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Sex Differences in the Use of Oral Anti-Coagulants for Atrial Fibrillation: A Report from the NCDR® PINNACLE Registry

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Abstract (Word Count = 250)

Background: Despite higher thromboembolism risk, women with atrial fibrillation (AF) have lower oral anticoagulation (OAC) use compared to men. The influence of the CHA_2DS_2-VASc score or the introduction of Non-Vitamin K oral anticoagulants (NOACs) on this relationship is not known.

Methods and Results: Using the PINNACLE National Cardiovascular Data Registry from 2008-2014, we compared the association of sex with OAC use (warfarin or NOAC) overall and by CHA_2DS_2-VASc score, and examined temporal trends in OAC use by sex. Multivariable regression models assessed the association between sex and OAC use in those with CHA_2DS_2-VASc scores ≥ 2. Temporal analyses assessed changes in OAC use by sex over time. Of the 691,906 AF patients, 48.5% were women. Women were significantly less likely than men to use any OAC overall (56.7% vs. 61.3%; p = <0.001) and at all levels of CHA_2DS_2-VASc score (adjusted RR 9%- 33% lower, all p<0.001). Compared to other thromboembolic risk factors, female sex was associated with lower use of OAC (RR 0.90, 95% CI 0.90-0.91). Over time, NOAC use increased at a slightly higher rate in women (56.2% increase per year, 95% CI 54.6%-57.9%) compared to men (53.6% increase per year, 95% CI 52.0%-55.2%), yet, women remained less likely to receive any OAC at all time points (p< 0.001).

Conclusions: Among patients with AF, women were significantly less likely to receive OAC at all levels of the CHA_2DS_2-VASc score. Despite increasing NOAC use, women had persistently lower rates of OAC use compared to men over time.

Keywords: Sex Differences, Atrial Fibrillation, Anticoagulants, Warfarin, Novel Oral Anticoagulants, women

Clinical Perspective

What is new?

- Women with non-valvular atrial fibrillation are significantly less likely to receive oral anticoagulation (warfarin or NOAC) compared to men at all levels of thromboembolic risk.
- NOAC use has increased in women at a slightly faster pace than in men; yet, women remained significantly less likely to receive any oral anticoagulation over time.

What are the clinical implications?

- A risk-treatment paradox for women with atrial fibrillation exists, suggesting those at increased thromboembolic risk are less likely than men to receive guideline concordant therapy.
- Under recognition of female sex as a thromboembolic risk factor does not fully explain these sex differences suggesting clinical guidelines may be applied differently in women and men.
- Interventions aimed at increasing appropriate oral anticoagulation use, particularly in women, are needed.

Introduction

Despite a higher risk of stroke, women with non-valvular atrial fibrillation (AF) receive less oral anticoagulation (OAC) than men.[1-10] Possible explanations for decreased OAC use in women include under-recognition of their higher thromboembolic risk or concern for bleeding risk on warfarin in female patients.[11, 12]

Recent advancements in AF care may have addressed these concerns. First, the CHA_2DS_2-VASc score for thromboembolic risk stratification incorporates female sex as an independent risk factor for thromboembolic events.[13] Its incorporation into current AF guidelines may have increased provider awareness of higher thromboembolic risk in women and thus increased OAC use.[14, 15] Second, the development of Non-Vitamin K oral anticoagulants (NOAC) has expanded treatment options for patients with AF. NOACs have a lower risk of major bleeding and equivalent stroke rates compared to

warfarin.[16-20] Therefore, it is possible that sex differences in OAC use have diminished with the introduction of NOACs.

To assess the impact of these advancements on OAC use in female AF patients, we examined the relative impact of individual thromboembolic risk factors on OAC use in the National Cardiovascular Data Registry (NCDR) PINNACLE Registry of outpatient cardiology practices. Rates of OAC use were evaluated by sex according to their CHA_2DS_2-VASc score and controlling for estimated bleeding risk. Finally, temporal trends in overall and individual OAC (warfarin and NOAC) use by sex were assessed. Understanding these relationships can determine the influence of the CHA_2DS_2-VASc score and NOAC use on the sex gap in OAC provision, and suggest future directions for improvement.

