Journal of
Clinical Medicine

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Lack of Sex Disparity in Oral Anticoagulation in Atrial Fibrillation Patients Presenting with Ischemic Stroke in a Rural Population

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Abstract: Various studies on oral anticoagulants (OAC) use among atrial fibrillation (AF) patients have shown high rates of undertreatment and the presence of sex disparity. This study used the 'Geisinger Neuroscience Ischemic Stroke' (GNSIS) database to examine sex differences in OAC treatment among ischemic stroke patients with the pre-event diagnosis of AF in rural Pennsylvania between 2004 and 2019. We examined sex disparities in OAC undertreatment and associated risks based on age group and ischemic stroke year. A total of 1062 patients were included in the study and 1015 patients (96%) had CHA_2DS_2-VASc score ≥ 2, of which 549 (54.1%) were women. Undertreatment rates were not statistically significant between men and women in the overall cohort (50.0% vs. 54.5%, $p = 0.18$), and male sex was not found to be a significant factor in undertreatment (OR 0.82, 95% CI 0.62–1.09, $p = 0.17$). The result persisted even when patients were divided into four age groups and two groups based on the study time period. The undertreatment rates in both sex groups remained consistent following the introduction of novel oral anticoagulants. In conclusion, there was no evidence of sex disparity with respect to OAC treatment, even after stratifying the cohort by age and ischemic stroke year.

Keywords: ischemic stroke; atrial fibrillation; oral anticoagulants; undertreatment; sex disparity; CHA_2DS_2-VASc

Citation: Koza, E.; Diaz, J.; Chaudhary, D.; Shahjouei, S.; Li, J.; Abedi, V.; Zand, R. Lack of Sex Disparity in Oral Anticoagulation in Atrial Fibrillation Patients Presenting with Ischemic Stroke in a Rural Population. *J. Clin. Med.* **2021**, *10*, 4670. https://doi.org/10.3390/jcm10204670

Academic Editors: Aaron S. Dumont and Roberto De Ponti

Received: 27 August 2021
Accepted: 30 September 2021
Published: 12 October 2021

1. Introduction

Atrial fibrillation (AF) is a major risk factor for stroke incidence and the most significant cardiac arrhythmia worldwide [1,2]. It is estimated that around 7.6 million Americans have suffered a stroke, with women carrying a higher lifetime risk when compared to men [2]. The increased risk in women has been translated to the clinical practice through the inclusion of female sex within risk stratification models for stroke management, such as the CHA_2DS_2-VASc score [3–6]. Current guidelines by the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) recommend oral anticoagulation (OAC) therapy for all AF patients with a CHA_2DS_2-VASc ≥ 2, and those with a CHA_2DS_2-VASc of 1 should be considered for treatment with OAC or antiplatelets [3].

Despite the AHA/ACC/HRS guidelines for the management of patients with atrial fibrillation [3], some studies have suggested that women have a higher risk of OAC undertreatment than men [7–10], while others have reported no significant differences [11,12].

A previous study using a national registry in the United States found that women had a higher risk of undertreatment across all CHA_2DS_2-VASc scores [9], while an investigation in Europe found that a higher proportion of female patients received OAC treatment in contrast to males [13]. Further, a recent international study found no differences in anticoagulation use between women and men globally except for a sex disparity specific to North America [11]. While the authors attributed these results to differences in guideline recommendations [11], there is still uncertainty about sex inequalities in OAC treatment due to the combined contradictory findings.

In a previous study, we investigated the prevalence and factors associated with AF undertreatment in patients with stroke outcomes [14]. The current analysis aimed to determine whether sex influenced AF treatment among a rural population of stroke patients in central and northeast Pennsylvania, USA. The study examined sex disparities by evaluating undertreatment rates and risk associations, stratifying patients based on age groups and index stroke dates, mainly considering the introduction of non-vitamin K antagonist oral anticoagulants (NOACs) in 2010.

