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Research Paper

Racial and sex differences in optimizing anticoagulation therapy for patients with atrial fibrillation

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ABSTRACT

Study objective: Atrial fibrillation (AF) is the most common cardiac rhythm disorder, responsible for 15 % of strokes in the United States. Studies continue to document underuse of anticoagulation therapy in minority populations and women. Our objective was to compare the proportion of AF patients by race and sex who were receiving non-optimal anticoagulation as determined by an Atrial Fibrillation Decision Support Tool (AFDST).
Design, setting, and participants: Retrospective cohort study including 14,942 patients within University of Cincinnati Health Care system. Data were analyzed between November 18, 2020, and November 20, 2021.
Main outcomes and measures: Discordance between current therapy and that recommended by the AFDST.
Results: In our two-category analysis 6107 (41 %) received non-optimal anticoagulation therapy, defined as current treatment category ≠ AFDST-recommended treatment category. Non-optimal therapy was highest in Black (42 % [$n = 712$]) and women (42 % [$n = 2668$]) and lower in White (39 % [$n = 4748$]) and male (40 % [$n = 3439$]) patients. Compared with White patients, unadjusted and adjusted odds ratios of receiving non-optimal anticoagulant therapy for Black patients were 1.13; 95 % CI, 1.02–1.30, $p = 0.02$; and 1.17; 95%CI, 1.04–1.31, $p = 0.01$; respectively, and 1.10; 95 % CI 1.03–1.18, $p = 0.005$; and 1.36; 95 % CI, 1.25–1.47, $p < 0.001$; for females compared with males.
Conclusions and relevance: In patients with atrial fibrillation in the University of Cincinnati Health system, Black race and female sex were independently associated with an increased odds of receiving non-optimal anticoagulant therapy.

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1. Introduction

Atrial fibrillation (AF) is the most common significant cardiac rhythm disorder and is also a significant and common risk factor for stroke: about 15 % of all strokes in the U.S. are attributable to AF [1]. Its frequency increases with age, reaching a prevalence of 10 % in persons over age 80. With the aging of the U.S. population, the prevalence of AF is increasing steadily from over 8.7 million (in 2021) to >12 million in 2030 [2]. Randomized trials have established that anticoagulation can reduce stroke risk posed by AF [3]. However, there is widespread underutilization of this therapy [4,5], particularly in community settings where there is wide variation in adherence to practice guidelines [6].

Prior studies also have documented racial and sex differences in the use of oral anticoagulation therapy in patients with AF. Earlier analyses focusing on anticoagulation with warfarin reported a lower odds of anticoagulation among Black patients, ranging between 0.5 and 0.75 [7–13]. More contemporary studies have examined differences in the prescribing of direct oral anticoagulants (DOACs), with results suggesting higher odds of DOAC prescriptions being made for non-Hispanic white patients [14], and decreased odds of DOAC prescriptions among non-Hispanic Blacks, Asians, and Hispanic Medicare recipients compared with non-Hispanic White patients [15]. Studies also have shown that Black patients were less likely to be switched from warfarin to DOACs for their anticoagulation management [16,17].

Most studies have focused exclusively on anticoagulation prescribing among patients with newly incident AF [13,18–22]. However, the balance of risk factors for stroke and bleeding while taking anticoagulant therapy are dynamic and change over time. Thus, the decision about net benefit and whether a patient should receive anticoagulant therapy needs to be made repeatedly over time. Furthermore, many of these studies report only on anticoagulation use overall, or use stroke risk, as measured by the $CHADS_2$ or CHA_2DS_2VASc [23] as the sole determinant of appropriateness for anticoagulation. They do not consider the balance of risk and benefit for anticoagulation therapy among individual patients, nor do they account for competing risks of death from either advanced age or comorbid health conditions that may limit the net benefit of anticoagulation.

We have developed an Atrial Fibrillation Decision Support Tool (AFDST) that uses a decision analytic model to examine anticoagulation strategies for individual patients [24,25]. Using clinical and demographic information extracted into a datastore from our electronic health record (EHR), we calculate the net benefit or loss of a variety of anticoagulation strategies compared with no anticoagulation. Our goal was to use this tool to analyze race and sex differences in anticoagulation therapy for our health system's roughly 15,000 patients with prevalent AF. While the AFDST is available to our clinicians as a real-time decision aid, this study was entirely observational, using the AFDST "offline" to determine whether patients were receiving optimal anticoagulation therapy at the time of the data pull.

2. Methods

2.1. Basic design and data source

This was a retrospective study of 14,942 adult aged 20 to 99 with non-valvular AF or flutter seen in our University of Cincinnati Health system. Our AF clinical data store contains patients with International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnoses of I48.x and age ≥ 18 years. As shown in Fig. 1, we exclude patients with diagnoses of mitral valve disease (I05*), aortic valve disease (I06*), mitral and aortic valve disease (I08*), nonrheumatic mitral valve disease (I34*), nonrheumatic aortic valve disease (I35*), or presence of prosthetic heart valve (Z95.2), or presence of xenogenic heart valve (Z95.3). We also include a number of ICD-10 procedure coding system codes for valve repair or replacement (PCS 02AF*, 02QG*, 02QH*, 02QJ*, 02RF*, 02RG*, 02RH*, 02RJ*). In addition, we measured covariates related to perceived barriers to clinicians' prescribing anticoagulants. These included psychiatric diagnoses, alcohol or other drug abuse that might impact medication adherence; and other potential barriers to adherence and clinical follow-up such as homelessness, inadequate housing, lack of other household member to render care, or a personal history of non-compliance. We also obtained information on covariates associated with a predisposition to falls, including epilepsy, narcolepsy, syncope, orthostatic hypotension, prior fall from stairs, among others. See supplement table 1 for a full listing of ICD-10-CM codes and clinical data sources used in the analysis. We took a snapshot of AF patients in our datastore who were alive on November 18, 2020. Information needed to calculate stroke risk using CHA_2DS_2VASc [23], major hemorrhage using HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, concomitant drugs and alcohol) [26], and intracerebral hemorrhage [27] was extracted from the clinical data store using the active problem list and a combination of laboratory values and clinical measurements. Information on current antithrombotic therapy was retrieved from the active medication list. Fifty-eight percent of our patients were male, 81 % were White and 11 % were Black. The 8 % of patients who were categorized as Other, included Asian, Hispanic, American Indian, Multiracial, and Native Hawaiian patients (see Table 1 for patient characteristics). Data are stored on a secure server at the Center for Health Informatics, University of Cincinnati, as discrete elements hosted on MySQL (Oracle Corporation, Cupertino, CA). SAS (SAS Institute, Inc., Cary, NC). Data files were created as necessary for statistical analyses using unique

