use being −0.5% (95% CI, −1.8%, 0.8%) [Table S1]. Anticoagulant choice was similar between genders: 32.8% women and 31.9% men were prescribed VKAs (NOACs 46.8 % and 48.3%). Overall, 8.1% of women and 7.6% men were given no antithrombotic therapy, while aspirin was prescribed to 11.3% of both genders.

Antithrombotic Therapy in Relation to Stroke and Bleeding Risks

Antithrombotic therapies in relation to thromboembolic risk are presented in Figure 1, Panel A. For CHA_2DS_2-VASc=1, 46.1% of women and 69.8% of men were prescribed anticoagulants, whereas the corresponding proportions for CHA_2DS_2-VASc score ≥2 were 81.4% and 83.0%, respectively. Detailed treatment strategies according to stroke risk (as per CHA_2DS_2-VASc score 1-9) are presented in Figure 2, separately for women (Panel A) and men (Panel B).

Of the studied population, 18.3% of women and 17.0% men at low risk of bleeding (HAS-BLED score of 0-2) were not anticoagulated, whereas the corresponding proportions for those at high risk of hemorrhage (HAS-BLED ≥3) were 34.7% and 31.6%, respectively (Figure 1, Panel B). Aspirin was the most commonly prescribed antithrombotic drug in both women (28.3%) and men (27.1%) at high risk of bleeding.

Antithrombotic Treatment by Geographic Region

Apart from evident between-region differences in overall anticoagulant use and choice of specific anticoagulant agents, oral anticoagulation by gender was similar within particular regions (Figure 3). The exception was noted in North America, where fewer women (75.9%) than men (80.4%) were anticoagulated. The corresponding proportions for anticoagulant use by females and males in other regions were as follows: 54.4 vs 55.8% in Asia; 89.9 vs 90.2% in Europe, 86.8 vs 84.1% in Latin America and 88.7 vs 86.3% for Africa/Middle East, respectively.

Gender Difference in Anticoagulation Prescription by Covariates

Gender differences in oral anticoagulant prescription within strata defined by variables of clinical relevance and their interaction term associated with prescription of anticoagulation against no anticoagulation are presented in Figure 1, Panel C and Table S2. Between-gender (women *versus* men) differences in anticoagulant use were found for (by decreasing order of magnitude of the difference): CHA_2DS_2-VASc score=1; $CHADS_2$ score=0; previous bleeding; age <65 years; no history of hypertension; myocardial infarction; coronary artery disease; North America region; and specialist office setting.

Discussion

The principal finding of our study is that globally similar proportions of women (79.7%) and men (80.2%) are prescribed oral anticoagulation for stroke prevention in atrial fibrillation. Second, oral anticoagulant choice is unaffected by gender (approximately 1/3 and 1/2 are prescribed VKAs and NOACs, respectively). Third, when exploring subgroups, the most

important difference in anticoagulant use identified between women and men is for patients with a CHA_2DS_2-VASc score of 1 (46.1% of women and 69.8% of men, respectively); this difference may be linked to guideline recommendations for atrial fibrillation, hence the decision to prescribe anticoagulation is not gender-dependent, but may rely predominately upon clinical stroke risk factors.

Although we found no confounders for the association between gender and anticoagulant use as well as global anticoagulation was nearly identical amongst women and men, we identified several factors of clinical relevance to interact with gender and anticoagulants prescription (*i.e.,* thromboembolic risk, previous bleeding, age, geographic region, health care setting, comorbid coronary artery disease, myocardial infarction or hypertension).

The largest between-gender difference in anticoagulant use (46.1% and 69.8% for women and men, respectively) was found for CHA_2DS_2-VASc score of 1. This reflects a different clinical approach to a score of 1 in both genders, rather than an underuse of anticoagulation in women compared with men. On the contrary, women with this score seem over-treated with anticoagulants. Indeed, past European guidelines (in effect during enrolment period for Phase II of GLORIA-AF, 2011-2014) as well as present guidelines in Europe state that women with CHA_2DS_2-VASc=1 (1 point for female gender only) are at "truly low-risk" for stroke and should not be anticoagulated as this brings no benefit but may cause harm.[9–11] By contrast, anticoagulation should be considered in patients with 1 non-gender related risk factors for stroke, that is CHA_2DS_2-VASc=1 for men and CHA_2DS_2-VASc=2 for women.[9,10] We observed similar proportions of women and men with one non-gender related risk factor being anticoagulated (71.9% and 69.1%, respectively).