2. Materials and Methods

2.1. Data Source and Study Population

The study used a retrospective cohort analyzing data from the "Geisinger Neuroscience Ischemic Stroke (GNSIS)" registry, a database of ischemic stroke patients at Geisinger which includes demographics, family history, and clinical and past medical history. Geisinger is an integrated system delivering healthcare in rural Pennsylvania to approximately 2.6 million people throughout 43 counties. Patients were included in GNSIS if they had a primary diagnosis of ischemic stroke based on the International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification (ICD-9-CM or ICD-10-CM) during a hospital encounter of at least 24 h, and a magnetic resonance imaging of the brain in the same encounter. Further details on the data extraction and pre-processing for the GNSIS database are provided in previously published study articles [14–16]. The Geisinger Institutional Review Board reviewed and approved this study as a "non-human subject research" for using de-identified information.

2.2. Evaluation of Sex Disparities

The study included ischemic stroke patients $\geq$ 18 years old with an AF diagnosis ICD (ICD-9-CM and ICD-10-CM) code at any time before the stroke index date, and it excluded patients with an AF diagnosis on the index stroke date. The study analyzed point prevalence among men and women, and patients' distribution according to CHA_2DS_2-VASc score. Sex was studied as a risk factor for undertreatment in patients with CHA_2DS_2-VASc $\geq$ 2 stratified based on age group or NOACs use. Alternatively, $CHADS_2$ was employed for risk stratification with a score of $\geq$2 denoting patients at high risk of stroke.

To study the impact of NOACs on sex disparity in undertreatment, patients were stratified based on their index stroke date. The first group contained patients with an index stroke date between 2004 and 2010, while the second group included patients with an index stroke date between 2011 and 2019. To examine the sex disparity in OAC treatment in different age groups, the patients were also divided into four subgroups based on age, and undertreatment was examined in each subgroup.

The HAS-BLED score is used by clinicians to evaluate the risk of bleeding in AF patients and assesses the history of uncontrolled hypertension, renal or liver disease, stroke, bleeding, labile INR, age $\geq$ 65 years, medications, and alcohol use [3]. For this study, a limited HAS-BLED score was calculated from the liver and renal function, age, medications predisposing to bleeding, and history of stroke, TIA, and bleeding diagnoses. The differences in the limited HAS-BLED scores between the male and female patients were examined along with its association with sex disparity in undertreatment.

2.3. Statistical Analysis

In the study, demographic and comorbidity characteristics for the population were summarized using descriptive statistics. Continuous variables were presented as mean ± standard deviation or median with interquartile range (IQR), and categorical variables were presented as counts and percentages. Statistical analysis among groups included Pearson's chi-squared test or Fisher's exact test for the categorical variables, and analysis of variance (ANOVA) or the Kruskal–Wallis test for continuous variables. Multiple logistic regression was performed to examine the association of gender with undertreatment in AF patients, adjusting for age and comorbidities, while the goodness of fit was evaluated using the Hosmer–Lemeshow test. Variables with missingness, such as the National Institutes of Health Stroke Scale (NIHSS), were not included in regression analysis. The alpha value for all *p*-values was set to 0.05. R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses.

3. Results

3.1. Patient Characteristics of Study Population

Evaluation of ischemic stroke patients from the GNSIS database yielded 1062 patients with an AF diagnosis before the index stroke date (Figure 1). Of these patients, 506 (47.6%) were men, and 556 (52.4%) were women (Table 1). The median age at AF diagnosis was 72.3 years (IQR 64.4–79.2) for men and 78.9 years (IQR 69.8–84.5) for women ($p < 0.001$). The median age at the index date of stroke was 76.9 years (IQR 68.1–82.9) for men and 82.6 years (IQR 74.9–88.3) for women ($p < 0.001$). Additional patient characteristics are summarized in Table 1. In terms of medication, there were no significant differences between men and women using antiplatelets only (116 (22.9%) vs. 115 (20.7%); $p = 0.418$), anticoagulants only (129 (25.5%) vs. 146 (26.3%); $p = 0.830$), or anticoagulants and antiplatelets (120 (23.7%) vs. 106 (19.1%); $p = 0.076$). There was a significant difference between the $CHA2DS_2$-VASc median score (male median, 4; IQR, 3–5 vs. female median, 5; IQR, 4–6; $p < 0.001$). Further comparison of $CHA2DS_2$-VASc scores distribution based on sex can be seen in Figure 2.

