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Clinical Research Study

Oral anticoagulation use in non-valvular atrial fibrillation patients in rural setting

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ABSTRACT

Background: The 2019 ACC/AHA/HRS guidelines established direct oral anticoagulants (DOACs) as first line therapy over warfarin for non-valvular atrial fibrillation (AF).

Methods: Ambulatory clinic patients with non-valvular AF or atrial flutter seen between 10/1/2019-7/12/2020 included. High-risk AF defined as males CHA_2DS_2-VASc score ≥2 and females ≥3. Patients were separated into: warfarin, DOAC, or no oral anticoagulation (OAC). ATRIA bleed score calculated. A provider survey assessing knowledge and barriers to anticoagulation completed via REDCap between 3/5-4/16/2020.

Results: Of 12,014 subjects with AF, 8,032 were high risk (mean age 75.9 ± 9.8 years; 57.5% male). There were 4,619 (57.1%) ≥ 75 years and 63.4% were rural dwelling. There was no significant difference between the number of subjects on anticoagulation before and after the guideline publication (75.6% vs. 75.7%, $p = 0.79$). Warfarin use decreased 2.3% over 1 year (39.3% to 37.0%), while DOACs increased 2.4% (36.2% to 38.7%, $p < 0.001$ for both). At 1-year, age, male gender, CHA_2DS_2-VASc score 4-6, hypertension, stroke and cardiology consult increased prescription of OAC ($p<0.05$). Vascular disease, high risk ATRIA bleed, renal disease, prior hemorrhage, and left atrial appendage occlusion were associated with decreased OAC use ($p < 0.05$). Left atrial appendage occlusion device use was low (<1%). In a survey, majority of providers noted bleeding risk (35.1%) and cost (25.0%) to be the biggest barriers to DOAC use.

Conclusions: The new guidelines caused a slight increase in DOACs over time. Significant barriers to DOAC use exist in rural areas; one in four high risk AF patient remains without OAC therapy.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia globally, and its prevalence increases with age.[1-3] Approximately 6–12 million people in the United States will suffer from AF by 2050.[4] Due to the aging population, the total number of AF cases continues to rise, even while the age standardized prevalence of AF is decreasing over time.[5–7] AF is associated with an approximate 5-fold increase in the risk of thromboembolism (TE) with no differences between males and females,[7–11] thus leading to an increased risk of morbidity and mortality if left untreated.[10,12–14] Management with oral anticoagulation (OAC) is important to reduce the risk of stroke.[1,12]

The 2019 American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines updated the recommendations for OAC use in patients with non-valvular AF. The first line therapy for non-valvular AF patients is now direct oral anticoagulants (DOACs; in DOAC-eligible patients) instead of warfarin[15] as DOACs were found to be noninferior to warfarin.[16–20]

The ACC/AHA/HRS guidelines changed the definition of high risk for females.[15] The CHA_2DS_2-VASc risk score is recommended for all pa-

Abbreviations: ACC/AHA/HRS, American college of cardiology/American heart association/heart rhythm society; AF, atrial fibrillation; ATRIA, anticoagulation and risk factors in atrial fibrillation; CHA_2DS_2-VASc, congestive heart failure/left ventricular dysfunction, hypertension, Age ≥ 75, diabetes mellitus, stroke/transient ischemic attack/thromboembolism, vascular disease, age 65-74, sex category (female gender); CHF, congestive heart failure; EHR, electronic health record; LAAO, left atrial appendage occlusion; DOAC, direct oral anticoagulant; OAC, oral anticoagulation; TE, thromboembolism.

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tients with AF (except those with moderate or severe mitral stenosis, or mechanical or bioprosthetic heart valves) and is used to estimate the risk of TE;[15,21,22] as the risk of TE increases stepwise with increasing CHA_2DS_2-VASc score.[7] Despite clear evidence that warfarin and DOACs reduce risk of stroke, studies demonstrate that these medications continue to be underutilized among high-risk AF patients.[23,24] Patient and provider barriers which influence the use of DOACs include cost, insurance coverage, presumed lack of availability of reversal age, patient compliance, and lack of knowledge.[25–28]

The primary aim was to demonstrate trends in OAC therapy across a largely rural healthcare system in northern Minnesota. The secondary aim was to determine what factors were associated with use or lack of use of OAC therapy. Lastly, we aimed to assess the impact of the new 2019 guideline-recommended use of DOACs as first line OAC therapy over warfarin in real-world clinical practice.

Methods

Study population

This is a retrospective cohort study of patients seen in outpatient primary care or cardiology at Essentia Health between 10/1/2019 and 7/1/2020, who had a diagnosis of AF or atrial flutter on their electronic health record (EHR, Epic®) problem list. Essentia Health serves patients in Northern Minnesota, Northern Wisconsin, and North Dakota, USA, with an approximately 65% rural population. The baseline AF cohort was obtained on 7/1/2020 and included all AF patients and a baseline CHA_2DS_2-VASc score at time of clinic visit. The 1-year follow-up data was captured on the same AF cohort on 7/12/2021.

Inclusion and exclusion criteria

Adults aged 18 years or older were included in the baseline cohort. Prevalent AF was identified using diagnostic codes (ICD-10 codes I48.0, I48.1, I48.2, I48.3, I48.4, I48.91, and I48.92.) Patients with moderate to severe rheumatic mitral stenosis and mechanical heart valves on the problem list were excluded, as it is recommended that these patients take warfarin regardless of CHA_2DS_2-VASc risk scores.[15,29] Patients who were deceased (N = 1,073) or had missing 1-year follow-up data (N = 665) were excluded (Fig. 1).

Baseline demographic, clinical, and medication data were obtained at time of encounter. Cardiology visit was defined as any office visit with a cardiology provider in the 3 years prior to their encounter. Baseline variables included results from an automated CHA_2DS_2-VASc calculator in EHR and risk factors included in the atrial fibrillation (ATRIA) bleed score.[30] Patients missing a CHA_2DS_2-VASc score were excluded from analysis (N = 429).

CHA_2DS_2-VASc calculator

Systemwide implementation of the CHA_2DS_2-VASc automated calculator occurred on 5/27/2020 after undergoing testing and internal validation in 300 patients with known AF. During the study period, the CHA_2DS_2-VASc calculator was visible to the provider and would update at every clinic visit. The calculator was located next to the EHR problem list (Fig. 2).

The CHA_2DS_2-VASc score was calculated as follows: 1 point for congestive heart failure (CHF) defined as having ejection fraction < 40% on echocardiography or by ICD-10 code (see Appendix A), hypertension, diabetes mellitus, vascular disease, age 65-74 years, or female sex and 2 points for age ≥ 75 years or prior stroke/transient ischemic attack (TIA)/TE. High-risk CHA_2DS_2-VASc score was defined as ≥ 2 for males and ≥ 3 for females.[15]

ATRIA bleed score

The ATRIA bleed score was verified by using ICD-10 codes for prior hemorrhage. ATRIA bleed score was validated previously[31] and is calculated as follows: 1 point for any prior bleeding episode, or current or prior diagnosis of hypertension, 2 points for age ≥ 75 years, and 3 points for severe renal disease with eGFR <30 ml/min or end-stage renal disease (dialysis-dependent), or anemia with hemoglobin <13 g/dL in men and <12 g/dL in women. ATRIA bleed score was divided into low (0-3), intermediate (4), and high risk (5-10). Although the HAS-BLED score more accurately predicts major bleeding episodes compared to ATRIA, variables from ATRIA bleed score were all obtainable in the EHR.[31,32] Variable definitions and ICD codes are shown in Appendix A.