Methods

Data Source

The NCDR PINNACLE Registry consists of consecutive patients from cardiology practices in the United States (U.S.) that voluntarily participate and submit data as part of a national office-based cardiovascular quality improvement program.[21, 22] Data is collected at the point of care using a validated electronic medical record-mapping algorithm for patients with hypertension (HTN), coronary artery disease (CAD), congestive heart failure (CHF), and AF.[23, 24] Registry data quality is maintained through data definitions, standard data collection and transmission, and periodic data quality checks.[23-25]

Study Population

Between May 1, 2008 to December 31, 2014, 848,931 patients with their first documented AF diagnosis within the registry were identified. Patients were excluded for missing sex (n=1,439, 0.2%), reversible causes of AF (cardiac surgery, hyperthyroidism, pregnancy, pneumonia) (n=1,100, 0.1%), other indications for OAC (mechanical heart valve, valvular heart surgery, systemic embolization; n=6,206, 0.7 %), or documented contraindication to OAC (medical reasons or patient preference; n=24,893, 2.9%) as these would have impacted decisions to initiate OAC. Patients were excluded if they had a CHA_2DS_2-VASc score ≤1 (n=123,387 14.5%) leaving a final study cohort of 691,906 patients with high thromboembolic risk.[14, 15] (Figure 1)

Outcomes

The primary predictor variable for all analyses was patient sex. The primary outcome was prescription of any OAC defined as warfarin or NOAC (apixaban, dabigatran, and rivaroxaban) within 1 year of the patient's first encounter recorded in the PINNACLE registry with documented AF. Secondary outcomes of interest were use by OAC class (warfarin or NOACs). For patients with multiple OAC prescriptions within the first year of AF, the first prescribed OAC class was used.

Estimation of Thromboembolic Risk

According to practice guidelines, a CHA_2DS_2-VASc score was calculated for each patient as the summation of his or her risk factor points.[13] Risk factors receiving 1 point per factor included: female sex, age 65-74 years, history of CHF, HTN, diabetes mellitus, or vascular disease. Risk factors receiving 2 points per factor included: age ≥ 75 years or a history of prior transient ischemic attack or stroke. [13] The variables included in the CHA_2DS_2-VASc score were defined according to NCDR PINNACLE standards.[13, 26] CHF was defined as symptoms of heart failure or left ventricular ejection fraction < 40%. Vascular disease was defined by the presence of any of the following: peripheral arterial disease, peripheral vascular disease, history of myocardial infarction, prior coronary artery bypass surgery, percutaneous coronary angioplasty or percutaneous coronary intervention.[13]

Estimation of Bleeding Risk

Bleeding risk was estimated using the modified HAS-BLED score (mHAS-BLED).[27] The mHAS-BLED score is a total of the patient's bleeding risk factors including: HTN (diagnosis of hypertension, or at least two prior encounters with systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg within two years), abnormal renal function (creatinine ≥ 2.3 mg/dL), previous stroke, major bleeding history (intracranial hemorrhage or non-intracranial major hemorrhage) or anemia, age ≥ 65 years, concomitant use of medications predisposing to bleeding (anti-platelets or nonsteroidal anti-inflammatory drugs), and alcohol abuse history.

Statistical Analysis

Patient and practice level characteristics were compared between women and men using chi-square tests for categorical variables and Student's t-test for continuous variables. Continuous variables were summarized as median (interquartile range [IQR]) or mean ± SD while categorical variables were summarized as percentages and frequencies.

First, the associations of female sex and the other components of the CHA_2DS_2-VASc score with OAC use were examined. Models were adjusted for individual components of the CHA_2DS_2-VASc score (CHF, HTN, age, etc.) and additional patient (race, insurance type [private vs. non-private], mHAS-BLED, and rhythm control therapy), provider (physician vs. other provider), and clinic (total number of physicians at site and proportion of female patients at site) characteristics. Next, the fully adjusted models were stratified by CHA_2DS_2-VASc strata (score = 2, 3, 4, 5 and ≥6) with the individual components of the score removed as covariates to estimate adjusted risk ratios (RR) by sex within each CHA_2DS_2-VASc strata.