Table 1. Male and female ischemic stroke patient characteristics with a diagnosis of atrial fibrillation before index stroke event.

Variable	Overall	Female	Male	*p*-Value
Number of patients	1062	556	506	
Age at atrial fibrillation diagnosis in years, median (IQR)	75.5 (67.3, 82.5)	78.9 (69.8, 84.5)	72.3 (64.4, 79.2)	<0.001 *
Age at index stroke event in years, median (IQR)	80.0 (71.5, 86.3)	82.6 (74.9, 88.3)	76.9 (68.1, 82.9)	<0.001 *
CHA_2DS_2-VASc at baseline, median (IQR)	4.0 (3.0, 6.0)	5.0 (4.0, 6.0)	4.0 (3.0, 5.0)	<0.001 *
CHA_2DS_2-VASc				<0.001 *
0	10 (0.9)	0 (0.0)	10 (2.0)	
1	37 (3.5)	7 (1.3)	30 (5.9)	
2+	1015 (95.6)	549 (98.7)	466 (92.1)	
Dyslipidemia, *n* (%)	740 (69.7)	368 (66.2)	372 (73.5)	0.011 *
Heart failure, *n* (%)	397 (37.4)	209 (37.6)	188 (37.2)	0.934
Hypertension, *n* (%)	900 (84.7)	472 (84.9)	428 (84.6)	0.957
Diabetes, *n* (%)	392 (36.9)	188 (33.8)	204 (40.3)	0.033 *
Past ischemic stroke, *n* (%)	115 (10.8)	66 (11.9)	49 (9.7)	0.295
Transient ischemic attack, *n* (%)	135 (12.7)	74 (13.3)	61 (12.1)	0.603
Other thromboembolism, *n* (%)	79 (7.4)	46 (8.3)	33 (6.5)	0.332

Table 1. *Cont.*

Variable	Overall	Female	Male	*p*-Value
Myocardial infarction, *n* (%)	215 (20.2)	84 (15.1)	131 (25.9)	<0.001 *
Peripheral vascular disease, *n* (%)	275 (25.9)	119 (21.4)	156 (30.8)	0.001 *
Hypercoagulative State, *n* (%)	13 (1.2)	9 (1.6)	4 (0.8)	0.271
Chronic liver disease, *n* (%)	42 (4.0)	16 (2.9)	26 (5.1)	0.084
Cirrhosis, *n* (%)	12 (1.1)	6 (1.1)	6 (1.2)	1.000
Chronic kidney disease, *n* (%)	391 (36.8)	217 (39.0)	174 (34.4)	0.133
End-stage renal disease ESRD, *n* (%)	35 (3.3)	13 (2.3)	22 (4.3)	0.097
Past hemorrhagic stroke, *n* (%)	37 (3.5)	18 (3.2)	19 (3.8)	0.770
Medications				
Antiplatelets, *n* (%)	231 (21.8)	115 (20.7)	116 (22.9)	0.418
Anticoagulants, *n* (%)	275 (25.9)	146 (26.3)	129 (25.5)	0.830
Anticoagulant and Antiplatelet, *n* (%)	226 (21.3)	106 (19.1)	120 (23.7)	0.076
Statins, *n* (%)	501 (47.2)	242 (43.5)	259 (51.2)	0.015 *
Antihypertensives, *n* (%)	546 (51.4)	272 (48.9)	274 (54.2)	0.101
Medical insurance type, *n* (%) †				<0.001 *
Commercial	132 (12.8)	55 (10.2)	77 (15.7)	
Health Maintenance Organization (HMO)	352 (34.1)	174 (32.2)	178 (36.2)	
Medicaid	13 (1.3)	7 (1.3)	6 (1.2)	
Medicare	518 (50.2)	297 (55.0)	221 (44.9)	
Self-Pay	1 (0.1)	1 (0.2)	0 (0.0)	
Special Billing	9 (0.9)	6 (1.1)	3 (0.6)	
Veterans Affairs (VA)	7 (0.7)	0 (0.0)	7 (1.4)	
Smoking status, *n* (%)				<0.001 *
Current smoke	87 (8.2)	25 (4.5)	62 (12.3)	
Past smoker	408 (38.4)	140 (25.2)	268 (53.0)	
Never smoker	520 (49.0)	368 (66.2)	152 (30.0)	
Unknown	47 (4.4)	23 (4.1)	24 (4.7)	
NIHSS at index stroke event, median (IQR) #	5.0 (2.0, 9.0)	6.0 (3.0, 12.0)	4.0 (2.0, 6.0)	0.001 *
All-cause mortality within 1 year of index stroke, *n* (%)	303 (28.5)	164 (29.5)	139 (27.5)	0.508
Recorded encounter count per year between diagnosis of atrial fibrillation and index stroke, median (IQR)	6.3 (3.0, 11.0)	6.9 (3.0, 11.0)	6.0(3.0, 10.8)	0.404
Time in years between diagnosis of atrial fibrillation and index stroke, median (IQR)	2.8 (1.0, 5.6)	2.9 (1.0, 5.5)	2.6 (1.0, 5.6)	0.899