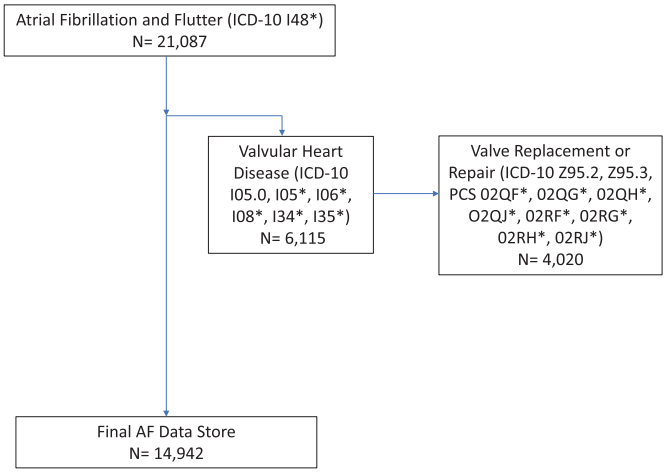

Fig. 1. Study flow diagram – the AF datastore was created on November 18, 2020. At that time, 21,087 patients in the UC Health system had a diagnosis of atrial fibrillation or atrial flutter. Of those, 6115 had a diagnosis of valvular heart disease and were excluded from the AF datastore, leaving 14,942 patients in our study. Of interest, an estimated 4020 of the 6115 patients with valvular heart disease had valve replacements or repairs.
Note: The AF datastore created on November 18, 2020 contained 14,942 patients. We did not have data at that time for the number of patients who were excluded from the datastore due to a diagnosis of valvular heart disease. Therefore, in order to estimate the total number of patients in our health system with atrial fibrillation or atrial flutter along with the number of those with valvular heart disease exclusions we calculated the proportion of AF patients in our UC Health system on April 22, 2022 who had valvular heart disease or a repaired or replaced heart valve and then used those percentages to back-calculate the missing data based on the 14,942 patients in our study. Of the 22,340 AF patients in our healthcare system on April 22, 2022, 6510 had valvular heart disease (29 %), and 4280 had valve repair or replacement (66 % of those with valvular heart disease). Applying these percentages, we estimated a total of 21,087 AF patients, of whom 6115 were excluded for having valvular heart disease, resulting in the cohort of 14,942 AF patients assembled on November 18, 2020 in our study.

Table 1
Patient characteristics for 14,942 atrial fibrillation patients in UC health cohort.

Characteristic	All (N = 14,942)	Male (N = 8649) 58 %	Female (N = 6293) 42 %	White (N = 12,045) 81 %	Black (N = 1677) 11 %	Other[a] (N = 1220) 8 %	White/ Black p	Sex p
Sex							0.007	
Male (%)	8649 (58)			7054 (59)	924 (55)	671(55)		
Female (%)	6293 (42)			4991 (41)	753 (45)	549 (45)		
Race								0.007
White (%)	12,045 (81)	7054 (82)	4991 (49)					
Black (%)	1677 (11)	924 (11)	753 (12)					
Other (%)	1220 (8)	671 (8)	549 (9)					
Age, y (SD)	76.12 (14.4)	73.5 (14.4)	79.8 (13.6)	76.7 (14.0)	68.7 (14.9)	81.1 (14.4)	<0.001	<0.001
Marital status							<0.001	<0.001
Single (%)	2196 (15)	1407 (16)	789 (13)	1480 (12)	621 (37)	95 (8)		
Married or significant other (%)	7570 (51)	5322 (62)	2248 (36)	6518 (54)	507 (30)	545 (45)		
Divorced or legally separated (%)	1489 (10)	795 (9)	694 (11)	1187 (10)	260 (16)	42 (3)		
Widowed (%)	3164 (21)	859 (10)	2305 (37)	2699 (22)	264 (16)	201 (17)		
Other/Unknown (%)	523 (4)	266 (3)	257 (4)	161 (1)	25 (1)	337 (28)		
Insurance							<0.001	<0.001
Commercial (%)	2210 (15)	1558 (18)	652 (10)	1816 (15)	297 (18)	97 (8)		
Medicare, including managed Medicare (%)	8375 (56)	4542 (53)	3833 (61)	7239 (60)	904 (54)	232 (19)		
Medicaid, including managed Medicaid (%)	642 (4)	405 (5)	237 (4)	394 (3)	205 (12)	43 (4)		
Self-pay (%)	468 (3)	321 (4)	147 (2)	339 (3)	66 (4)	63 (5)		
Other (%)	220(1)	177 (2)	43 (1)	172 (1)	39 (2)	9 (1)		
N/A (%)	3027 (20)	1646 (13)	1381 (22)	2085 (17)	166 (10)	776 (64)		
Comorbidities								
Hypertension (%)	9610 (64)	5420 (63)	4190 (67)	7484 (62)	1341 (80)	785 (64)	<0.001	<0.001
Poorly controlled hypertension (%)	1014 (7)	535 (6)	479 (8)	727 (6)	259 (15)	28 (2)	<0.001	<0.001
Congestive heart failure (%)	3415 (22)	2003 (23)	1412 (22)	2536 (12)	635 (38)	244 (20)	<0.001	0.30
Diabetes mellitus (%)	3933 (26)	2379 (28)	1554 (25)	3018 (25)	615 (37)	300 (25)	<0.001	<0.001
Prior stroke or TIA (%)	3116 (21)	1671 (19)	1445 (23)	2481 (21)	448 (27)	187 (15)	<0.001	<0.001
Vascular disease (%)	5597 (37)	3655 (42)	1942 (31)	4579 (38)	683 (41)	335 (28)	0.03	<0.001
Abnormal renal function (%)	973 (6)	642 (7)	331 (5)	652 (5)	277 (17)	44 (4)	<0.001	<0.001
eGFR (ml/min) (SD)	67.5 (13.7)	67.8 (14.3)	67.2 (12.8)	67.8 (12.6)	65.4 (20.6)	67.7 (11.6)	<0.001	<0.001
End stage kidney disease (%)	472 (3)	313 (4)	159 (3)	298 (2)	135 (8)	39 (3)	<0.001	<0.001
Abnormal liver function (%)	942 (6)	640 (7)	302 (5)	746 (6)	161 (10)	35 (3)	<0.001	<0.001
Bleeding history (%)	2433 (16)	1450 (17)	983 (16)	1942 (16)	379 (23)	112 (9)	<0.001	0.06
Prior intracerebral hemorrhage (%)	517 (3)	316 (4)	201 (3)	437 (4)	63 (4)	17 (1)	0.78	0.13
Coronary artery disease (%)	5010 (34)	3311 (38)	1699 (27)	4103 (34)	618 (37)	289 (24)	0.03	<0.001
History of myocardial infarction (%)	1676 (11)	1074 (12)	602 (10)	1323 (11)	290 (17)	63 (5)	<0.001	<0.001
Labile INR (%)	1068 (7)	651 (8)	417 (7)	804 (7)	234 (14)	30 (2)	<0.001	0.04
Perceived barriers to adherence or safety								
Psychiatric diagnoses (%)	87 (1)	43 (0)	44 (1)	70 (1)	14 (1)	3 (0)	0.24	0.12
Intellectual disabilities (%)	9 (0)	6 (0)	3 (0)	4 (0)	5 (0)	0 (0)	0.002	0.74
Developmental disorders (%)	13 (0)	6 (0)	7 (0)	11 (0)	2 (0)	0 (0)	0.67	0.41
Alcohol and/or drug abuse (%)	919 (6)	674 (8)	245 (4)	650 (5)	222 (13)	47 (4)	<0.001	<0.001
Other barriers to adherence[b] (%)	49 (0)	28 (0)	21 (0)	17 (0)	30 (2)	2 (0)	<0.001	1.00
Predisposition to falls[c] (%)	1910 (13)	1055 (12)	855 (13)	1512 (13)	321 (19)	77 (6)	<0.001	0.01
CHA_2DS_2VASc score (SD)	3.7 (1.8)	3.2 (1.8)	4.4 (1.7)	3.7 (1.8)	3.9 (2.0)	3.7 (1.7)	<0.001	<0.001
HASBLED score (SD)	1.9 (1.1)	1.9 (1.2)	1.9 (1.1)	1.9 (1.1)	2.2 (1.4)	1.4 (0.9)	<0.001	0.29
Mean ICH risk, events per year (SD)	0.0051 (0.016)	0.0059 (0.018)	0.0040 (0.013)	0.0053 (0.017)	0.0048 (0.015)	0.0034 (0.012)	<0.001	<0.001
Current Antithrombotic Therapy							<0.001	<0.001
None (%)	5393 (36)	2971 (34)	2422 (38)	4032 (33)	468 (28)	893 (89)		
Aspirin[d] (%)	2873 (19)	1798 (21)	1075 (17)	2378 (20)	400 (24)	95 (8)		
Warfarin (%)	2670 (18)	1601 (19)	1069 (17)	2264 (19)	314 (19)	92 (9)		
Apixaban (%)	2374 (16)	1326 (15)	1048 (17)	1983 (16)	308 (18)	83 (8)		
Rivaroxaban (%)	1404 (9)	819 (9)	585 (9)	1176 (10)	180 (11)	48 (5)		
Dabigatran (%)	222 (1)	133 (2)	89 (1)	208 (2)	6 (0)	8 (1)		
Edoxaban (%)	6 (0)	1 (0)	5 (0)	4 (0)	1 (0)	1 (0)		
Any DOAC (%)	4006 (27)	2279 (26)	1728 (27)	3372 (28)	495 (30)	140 (14)		
Any oral anticoagulant	6676 (45)	3880 (45)	2797 (44)	5636 (47)	809 (48)	232 (19)		
Receiving "non-optimal anticoagulation therapy"[e] (%)	6107 (41)	3439 (40)	2668 (42)	4748 (39)	712 (42)	647 (53)	0.02	0.001
Average gain among those not receiving optimal anticoagulation treatment (QALYs)[e] (SD)	0.69 (0.76)	0.57 (0.54)	0.85 (0.94)	0.68 (0.72)	0.88 (1.05)	0.59 (0.62)	0.001	<0.001