Anticoagulation groups

Patients were separated into three treatment groups: warfarin, DOAC, or no OAC. No OAC included patients on aspirin monotherapy or patients without anticoagulation or antiplatelet therapies on their medication list. Patients who had both a DOAC and warfarin on their medication list underwent chart review to determine what OAC therapy was most recently prescribed.

Study outcomes

The outcome for this study was to determine trends in OAC therapy in patients with AF at high-risk of stroke from baseline to 1-year follow-up. Time trend comparisons were made by comparing CHA_2DS_2-VASc and ATRIA bleed scores, as well as OAC use versus no OAC use.

Barriers to anticoagulation treatment in AF provider survey

A modified version of the 2014 Heart Rhythm Society/National Stroke Association survey was used to better understand the barriers to appropriate use of OAC therapy from prescribing providers. The survey was IRB approved by Essentia Health. An email with a link to an electronic REDcap survey (Appendix B) was sent to all primary care and cardiology providers at Essentia Health (n=894) between March 5-April 16, 2020, with a response rate of 17%. Providers were grouped into 3 categories: cardiology, primary care, and other. Primary care included providers who selected primary care or hospital medicine as their specialty. Other included emergency medicine, neurology, and other specialties. Surveys included both fixed-response and open-ended questions. Providers were asked how they would manage a hypothetical patient with AF: 67-year-old female with hypertension, recurrent episodes of paroxysmal AF, no other medical history. Answer options included aspirin, warfarin, or DOAC. Demographic data were obtained along with answers to questions assessing barriers to anticoagulation use and patient education. Responses were excluded if provider reported they did not see AF patients (N = 11), were a nurse (N = 29), a pharmacist (N = 18), or did not complete the survey (N = 33).

Statistical analysis

Categorical variables were expressed as numbers (percentages) and compared using $\chi 2$ tests. Continuous variables were presented as mean ± standard deviation (SD) and compared using ANOVA F tests. For all analyses, a p-value <0.05 was considered statistically significant. Generalized logistic regression models were used to calculate odds ratios and corresponding 95% confidence intervals (CI) to determine the independent association between variables and OAC status. A univariate regression model compared each variable to OAC status and was adjusted for age and sex only. A multivariable regression model with the outcomes: any OAC (warfarin and/or DOACs use) versus no

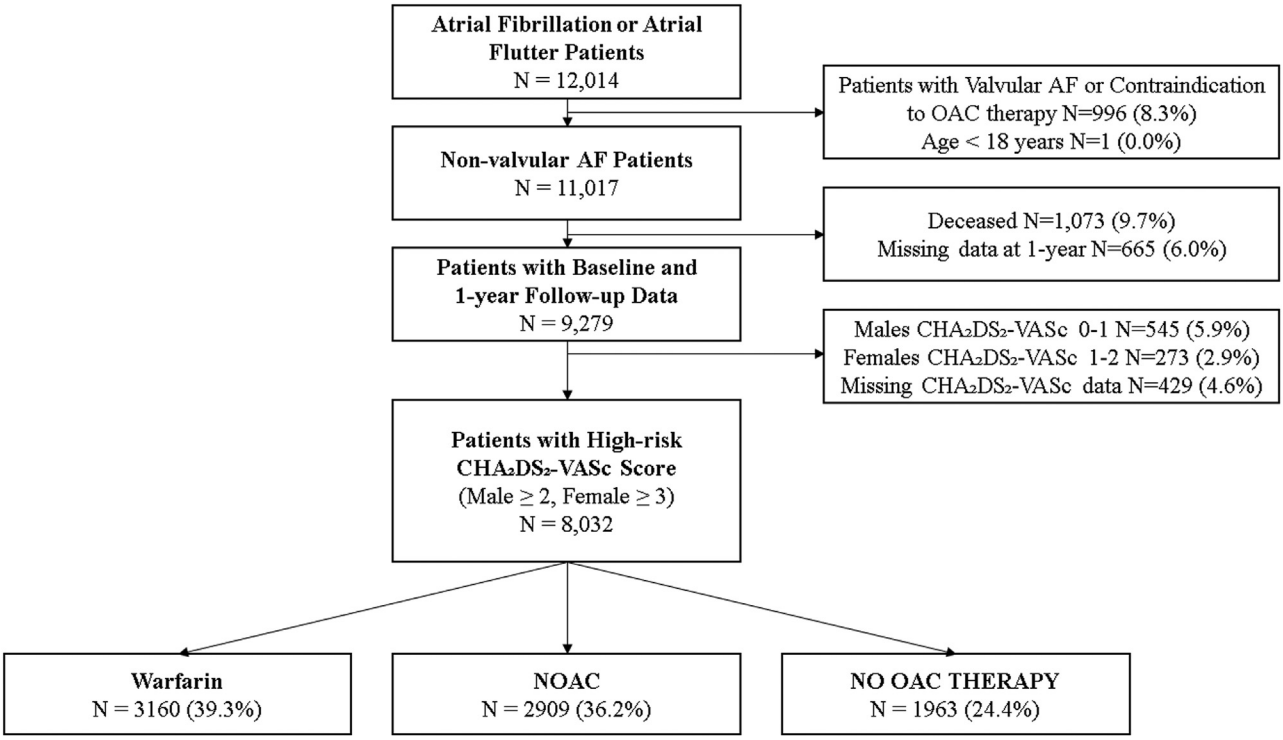


Fig. 1. Flow diagram of the study cohort review process and categorization of atrial fibrillation patients' anticoagulation treatment regimens at baseline. AF indicates atrial fibrillation; NOAC, non-vitamin K oral anticoagulant; OAC, oral anticoagulation. CHA_2DS_2-VASc conditions key: C: Congestive Heart Failure, H: Hypertension, Age ≥75, D: Diabetes Mellitus, S: Stroke or Transient Ischemic Attack, V: Vascular Disease, A: 65 to 74 years, S: Female.

OAC therapy were used against select variables: age, sex, CHA_2DS_2-VASc score, ATRIA bleed score, CHF, hypertension, diabetes mellitus, stroke/TIA/TE, vascular disease, severe renal disease, prior hemorrhage, cardiology visit, and left atrial appendage occlusion (LAAO) device (WATCHMAN). All statistical analyses were performed with Microsoft Excel (version 2102, Redmond, WA, 2021) and RStudio (version 1.4.1717, Boston, MA, 2020).

This study was approved by the Institutional Review Board at Essentia Health. The need to obtain informed consent was waived for the collection, analysis, and publication of the retrospectively obtained and anonymized data for this non-interventional study.