* Significant *p*-value; † Medical insurance data available for 1032 patients (540 female and 492 male patients); # NIHSS available for only 261 patients (136 female and 125 male patients).

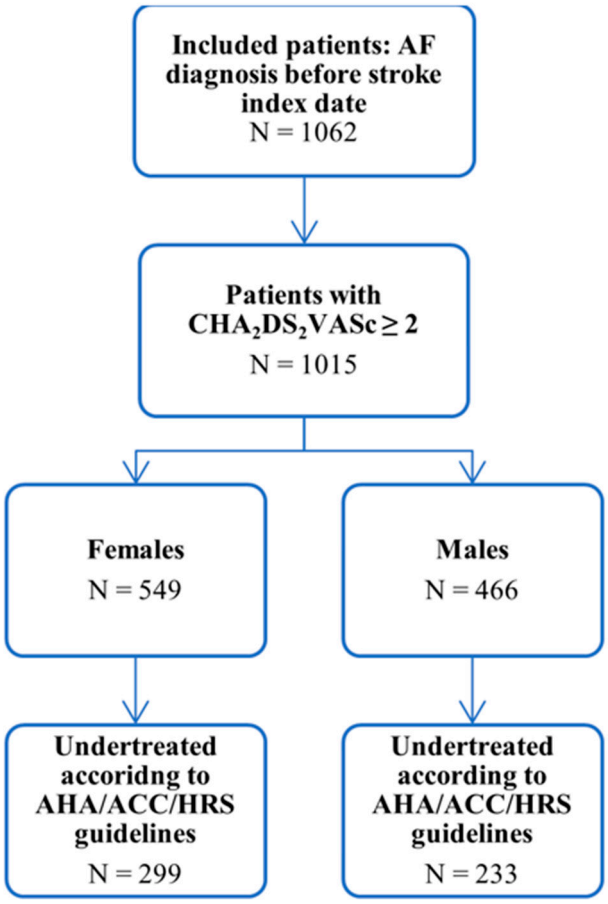

Figure 1. Flowchart of patients with atrial fibrillation in the study.