Abbreviations: ICH – intracerebral hemorrhage.
P-values from Fisher exact tests on 2 × 2 tables, chi-squares on larger tables, and Wilcoxon rank-sum tests on continuous variables.

[a] Category includes – Other (1092), unknown (109), and patient refused (19).

[b] Other barriers to adherence includes – homelessness, inadequate housing, inadequate material resources, person living alone, no other household member able to render care, other specified or unspecified housing or economic circumstances.

[c] Predisposition to falls include diagnoses of – senile and presenile organic conditions, epilepsy, cataplexy/narcolepsy, orthostatic hypotension, syncope and collapse, convulsions, fall on or from stairs or steps.

[d] Patients listed in table as taking aspirin do not include those receiving aspirin and an oral anticoagulant.

[e] Non-optimal therapy defined as current treatment category ≠ recommended treatment category, and recommended treatment would result in a net gain ≥0.1 quality-adjusted life years, using two treatment categories of None/Aspirin vs. Warfarin/DOAC.

coded participant identifiers. Further details are described elsewhere [25]. See the supplement Table 1 for detailed information regarding diagnostic codes and laboratory information used to define model variables.

2.2. Decision analytic model

Treatment recommendations are made using the AFDST. The computational engine of the AFDST is an individual-specific decision analytic model consisting of a 29-state Markov simulation that projects quality-adjusted life expectancy for each of seven strategies (1) no antithrombotic therapy, (2) aspirin, (3) warfarin, (4) dabigatran, (5) apixaban, (6) rivaroxaban, and (7) edoxaban for each individual [25]. The decision model uses information from the electronic health record to integrate individual-specific risk factors for stroke and hemorrhage in its calculations (see supplement Table 2 for a complete listing of the data elements extracted from the EHR as inputs to the decision analytic model). Decision model construction and analysis was performed using a standard computer program (Decision Maker, Boston, MA). During each monthly cycle of the Markov simulation, patients face a chance of stroke and hemorrhage, either of which may lead to death, long-term morbidity, or resolution. Efficacy of treatment and relative risk of complications including major bleeding and intracerebral hemorrhage (ICH) were informed by literature review including meta-analyses