Results

Of the 12,014 patients in the baseline AF cohort, we identified 8,032 (mean age 75.9 ± 9.8 years, 42.5% female) who met inclusion criteria: non-valvular AF, high-risk CHA_2DS_2-VASc score, and had 1-year follow-up data (Fig. 1). Patients in the warfarin group were more likely to be ≥ 75 years of age (67.2%) compared to the DOAC (49.9%) or no OAC treatment (51.6%) groups ($p < 0.001$) (Table 1).

The mean CHA_2DS_2-VASc score was higher in patients in the warfarin group (4.3 ± 1.3) compared to DOACs (4.1 ± 1.4) or no OAC therapy (3.8 ± 1.4) ($p < 0.001$). The prevalence of CHF (17.1%), hypertension (85.3%), diabetes (35.0%), and vascular disease (30.4%) was also higher in patients in the warfarin group compared to DOACs and no OAC therapy ($p < 0.001$). The mean ATRIA bleed score was higher in patients in the warfarin group (3.1 ± 1.8) compared to DOACs (2.7 ± 1.9) or no OAC therapy (2.7 ± 2.) ($p < 0.001$).

Severe renal risk and prior hemorrhage (1.4% and 10.3%, respectively) ($p < 0.001$), and current daily smoking (8.0%) ($p < 0.001$) were higher in patients on no OAC therapy compared to warfarin and DOACs groups. Prevalence of LAAO device (WATCHMAN) was low (1.1%) but higher in patients in the no OAC therapy compared to warfarin and DOACs groups ($p < 0.001$). Patients in the warfarin (60.5%) or DOACs (68.6%) groups were more likely to have had a prior cardiology visit compared to the no OAC therapy group (47.5%) ($p < 0.001$) (Table 1).

Adherence to guidelines and prescription of DOACs

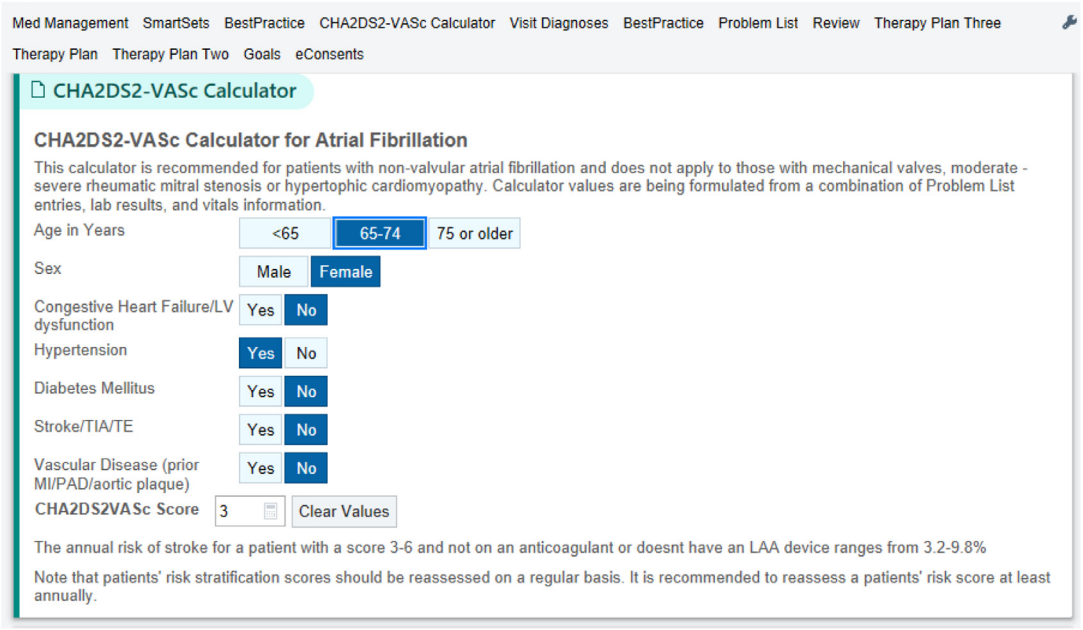
Baseline OAC use by sex and CHA_2DS_2-VASc risk scores is shown in Fig. 3.

Females, at every CHA_2DS_2-VASc score, were less likely to be on any OAC compared to males in the respective score. Among the 8,032 high-risk non-valvular AF patients, OAC use at baseline and 1-year follow up was unchanged (75.6% to 75.7% at 1-year; $p = 0.79$). However, there was a non-significant trend in decreasing warfarin use (39.3% to 37.0% at 1-year; $p = 0.19$), while DOAC use increased overall (36.2% to 38.7%; $p = 0.07$). Of the patients taking DOACs at baseline, 56.0% were on apixaban (Eliquis), increasing to 57.9% at 1-year; 40.3% on rivaroxaban (Xarelto), decreasing to 39.1% at 1-year; and 3.7% on dabigatran (Pradaxa), decreasing to 3.0% at 1-year. Approximately one in four high risk patients were not on any OAC therapy at baseline and this did not change over time (24.4% at baseline to 24.3% at 1-year).

Anticoagulation use by age

In the age group < 65 years, 22.8% were on warfarin, 19.7% apixaban, 23.8% rivaroxaban, and 1.8% dabigatran. In the age group 65-74 years, 32.6% were on warfarin, 21.7% apixaban, 18.0% rivaroxaban, and 1.6% dabigatran. In the age group 75-84 years 45.2% were on warfarin, 20.7% apixaban, 13.0% rivaroxaban, and 1.1% dabigatran. In the age group ≥ 85 years 48.2% were on warfarin, 17.5% apixaban, 7.1% rivaroxaban, and 1.1% dabigatran ($p < 0.001$). Patients were more likely to be on warfarin as they aged: 22.8% (age < 65 years) versus 48.2% (age ≥85 years). Patients that were younger were more likely to be on no OAC therapy: 31.9% (age < 65 years) versus 26.1% (age 65-74 years) and 19.9% (age ≥75 years).

A.