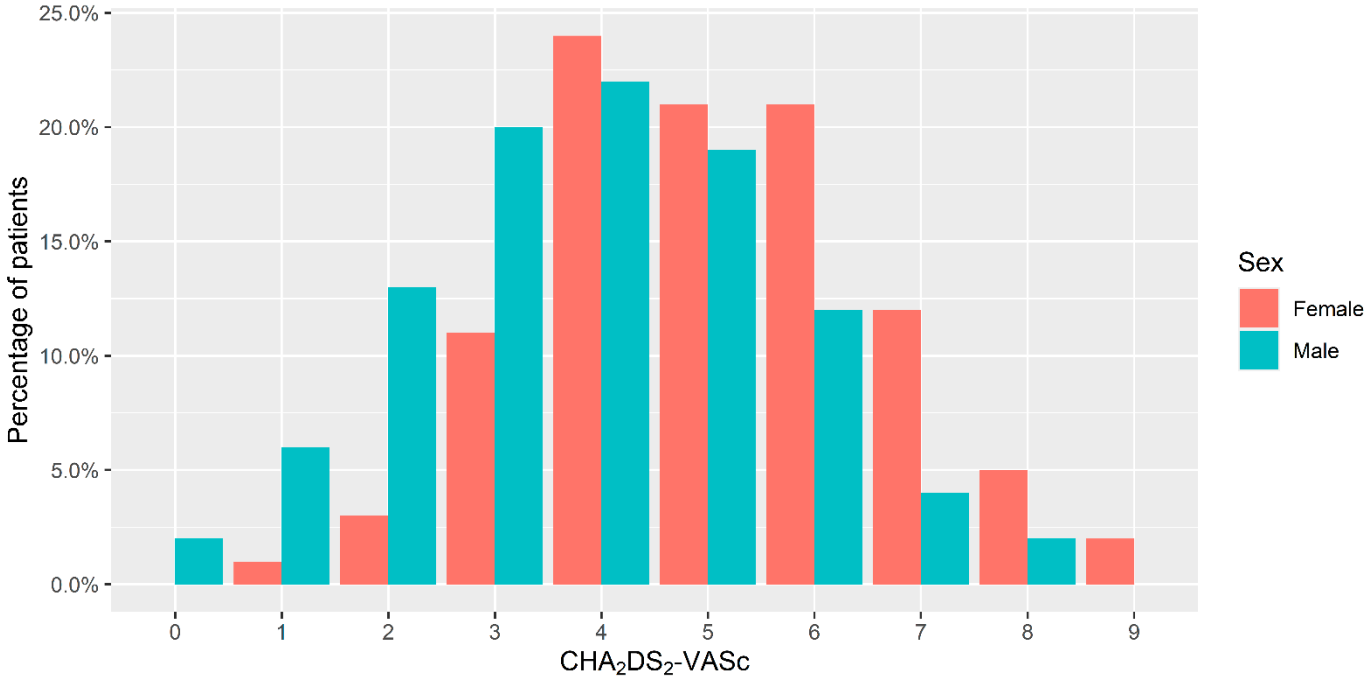

Figure 2. CHA_2DS_2-VASc score patient distribution based on sex.

3.2. Undertreatment of Atrial Fibrillation

After dividing the distribution of CHA2DS$_2$-VASc into three categories, 0, 1, and 2+ (Table 1), 1015 (95.6%) patients were included in the 2+ category. Of the 1015 patients, 466 (45.9%) were men, and 549 (54.1%) were women (Figure 1). Further evaluation of these patients showed that based on current treatment guidelines, 233 (50.0%) men were not receiving adequate therapy, while 299 (54.5%) women were also not receiving adequate therapy (p = 0.18), as seen in Table 2. Overall, the male sex was not found to have a statistically significant association with undertreatment in multiple logistic regression (OR 0.82, 95% CI 0.62–1.09, p = 0.17) (Figure 3).