Due to the degree of missing variables for estimating bleeding risk, we conducted a sensitivity analysis excluding the mHAS-BLED estimate from the multivariable models. Since the CHA_2DS_2-VASc was incorporated into the American Heart Association/ American College of Cardiology/Heart Rhythm Society (AHA/ACC) guidelines towards the end of the study timeframe (2014), we performed a sensitivity analysis stratifying by the $CHADS_2$ score, which does not include female sex, vascular disease or the age category 65-74 as risk factors.[28, 29]

To assess temporal trends in OAC use overall and by class in women and men over the study period, we used multivariable regression with calendar quarter as a categorical independent variable, and the first quarter of 2010 as our referent group. For this OAC class analysis, the cohort was limited to patients who received an OAC prescription after 2010 when the Federal Drug Administration approved the first NOAC (dabigatran). In both women and men, we multiplied the adjusted RR for each quarter by the observed OAC use for the reference quarter to obtain quarterly risk-adjusted proportions of patients receiving OAC. A sex by quarter interaction term was included in the models to test whether the uptake in OAC use differed in women and men. To examine whether OAC use by sex changed significantly after guideline updates were published, we examined these relationships using the quarter prior to publishing of the

guidelines as the reference quarter (July-September 2010 for European Society of Cardiology (ESC) and January- March 2014 for AHA/ACC) and compared rates of OAC use in the subsequent 4 quarters.

All models accounted for clustering of patients by provider nested within practice using Generalized Estimating Equations. To directly estimate RRs, we used Zou's method by specifying a Poisson distribution and including a robust variance estimate in our models.[30-33]

All analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina). The Harvard Clinical Research Institute was the primary analytic center for this analysis.

Results

Baseline Characteristics in Women and Men

Our final study cohort included 691,906 patients with AF and indications for OAC of which 48.5% were women (Figure 1). Women were older, had lower BMI, and had a lower prevalence of CAD and higher ejection fraction compared to men. Men had a higher prevalence of many of the CHA_2DS_2-VASc risk factors. (Table 1)

The median estimated thromboembolic risk was higher in women than in men (median CHA_2DS_2-VASc score 4.0; IQR, 3.0-5.0, vs 3.0; IQR, 2.0-4.0, respectively, $p < 0.001$), and a larger proportion of women than men were in the higher risk CHA_2DS_2-VASc strata. (Table 1) The estimated bleeding risk (mHAS-BLED score) was slightly lower in women compared to men (median score 2; IQR, 2.0-3.0, vs. 2; IQR, 2.0-3.0, $p <0.001$).

Association of Sex and CHA_2DS_2-VASc Components with OAC Use

Overall, 59.1% of the study cohort with an indication for OAC was prescribed OAC; women were significantly less likely to receive OAC compared to men (56.7% vs. 61.3%, unadjusted RR 0.92, 95% CI 0.92-0.93). (Figure 2) Among individual components of CHA_2DS_2-VASc risk score, female sex and vascular disease were associated with significantly decreased OAC prescriptions (adjusted RR 0.90, 95% CI 0.90-0.91 and RR 0.97, 95% CI 0.96-0.98, respectively). Factors associated with increased OAC prescription were HTN (RR 1.52, 95% CI 1.50-1.54), age 65-74 (RR 1.68, 95% CI 1.66-1.71), and age ≥ 75 years (RR 1.70, 95% CI 1.67-1.72). (Figure 3)

OAC Use in Women and Men by CHA_2DS_2-VASc score

In analysis stratified by CHA_2DS_2-VASc score, women had significantly lower rates of OAC use compared to men at all strata (adjusted RR 9%- 33% lower, all p <0.001). (Figure 4) For example, in the fully adjusted models, women with a CHA_2DS_2-VASc score = 5 were 12% less likely to have OAC prescribed than men with CHA_2DS_2-VASc score = 5 (adjusted RR 0.88, 95% CI 0.87-0.89). In sensitivity analysis, these relationships persisted when stratifying by the $CHADS_2$ score. (Figure 5) Similarly, removal of the mHAS-BLED score from the multivariable models did not significantly change the results. (not shown)