A similar pattern (less anticoagulant use for women than men) was noted for those aged <65 years with no history of hypertension, which seems to reflect treatment strategy for low risk patients. We observed no between-gender differences for patients ≥65 years of age or with comorbid hypertension. Indeed, on the other side of the stroke risk continuum (high-risk cohort), as defined by the CHA_2DS_2-VASc ≥2 (regardless of gender), we observed a similar anticoagulation by women and men, at 81.4% and 83.0%, respectively. Nonetheless, we found that fewer women than men were anticoagulated if they had a previous bleeding event, even though no major between-gender differences were noted with regard to bleeding risk, as per HAS-BLED scheme. The reasons for this disparity in anticoagulation patterns between men and women are not fully understood, but perhaps may reflect a differently perceived (higher in women) risk of bleeding complications in relation to gender. Importantly, the net clinical benefit of anticoagulation, when balancing stroke risk reduction versus increased risk of bleeding, is positive and even greater in patients at increased risk of bleeding.[21,22]

Regional disparities in anticoagulant use by gender may result from various guideline recommendations issued by different societies, largely due to different thresholds for anticoagulation initiation.[23,24] We found that fewer women than men were anticoagulated in North America. Our findings are consistent with recent report of the PINNACLE Registry, which found that in North America women are less likely to be anticoagulated.[25] Unlike European guidelines, the American recommendations offer OAC, aspirin or no stroke prophylaxis to patients with CHA_2DS_2-VASc=1 (regardless of gender), whereas anticoagulation is recommended for those with the score ≥2.[11,26] By considering female

gender as a risk factor for those with CHA_2DS_2-VASc=1, the American guidelines (in contrast to European guidelines) could potentially be recommending anticoagulation for women who may be at truly low risk for stroke (thus, potential drug overuse), whereas anticoagulants may be underused in men at moderate risk of stroke.[24,27,28] Although the difference in anticoagulation rates amongst women versus men in North America is modest, patients with one risk factor for stroke constitute only the minority of atrial fibrillation population, for example only 13.9% in the present analysis (and taking into account the fact that men with CHA_2DS_2-VASc=0 were not recruited by GLORIA-AF). Importantly, though 1-year stroke rates in untreated patients with only 1 risk factor for stroke (beyond gender) vary amongst studies, the majority of reports show evident clinical benefit of anticoagulation versus no anticoagulation.[24,27–30] The same reports show also no benefit of anticoagulation in patients with no stroke risk factors, that is men with CHA_2DS_2-VASc=0 and women with CHA_2DS_2-VASc=1 (one point for female gender only).

In Canada, female gender is not perceived as a stroke risk factor and anticoagulation is recommended for patients with $CHADS_2$ ≥1 (Congestive Heart Failure, Hypertension, Age≥75, Diabetes, Stroke/TIA).[31] We observed no difference in anticoagulant use by gender for $CHADS_2$ ≥1, but fewer women than men were anticoagulated if $CHADS_2$ score was 0. In contrast to CHA_2DS_2-VASc scoring system, employment of $CHADS_2$ scheme may underestimate the risk of stroke in patients categorized as low risk (score=0).[32] Indeed, in Canada, a woman age <65 years with vascular disease is not recommended anticoagulation ($CHADS_2$=0), whereas in Europe anticoagulation is considered/indicated (CHA_2DS_2-VASc=2) for such women.[9–12] Importantly, women versus men with vascular disease (i.e. coronary

artery disease and prior myocardial infarction) in the present analysis were less likely to be anticoagulated.

A recent report from 3 nationwide registries suggests that female gender is a "stroke risk modifier" rather than a "stroke risk factor" and although stroke risk may be higher in women versus men it seems that "female gender" may be safely omitted in decision making on oral anticoagulation prescription.[33] Thus, use of a CHA_2DS_2-VA score (i.e. excluding gender criterion) may be considered.

Limitations

Per study protocol, GLORIA-AF recruited patients with CHA_2DS_2-VASc score ≥1. Thus, no data on males with score zero (low-risk of stroke) were available. Our analyses are based on the prescription of baseline anticoagulation in relation to gender, and thus we could assess neither quality of anticoagulation nor changes in practice patterns over time. Only patients with new onset atrial fibrillation (not all-comers) were recruited. Both patients and physicians knew they were participants of a registry program and patients could join the study only after signing an informed consent. This might have led to higher overall anticoagulation rates compared with general population.

In order to analyze many clinically important factors affecting decision making on anticoagulation prescription, we have performed a log-binomial analysis of anticoagulant use against no anticoagulant use, instead of analyzing the use of each of the anticoagulants separately. Also, we did not analyze the associations between anticoagulant use and concomitant dual antiplatelet therapy use by gender. A detailed analysis of various combinations of antiplatelet therapy use ± anticoagulant use that may have varying

durations of use is beyond the scope of the current analysis that focuses on gender differences.

We used a 10% absolute change in the coefficient of gender as a cut-off for identification of confounders of the association between gender and anticoagulant use. More typically, a 10% relative change is used. We opted for an absolute cut-off because the effect of gender on anticoagulant use seems nearly null. The results would have been unchanged for any absolute change threshold above 2.3% (Table S1). With the threshold 2.3% (or any above 1.1%), the retained model would have adjusted for CHA_2DS_2–VASc score and the resulting absolute difference in anticoagulation between women and men would have shifted from -0.5% (95% CI −1.8, 0.8) to -2.8% (−4.0,−1.5) (Table S1), which would still support our principal finding that the oral anticoagulant use is globally similar between women and men. In addition, a model estimating the effect of gender when adjusting for all other factors has been reported;[34] the effect of gender on anticoagulation was not affected by the adjustments (relative risk of anticoagulant prescription for females compared with males: 0.99 unadjusted vs. 0.99 adjusted for all other factors). We have therefore no reason to suspect that our results were sensitive to this choice.