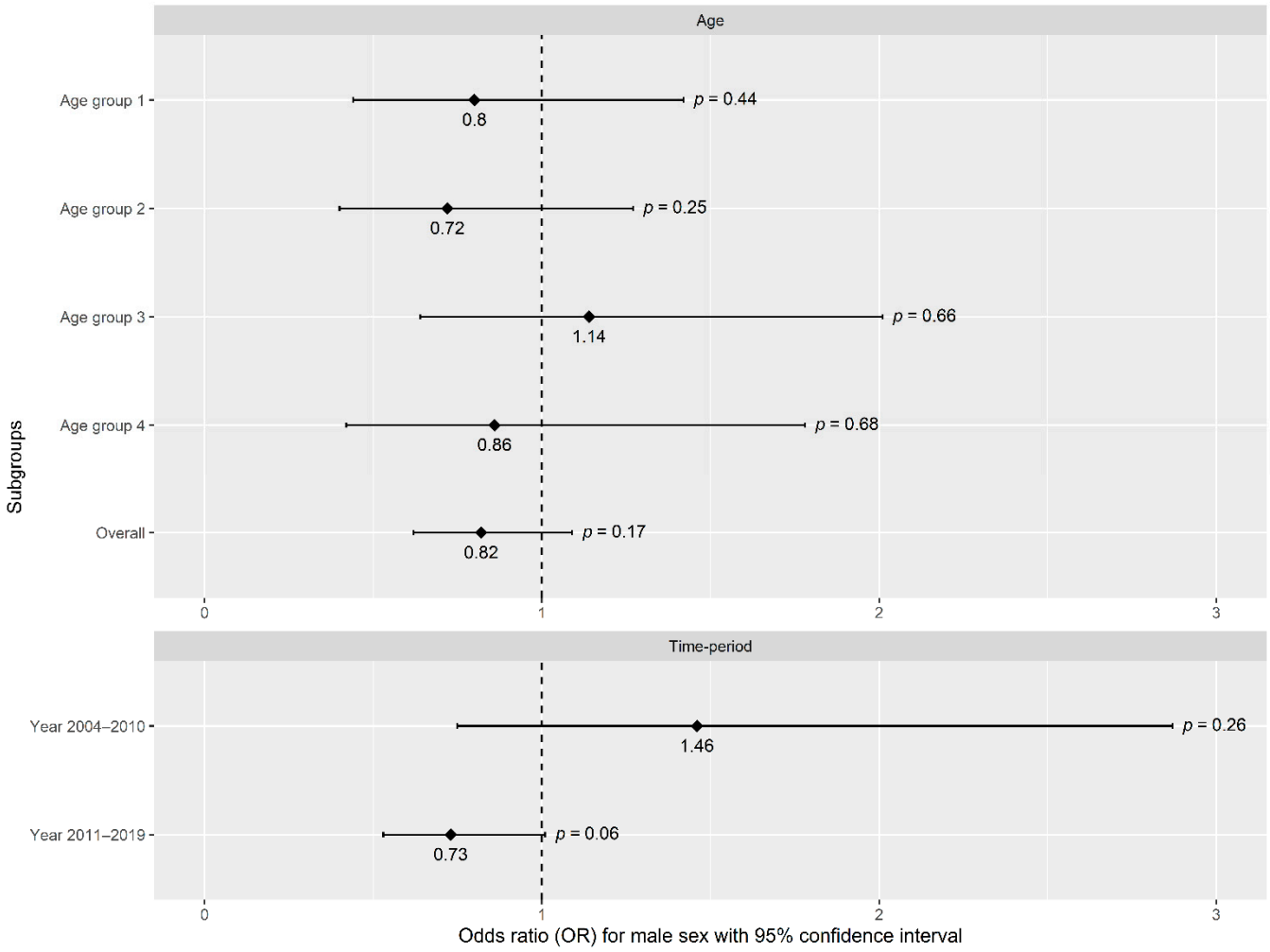

Figure 3. Logistic regression for patients with a CHA$_2$DS$_2$-VASc score $\geq$ 2 stratified by age groups and index stroke date.

3.3. Anticoagulant Undertreatment Rate Based for Different Age Groups

To examine sex differences in atrial fibrillation, patients were first stratified into four groups based on age quartiles (Table 2). Group 1 consisted of 254 patients aged 44.4–72.8 years, Group 2 had 254 patients aged 72.8–80.6 years, Group 3 included 254 patients aged 80.6–86.6 years, and Group 4 with 253 patients older than 86.6 years. The OAC undertreatment rate was not significantly different in any of the four age groups (Table 2), nor was male sex a significant predictor in the multiple logistic regression on undertreatment (Figure 3).

Table 2. Anticoagulant undertreatment rates for patients with a CHA_2DS_2-VASc score ≥ 2 stratified by age groups and index stroke date.