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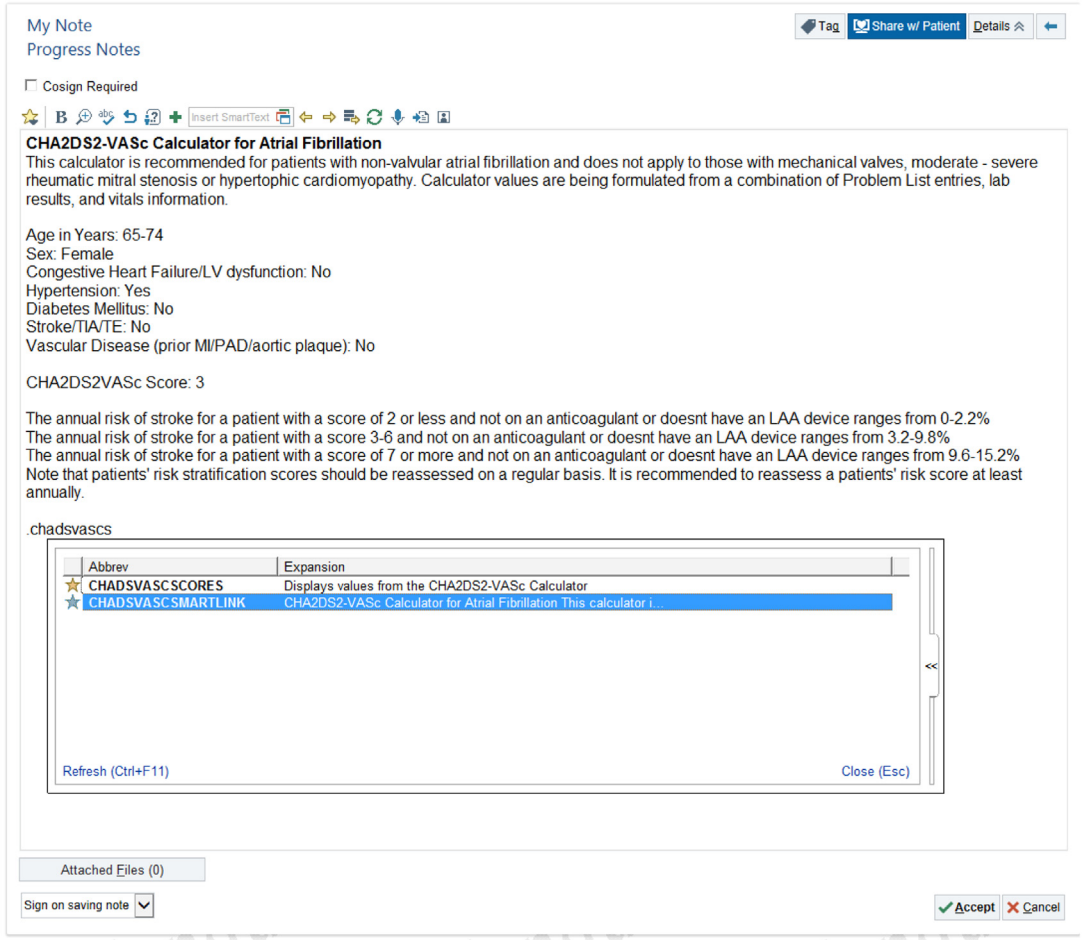

Fig. 2. Example of the automatic CHA_2DS_2-VASc calculator and smart phrase available in the electronic health record (EHR) for providers to use. A, Sample pop-up CHA_2DS_2-VASc calculator. B, smart phrase available in the EHR to auto populate the recording of the CHA_2DS_2-VASc score into the provider's note. **A)** LAA indicates left atrial appendage; LV, left ventricular; MI, myocardial infarction; PAD, peripheral artery disease; TE, thromboembolism; TIA, transient ischemic attack. **B)** LV indicates left ventricular; MI, myocardial infarction; PAD, peripheral artery disease; TE, thromboembolism; TIA, transient ischemic attack. CHA_2DS_2-VASc conditions key: C: Congestive Heart Failure, H: Hypertension, Age ≥75, D: Diabetes Mellitus, S: Stroke or Transient Ischemic Attack, V: Vascular Disease, A: 65 to 74 years, S: Female.

Table 1
Baseline characteristics of patients with non-valvular atrial fibrillation or atrial flutter in a large ambulatory health care system (Essentia Health, Duluth, MN, US); identified by a high-risk CHA_2DS_2-VASc score with 1-year follow-up data and stratified into groups based on anticoagulation therapy at baseline.

Measurement	All AF patients *N* = 8032	Warfarin *N* = 3160	DOAC *N* = 2909	No OAC therapy *N* = 1963	*p*-Values
Demographics					
Age, years	75.9 ± 9.8	78.0 ± 8.7	74.3 ± 9.5	75.0 ± 11.1	< 0.001
Age groups					
< 65 years	852 (10.6)	194 (6.1)	386 (13.3)	272 (13.9)	
65-74 years	2595 (32.3)	845 (26.7)	1072 (36.9)	678 (34.5)	
75-84 years	2975 (37)	1345 (42.6)	1037 (35.6)	593 (30.2)	
≥ 85 years	1610 (20.1)	776 (24.6)	414 (14.2)	420 (21.4)	
Male	4619 (57.5)	1784 (56.5)	1714 (58.9)	1121 (57.1)	0.14
Rural dwelling	5095 (63.4)	2088 (66.1)	1791 (61.6)	1216 (61.9)	< 0.001
Clinical Diagnoses					
Atrial fibrillation	7200 (89.6)	2874 (90.9)	2579 (88.7)	1747 (89.0)	<0.001
Atrial flutter	435 (5.4)	114 (3.6)	168 (5.8)	153 (7.8)	<0.001
Atrial fibrillation and flutter	397 (4.9)	172 (5.4)	162 (5.6)	63 (3.2)	<0.001
Current daily smoker	541 (6.7)	189 (6.0)	195 (6.7)	157 (8.0)	<0.001
Current e-cigarette use	15 (0.2)	3 (0.1)	29 (1.0)	22 (1.1)	<0.001
CHA_2DS_2-VASc Score					
Score, mean ± SD	4.1 ± 1.4	4.3 ± 1.3	4.1 ± 1.4	3.8 ± 1.4	<0.001
CHF/ LVD	1180 (14.7)	541 (17.1)	431 (14.8)	208 (10.6)	< 0.001
Hypertension	6160 (76.7)	2695 (85.3)	2184 (75.1)	1281 (65.2)	< 0.001
Diabetes	2489 (31.0)	1106 (35.0)	908 (31.2)	475 (24.2)	< 0.001
Stroke/TIA/TE	543 (6.8)	238 (7.5)	240 (8.3)	65 (3.3)	< 0.001
Vascular disease	2157 (26.9)	962 (30.4)	754 (25.9)	441 (22.5)	< 0.001
ATRIA Bleed Score					
Average Score	2.8 ± 1.9	3.1 ± 1.8	2.7 ± 1.9	2.7 ± 2.0	<0.001
Anemia	2041 (25.4)	819 (25.9)	720 (24.7)	502 (25.6)	1
Severe renal risk	58 (0.7)	15 (0.5)	16 (0.6)	27 (1.4)	<0.001
Prior hemorrhage	654 (8.1)	226 (7.2)	226 (7.8)	202 (10.3)	<0.001
Hypertension	6645 (82.7)	2706 (85.6)	2408 (82.8)	1531 (78.0)	<0.001
Device					
LAAO (WATCHMAN)	27 (0.3)	0 (0.0)	5 (0.2)	22 (1.1)	<0.001
Other					
Cardiology visit	4840 (60.3)	1911 (60.5)	1997 (68.6)	932 (47.5)	<0.001

Categorical variables are reported as n (%). Continuous data are reported as mean ± standard deviation. AF indicates atrial fibrillation; ATRIA bleed score, Anticoagulation and Risk Factors in Atrial Fibrillation; CHA_2DS_2-VASc conditions key: C: Congestive Heart Failure, H: Hypertension, A: Age ≥75 years, D: Diabetes Mellitus, S: Stroke or Transient Ischemic Attack, V: Vascular Disease, A: 65 to 74 years, S: Female sex; CHF, congestive heart failure; LAAO, left atrial appendage occlusion device; LVD, left ventricular dysfunction; DOAC, non-vitamin K oral anticoagulant; OAC, oral anticoagulation; SD, standard deviation; TE, thromboembolism; TIA, transient ischemic attack.