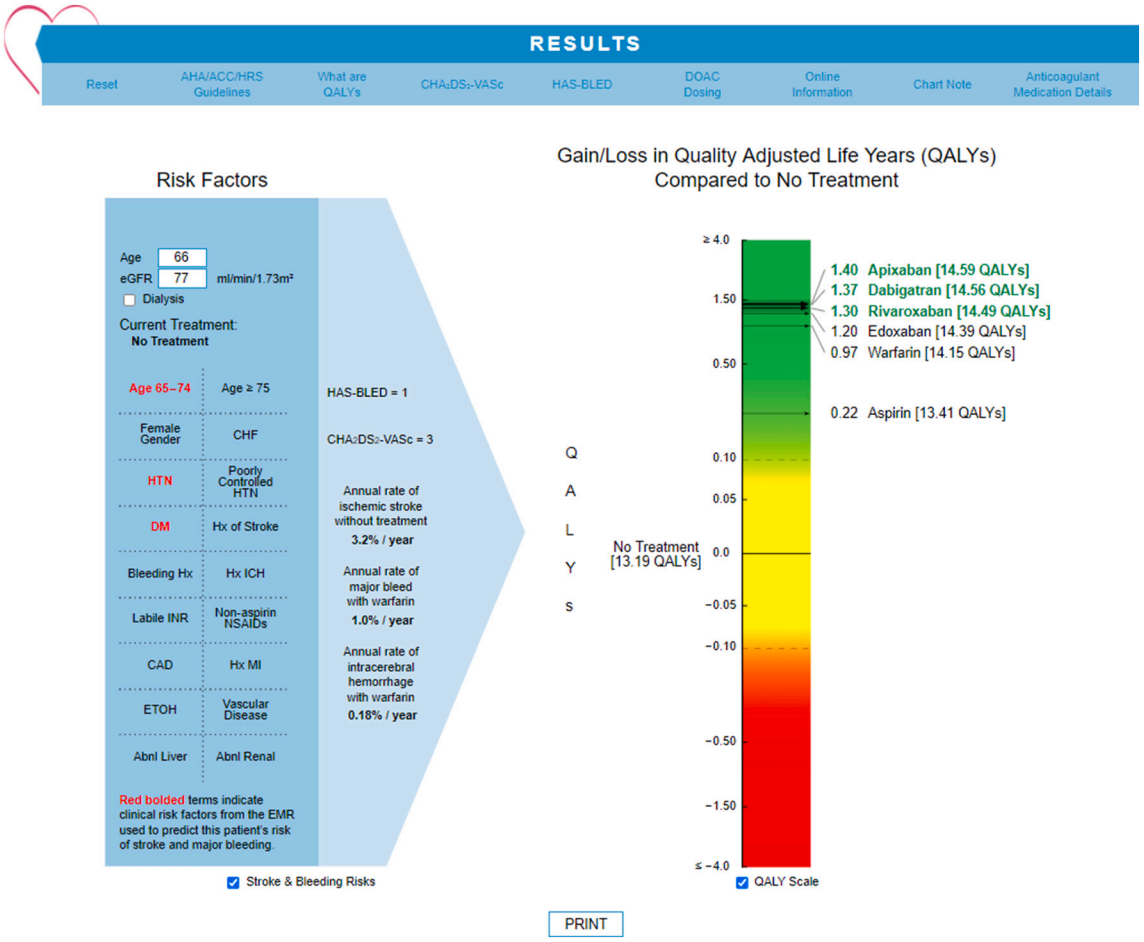

Fig. 2. Sample report from the AFDST for a patient with atrial fibrillation. Screen shot of report that appears in Epic Hyperspace frame when AFDST is launched from a patient's chart. Red, bolded items indicate clinical risk factors extracted from the AF data-mart used to predict the patient's risk of stroke, major bleeding, intracranial bleeding, and QALYs for each of the considered treatments. In this example, the patient is a 66-year-old woman with a history of hypertension and type 2 diabetes. Her most recent eGFR is 77 mL/min/1.73 m2. Her CHA_2DS_2VASc score is 3, corresponding to an annual rate of ischemic stroke without thromboprophylaxis of 3.2 %. Her HAS-BLED is 1, corresponding to an annual rate of major non–central nervous system bleeding while taking warfarin of 1.0 % (note: this is an upper limit on risk of major bleeding, as the relative hazard of major bleeding is <1 for several of the DOACs). A separate model predicts the annual rate of ICH while taking warfarin, 0.18 % for this patient. This also is an upper limit, as the relative hazard of ICH is <1 for all of the DOACs. The graphic to the far right indicates gain or loss in QALYs for each of the considered strategies compared with no treatment. The visual analog scale is divided into 3 regions: green, indicating a clinically significant gain; red, indicating a clinically significant loss; and yellow, indicating a gain or loss <0.1 QALY, which makes treatment too close to call as a recommended strategy compared with no treatment. For this patient, aspirin provides minimal benefit, whereas the 4 DOACs and warfarin all fall well into the green range, providing net gains of 0.97 to 1.40 QALYs compared with no treatment. In particular, apixaban, dabigatran and rivaroxaban all fall within 0.1 QALYs of each other, making them indistinguishable from a decision analytic perspective. In this example, all of the oral anticoagulants are reasonable choices. When used in clinical practice, the patient's decision between these agents needs to be guided by other more nuanced factors such as out-of-pocket cost, availability of reversal agent, number of doses per day, need for routine laboratory testing, and others. The clinician can click on the tab labeled "Print" to give the patient a copy of the report to take home. To facilitate this discussion in a typical shared decision-making encounter, the clinician would next click on the tab at the far right of the top ribbon, labeled "Anti-coagulant Medication Details." (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

[28,29] and network meta-analyses [30–32] of DOACs in general populations and in the elderly [33–35] along with systematic reviews given the absence of head-to-head trials comparing DOACs to one another [30,31]. The simulation runs for the entire life expectancy of the patient, adjusted for age, sex, and excess mortality risk from significant comorbid diagnoses, such as heart failure, CKD, diabetes mellitus, and hypertension. The strategy recommended by the decision support tool is the one resulting in the largest expected utility in quality-adjusted life years (QALYs). QALYs are particularly useful when a model considers outcomes with very different implications and impact upon quality of life, such as stroke or extracranial major bleeding events [36–38]. A strategy is not considered to be better if it results in a gain of <0.1 QALYs (see below) [39].

Current guidelines for anticoagulant therapy are based upon stroke risk as calculated by the CHA_2DS_2VASc scores (European Society of Cardiology and more recently American Heart Association/American College of Cardiology) [40,41]. While mentioning that bleeding risk is a consideration, these guidelines do not integrate bleeding risk in a formal, quantitative manner. If one makes decisions based upon overall event rates for bleeding and stroke, choosing to treat with anticoagulants only if the stroke risk in untreated patients exceeds the risk of major hemorrhage in treated patients, there is an implicit assumption that outcomes following both stroke and bleeding events are equivalent. However, most bleeds are extracranial and have less significant long-term consequences than strokes. Furthermore, ICH while receiving anticoagulant therapy generally results in worse clinical outcomes than ischemic stroke [42]. Singer and colleagues dealt with this later issue by differentially weighting ischemic stroke and ICH in their calculations of net clinical benefit of warfarin anticoagulation, using an impact weight of 1.5 for the latter [43]. The AFDST is able to integrate both stroke risk and bleeding risk along with their longer term sequelae in a formal quantitative manner by utilizing a decision model as the analytical "engine." The projections of quality-adjusted life expectancy generated by the AFDST for each individual patient and therapeutic alternative capture both the differential clinical outcomes following these events and their impact on patients' quality of life. Fig. 2 shows an example of a personalized report from the AFDST for a 66-year-old woman, with comorbidities of hypertension and type II diabetes mellitus. Her most recent eGFR was 77 ml/min/1.73m^2. Further details of the individual-specific decision analytical model are described elsewhere [25,44].