		All Patients			Undertreated			
		Total	**Female**	**Male**	**Total**	**Female**	**Male**	***p*-Value**
	All Groups	1015	549	466	532 (52.4%)	299 (54.5%)	233 (50.0%)	0.175
Stratified by Age	**Group 1 (44.4–72.8 years)**	254	110	144	141 (55.5%)	64 (58.2%)	77 (53.5%)	0.535
	Group 2 (72.8–80.6 years)	254	112	142	120 (47.2%)	59 (52.7%)	61 (43.0%)	0.157
	Group 3 (80.6–86.6 years)	254	138	116	122 (48.0%)	64 (46.4%)	58 (50.0%)	0.653
	Group 4 (>86.6 years)	253	189	64	149 (58.9%)	112 (59.3%)	37 (57.8%)	0.955
Stratified by Index Date	**2004–2010**	221	108	113	112 (50.7%)	54 (50.0%)	58 (51.3%)	0.950
	2011–2019	794	441	353	420 (52.9%)	245 (55.6%)	175 (49.6%)	0.108

3.4. Anticoagulant Undertreatment Rate Based on Index Stroke Year

When grouping the patients based on the index stroke year, the first group (2004–2010) contained 221 patients with 112 (50.7%) identified as undertreated with anticoagulants, 58 (51.3%) men, and 54 (50.0%) women (Table 2). Undertreatment rates between the sexes did not show a statistically significant difference ($p = 0.95$). Additionally, sex was not associated with undertreatment rate (OR 1.46, 95% CI 0.75–2.87, $p = 0.26$) in Figure 3. In the second group (2011–2019), there were 794 patients, of which 420 (52.9%) were undertreated with anticoagulants, 175 (49.6%) men and 245 (55.6%) women (Table 2). No statistically significant difference was observed between the undertreatment of men and women ($p = 0.11$) in Table 2, nor with the association of male sex and undertreatment in multiple logistic regression (OR 0.73, CI 0.53–1.01, $p = 0.06$) in Figure 3. Overall, undertreatment rates following the introduction of NOACs were comparable to previous years without significant differences in OAC usage between sex groups.

4. Discussion

The results from our rural AF patient population with ischemic stroke outcomes indicate the presence of undertreatment according to guideline-recommended OAC of about 50% in men and 55% in women with a CHA_2DS_2-VASc ≥ 2; however, sex was not shown to be a statistically significant risk factor for OAC undertreatment. When dividing the population based on age and index stroke year, both analyses revealed no apparent sex disparity and no risk association between sex and undertreatment. Following the introduction of NOACs in 2010, the undertreatment rates remained consistent between the 2004–2010 and 2010–2019 groups, without significant sex disparities or associated risk. Similarly, risk stratification using $CHADS_2$ scores did not show a sex disparity or risk association with undertreatment (Supplemental Result R1, Table S1). Several associated factors were more prevalent in men, such as dyslipidemia, diabetes, peripheral vascular disease, and a history of myocardial infarction. Women were diagnosed with AF at an older age, had an older age at index stroke date, and a higher median baseline CHA2DS2-VASc, which aligned with populations in similar studies [5,9,10,12,13,17,18].

In contrast, recent studies have identified potential sex disparities in OAC undertreatment (Supplemental Table S2). Retrospectives studies have found lower odds of OAC initiation and an increased likelihood of undertreatment among high-risk female patients with Medicare and commercial insurance [7,8]. Similarly, a study using the PINNACLE

National Cardiovascular Data Registry found that women had a higher risk of undertreatment across all levels of the CHA_2DS_2-VASc scores [9], while a study from the Euro Observational Research Programme Pilot survey on atrial fibrillation (EORP-AF) reported that more women with CHA_2 DS_2-VASc $\geq$ 2 received OAC than men [13]. However, other researchers have found comparable results to those presented in this study (Supplemental Table S2). A prospective cohort study in China reported no sex difference in OAC treatment among AF patients with CHA_2DS_2-VASc $\geq$ 2, but women represented a smaller percentage of the patient population [12]. Two international studies found no significant sex disparities in OAC therapy worldwide [11,19]. In one of these studies, the authors described a sex disparity specific to North America that was attributed to differences in thresholds for OAC initiation due to varying guideline recommendations [11].