A few variables had non-negligible proportions of missing values. For example, creatinine clearance had 21% missing, HAS-BLED score had 12% missing, and alcohol abuse had 8% missing. Multiple imputation to deal with missing values was not planned in the phase II analyses, which are mostly descriptive, but this will be considered for phase III.

Conclusion

Globally, the prevalence of anticoagulant use is similar in women and men. The decision to prescribe oral anticoagulation seems to depend predominantly upon guideline-related differences in stroke risk stratification rather than on gender.

Funding

This work was supported by Boehringer Ingelheim GmbH.

Conflict of interest:

M.M. declares no conflict of interest. M.V.H. has received honoraria for presentations and research grants from Boehringer Ingelheim, Bayer HealthCare, Pfizer, GlaxoSmithKline (GSK), and Actelion Pharmaceuticals. K.J.R. is an employee of RTI Health Solutions, an independent nonprofit research organization that does work for government agencies and pharmaceutical companies. H.C.D. has received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from: Abbott, Allergan, AstraZeneca, Bayer Vital, BMS, Boehringer Ingelheim, CoAxia, Corimmun, Covidien, Daiichi-Sankyo, D-Pharm, Fresenius, GSK, Janssen-Cilag, Johnson & Johnson, Knoll, Lilly, MSD, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo-Nordisk, Paion, Parke-Davis, Pfizer, Sanofi-Aventis, Schering-Plough, Servier, Solvay, St Jude, Syngis, Talecris, Thrombogenics, WebMD Global, Wyeth and Yamanouchi. Financial support for research projects was provided by AstraZeneca, GSK, Boehringer Ingelheim, Lundbeck, Novartis, Janssen-Cilag, Sanofi-Aventis, Syngis and Talecris. The Department of Neurology at the University Duisburg-Essen received research grants from the German Research Council (DFG), the German Ministry of Education and Research (BMBF), the European Union, the National Institutes of Health (NIH), the Bertelsmann Foundation, and the Heinz-Nixdorf Foundation; H.C.D. has no ownership interest and does not own stocks of any pharmaceutical company; within the past year H.C.D. served as the editor of Aktuelle Neurologie, Arzneimitteltherapie, Kopfschmerznews, Stroke News, as the co-editor of Cephalalgia and was on the editorial board of Lancet Neurology, Stroke, European Neurology and Cerebrovascular Disorders; H.C.D. chairs the Treatment Guidelines Committee of the German Society of Neurology and has contributed to the European Heart Rhythm Association (EHRA) and the European Society of Cardiology (ESC) guidelines for the treatment of atrial fibrillation. S.J.D. has received consultancy fees for serving as a steering committee member for Boehringer Ingelheim. He also holds research grants from St Jude Medical. J.L.H. is currently conducting research sponsored by Boehringer Ingelheim as a member of the Executive Steering Committee for the GLORIA-AF Registry, and has received consulting fees from Bayer HealthCare, Janssen-Ortho-McNeil, and Pfizer for advisory activities involving the development of anticoagulant drugs. M.P., C.T., K.Z., L.R.F. and S.L. are employees of Boehringer Ingelheim. G.Y.H.L. has been a consultant for Bayer/Janssen, Astellas, Merck, Sanofi, Bristol-Myers Squibb (BMS)/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo. He has also been a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo.

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Legends

Figure 1 Gender Differences in Antithrombotic Therapy Prescription by Stroke (Panel A) and Bleeding Risk (Panel B) and Covariates (Panel C)

ASA – aspirin; VKA – Vitamin K antagonists; Other – antiplatelets other than aspirin and combination of antithrombotic agents; HAS-BLED – missing values = 706 (10.3%) in women and 1083 (13.2%) in men

Figure 2 Antithrombotic Treatment in Relation to Stroke Risk in Females (Panel A) and Males (Panel B)

ASA – aspirin; OAC – oral anticoagulant; Other – antiplatelets other than aspirin and combination of antithrombotic agents; N/A – not applicable in men

Figure 3 Antithrombotic Treatment by Gender and Region

ASA – aspirin; NOAC - non-Vitamin K antagonist oral anticoagulants; VKA – Vitamin K antagonists; Other – antiplatelets other than aspirin and combination of antithrombotic agents