2.3. Statistical methods

We analyzed model recommendations for all 14,942 members of our UC Health AF cohort. The AFDST recommends the strategy resulting in the largest expected utility measured in QALYs. We used a 0.1 QALY threshold as the minimum clinically significant gain (MCSG) to consider one strategy better than another. The choice of a 0.1 gain in QALYs as our threshold for a MCSG is based upon prior work examining population and individual average change in QALYs with anticoagulation therapy at different CHA_2DS_2VASc cut points. We applied the Markov state transition model to 33,434 patients with incident AF in the ATRIA-CVRN (AnTicoagulation and Risk Factors In Atrial Fibrillation Cardiovascular Research Network) cohort [45]. Using ischemic stroke rates for each corresponding CHA_2DS_2VASc score, we calculated the net clinical benefit of oral anticoagulant therapy. The median net clinical benefit for patients with a CHA_2DS_2VASc score $\geq$ 2 was 0.1 QALYs [46]. To be consistent with AHA/ACC/HRS guidelines recommending anticoagulation for patients at "high ischemic stroke risk" with CHA_2DS_2-VASc scores of 2 or more, the AFDST uses a 0.1 QALY threshold for MCSG before it will recommend a change in treatment. Thus, the AFDST will not recommend one treatment over another unless the gain exceeds a threshold of 0.1 QALYs. We then identified patients whose current therapy was discordant from that recommended by the personalized decision analyses. From this point forward we refer to this as "non-optimal" anticoagulation therapy. In our base case analysis, we looked at categories of treatment – anticoagulation, consisting of any DOAC or warfarin, and no anticoagulation, consisting of either no oral anticoagulant or aspirin as the sole stroke preventive therapy. As an example, if the AFDST made a recommendation for apixaban but the patient was being treated with a different oral anticoagulant, such as warfarin, this would be considered concordant with recommendations. We also performed a 7-category analysis in which concordant therapy referred to the specific drug being recommended by the AFDST. Thus, if the AFDST recommended apixaban and a patient was receiving warfarin, and treatment with apixaban would result in a gain of $\geq$0.1 QALYs compared with the current therapy of warfarin, current treatment would be considered discordant from AFDST-recommended treatment.

Once again using a 0.1 QALY threshold for MCSG, we next examined the impact of race and sex on the likelihood of receiving non-optimal anticoagulation therapy. For this analysis we only included patients who were self-described as either White or Black (13,722). In order to control for confounding, we also considered a number of demographic, clinical, and socio-economic factors. We calculated unadjusted odds ratios for each of these factors, and then developed a multivariable logistic regression model from which we determined adjusted odds ratios for each covariate. We also analyzed the impact of race and sex in a logistic regression model using a more stringent threshold of 0.5 QALYs for a MCSG. For descriptive statistics we used Wilcoxon tests of significance for continuous variables and Chi-squares for categorical variables. We performed statistical analyses using SAS 9.4 (Cary, NC).

2.4. Ethical considerations

The study has been approved by the Institutional Review Board of the University of Cincinnati.

2.5. Role of the funding source

The study was funded by Bristol Myers Squibb-Pfizer Alliance through a grant from the Annual American Thrombosis Investigator Initiated Research Program (ARISTA). The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. BMS-Pfizer Alliance was given the opportunity to review the manuscript for medical and scientific accuracy as it relates to BMS-Pfizer Alliance substances, as well as intellectual property considerations. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. The authors are solely responsible for the design and conduct of this study, all study analyses and drafting and editing of the paper.

3. Results

Patient characteristics are summarized in Table 1, grouped by sex and race. Our AF cohort has significant comorbid diseases as reflected by mean CHA_2DS_2VASc and HAS-BLED scores of 3.7 and 1.9, respectively. Women have higher CHA_2DS_2VASc scores than men 4.4 vs 3.2, as do Black than White patients, 3.9 vs 3.7. As shown in Table 1, among the 6676 patients receiving anticoagulation therapy 2670 (40 %) were being treated with warfarin, while 4006 (60 %) were receiving a DOAC. Five thousand one hundred and ninety-four patients were receiving aspirin. Of those, 2321 were receiving aspirin and oral anticoagulant. Two thousand eight hundred and seventy-three patients were receiving aspirin as their only antithrombotic treatment to prevent stroke. Fig. 3 shows the proportion of patients receiving no anticoagulation, aspirin as the sole antithrombotic, warfarin, or a DOAC stratified by race and sex. Supplement tables 3a and 3b present baseline patient characteristics according to anticoagulation therapy status.

Our results showed that anticoagulation therapy had a greater expected utility (i.e., QALYs) than no anticoagulation or aspirin for 14,041 (94 %) of patients. However, when using the 0.1 QALY threshold for