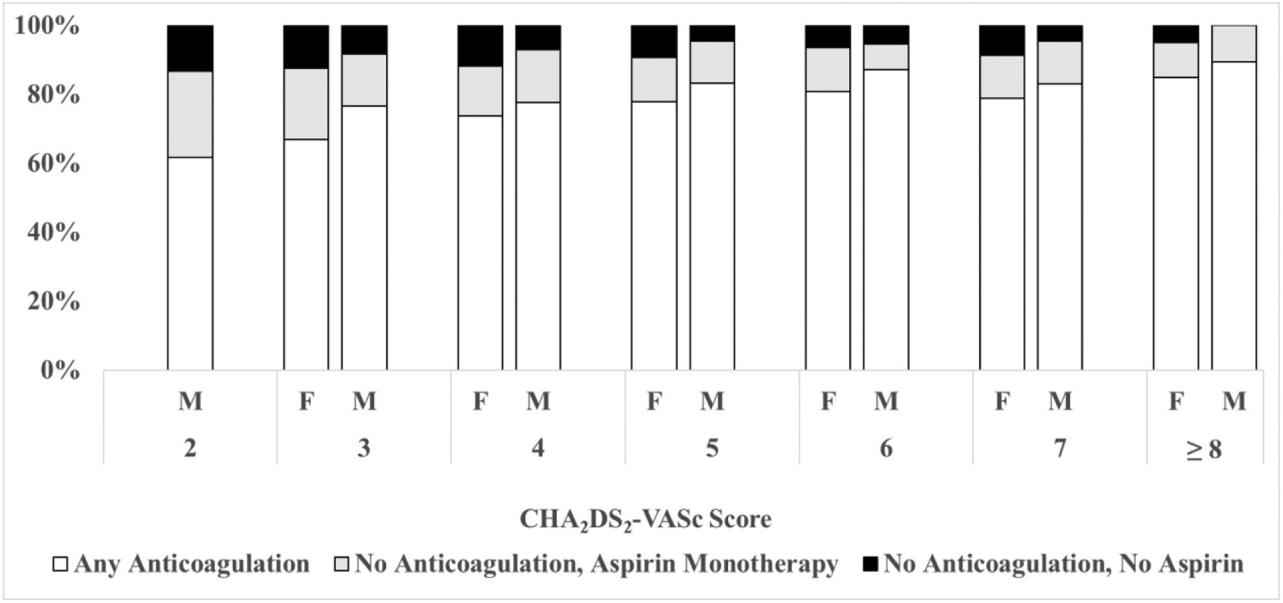

Fig. 3. Baseline prevalence of anticoagulation therapy in the study cohort (non-valvular atrial fibrillation or atrial flutter patients with a high-risk CHA_2DS_2-VASc score and 1-year follow-up data; *N* = 8,032), sorted by CHA_2DS_2-VASc score. M = male; F = female. CHA_2DS_2-VASc conditions key: C: Congestive Heart Failure, H: Hypertension, A: Age ≥75 years, D: Diabetes Mellitus, S: Stroke or Transient Ischemic Attack, V: Vascular Disease, A: 65 to 74 years, S: Female sex.

Table 2
Patients in the study cohort (non-valvular atrial fibrillation or atrial flutter patients with a high-risk CHA_2DS_2-VASc score and 1-year follow-up data; N = 8 032) on oral anticoagulation (warfarin or non-vitamin K oral anticoagulant) compared to those not on oral anticoagulation therapy, stratified by ATRIA bleed score at baseline and at 1-year.

	ATRIA Bleed Score		
Treatment Regimen	Low Risk0-3	Intermediate Risk4	High Risk5-10
Baseline (N = 8032)			
OAC (N = 6069, 75.6%)	4436 (55.2)	536 (6.7)	1097 (13.7)
No OAC Therapy (N = 1963, 24.4%)	1432 (17.8)	170 (2.1)	361 (4.5)
1-year Follow-up (N = 8032)			
OAC (N = 6083, 75.7%)	4310 (53.7)	505 (6.3)	1268 (15.8)
No OAC Therapy (N = 1949, 24.3%)	1354 (16.9)	152 (1.9)	443 (5.5)

Categorical variables are reported as n (%). ATRIA bleed score, Anticoagulation and Risk Factors in Atrial Fibrillation; OAC, oral anticoagulation.

Table 3
Multivariate predictors of oral anticoagulation use among patients in the study cohort (non-valvular atrial fibrillation or atrial flutter patients with a high-risk CHA_2DS_2-VASc score and 1-year follow-up data; N = 8 032). Assessed at baseline, July 2020.

	OAC vs. No OAC Multivariate	
Predictors	Odds Ratio (95% CI)	p-value
Age < 65 years	Reference	
Age 65-74 years	1.45 (1.21-1.73)	< 0.001
Age 75-84 years	1.98 (1.60-2.46)	< 0.001
Age ≥ 85 years	1.41 (1.12-1.77)	< 0.01
Male sex	1.31 (1.17-1.46)	< 0.001
CHA_2DS_2-VASc Score		
2-3	Reference	
4	1.23 (1.05-1.43)	< 0.05
5	1.40 (1.39-1.72)	< 0.01
6	1.52 (1.15-2.02)	< 0.01
7	1.17 (0.81-1.72)	0.41
≥ 8	1.15 (0.64-2.13)	0.65
Hypertension	1.87 (1.63-2.14)	< 0.001
Stroke/TIA/TE	1.98 (1.47-2.71)	< 0.001
Vascular Disease	0.86 (0.74-0.99)	< 0.05
ATRIA Bleed Score		
0-3	Reference	
4	1.05 (0.86-1.29)	0.62
5-10	0.84 (0.72-0.98)	< 0.05
Severe Renal Risk	0.33 (0.19-0.58)	< 0.001
Hemorrhage	0.63 (0.52-0.77)	< 0.001
LAAO (WATCHMAN)	0.06 (0.02-0.17)	< 0.001
Cardiology visit	1.93 (1.73-2.15)	< 0.001

ATRIA Bleed Score, Anticoagulation and Risk Factors in Atrial Fibrillation; CHA_2DS_2-VASc conditions key: C: Congestive Heart Failure, H: Hypertension, Age ≥75, D: Diabetes Mellitus, S: Stroke or Transient Ischemic Attack, V: Vascular Disease, A: 65 to 74 years, S: Female; CI, confidence interval; LAAO, left atrial appendage occlusion device; OAC, oral anticoagulation. TE, thromboembolism; TIA, transient ischemic attack.

Anticoagulation and ATRIA bleed score

At baseline there were 17.8% (N = 1432) of low bleeding risk patients not on OAC, decreasing by less than 1.0% (16.9%; N = 1354) at 1-year (Table 2).

At 1-year, patients at high bleeding risk increased by 3.1% (n = 1458 at baseline vs. n = 1711 at 1-year). Of the 443 patients at 1-year follow-up, who were not on OAC therapy and had a high bleeding risk, 85.6% (N = 379) had a very high CHA_2DS_2-VASc score (≥ 4) and only 3.6% (N = 16) had an LAAO (WATCHMAN) device.