Table 1 Baseline Characteristics

N (%) or median [Q1, Q3]	**All** n=15,092 (100%)	**Women** n=6872 (45.5%)	**Men** n= 8220 (54.5%)
Patient characteristics			
Age, years (median [Q1, Q3])	71.0 (64.0, 78.0)	73.0 (66.0, 80.0)	70.0 (62.0, 77.0)
<65 years	4064 (26.9)	1464 (21.3)	2600 (31.6)
65-74 years	5121 (33.9)	2261 (32.9)	2860 (34.8)
≥75 years	5907 (39.1)	3147 (45.8)	2760 (33.6)
Current-smoker	1428 (9.5)	320 (4.7)	1108 (13.5)
Past smoker	4376 (29.0)	1127 (16.4)	3249 (39.5)
Creatinine clearance [ml/min] (median [Q1, Q3])	73.5 (55.3, 97.0)	66.8 (50.4, 87.9)	80.4 (60.6, 103.9)
Medical history			
Hypertension	11255 (74.6)	5177 (75.3)	6078 (73.9)
Hyperlipidemia	6026 (39.9)	2671 (38.9)	3355 (40.8)
Diabetes mellitus	3487 (23.1)	1472 (21.4)	2015 (24.5)
Previous stroke/TIA	2147 (14.2)	1008 (14.7)	1220 (14.8)
Congestive heart failure	3647 (24.2)	1419 (20.6)	2228 (27.1)
Ejection fraction <40%[a]	1388 (38.1)	370 (26.1)	1018 (45.7)
Coronary artery disease	3068 (20.3)	1029 (15.0)	2039 (24.8)
Myocardial infarction	1600 (10.6)	464 (6.8)	1136 (13.8)
Peripheral artery disease	475 (3.1)	130 (1.9)	345 (4.2)
Chronic gastrointestinal diseases	1976 (13.1)	960 (14.0)	1016 (12.4)
Abnormal kidney function[b]	241 (1.6)	80 (1.2)	161 (2.0)
Previous bleeding event	842 (5.6)	382 (5.6)	460 (5.6)
Alcohol abuse, ≥8 units/week	996 (6.6)	158 (2.3)	838 (10.2)
Cancer	1401 (9.3)	619 (9.0)	782 (9.5)
Type of AF			
Paroxysmal	8052 (53.4)	3931 (57.2)	4121 (50.1)
Persistent	5362 (35.5)	2224 (32.4)	3138 (38.2)
Permanent	1678 (11.1)	717 (10.4)	961 (11.7)
Categorization of AF			
Symptomatic	4263 (28.2)	2157 (31.4)	2106 (25.6)
Minimally Symptomatic	6004 (39.8)	2896 (42.1)	3108 (37.8)
Asymptomatic	4825 (32.0)	1819 (26.5)	3006 (36.6)

Interventions in AF			
AF cardioversion	2431 (16.1)	1084 (15.8)	1347 (16.4)
AF ablation	161 (1.1)	61 (0.9)	100 (1.2)
Health-care setting			
GP/primary care	968 (6.4)	451 (6.6)	517 (6.3)
Specialist office	4567 (30.3)	2034 (29.6)	2533 (30.8)
Community hospital	3969 (26.3)	1870 (27.2)	2099 (25.6)
University hospital	5081 (33.7)	2286 (33.3)	2795 (34.0)
Outpatient health care center	239 (1.6)	113 (1.6)	126 (1.5)
Anticoagulation clinic	142 (0.9)	60 (0.9)	82 (1.0)
Other	126 (0.8)	58 (0.8)	68 (0.8)
Region			
Region 1 – Asia	3071 (20.3)	1337 (43.5)	1734 (56.5)
Region 2 – Europe	7108 (47.1)	3317 (46.7)	3791 (53.3)
Region 3 – North America	3403 (22.5)	1524 (44.8)	1879 (55.2)
Region 4 – Latin America	913 (6.0)	410 (44.9)	503 (55.1)
Region 5 – Africa/Middle East	597 (4.0)	284 (47.6)	313 (52.4)

AF = atrial fibrillation; GP = general practitioner; SD = standard deviation; TIA = transient ischemic attack

[a]For patients with congestive heart failure

[b]Defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 µmol/L

Unknown/missing values: 1188 for alcohol abuse, 565 for smoking status, 440 for hyperlipidemia, 243 for abnormal kidney function, 15 for physician specialty, 941 for medical reimbursement, 2 for TIA/stroke, 411 for coronary artery disease, 9 for myocardial infarction, 149 for congestive heart failure, 36 for hypertension, 133 for peripheral artery disease, 117 for cancer, 172 for chronic gastrointestinal diseases, 276 for prior bleeding, 220 for AF cardioversion, 145 for AF ablation, 3221 missing for creatinine clearance.