Temporal Trends in OAC Use

Over the study, there was a similar increase in overall OAC use in both women and men (women 3.0% increase per year, 95% CI 2.5%-3.5%; and men 2.8% increase per year, 95% CI 2.3%-3.3%; p-value for time by sex interaction 0.12). (Figure 6) Women remained significantly less likely to receive any OAC compared to men at all time points (all p <0.001). There was no significant change in overall OAC use after adoption of CHA_2DS_2-VASc into ESC or AHA/ACC guidelines (all p >0.05).

Beginning in 2010, NOAC use increased at a slightly higher rate in women (56.2% increase per year, 95% CI 54.6%- 57.9%) compared to men (53.6% increase per year, 95% CI 52.0%-55.2%; p-value for time by sex interaction <0.001). (Figure 6) By the second quarter of 2014, NOAC use surpassed the use of warfarin in both women and men. Over the same timeframe, warfarin use declined at a slightly higher rate in women (14.4% decrease per year, 95% CI 13.8%-15%) compared to men (13.8% decrease per year, 95% CI 13.1%-14.4%; p-value for time by sex interaction 0.003).

Discussion

In this contemporary cohort of U.S. patients with AF and indications for OAC, female sex was associated with significantly less OAC use compared to men across the spectrum of thromboembolic risk. Over the last decade, OAC use has gradually increased each year for both women and men. Warfarin use has been declining and NOAC use increasing; these changes have been slightly more pronounced in women

compared to men. Even with these shifts in therapy type, women remained significantly less likely than men to receive OAC at all time points. Despite the introduction of the CHA_2DS_2-VASc score and NOACs, a risk treatment paradox for OAC use in eligible women with AF persists.

Our study suggests female sex is under-emphasized as a thromboembolic risk factor. Compared to other thromboembolic risk factors in the CHA_2DS_2-VASc score (i.e. HTN or age), female sex was associated with relatively lower use of OAC. Further, women were significantly less likely than men to receive guideline-concordant OAC at all levels of estimated thromboembolic risk. In the CHA_2DS_2-VASc scoring system, women previously viewed as intermediate-risk ($CHADS_2$ =1) are now categorized as high-risk (CHA_2DS_2-VASc 2 or more).[34-37] In our study, differences in OAC use were most pronounced in lower CHA_2DS_2-VASc scores (i.e. CHA_2DS_2-VASc=2) supporting female sex as a thromboembolic risk factor has less weight on OAC use compared to other factors. However, in our sensitivity analysis stratified by $CHADS_2$ scores (sex not included as an independent risk factor), we found lower rates of OAC use in women across the spectrum of estimated thromboembolic risk. Taken together, women were consistently less likely to receive OAC compared to men independent of level or method of estimating thromboembolic risk. Therefore, our findings suggest factors beyond thromboembolic risk alone contribute to lower rates of OAC use in women.

We also examined whether expanded treatment options, specifically NOACs, has affected sex differences in OAC use over time. Compared to warfarin therapy, NOAC therapy offers potential benefits including standardized dosing regimens, lack of intensive laboratory monitoring, and lower rates of major bleeding.[17, 38] Our findings suggest that sex differences in OAC use may be primarily due to differences in the use of warfarin. Over the last 5 years, warfarin use has gradually decreased and NOAC use has increased by as much as 50% per year in both women and men with a slightly greater rate of increase for women. Prior studies assessing sex differences in OAC have been unable to assess the impact of NOACs by sex due to low rates of NOAC use.[39-41] As of 2014, 1 in 3 people with AF were prescribed a NOAC, representing >50% of those receiving some form of OAC for AF. Therefore, it is possible that if NOAC use continues to increase over time, sex differences in overall OAC use may decrease and eventually be eliminated.