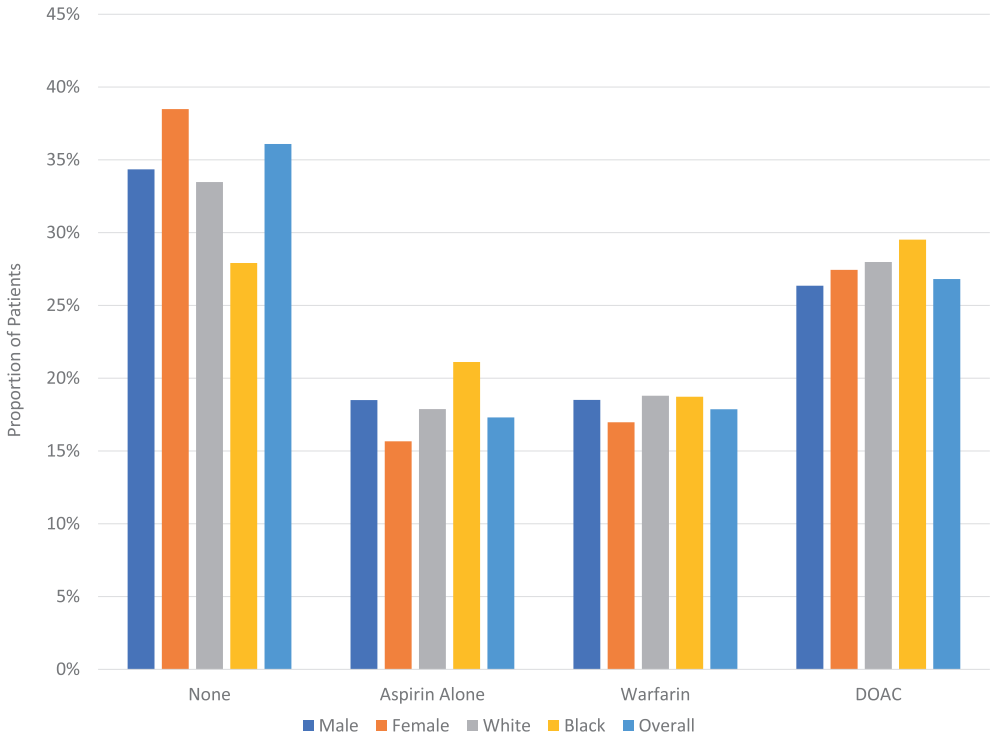

Fig. 3. Antithrombotic Therapy Stratified by Sex and Race - This figure shows the proportion of patients receiving no anticoagulation, aspirin as the sole antithrombotic, warfarin, or a DOAC stratified by race and sex. Females were more likely than males to be receiving no anticoagulation; while a higher proportion of White patients than Black patients were not receiving anticoagulation therapy. Black patients and men were more likely than White patients and women to be receiving aspirin as their sole antithrombotic therapy. Warfarin use was similar across sex and race, while Black patients and women were slightly more likely to receive DOACs than White patients and men.

minimal clinically significant benefit, anticoagulation was better than no anticoagulant therapy for 11,665 (78 %) patients (not shown in tables). Current therapy was discordant with AFDST recommendations for 6107 (41 %) patients when using the 0.1 QALY threshold for MCSG (Tables 1 and 2). Current therapy may be discordant from AFDST recommendations either due to overly conservative management and anticoagulation underuse, or overly aggressive anticoagulation of those at higher risk of bleeding who have a net loss in QALYs as a result of anticoagulation. However, the vast majority of recommendations that were discordant from actual care (95 %) were for patients who were not currently receiving anticoagulation therapy, using the 0.1 QALY minimal benefit threshold. Five percent of patients whose care was discordant from the AFDST recommendation would have gained 0.1 QALYs or more if their oral anticoagulation were discontinued. In the 7-category analysis, among the 7954 patients who would gain ≥0.1 QALYs if their treatment were changed to a DOAC, 5818 (73 %) were currently receiving no anticoagulation or aspirin, while 1575 (20 %) of these patients were currently receiving warfarin (Table 3). Thus, there is an opportunity not only to improve the use of anticoagulation therapy, but to transition patients from warfarin to a DOAC.

3.1. Racial and sex differences

Using a MCSG of 0.1 QALYs with non-optimal therapy defined by treatment category (i.e., oral anticoagulant versus no anticoagulation), 42 % of women and Blacks were receiving non-optimal anticoagulation therapy compared with 40 % of men and 39 % of Whites, respectively (Table 1). In addition, among the 6107 patients who could benefit from a change in treatment, women and Blacks had a larger average potential net gain of 0.85 and 0.88 QALYs, respectively, compared with men and Whites, 0.57 and 0.68 QALYs, respectively.

The following analyses focus only on patients who self-identified their race as Black or White (n = 13,722). Table 4 shows unadjusted odds ratios of non-optimal therapy, once again using just two categories (oral anticoagulant or not anticoagulated), for a number of clinical, demographic and socio-demographic factors, as well as adjusted odds ratios from a multivariable logistic regression model using a 0.1 QALY threshold for MCSG. In unadjusted analyses, black race and female sex were both associated with a greater likelihood of receiving non-optimal anticoagulant therapy, with odds ratios of 1.13 (95 % CI, 1.02–1.26, p = 0.02) and 1.10 (95 % CI, 1.03–1.18, p = 0.005), respectively. This

Table 2
Direction of non-optimal anticoagulation therapy.[a]

Current treatment category ≠ recommended treatment category	8037	Current treatment category ≠ recommended treatment category and gain ≥0.1 QALYs	6107
Anticoagulation recommended (%)	7616 (95)		5818 (95)
No anticoagulation recommended (%)	421 (5)		289 (5)

[a] This table includes all 14,942 patients in the AF cohort using two treatment categories of None/Aspirin vs. Warfarin/DOAC.

Table 3
Warfarin, DOAC, or No Anticoagulant/aspirin use Among Patients who would Gain ≥0.1 QALYs by Changing to a DOAC.

Characteristic	Male	Female	White	Black	Other	Total
Total	4399	3555	6304	947	703	7954
Current Treatment						
Warfarin (%)	877 (20)	698 (20)	1347 (21)	185 (20)	43 (6)	1575 (20)
DOAC[a] (%)	348 (8)	213 (6)	459 (7)	79 (8)	23 (3)	561 (7)
No AC or ASA (%)	3174 (72)	2644 (74)	4498 (71)	683 (72)	637 (91)	5818 (73)
Average (sd) Gain for those currently treated with warfarin (QALYs)	0.29 (0.19)	0.30 (0.25)	0.29 (0.21)	0.33 (0.25)	0.32 (0.23)	0.30 (0.22)

Note: percentages are for the columns. For instance, of the total 7954 patients who would gain ≥0.1 QALYs by changing to a DOAC, 1575 (20 %) are currently being treated with warfarin.

[a] Patients who would have a better predicted outcome on a different DOAC.

Table 4
Odds ratio estimates - receiving non-optimal anticoagulation therapy.