Predictors of outcomes

Predictors of OAC versus no OAC therapy are summarized in Table 3.

In the multivariate regression model, older age groups, male sex, CHA_2DS_2-VASc score of 4, 5, and 6, hypertension, prior stroke/TIA/TE, and a cardiology visit had an increased probability of any OAC therapy ($p < 0.05$).

Vascular disease, high risk ATRIA bleed score, severe renal risk, prior hemorrhage, and LAAO device (WATCHMAN) had a decreased probability of any OAC therapy ($p < 0.05$). CHA_2DS_2-VASc score of 7 or ≥ 8 and ATRIA bleed score of 4 were not significant predictors of anticoagulation therapy in the multivariate analysis.

Survey: provider characteristics

A total of 243 prescribing providers started the survey, with 148 completing the entire survey and case study (60.9% completion rate). Provider demographics are shown in Appendix C. Of the 148 providers who completed the case study, 75.0% correctly recommended treatment with a DOAC. Providers in cardiology were more likely than those in primary care and other specialties to select DOAC (cardiology 96.3% vs. primary care 68.3% vs. other 88.2%, respectively; $p < 0.05$). In response to the question "When using anticoagulants to reduce the risk of stroke resultant from atrial fibrillation, what are your primary concerns?" Majority (87.8%) of providers responded bleeding risk, cost (83.1%), and need for monitoring (63.5%). When asked which on they saw as their greatest concern, 35.1% chose bleeding risk and 25.0% chose cost as the number one factor.

Majority of providers cited that the top barriers to patient compliance with anticoagulation were concerns of cost (N=62, 43.7%) and monitoring anticoagulation effect (N = 31, 21.8%). There were no differences between specialty who reported the primary barrier was concerns of cost (cardiology 40.7% vs. primary care 43.3% vs. other 35.3%; $p = 0.8$). Providers noted the primary barrier to educating patients about their increased risk of stroke was: "They have trouble understanding what I am trying to explain to them" (25.0%), "They think that once their symptoms are being treated the risk of AF-related stroke goes away" (14.1%), and "I don't have enough time to fully discuss the issues with them" (14.1%). When asked "How many patients with atrial fibrillation have you referred for consideration of WATCHMAN (left atrial appendage occlusion device)?" majority of providers responded 0 (60.1%) or 1–5 (35.8%).

Discussion

Nearly one in four patients with non-valvular AF or atrial flutter in a largely rural health system with a high-risk CHA_2DS_2-VASc score are not on guideline recommended OAC therapy. Of these high-risk AF patients not on anticoagulation, 16.9% had a low-risk ATRIA bleed score at 1-year and OAC therapy would be recommended.[31-34]

The GLORIA-AF registry found at 30 days after AF diagnosis, 40%, 16%, and 8.6% of patients had DOAC, vitamin K antagonists, and an-

tiplatelet drugs initiated, respectively, and more patients were on warfarin than DOAC therapy at 1-year (37%).[35] Two large health systems (Kaiser) found that at 1-year 43% of new AF patients with CKD were on warfarin compared to 48% without CKD. Additionally, 8.6% of those with CKD were on DOAC compared to 15% of those without CKD.[36] However, a trend was seen with fewer patients on warfarin and more on DOAC therapy (36% vs. 39%). Our DOAC use is similar to the GLORIA-AF registry and higher than the study by Bansal et al. (2022). We found no significant increase in the percentage of AF patients receiving OAC therapy. Apixaban (Eliquis) was the most prevalent DOAC followed by rivaroxaban (Xarelto). Possible explanation for this trend in decreased warfarin use is the result of the 2019 ACC/AHA/HRS guideline update which established DOACs as first line therapy over warfarin for non-valvular AF as well as increasing provider familiarity with DOACs.[15] Another contributing factor to declining warfarin use may have been the COVID-19 pandemic and corresponding limited access to INR clinics. Monitoring future trends in DOAC use will be important for anticoagulation programs as patients shifting from warfarin to DOACs will lead to decreased need for warfarin-specific management teams and increased need for comprehensive anticoagulation programs.

Meta-analysis has shown that DOACs significantly reduce the risk of ischemic and hemorrhagic stroke/TE, intracranial bleeding, and other fatal bleeding events in comparison to warfarin.[19,37,38] The GLORIA-AF found no significant difference between DOAC and warfarin in ischemic stroke incidence.[39] With exception of apixaban, AF patients ≥ 75 years taking warfarin had a decreased risk of gastrointestinal bleeding in comparison to DOACs. [40,41] We found that 48% of patients ≥ 85 years were on warfarin compared to only 23% of patients < 65 years. DOAC use was similar throughout the younger age groups. However, in patients ≥ 85 years, use of rivaroxaban dropped from 24% to 7% after 1 year. Rivaroxaban and dabigatran have been shown to have an increase rate of gastrointestinal and other nonfatal bleeding when compared to warfarin and apixaban.[10,12-18,21,22,38,42,43]

While not a variable in the CHA_2DS_2-VASc score, prior studies have shown that current daily smoking is an independent predictor of stroke/TIA/TE.[13,44,45] Despite this, we did not find that current daily smoking was associated with either an increased or decreased odds of being on OAC therapy.

We found a substantial population of high-risk AF patients not on anticoagulation. This may reflect physician gap in knowledge and perceived bleeding risk.[46] In the Essentia Health Provider Survey, only 75.0% of providers responded correctly that they would prescribe a DOAC for a hypothetical patient with a CHA_2DS_2-VASc score of 3 with no contraindications to anticoagulation. Primary care providers were least likely to prescribe DOACs to the hypothetical patient with nearly 1 in 4 incorrectly treating the patient either antiplatelet or no anticoagulation, similar to Frankel et al.[47] The survey provided insight into barriers physicians have cited to anticoagulation therapy; the top barrier was patient's concern of cost, monitoring anticoagulation and bleeding risk - but bleeding risk scores have and continue to be subject to misinterpretation.[30,46,48] Similarly, the SATELLITE substudy found the most important factors cited by patients were reducing stroke and bleeding risk, as well as their healthcare providers recommendations.[49] However, there is research that using a shared-decision making tool at the encounter does not improve treatment decisions.[50] Bleeding risk is a dynamic measurement of the patient.[30] Head to head comparisons of the different DOACs has shown Rivaroxaban to have higher bleeding.[51] High-risk ATRIA bleed scores are not a reason to withhold OAC in high-risk non-valvular AF patients if the net benefit of ischemic stroke risk reduction is higher than risk of serious bleeding events.[30-33] Furthermore, if patients are at high bleeding risk, a LAAO device could be considered to lower stroke risk in lieu of long-term anticoagulation.[52] We found LAAO use was low in this largely rural cohort. Barriers to LAAO use include geography (limited access to this technology) with few (<5) trained cardiology providers to implant these devices. Besides limited access, our implanting providers often require patients to have failed a DOAC (not just warfarin) prior to implant. Many patients who tolerate DOAC may not need to undergo a procedure for a LAA device. Furthermore, we have a centralized anticoagulation program across our health system that manages warfarin and DOACs. The time in therapeutic range on warfarin is >70% for most patients. Primary care provider knowledge of LAAO as a treatment option is also a barrier. Majority of providers (60.1%) noted never referring a patient for LAAO and 35.8% had referred 1-5 patients.