Our findings differ from other AF specific registries that found no significant sex differences in OAC use.[40-42] The Outcomes Registry for Better Informed Treatment of

Atrial Fibrillation (ORBIT), Euro Observational Research Program (EORP), and Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD) registries prospectively enroll patients based on specific inclusion and exclusion criteria introducing the possibility of selection bias. In contrast, PINNACLE is a quality improvement program that captures data on all patients with a diagnosis of AF and may more closely reflect broad clinical practice. Another important difference between our study and the GARFIELD and EORP registries is that these studies were largely international cohorts. ESC guidelines included the CHA_2DS_2-VASc score in 2010 whereas the AHA/ACC guidelines included the score in 2014.[14, 15] Earlier diffusion of evidence in these countries supporting female sex as an independent risk factor for thromboembolic events may contribute to these differences.

In contemporary general U.S. cardiology practices, our study provides evidence for sex differences in OAC use among eligible patients with AF that are independent of thromboembolic risk and the introduction of NOACs. A potential reason for these observed sex differences might be differences in patient or provider preferences. For example, women may be more likely to decline OAC therapy, particularly warfarin, due to concerns for bleeding, inconvenience or lack of social support (i.e. transportation for INR check).[9] Additionally, providers may perceive increased frailty or bleeding risk in women compared to men since women have been shown to have higher rates of bleeding while on warfarin and after cardiac interventions.[6, 11, 16, 43-45] Our finding of greater increases in NOAC use in women compared to men may support the notion that higher bleeding risk contributed to past sex differences in OAC use when therapy options were more limited. However, in our study, sex differences persisted across our entire study timeframe after controlling for estimated bleeding risk and allowing for the introduction of NOACs. Finally, US cardiologists' may apply clinical guidelines at lower rates in women compared to men suggesting a bias in how care is delivered.[46-48] Future studies should examine these potential causes in order to understand and work to eliminate sex differences in OAC use.

Certain limitations must be considered when interpreting our study. First, whether the demonstrated statistically significant differences in OAC use correspond to clinically significant differences in patient outcomes was not investigated in this study and warrants further evaluation. However, prior studies have demonstrated that sex related differences in the risk of stroke decrease when OAC are used.[49] Also, sex differences were observed at the highest level of estimated thromboembolic risk

(CHA_2DS_2-VASc ≥6), suggesting that even small absolute differences in OAC use may translate into significant sex differences in clinical outcomes. Second, we were unable to determine whether all potential contraindications or provider or patient preferences regarding OAC use potentially differed by patient sex. However, we excluded patients with a documented contraindication for OAC use, either for personal preference or medical reasons, and we saw no sex differences in this exclusion (49.5% female vs. 50.5% male, p>0.05). Third, the CHA_2DS_2-VASc score was only incorporated into US clinical guidelines in 2014, thus many clinicians in the US may not have been using the CHA_2DS_2-VASc score for risk stratification during the cohort period. However, our findings were unchanged in sensitivity analysis stratified by $CHADS_2$ score, the previous guideline recommended risk stratification tool. Finally, reported OAC use may be lower than actual use due to under-reporting in the PINNACLE registry. We would not expect under-reporting to occur differentially according to patient sex. Further, we allowed one year of follow-up for OAC use to be documented increasing capture of OAC use and our observed rates of OAC use were similar to what has been seen in previous clinical cohorts.[41, 50, 51]

Conclusions

In this contemporary cohort of cardiology patients in the U.S. with AF and indications for anticoagulation, women were 9-33% less likely than men to receive OAC at all levels of thromboembolic risk. Despite the introduction of NOACs and their rapidly increased use over time, women remained significantly less likely to receive OAC at all time points. Under recognition of female sex as a thromboembolic risk factor does not fully explain these differences suggesting clinical guidelines may be applied differently in women and men. Further studies are needed to understand whether lower rates of OAC use in women are associated with differences in clinical outcomes and, if so, action is needed to eliminate unnecessary differences in OAC use by sex.