Variable	Adjusted Odds Ratios	95 % CI		*p*-Value	Unadjusted Odds Ratios	95 % CI		*p*-Value
RACE Black vs White	1.165	1.037	1.308	0.0102	1.134	1.022	1.258	0.02
Female	1.356	1.253	1.468	<0.0001	1.104	1.030	1.183	0.005
Age (per year)	0.974	0.970	0.977	<0.0001	0.987	0.985	0.990	<0.001
Clinical factors								
CHF	0.490	0.446	0.538	<0.0001	0.539	0.495	0.588	<0.001
DM	1.184	1.088	1.289	<0.0001	1.192	1.104	1.288	<0.001
HTN	1.195	1.103	1.294	<0.0001	1.120	1.043	1.204	0.002
Prior stroke	0.819	0.748	0.898	<0.0001	0.752	0.690	0.819	<0.001
Vascular disease	1.159	0.961	1.398	0.1236	1.056	0.984	1.133	0.13
Poorly controlled HTN	0.965	0.831	1.120	0.6406	0.833	0.728	0.953	0.008
Abnormal renal function	0.957	0.775	1.182	0.6822	0.728	0.632	0.839	<0.001
Abnormal liver function	1.370	1.184	1.586	<0.0001	1.244	1.087	1.425	0.002
History of bleeding	1.073	0.964	1.195	0.1967	0.942	0.860	1.033	0.2
Labile INR	0.542	0.462	0.635	<0.0001	0.530	0.460	0.611	<0.001
CHA_2DS_2VASc (per point)					0.951	0.934	0.969	<0.001
HASBLED (per point)					0.928	0.900	0.956	<0.001
History of intracerebral hemorrhage	1.117	0.902	1.383	0.3115	0.942	0.784	1.131	0.52
Coronary artery disease	1.220	1.004	1.484	0.0458	1.063	0.990	1.142	0.09
Prior myocardial infarction	0.980	0.860	1.116	0.7561	0.916	0.823	1.019	0.11
End stage kidney disease	0.697	0.521	0.932	0.0149	0.796	0.651	0.974	0.03
Marital status vs single				0.003				<0.001
Married or significant other	1.151	1.030	1.287	0.0130	1.032	0.934	1.140	0.5372
Divorced or separated	1.231	1.067	1.421	0.0045	1.142	0.997	1.308	0.0551
Other or unknown	1.258	0.914	1.732	0.1595	1.253	0.927	1.694	0.1419
Widowed	1.008	0.878	1.157	0.9107	0.791	0.705	0.888	<0.0001
Insurance Status vs Medicare				<0.001				<0.001
Commercial	0.931	0.829	1.046	0.2269	1.427	1.294	1.574	<0.0001
Medicaid	0.900	0.746	1.086	0.2704	1.405	1.187	1.663	<0.0001
N/A	3.321	2.991	3.687	<0.0001	2.740	2.490	3.015	<0.0001
Other	0.839	0.621	1.135	0.2549	0.974	0.728	1.301	0.8566
Self-Pay	1.362	1.103	1.682	0.0040	1.699	1.390	2.076	<0.0001
Perceived barriers to anticoagulation								
Alcohol or drug abuse	1.066	0.917	1.239	0.4079	1.175	1.023	1.350	0.02
Other barriers	0.709	0.377	1.334	0.2867	0.780	0.426	1.428	0.42
Predisposition to falls	1.184	1.061	1.321	0.0025	0.940	0.850	1.040	0.23

remained the case in multivariable logistic regression models, adjusting for confounding by other clinical, demographic, or socio-demographic factors, with adjusted odds ratios of 1.17 (95 % CI, 1.04–1.31, $p = 0.01$) and 1.36 (95 % CI, 1.25–1.47, $p < 0.001$), respectively. Other key factors associated with a higher likelihood of non-optimal anticoagulation therapy in the regression model were clinical diagnoses of diabetes mellitus, hypertension, coronary artery disease, and abnormal liver function. Among socio-demographic factors, patients who were married or had a significant other, and those who were divorced had a higher likelihood of receiving non-optimal therapy, compared with single patients. Insurance status was also an important predictor, with self-pay and none reported being associated with a higher likelihood of non-optimal therapy compared with Medicare patients. Among perceived barriers to anticoagulation, predisposition to falls was associated with an increased adjusted odds of non-optimal anticoagulation therapy. Clinical factors including increasing age, congestive heart failure, prior stroke, end stage kidney disease, and labile INR were associated with a lower likelihood of benefiting from a change in treatment. The c-statistic for this model was 0.66. Our goal in developing these regression models was not to optimize a predictive instrument for non-optimal anticoagulation therapy; rather we wished to explore potential confounding by other clinical or demographic factors. Thus, our final model including many variables whose adjusted odds ratios were not significant.

Once again, using all of the covariates and only two categories (oral anticoagulant versus not anticoagulated), we developed a separate logistic regression model using 0.5 QALYs as a more stringent threshold for MCSG (see supplement Table 4). Most interestingly, in this model, black race is no longer a statistically significant predictor, having an odds ratio of 1.04 (95 % CI, 0.88–1.22, $p = 0.67$). However, hypertension, diabetes and vascular disease, all highly prevalent among Black patients, became more important predictors in this model. Female sex is a stronger predictor, odds ratio of 2.58 (95 % CI, 2.30–2.88, $p < 0.001$).

Finally, we also developed logistic regression models in which we used more precise matches between current and recommended therapy by expanding categories of anticoagulation treatment from the 2 categories in the previous models (no anticoagulation or aspirin alone, and oral anticoagulant therapy, which included warfarin and the DOACs) to 7 categories (no anticoagulation, aspirin alone, warfarin, apixaban, dabigatran, rivaroxaban, or edoxaban). As before we constructed two versions of this model, one based upon a MCSG of 0.1 QALYs and the second using a 0.5 QALY threshold. Results were similar to the 2 category models, in that Black race and female sex were both significant predictors in the model using a 0.1 QALY threshold, while in the model using a more stringent threshold for MCSG of 0.5, female sex remained a significant predictor, while black race did not. Additional details are presented in supplement tables 5–6.

As the DOACs have become increasing accepted as more convenient forms of oral anticoagulant therapy, we also explored the impact of race and sex on prescribing of DOACs versus warfarin among patients for whom the AFDST determined that anticoagulation therapy was best. As shown in Table 3, there were no clinically significant differences in the proportion of these patients receiving warfarin rather than a DOAC among men and women or among blacks and whites.

4. Discussion

In summary, this cohort study found that in patients with AF in the University of Cincinnati Health system, Black race and female sex were independently associated with an increased odds of receiving non-optimal anticoagulant therapy. In addition, we found that a large proportion of patients overall, 40.2 %, could gain 0.1 QALYs or more from a change in their current anticoagulation category. In most cases (96 %), this involves starting an oral anticoagulant for patients who are

currently receiving no anticoagulant therapy or aspirin as a sole antithrombotic therapy. In a small proportion of cases (4 %), patients currently receiving anticoagulant therapy would fare better not receiving anticoagulants. Many of these patients might be good candidates for left atrial occlusive devices, although anticoagulation is still needed for 45 days, followed by 6 months of dual antiplatelet therapy.

These numbers are consistent with current trends [47]. In one of the more recent cross-sectional registry studies of 429,417 outpatients with AF, oral anticoagulants were prescribed for only 44.9 % of patients. Even among patients at higher risk for stroke, men with CHA_2DS_2VASc scores $\geq$2 and women with scores $\geq$3, roughly 50 % were prescribed oral anticoagulant therapy [48]. However, some registry and intervention studies (e.g., ORBIT and American Heart Association's GWTG-Afib registry) have documented higher proportions of oral anticoagulant use in higher risk patients [49,50]. Unfortunately, the situation among women and Blacks is even worse. Among higher risk patients enrolled in the PINNACLE registry, women were more likely than men to receive aspirin as the sole antithrombotic agent instead of oral anticoagulants [51]. Women also were significantly less likely to receive oral anticoagulation compared with men (56.7 % versus 61.3 %). Similar differences were noted at all levels of stroke risk as measured by the CHA_2DS_2VASc. In a multivariable model using components of the CHA_2DS_2VASc score as covariates, female sex was associated with a significantly decreased relative risk of being prescribed and oral anticoagulant, 0.9 (95 % CI, 0.90–0.91) [52].