Table 2 Thromboembolic/Bleeding Risk and Antithrombotic Therapy by Gender

N (%) or median [Q1, Q3]	**All** n=15,092 (100%)	**Women** n=6872 (45.5%)	**Men** n= 8220 (54.5%)
$CHADS_2$ (median [Q1, Q3])	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	2.0 (1.0, 2.0)
Low Risk (score 0)	1221 (8.1)	730 (10.6)	491 (6.0)
Moderate Risk (score 1)	5150 (34.1)	2086 (30.4)	3064 (37.3)
High Risk (score≥2)	8719 (57.8)	4055 (59.0)	4664 (56.7)
Missing data	2 (0.0)	1 (0.0)	1 (0.0)
CHA_2DS_2-VASc (median [Q1, Q3])	3.0 (2.0, 4.0)	4.0 (3.0, 5.0)	3.0 (2.0, 4.0)
Low Risk (score 1 in women)	332 (2.2)	332 (4.8)	-
Moderate Risk (score 1 in men)	1761 (11.7)	-	1761 (21.4)
High Risk (score≥2)	12999 (86.1)	6540 (95.2)	6459 (78.6)
HAS-BLED (median [Q1, Q3])	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)
Low Risk (score 0-2)	11927 (79.0)	5590 (81.3)	6337 (77.1)
High Risk (score≥3)	1376 (9.1)	576 (8.4)	800 (9.7)
Missing Data	1789 (11.9)	706 (10.3)	1083 (13.2)
Antithrombotic Therapy			
None	1182 (7.8)	558 (8.1)	624 (7.6)
ASA	1706 (11.3)	774 (11.3)	932 (11.3)
VKA	4878 (32.3)	2255 (32.8)	2623 (31.9)
NOAC	7187 (47.6)	3219 (46.8)	3968 (48.3)
Dabigatran	4767 (31.6)	2122 (30.9)	2645 (32.2)
Rivaroxaban	1726 (11.4)	761 (11.1)	965 (11.7)
Apixaban	694 (4.6)	336 (4.9)	358 (4.4)
Other	139 (0.9)	66 (0.9)	73 (0.9)
Overall oral anticoagulation	12065 (79.9)	5474 (79.7)	6591 (80.2)

ASA = aspirin; NOAC = non-Vitamin K antagonist oral anticoagulants; VKA = Vitamin K antagonists; Other = antiplatelets other than aspirin and combination of anticoagulant agents; SD = standard deviation

Unknown/missing values: 2 for $CHADS_2$ score class, 1786 for HAS-BLED risk score class.

Table S1 Binomial Regression Analysis to Select Confounding Variables For Gender Analysis Using Change−in−Estimate Method with 0.10 cut-off For Absolute Change − Dependent Variable in the Models is the Proportion of OAC Prescription (VKA, NOAC)

Gender models	**Gender difference of OAC prescription** coefficient of sex % (95% CI)	**Absolute change in estimate of sex coefficient**
No adjustment for other variable	−0.5 (−1.8, 0.8)	0.0
Adjustment of Age	−1.2 (−2.4, 0.1)	0.7
Adjustment of Type of AF	0.2 (−1.0, 1.4)	0.7
Adjustment of Categorization of AF	−0.4 (−1.7, 0.8)	0.1
Adjustment of AF cardioversion	−0.5 (−1.8, 0.8)	0.0
Adjustment of Hypertension	−0.3 (−1.6, 0.9)	0.2
Adjustment of Diabetes mellitus	−0.4 (−1.7, 0.8)	0.1
Adjustment of Previous stroke/TIA	−0.5 (−1.7, 0.8)	0.0
Adjustment of Congestive heart failure	−0.5 (−1.8, 0.8)	0.0
Adjustment of Coronary artery disease	−1.0 (−2.3, 0.3)	0.5
Adjustment of Myocardial infarction	−0.7 (−2.0, 6.0)	0.2
Adjustment of Peripheral artery disease	−0.4 (−1.7, 0.9)	0.1
Adjustment of Previous bleeding events	−0.4 (−1.7, 0.9)	0.1
Adjustment of Creatinine clearance <60ml/min	−0.2 (−1.6, 1.3)	0.3
Adjustment of Alcohol abuse	−1.0 (−2.4, 0.3)	0.5
Adjustment of Cancer	−0.5 (−1.7, 0.8)	0.0
Adjustment of Chronic gastrointestinal diseases	−0.4 (−1.7, 0.8)	0.1
Adjustment of No coverage for medications	−0.9 (−2.2, 0.4)	0.4
Adjustment of $CHADS_2$	0.1 (−1.1, 1.4)	0.6
Adjustment of CHA_2DS_2−VASc	−2.8 (−4.0,−1.5)	2.3
Adjustment of HAS−BLED	−1.6 (−3.0,−0.3)	1.1
Adjustment of Region	−0.7 (−1.9, 0.4)	0.2
Adjustment of Type of site	−0.5 (−1.8, 0.7)	0.0
Adjustment of Physician specialty	−0.6 (−1.9, 0.7)	0.1

For abbreviations and unknown/missing values please refer to footnotes of Table 1-2; 12 patients who were prescribed a combination of OACs and patients with unknown/missing values were excluded from the binomial regression analyses.