Based on the 2019 ACC/AHA/HRS guidelines, DOACs are preferred over warfarin if the patient is eligible for DOAC.[15] However, increasing DOAC use continues to be a challenge due to patient and provider barriers. DOACs are more expensive, and the target-specific reversal agents such as idarucizumab (Praxbind) and andexanet alfa (Andexxa), are not reliably accessible, especially in rural critical access hospitals, compared to vitamin K or 4F-PCC (Kcentra).[48] The superiority of DOACs to warfarin in regard to lower incident of intracranial bleed, was demonstrated without the use of DOAC antidotes.[16-18,23,40,41] The perception of necessity of having the antidote available at hand before initiating the DOAC treatment remains misconstrued. As the population continues to age, the prevalence of AF will continue to rise.[4,5] There is an increasing need for appropriate and up to date OAC therapy and improved AF management in high-risk patients. As DOACs have been introduced to the market since 2010, some if not all the currently used DOAC agents will become generic over the next 5-10 years which in turn will increase their use. Majority of providers reported patient cost as a significant barrier to patient anticoagulation use in the provider survey. While many insurance plans cover DOACs, it is our experience that the combination of the patient deductible that has to be met and then the Medicare Coverage Gap (or donut hole) are the biggest barriers to patient use. Many Medicare Part D plans have reasonable copays for DOAC, but the initial deductible can be a barrier. Provider's lack of understanding of the intricacies of insurance coverage and deductibles and lack of transparency when ordering medications are also potential barriers. Some providers cite the high co-pay as the barrier but in reality, that is the high patient deductible for the first month due, but the DOAC co-pay may be affordable for the patient in subsequent months. This predictable trend places further emphasis in transitioning the warfarin clinics to comprehensive anticoagulation clinics.

Limitations

There are several limitations of this study. First, groups were defined based on EHR medication list, not pharmacy dispensing data. Most of these patients had multiple visits during this time but medication adherence and duration of use was not measured in this retrospective study. Second, we included clinically meaningful AF. We did not confirm AF diagnosis by electrocardiogram nor determine timing or duration of AF episodes nor exclude secondary causes of AF.[42] If AF or atrial flutter was on the active problem list at the time of the visit, the patient was considered to have AF and was entered into the cohort. Third, we used the ATRIA bleed score, a measurement of bleeding risk that includes variables easily captured in the EHR. [30-32] Lastly, there is commonly a delay after publication of a new guideline until the widespread implementation in the medical community. The time frame for our observation was only 1 year, and only 2 years after the publication of the new guidelines. It is possible that the changes in the trend of administration of OAC would be different if a longer timeframe was chosen.

Conclusion

Implementation of the 2019 ACC/AHA/HRS guideline recommendation that DOACs are first line therapy over warfarin for high-risk non-valvular AF resulted in an increase in DOAC use. There was a non-significant trend in decreasing warfarin use. Apixaban (Eliquis) was the most prevalent DOAC. Although trends showed that anticoagulation use

slightly increased over the 1-year study period, one in four high-risk patients were not on any OAC therapy. Barriers to anticoagulation use include concerns of bleeding and patient cost. These results present further opportunities for research, discussion, and education of providers and patients on the risk of stroke associated with non-valvular AF. Future studies on barriers and facilitators of OAC therapy for AF needs to be prioritized.

Disclosures

The authors declare that they have no conflicts of interest or disclosures to report.

IRB/ethical approval

The survey was IRB approved by Essentia Health.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ajmo.2022.100026.