With regards to racial differences in anticoagulation for AF, one of the more contemporary studies using data from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT) II, found that of 12,417 patients, Blacks were less likely than Whites to receive any oral anticoagulation therapy, with an adjusted odds ratio of 0.75 (95 % CI, 0.56–0.99). They also found that Blacks were less likely than Whites to receive a DOAC if anticoagulant therapy was prescribed (adjusted odds ratio of 0.63 [95 % CI, 0.49–0.83]) [53]. In contrast, our study found no significant differences between the proportion of Whites and Blacks or men and women who were receiving DOACs.

In our study, Blacks and women both had a higher likelihood of getting non-optimal anticoagulation therapy. Our study also showed beyond differences in the proportion of patients receiving optimal or non-optimal anticoagulation therapy, women and Blacks on average stand to benefit more than men and Whites, were they to receive optimal treatment.

A unique contribution of our study was the inclusion of several socioeconomic determinants of health. Given the high out-of-pocket cost of the DOACs, ranging between $387 and $525 for a one-month supply, one might anticipate that insurance status would be important predictor of optimal anticoagulation management [54]. Indeed, we found that patients without health care insurance (i.e., self-pay) compared with Medicare recipients were more likely to have non-optimal anticoagulant therapy. In unadjusted analyses this also was the case for patients with both Medicaid (including managed Medicaid) and commercial insurance, compared with Medicare recipients.

Finally, we also examined a number of perceived barriers to anticoagulation including a history of alcohol or drug abuse, predisposition to falls, or other miscellaneous barriers. In unadjusted analyses, a history of alcohol or drug abuse was associated with an increased likelihood of non-optimal anticoagulation therapy. However, when controlling for other factors in a multivariable logistic regression model, only predisposition to falls was significant.

How best to validate a decision analytic model that informs a decision support tool is a tricky matter. One approach is to assess the calibration of the patient-specific probability estimates the model makes for major clinical outcomes that drive the ultimate recommendation. For an earlier version of the AFDST, we tested the calibration of the underlying decision analytic model by simulating an observational study of future events in our cohort (using first order Monte Carlo simulations), comparing event rates for ischemic stroke and ICH across strata of stroke risk to those reported in a contemporary AF cohort, ATRIA over a similar period of time [43]. Stroke and ICH risk in all strata were not significantly different, indicating good calibration [44]. As part of an ongoing prospective randomized clinical study evaluating the effectiveness of adding a best practice advisory to the AFDST, we are collecting clinical outcomes for roughly 600 AF patients. We plan to do an analysis comparing major clinical outcomes (ischemic stroke, ICH, and extracranial gastrointestinal bleeds) among risk-adjusted strata of patients whose anticoagulation therapy is AFDST-concordant versus AFDST-discordant. This should help answer the question of whether better clinical outcomes are associated with anticoagulant therapy that is concordant with AFDST recommendations.

Our analysis had a number of limitations inherent to the study design and data available. First, the cohort we examined through the decision analytic model (AFDST) was created from a population of patients cared for in an academic medical center in Southwestern Ohio. While such a population has a broad age, sex, and racial/ethnic diversity, it may not be completely generalizable to all populations in the United States. However, use of an AF cohort that includes patients seen in ambulatory and inpatient settings is more generalizable than samples selected entirely from hospitals. In addition, the proportion of Black patients in our sample (11 %) was less than that shown in the most recent census data which reported in 2020 that 40 % of individuals in Cincinnati were Black. Prior studies have reported that the prevalence of clinically detected AF is substantially lower among Blacks than Whites [55]. Interestingly, in this same analysis similar proportions of Black and White patients were found to have AF using ambulatory monitoring. This suggests that there may be differences in clinical recognition and detection of AF by race, creating even further disparities in AF management. Second, the identification of risk factors used to inform the CHA_2DS_2VASc and HAS-BLED scores used by the AFDST was through our EHR's active problem list. It is possible that inaccurate information gets entered into the medical record at the level of provider data entry. However, in prior studies of the real time use of the AFDST in our healthcare system, it was rare that clinicians corrected information that had been automatically populated in the AFDST [25].

Finally, since the data source for our analyses was our health system's EHR, we were unable to examine other potentially important contributors to these differences that are not routinely captured, such as patient preferences, health literacy, numeracy, educational level, household income, or access to transportation. We also were not able to capture text data from diagnostic studies such as brain MRIs which might have revealed clinically silent microhemorrhages on gradient echo imaging, which conceivably may have led clinicians to avoid anticoagulation therapy.

5. Conclusion

In conclusion, we found differences in the anticoagulation management of patients with AF associated with Black race and female sex. The reasons for such persistent differences remain unclear, although they seem to persist despite controlling for confounding by sociodemographic factors, insurance status, or other factors that might be perceived barriers to anticoagulation therapy. Finally, we do not know from our analysis, whether these differences are associated with differences in clinical outcomes. This should be the subject of further study.

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CRediT authorship contribution statement

Mark Eckman – conceptualization, methodology, formal analysis, investigation, writing original draft, writing review and editing, visualization, supervision, project administration and funding acquisition.

Ruth Wise – writing review and editing, visualization, project administration, data collection.

Anthony C. Leonard – methodology, formal analysis, writing review and editing.

Pete Baker – software, data curation, writing review and editing, data collection.

Rob Ireton - software, data curation, writing review and editing, data collection.

Brett M. Harnett - software, data curation, writing review and editing, data collection.

Estrelita Dixon – resources, writing review and editing.

Bi Awosika - writing review and editing.

Chika Ezigbo - writing review and editing.

Matthew L. Flaherty - writing review and editing.

Adeboye Adejare – software, writing review and editing.

Carol Knochelmann - writing review and editing, data collection.

Rachael Mardis - writing review and editing, data collection.

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Alexandru Costea - writing review and editing.

Dawn Kleindorfer - writing review and editing.

Heidi Sucharew – data analysis, administration, writing review and editing.

Amy Costanzo – methodology, formal analysis, data collection, writing review and editing.

Lora Anderson - methodology, formal analysis, data collection, writing review and editing.

John Kues - methodology, formal analysis, data collection, writing review and editing.

Declaration of competing interest

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Adeboye Adejare now works for Janssen Pharmaceuticals.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2022.100170.

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