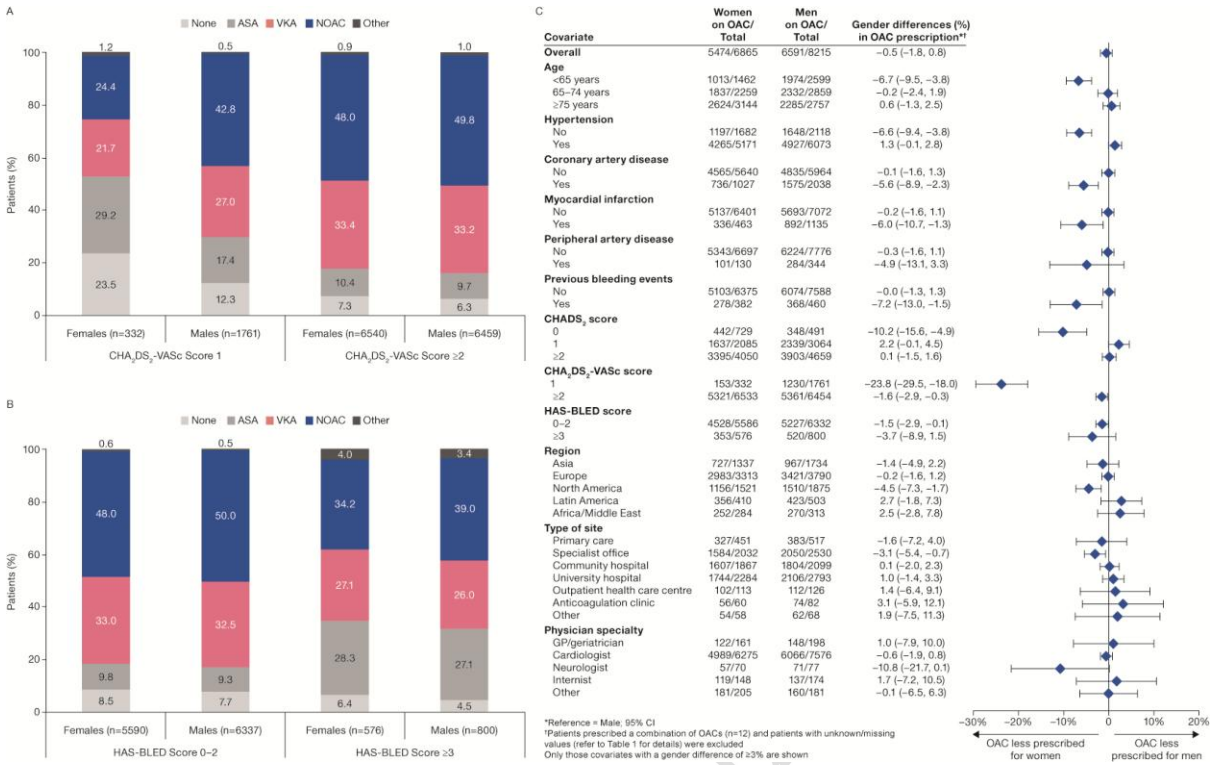
Table S2 Multivariable Analysis For Gender Differences by Covariates – Binomial Regression Analysis with 2 Risk Factors (Gender and Another Risk Factor) and Their Interaction Term Associated with Prescription of OAC against No OAC

Strata defined by covariates		**Men** Number of pts (on OAC/total)	**Women** Number of pts (on OAC/total)	**Gender difference of OAC prescription** (Reference = Male; %, 95% CI)
Age category				
	<65 years	1974/2599	1013/1462	−6.7 (−9.5,−3.8)
	65-74 years	2332/2859	1837/2259	−0.2 (−2.4, 1.9)
	≥75 years	2285/2757	2624/3144	0.6 (−1.3, 2.5)
Type of AF				
	Paroxysmal	3085/4117	2952/3927	0.2 (−1.7, 2.1)
	Persistent	2626/3137	1864/2221	0.2 (−1.8, 2.2)
	Permanent	880/961	658/717	0.2 (−2.5, 2.9)
Categorization of AF				
	Symptomatic	1704/2106	1784/2155	1.9 (−0.4, 4.2)
	Minimally Symptomatic	2455/3106	2244/2894	−1.5 (−3.6, 0.6)
	Asymptomatic	2432/3003	1446/1816	−1.4 (−3.7, 1.0)
AF cardioversion				
	No	5379/6738	4526/5695	−0.4 (−1.8, 1.1)
	Yes	1109/1347	876/1080	−1.2 (−4.3, 1.9)
Hypertension				
	No	1648/2118	1197/1682	−6.6 (−9.4,−3.8)
	Yes	4927/6073	4265/5171	1.3 (−0.1, 2.8)
Diabetes mellitus				
	No	4909/6203	4270/5394	0.0 (−1.5, 1.5)
	Yes	1682/2012	1204/1471	−1.7 (−4.3, 0.8)
Previous stroke/TIA				
	No	5612/7035	4675/5898	−0.5 (−1.9, 0.9)
	Yes	978/1179	799/966	−0.2 (−3.4, 3.0)
Congestive heart failure				
	No	4697/5898	4281/5388	−0.2 (−1.7, 1.3)
	Yes	1830/2228	1142/1417	−1.5 (−4.1, 1.1)
Coronary artery disease				
	No	4835/5964	4565/5640	−0.1 (−1.6, 1.3)
	Yes	1575/2038	736/1027	−5.6 (−8.9,−2.3)
Myocardial infarction				
	No	5693/7072	5137/6401	−0.2 (−1.6, 1.1)
	Yes	892/1135	336/463	−6.0 (−10.7,−1.3)
Peripheral artery disease				
	No	6224/7776	5343/6697	−0.3 (−1.6, 1.1)