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Table 1: Baseline Characteristics by Sex

Characteristic	**Women** (n= 335,756)	**Men** (n= 356,150)	**p-value**
Demographics			
Age (years)	75.4±11.0	73.9± 10.2	<0.001
Race			<0.001
White	64.4%	66.1%	
Black	3.4%	2.6%	
Asian	0.6%	0.6%	
American Indian/Alaskan Native	0.3%	0.4%	
Native Hawaiian/Pacific Islander	0.1%	0.1%	
Mixed	0.2%	0.2%	
Missing	31.1%	30.1%	
Insurance			<0.001
Private	45.1%	47.6%	
Military	2.0%	2.3%	
Medicare	60.3%	59.0%	
Medicaid	4.1%	2.5%	
Other	2.0%	2.1%	
None	5.0%	5.4%	
Missing	21.4%	21.3%	
Clinical Characteristics			
CHA_2DS_2-VASc (median [IQR])	4.0 (3.0-5.0)	3.0 (2.0-4.0)	<0.001
CHA_2DS_2-VASc Score			<0.001
2	11.6%	27.5%	
3	21.3%	31.5%	
4	31.3%	22.5%	
5	19.9%	11.6%	
6+	15.8%	6.8%	
Thromboembolic Risk Factors			
CHF	23.3%	30.5%	<0.001
Hypertension	80.3%	81.4%	<0.001
Age 65-74 (years)	27.7%	33.7%	<0.001

Age ≥ 75 (years)	57.7%	51.3%	<0.001
Diabetes	20.3%	27.8%	<0.001
Ischemic Stroke	1.1%	1.2%	<0.001
TIA	1.6%	1.6%	0.48
CVA	10.2%	11.3%	<0.001
CAD	39.0%	59.9%	<0.001
PAD	6.8%	10.6%	<0.001
Bleeding Risk Factors			
mHASBLED Score (median [IQR])	2.0 (2.0-3.0)	2.0 (2.0-3.0)	<0.001
Renal Dysfunction	0.3%	0.5%	<0.001
Bleeding History	1.4%	1.6%	<0.001
Anti-platelet or NSAID Drug Use	51.4%	59.9%	<0.001
Age ≥ 65 years	85.4%	83.1%	<0.001
Heavy ETOH Use	0.1%	0.3%	<0.001
Hemorrhagic Stroke	0.09%	0.12%	<0.001
Intracranial Hemorrhage	1.1%	1.3%	<0.001
Vascular Complications	0.8%	1.1%	<0.001
Other Clinical Characteristics			
BMI	28.9±6.9	29.7±5.8	<0.001
LVEF	57.4±12.1	50.9±13.9	<0.001
Hyperlipidemia	55.3%	65.9%	<0.001
History of Tobacco Use	46.7%	66.4%	<0.001
Practice Site Variables			
Practice Size (Number of Providers)	25.1±19.5	24.7±19.1	<0.001
Provider Type			<0.001
Physician	89.4%	89.8%	
Other	10.6%	10.2%	

* Continuous variables reported as Mean ± SD, expect where noted as Median [IQR], all categorical variables presented as percentage

† Abbreviations: BMI= body mass index; CAD= coronary artery disease; CHF= congestive heart failure; CVA= cerebrovascular attack; Heavy ETOH = Alcohol use (defined at > 8 drinks/day); IQR= Interquartile Range; LVEF= left ventricular ejection fraction; NSAID = Nonsteroidal anti-inflammatory medication; PAD= peripheral arterial disease; SD= Standard Deviation; TIA= transient ischemic attack

Figure Legends:

Figure 1: Study Cohort

Figure 2: Unadjusted Rates of Oral Anticoagulant use for Non-Valvular Atrial Fibrillation in Women and Men by CHA_2DS_2-VASc Score
*OAC=Oral Anticoagulants

Figure 3: Adjusted Association Between Individual CHA_2DS_2-VASc Factors and OAC Use Among those with CHA_2DS_2-VASc ≥ 2

*Analysis were adjusted for: other CHA_2DS_2-VASc variables, Race, Insurance (private vs non-private), mHASBLED score, rhythm control therapy, Total Number Physicians at Site, Provider Type (MD vs Other), Proportion of Female Patients at Site, and clustering by practice and provider.