References

1. Lakshminarayan K, Anderson DC, Herzog CA, Qureshi AI. Clinical epidemiology of atrial fibrillation and related cerebrovascular events in the United States. *Neurologist*. 2008;14(3):143–150.
2. Staerk L, Sherer JA, Ko D, Benjamin EJ, Helm RH. Atrial fibrillation: epidemiology, pathophysiology, and clinical outcomes. *Circ Res*. 2017;120(9):1501–1517.
3. Williams BA, Chamberlain AM, Blankenship JC, Hylek EM, Voyce S. Trends in atrial fibrillation incidence rates within an integrated health care delivery system, 2006 to 2018. *JAMA Netw Open*. 2020;3(8):e2014874.
4. Lippi G, Sanchis-Gomar F, Cervellin G. Global epidemiology of atrial fibrillation: an increasing epidemic and public health challenge. *Int J Stroke*. 2021;16(2):217–221.
5. Benziger CP, Roth GA, Moran AE. The global burden of disease study and the preventable burden of NCD. *Glob Heart*. 2016;11(4):393–397.
6. Prevention CfDCa. Atrial fibrillation. 2020.
7. Kornej J, Börschel CS, Benjamin EJ, Schnabel RB. Epidemiology of atrial fibrillation in the 21st century: novel methods and new insights. *Circ Res*. 2020;127(1):4–20.
8. Lip GY, Frison L, Halperin JL, Lane DA. Identifying patients at high risk for stroke despite anticoagulation: a comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. *Stroke*. 2010;41(12):2731–2738.
9. Stroke NIoNDa. Atrial fibrillation and stroke. 2019.
10. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol*. 2014;6:213–220.
11. Evers-Dörpfeld S, Aeschbacher S, Hennings E, et al. Sex-specific differences in adverse outcome events among patients with atrial fibrillation. *Heart*. 2022;108(18):1445–1451.
12. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22(8):983–988.
13. Maeda T, Nishi T, Funakoshi S, et al. Risks of bleeding and stroke based on CHA2DS2-VASc Scores in Japanese patients with atrial fibrillation: a large-scale observational study using real-world data. *J Am Heart Assoc*. 2020;9(5):e014574.
14. Markides V, Schilling RJ. Atrial fibrillation: classification, pathophysiology, mechanisms and drug treatment. *Heart*. 2003;89(8):939–943.
15. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American college of cardiology/American heart association task force on clinical practice guidelines and the heart rhythm society. *Heart Rhythm*. 2019.
16. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883–891.
17. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981–992.
18. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139–1151.
19. Hicks T, Stewart F, Eisinga A. NOACs versus warfarin for stroke prevention in patients with AF: a systematic review and meta-analysis. *Open Heart*. 2016;3(1):e000279.
20. Staerk L, Fosbøl EL, Lip GYH, et al. Ischaemic and haemorrhagic stroke associated with non-vitamin K antagonist oral anticoagulants and warfarin use in patients with atrial fibrillation: a nationwide cohort study. *Eur Heart J*. 2017;38(12):907–915.
21. Kaplan RM, Koehler J, Ziegler PD, Sarkar S, Zweibel S, Passman RS. Stroke risk as a function of atrial fibrillation duration and CHA. *Circulation*. 2019;140(20):1639–1646.
22. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Rev Esp Cardiol*. 2017;70(1):50 *(Engl Ed)*.
23. Darkow T, Vanderplas AM, Lew KH, Kim J, Hauch O. Treatment patterns and real–world effectiveness of warfarin in nonvalvular atrial fibrillation within a managed care system. *Curr Med Res Opin*. 2005;21(10):1583–1594.
24. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *Am J Med*. 2010;123(7):638–645 e634.
25. Gebreyohannes EA, Mill D, Salter S, Chalmers L, Bereznicki L, Lee K. Strategies for improving guideline adherence of anticoagulants for patients with atrial fibrillation in primary healthcare: a systematic review. *Thromb Res*. 2021;205:128–136.
26. Hess PL, Mirro MJ, Diener HC, et al. Addressing barriers to optimal oral anticoagulation use and persistence among patients with atrial fibrillation: proceedings, Washington, DC, December 3-4, 2012. *Am Heart J*. 2014;168(3):239–247 e231.
27. Mujer MTP, Rai MP, Atti V, et al. An update on the reversal of non-vitamin K antagonist oral anticoagulants. *Adv Hematol*. 2020;2020:7636104.
28. Saraiva JFK. Stroke prevention with oral anticoagulants: summary of the evidence and efficacy measures as an aid to treatment choices. *Cardiol Ther*. 2018;7(1):15–24.
29. Iung B, Leenhardt A, Extramiana F. Management of atrial fibrillation in patients with rheumatic mitral stenosis. *Heart*. 2018;104(13):1062–1068.
30. Lip GYH, Skjøth F, Nielsen PB, Kjældgaard JN, Larsen TB. The HAS-BLED, ATRIA, and ORBIT bleeding scores in atrial fibrillation patients using non-vitamin K antagonist oral anticoagulants. *Am J Med*. 2018;131(5):574.e513 574.e527.
31. Fang MC, Go AS, Chang Y, et al. A new risk scheme to predict warfarin-associated hemorrhage: the ATRIA (Anticoagulation and risk factors in atrial fibrillation) study. *J Am Coll Cardiol*. 2011;58(4):395–401.
32. Roldán V, Marín F, Fernández H, et al. Predictive value of the HAS-BLED and ATRIA bleeding scores for the risk of serious bleeding in a "real-world" population with atrial fibrillation receiving anticoagulant therapy. *Chest*. 2013;143(1):179–184.
33. Chang G, Xie Q, Ma L, et al. Accuracy of HAS-BLED and other bleeding risk assessment tools in predicting major bleeding events in atrial fibrillation: a network meta-analysis. *J Thromb Haemost*. 2020;18(4):791–801.
34. Senoo K, Proietti M, Lane DA, Lip GY. Evaluation of the HAS-BLED, ATRIA, and ORBIT bleeding risk scores in patients with atrial fibrillation taking warfarin. *Am J Med*. 2016;129(6):600–607.
35. Bayer V, Kotalczyk A, Kea B, et al. Global oral anticoagulation use varies by region in patients with recent diagnosis of atrial fibrillation: the GLORIA-AF phase III registry. *J Am Heart Assoc*. 2022;11(6):e023907.
36. Bansal N, Zelnick LR, Reynolds K, et al. Management of adults with newly diagnosed atrial fibrillation with and without CKD. *J Am Soc Nephrol*. 2022;33(2):442–453.
37. Silverio A, Di Maio M, Prota C, et al. Safety and efficacy of non-vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation: systematic review and meta-analysis of 22 studies and 440 281 patients. *Eur Heart J Cardiovasc Pharmacother*. 2021;7(FI1):f20–f29.
38. Chan YH, Chao TF, Lee HF, et al. Clinical outcomes in atrial fibrillation patients with a history of cancer treated with non-vitamin K antagonist oral anticoagulants: a nationwide cohort study. *Stroke*. 2021;52(10):3132–3141. doi:10.1161/STROKEAHA.120.033470. Epub 2021 Jul 8. PMID: 34233467.
39. Ding WY, Lane DA, Gupta D, Huisman MV, Lip GYH. Investigators G-A. Incidence and risk factors for residual adverse events despite anticoagulation in atrial fibrillation: results from phase II/III of the GLORIA-AF registry. *J Am Heart Assoc*. 2022;11(15):e026410.
40. Lip GYH, Keshishian A, Li X, et al. Effectiveness and safety of oral anticoagulants among nonvalvular atrial fibrillation patients. *Stroke*. 2018;49(12):2933–2944.
41. Carnicelli AP, Hong H, Connolly SJ, et al. Direct Oral anticoagulants versus warfarin in patients with atrial fibrillation: patient-level network meta-analyses of randomized clinical trials with interaction testing by age and sex. *Circulation*. 2022;145(4):242–255.
42. Go AS, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Ann Intern Med*. 1999;131(12):927–934.
43. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137(2):263–272.
44. Pan B, Jin X, Jun L, Qiu S, Zheng Q, Pan M. The relationship between smoking and stroke: a meta-analysis. *Medicine*. 2019;98(12):e14872 *(Baltimore)*.
45. Chamberlain AM, Agarwal SK, Folsom AR, et al. Smoking and incidence of atrial fibrillation: results from the Atherosclerosis Risk in Communities (ARIC) study. *Heart Rhythm*. 2011;8(8):1160–1166.
46. Dharmarajan TS, Varma S, Akkaladevi S, Lebelt AS, Norkus EP. To anticoagulate or not to anticoagulate? A common dilemma for the provider: physicians' opinion poll based on a case study of an older long-term care facility resident with dementia and atrial fibrillation. *J Am Med Dir Assoc*. 2006;7(1):23–28.
47. Frankel DS, Parker SE, Rosenfeld LE, Gorelick PB. HRS/NSA 2014 survey of atrial fibrillation and stroke: gaps in knowledge and perspective, opportunities for improvement. *Heart Rhythm*. 2015;12(8):e105–e113.

48. Zaidel EJ, Leng X, Adeoye AM, et al. Inclusion in the World Health Organization model list of essential medicines of non-vitamin K anticoagulants for treatment of non-valvular atrial fibrillation: a step towards reducing the burden of cardiovascular morbidity and mortality. *Glob Heart.* 2020;15(1):52.
49. Ali-Ahmed F, Pieper K, North R, et al. Shared decision-making in atrial fibrillation: patient-reported involvement in treatment decisions. *Eur Heart J Qual Care Clin Outcomes*. 2020;6(4):263–272.
50. Kunneman M, Branda ME, Hargraves IG, et al. Assessment of shared decision-making for stroke prevention in patients with atrial fibrillation: a randomized clinical trial. *JAMA Intern Med*. 2020;180(9):1215–1224.
51. Lip GYH, Kotalczyk A, Teutsch C, et al. Comparative effectiveness and safety of non-vitamin K antagonists for atrial fibrillation in clinical practice: GLORIA-AF registry. *Clin Res Cardiol*. 2022;111(5):560–573.
52. Korsholm K, Valentin JB, Damgaard D, et al. Clinical outcomes of left atrial appendage occlusion versus direct oral anticoagulation in patients with atrial fibrillation and prior ischemic stroke: a propensity-score matched study. *Int J Cardiol*. 2022;363:56–63.