Our statistical analysis and logistic regression models of undertreatment showed no association for male sex with a decreased risk of OAC undertreatment, differing from previous studies (Supplemental Table S2). Two investigations in Italy and Sweden stratified AF patients based on age and year cohorts found that women in the $\geq$75 age group had an increased risk of OAC undertreatment, even with the emergence of NOACs and updated European Society of Cardiology Guidelines [10,20–22]. In general, prior studies concur that increasing age seems to correlate to an increased risk of AF undertreatment, especially among patients $\geq$70 or 80 years old [23–27]. There have been reports of an aging paradox, where patients $\geq$70 or 80 years old were less likely to receive OAC therapy despite a heightened risk of stroke [23–27]. Our previous study using the GNSIS registry found that less than half of our high-risk patients received OAC treatment according to guidelines [14]. These results were comparable to other studies in the USA [23,24]. However, we did not observe an increased risk of undertreatment associated with age [14].

There were several strengths and limitations present within our study. The EHR data collected provided a wealth of variables for each patient, as well as a wide time frame for evaluation, allowing a more robust analysis of differences in patient characteristics between sexes. While we had a large cohort comprised of patients from multiple study centers, our cohort lacked racial and socioeconomic diversity seen in previous related studies [7,9,10,17], in addition to the patient population being restricted to only rural areas, thus possibly limiting the external validity of our results.

Another limitation may be the use of CHA_2 DS_2-VASc to assess stroke risk and undertreatment rates in AF patients from 2004 to 2019. In the United States, CHA_2 DS_2-VASc was implemented in 2014, and prior to this guideline update, $CHADS_2$ was used for risk stratification [3]. However, in our previous study, we found similar undertreatment rates using CHA_2 DS_2-VASc and $CHADS_2$ scores [14], and our results in this study are consistent even when using $CHADS_2$ for risk stratification. Other limitations include the lack of a complete HAS-BLED score (Supplemental Results R2), used by clinicians to identify patients at risk for bleeding [3,6,28] and to potentially examine sex disparities [7–9,11,13,19].

Lastly, the use of ICD-9-CM and ICD-10-CM posed potential constraints. AF diagnosis was measured using ICD codes without electrocardiogram (EKG) confirmation. Furthermore, ICD codes do not provide detailed clinical information and sex-related preferences. Previous studies have found that women tend to present with more symptoms, older age, and receive more conservative treatments [12,13]. Additionally, ICD codes fail to give insight into other possible external factors affecting treatment, such as specific patient and physician preferences, and the decision process in treatment choice, as well as accurate insurance information. While medication data in EHR can provide information on whether a patient was prescribed a certain medication, determining the patient compliance remains a challenge [29].

5. Conclusions

This study found that OAC treatment for AF in ischemic stroke patients remains low according to guidelines in both men and women; however, there does not appear to be a

sex disparity, even when stratifying patients by age and index ischemic stroke date. Sex was not associated with OAC undertreatment in our rural population.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/jcm10204670/s1, Result R1. Risk stratification by CHADS2 score, Table S1. Anticoagulant undertreatment rates and logistic regression for patients with a CHADS2 score ≥ 2 stratified, Result R2. Risk of bleeding using limited HAS-BLED, Table S2. Summary of Relevant Studies.

Author Contributions: Conceptualization, R.Z.; Data curation, D.C.; Formal analysis, E.K., J.D., D.C., S.S., J.L., V.A. and R.Z.; Investigation, E.K., J.D. and D.C.; Methodology, J.L., V.A. and R.Z.; Supervision, V.A. and R.Z.; Writing—original draft, E.K. and J.D.; Writing—review & editing, D.C., S.S., J.L., V.A. and R.Z. All authors have read and agreed to the published version of the manuscript.

Funding: This study had no specific funding. VA had financial research support from the National Institute of Health (NIH) grant No. R56HL116832 sub-awarded to Geisinger during the study period. RZ had financial research support from Bucknell University Initiative Program, Roche—Genentech Biotechnology Company, the Geisinger Health Plan Quality fund, and receives institutional support from Geisinger Health System during the study period. The funders had no role in the study design, data collection, and analysis, or preparation of the manuscript.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Geisinger Institutional Review Board (IRB No. 2019-0470, 5/22/2019).

Informed Consent Statement: Patient consent was waived as the study only utilized de-identified data.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to institutional policies requiring data-sharing agreement.

Conflicts of Interest: The authors declare no competing interest.

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