† CHF= congestive heart failure; OAC = oral anticoagulant; TIA = transient ischemic attack; Vascular Disease = peripheral vascular disease, history of myocardial infarction, prior coronary artery bypass, or prior percutaneous coronary intervention

Figure 4: Adjusted Rates of Oral Anticoagulant use for Non-Valvular Atrial Fibrillation In Women and Men by CHA_2DS_2-VASc Score
*Analysis were adjusted for sex, CHA_2DS_2-VASc score, interaction of sex x CHA_2DS_2-VASc score, race, insurance type (private vs non-private), modified HAS-BLED score, rhythm control therapy, number of physicians at site, number of physician vs other, proportion female patients at site, and clustering by practice and provider.

† F = female; M= male; OAC= oral anticoagulant (warfarin or Non-Vitamin K oral anticoagulant); RR= Risk Ratio

Figure 5: Adjusted Rates of Oral Anticoagulant use for Non-Valvular Atrial Fibrillation In Women and Men Stratified by $CHADS_2$ Score

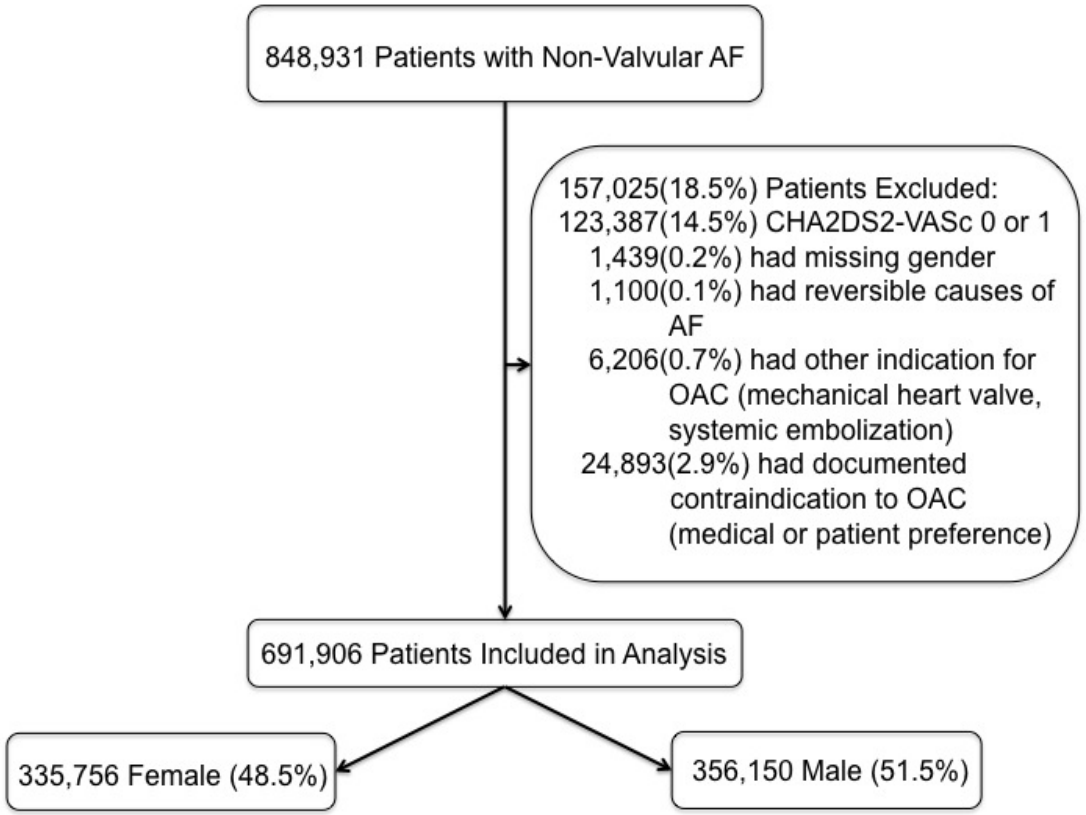
Analysis adjusted for race, insurance (private vs non-private), mHAS-BLED score, rhythm control; therapy, total number of physicians at site, provider type (MD vs other), proportion of female patients at site. P value for sex$CHADS_2$ interaction <0.001.