	Yes	284/344	101/130	−4.9 (−13.1, 3.3)
Previous bleeding events				
	No	6074/7588	5103/6375	−0.0 (−1.3, 1.3)
	Yes	368/460	278/382	−7.2 (−13.0,−1.5)
Creatinine clearance <60ml/min				
	No	3917/4849	2627/3312	−1.5 (−3.2, 0.3)
	Yes	1210/1549	1737/2149	2.7 (0.1, 5.4)
Alcohol abuse				
	No	5343/6639	4973/6259	−1.0 (−2.4, 0.4)
	Yes	683/838	127/157	−0.6 (−7.3, 6.1)
Cancer				
	No	5882/7369	4915/6197	−0.5 (−1.9, 0.9)
	Yes	648/781	512/617	0.0 (−4.0, 4.0)
Chronic gastrointestinal diseases				
	No	5690/7106	4640/5828	−0.5 (−1.8, 0.9)
	Yes	814/1016	765/958	−0.3 (−3.8, 3.3)
No reimbursement for medications				
	No	5758/7123	4746/5940	−0.9 (−2.3, 0.4)
	Yes	443/591	363/485	−0.1 (−5.3, 5.1)
$CHADS_2$ score				
	Score 0	348/491	442/729	−10.2 (−15.6,−4.9)
	Score 1	2339/3064	1637/2085	2.2 (−0.1, 4.5)
	Score ≥2	3903/4659	3395/4050	0.1 (−1.5, 1.6)
CHA_2DS_2-VASc score				
	Score 1	1230/1761	153/332	−23.8 (−29.5,−18.0)
	Score ≥2	5361/6454	5321/6533	−1.6 (−2.9,−0.3)
HAS-BLED score				
	Score 0-2	5227/6332	4528/5586	−1.5 (−2.9,−0.1)
	Score ≥3	520/800	353/576	−3.7 (−8.9, 1.5)
Region				
	Region 1 - Asia	967/1734	727/1337	−1.4 (−4.9, 2.2)
	Region 2 - Europe	3421/3790	2983/3313	−0.2 (−1.6, 1.2)
	Region 3 - North America	1510/1875	1156/1521	−4.5 (−7.3,−1.7)
	Region 4 - Latin America	423/503	356/410	2.7 (−1.8, 7.3)
	Region 5 - Africa/Middle East	270/313	252/284	2.5 (−2.8, 7.8)
Type of site				
	Primary care	383/517	327/451	−1.6 (−7.2, 4.0)
	Specialist office	2050/2530	1584/2032	−3.1 (−5.4,−0.7)
	Community hospital	1804/2099	1607/1867	0.1 (−2.0, 2.3)
	University hospital	2106/2793	1744/2284	1.0 (−1.4, 3.3)
	Outpatient health care center	112/126	102/113	1.4 (−6.4, 9.1)

	Anticoagulation clinic	74/82	56/60	3.1 (−5.9, 12.1)
	Other	62/68	54/58	1.9 (−7.5, 11.3)
Physician specialty				
	GP/Geriatrician	148/198	122/161	1.0 (−7.9, 10.0)
	Cardiologist	6066/7576	4989/6275	−0.6 (−1.9, 0.8)
	Neurologist	71/77	57/70	−10.8 (−21.7, 0.1)
	Internist	137/174	119/148	1.7 (−7.2, 10.5)
	Other	160/181	181/205	−0.1 (−6.5, 6.3)

For abbreviations and unknown/missing values please refer to footnotes of Table 1-2; 12 patients who were prescribed a combination of OACs and patients with unknown/missing values were excluded from the binomial regression analyses.