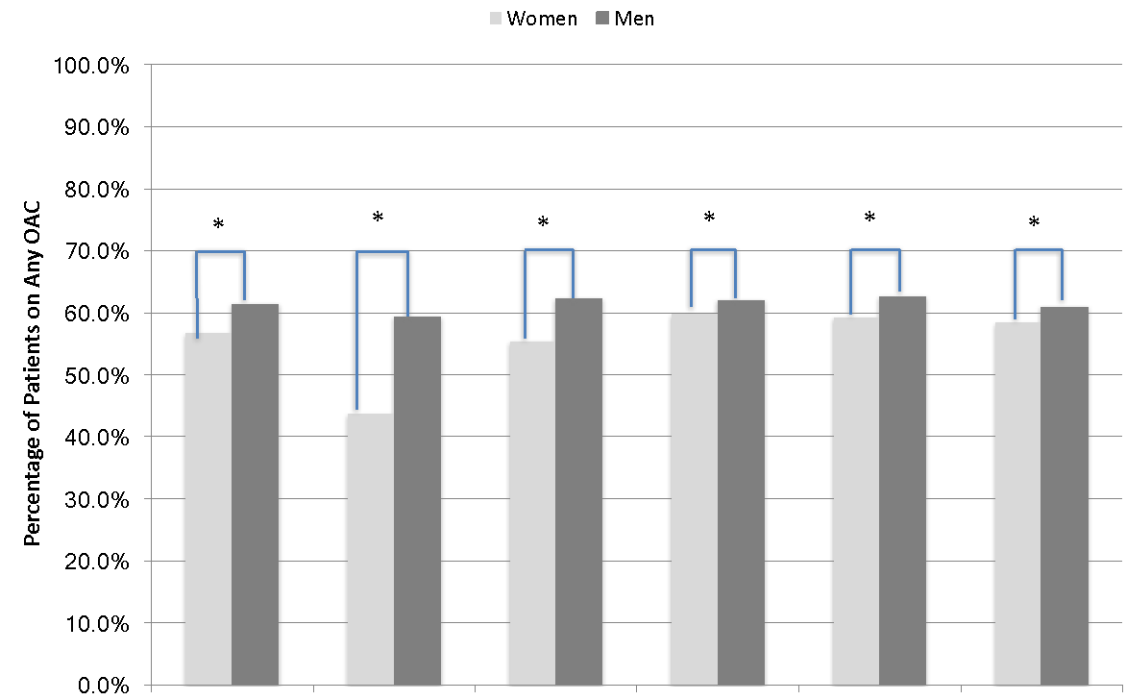
† RR= Risk Ratio

Figure 6: Trends in Oral Anticoagulant Use from 2010- 2014 by Anticoagulant Type in Women and Men

*There was no significant change in OAC use for women or men following introduction of ESC guidelines in 2010 or AHA/ACC guidelines in 2014 (all p <0.05). For NOAC and warfarin temporal analysis is from January 2010-December 2014, for NOAC January 2011-December 2014. Analysis were adjusted for: race, insurance type (private vs non-private), CHA_2DS_2-VASc score, modified HAS-BLED score, rhythm control therapy, total number of physicians at site, provider type (physician versus other provider), proportion of female subjects at site, and clustering by provider and practice.

† OAC= Oral Anticoagulant, NOAC= Non-Vitamin K oral anticoagulant





Treatment No (%)	Overall	2	3	4	5	≥6
Women	190,321 (56.7%)	17,057 (43.7%)	39,653 (55.4%)	62,879 (59.8%)	39,686 (59.3%)	31,046 (58.4%)
Men	218,308 (61.3%)	58,045 (59.3%)	69,721 (62.2%)	49,554 (61.9%)	26,223 (62.5%)	14,765 (60.9%)

* All P <0.001