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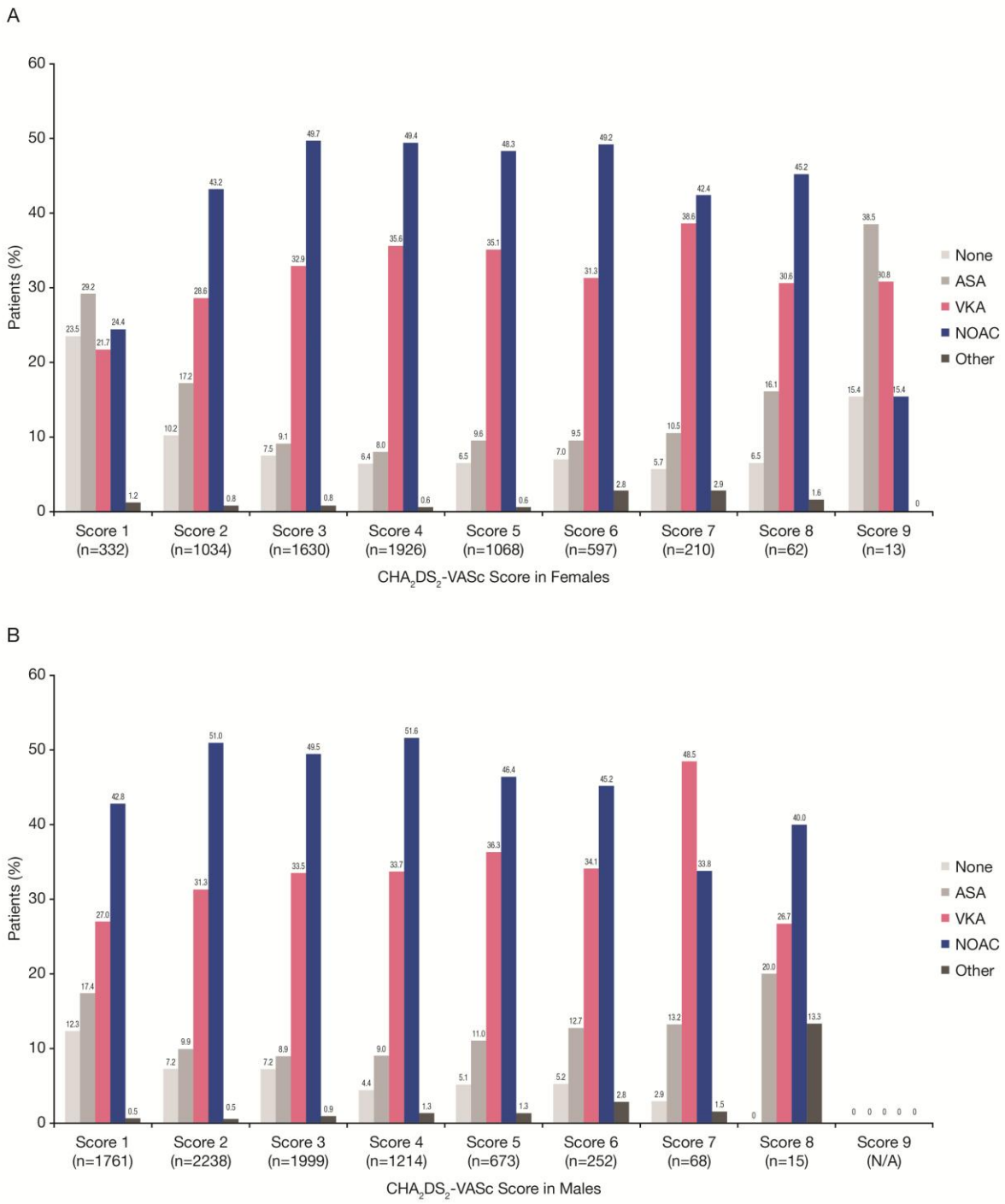

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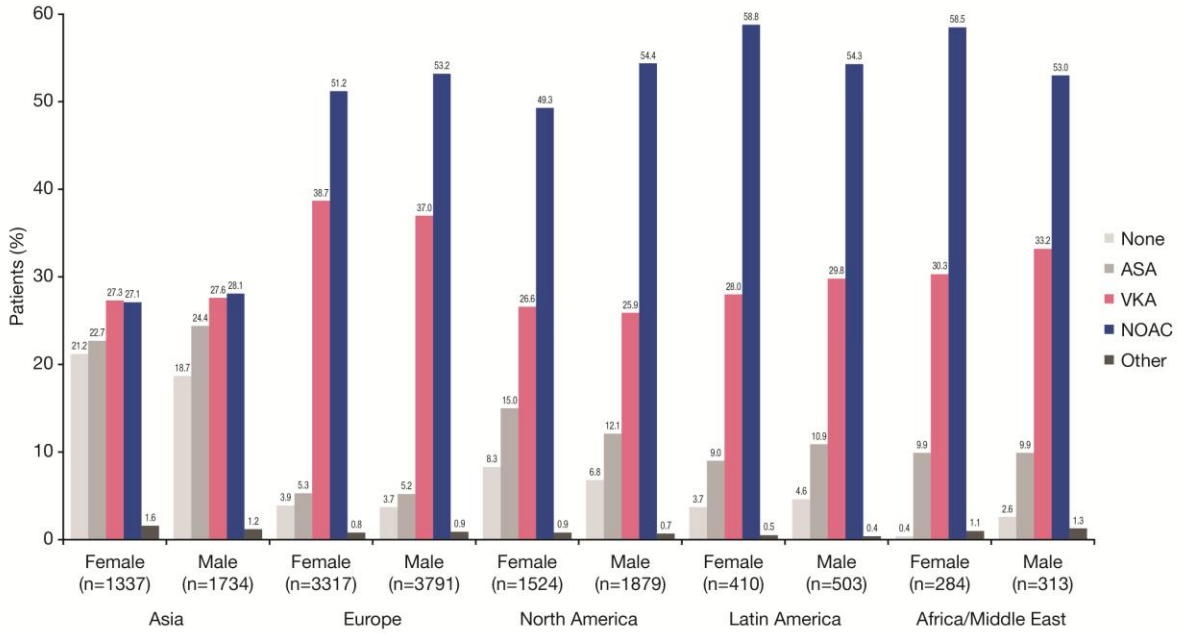

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