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ORIGINAL RESEARCH

Management of Atrial Fibrillation in Older Patients by Morbidity Burden: Insights From Get With The Guidelines-Atrial Fibrillation

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BACKGROUND: Knowledge is scarce regarding how multimorbidity is associated with therapeutic decisions regarding oral anticoagulants (OACs) in patients with atrial fibrillation.

METHODS AND RESULTS: We conducted a cross-sectional study of hospitalized patients with atrial fibrillation using the Get With The Guidelines-Atrial Fibrillation registry from 2013 to 2019. We identified patients ≥65 years and eligible for OAC therapy. Using 16 available comorbidity categories, patients were stratified by morbidity burden. A multivariable logistic regression model was used to determine the odds of receiving OAC prescription at discharge by morbidity burden. We included 34 174 patients with a median (interquartile range) age of 76 (71–83) years, 56.6% women, and 41.9% were not anticoagulated at admission. Of these patients, 38.6% had 0 to 2 comorbidities, 50.7% had 3 to 5 comorbidities, and 10.7% had ≥6 comorbidities. The overall discharge OAC prescription was high (85.6%). The prevalence of patients with multimorbidity increased from 59.7% in 2014 to 64.3% in 2019 (*P* trend=0.002). Using 0 to 2 comorbidities as the reference, the adjusted odds ratio (95% CI) of OAC prescription were 0.93 (0.82, 1.05) for patients with 3 to 5 comorbidities and 0.72 (0.60, 0.86) for patients with ≥6 comorbidities. In those with ≥6 comorbidities, the most common reason for nonprescription of OACs were frequent falls/frailty (31.0%).

CONCLUSIONS: In a contemporary quality-of-care database of hospitalized patients with atrial fibrillation eligible for OAC therapy, multimorbidity was common. A higher morbidity burden was associated with a lower odds of OAC prescription. This highlights the need for interventions to improve adherence to guideline-recommended anticoagulation in multimorbid patients with atrial fibrillation.

Key Words: anticoagulation ■ atrial fibrillation ■ comorbidities ■ multimorbidity ■ oral anticoagulants ■ prescription ■ quality of care

Older patients with atrial fibrillation (AF) often present with multiple chronic conditions, so-called multimorbidity.[1–4] Multimorbidity has been identified as one of the major healthcare system concerns of the current century.[5] Older patients with AF are at higher risk of stroke, and this risk is further increased with multimorbidity.[6,7] The risk of stroke can be mitigated by treating the patient with oral anticoagulants (OACs), which in turn increases the risk of bleeding. Importantly, the net clinical benefit seems to be in favor of OAC treatment even in octogenarians or older patients, but randomized data are lacking.[8,9] However, multimorbidity may influence therapeutic choices and potentially quality of care.[6,10] Evidence

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CLINICAL PERSPECTIVE

What Is New?

- In a contemporary quality-of-care database of hospitalized older patients with atrial fibrillation, multimorbidity (≥3 comorbidities) was highly prevalent and the multimorbidity burden increased significantly from 59.7% in 2014 to 64.3% in 2019.
- A high morbidity burden was associated with lower odds of oral anticoagulant prescription, the most common reason for nonprescription was frequent falls/frailty.

What Are the Clinical Implications?

- These results reveal a gap between current knowledge and clinical practice and the need for educational implementation tools to increase guideline-recommended oral anticoagulants therapy in patients with multimorbidity and atrial fibrillation.

Nonstandard Abbreviations and Acronyms

GWTG-AFIB	Get With The Guidelines-Atrial Fibrillation
NOACs	novel oral anticoagulants
OACs	oral anticoagulants
VKA	vitamin K antagonist

suggests that physicians may underestimate the benefit of stroke prevention and overestimate the risk of bleeding, thus potentially refraining from prescribing OACs in patients with multimorbidity.[11] How multimorbidity is associated with therapeutic choices such as OAC therapy for patients with AF is uncertain.[12,13] To address this uncertainty, we used the GWTG-AFIB (Get With The Guidelines-Atrial Fibrillation) registry to determine whether morbidity burden is associated with therapeutic decisions regarding anticoagulation.

METHODS

Data Sources

We will make our analytic methods available to other researchers, but we are not able to make the data or other study materials available to them because of our lack of ownership of the data.

Data collected through the GWTG-AFIB registry were used. The registry was started in 2013 by the American Heart Association as a quality improvement database of inpatients with AF to specifically improve the implementation of class 1 recommendations of stroke prevention. Quality interventions by GWTG-AFIB include educational workshops and webinars, provider education, performance assessment, and feedback. Details of the registry have been described previously.[14] In brief, patients aged ≥18 years were included from 161 participating sites if they were admitted for at least 1 overnight stay and diagnosed with preexisting or new AF (consisting of both AF and atrial flutter).

Personnel at each hospital used an online data management tool to enter data on demographics, comorbidities, laboratory tests, in-hospital treatment, AF-related procedures such as ablation and cardioversions, and discharge medications. CHA_2DS_2-VASc and HAS-BLED (hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol) scores for stroke and bleeding risk were entered, as well as a prespecified list of contraindications to OAC therapy. The American Heart Association/American College of Cardiology guidelines at the time of this analysis recommended anticoagulation for patients with a CHA_2DS_2-VASc score ≥2.[15]

Participating institutions in GWTG-AFIB are required to comply with local regulatory and privacy guidelines and to obtain institutional review board approval if required. Because data were used primarily at the local site for quality improvement, sites were granted a waiver of informed consent under the Common Rule. IQVIA serves as the data collection and registry coordinating center (through their Patient Management Tool) for GWTG. The Duke Clinical Research Institute serves as the data analysis center and has an agreement to analyze the aggregate de-identified data for research purposes. Institutional review board approval was granted to analyze aggregate de-identified data for research purposes.

Study Population and Covariates

In this cross-sectional analysis, we included patients aged ≥65 years with any admission for AF (but not lone atrial flutter) from January 2013 to June 2019. We excluded patients with missing information on discharge disposition, valvular AF (mechanical valve or mitral stenosis), those categorized as new-onset AF but also categorized as having a prior AF procedure (as these may have been categorized incorrectly), atrial flutter (as many of these patients undergo curative ablation, and as a result oral anticoagulation is often discontinued), patients prescribed nonoral anticoagulation (eg, heparin), CHA_2DS_2-VASc <2, and strict contraindications to OAC treatment as previously defined and that included prior bleeding

events, prior intracranial hemorrhage, allergy, recent operation, or severe comorbid illness (eg, severe renal or liver disease).[16] A wide range of comorbidities are captured in the GWTG-AFIB. We included 16 comorbidities as listed: hypertension; heart failure (medical history of/first detected heart failure, cardiac transplant or cardiomyopathy); coronary artery disease (medical history of/first detected coronary artery disease, a prior myocardial infarction or myocardial infarction this hospitalization, percutaneous coronary intervention; diabetes mellitus (medical history of/first detected); hypo- or hyperthyroidism; obstructive sleep apnea; chronic obstructive pulmonary disease; cancer; cerebral vascular disease (medical history of/first detected carotid disease, transient ischemic attack, stroke, intracranial hemorrhage); depression; anemia (hemoglobin <10 mg/dL); renal disease (medical history of renal disease or dialysis); peripheral vascular disease (medical history of/first detected atherosclerotic vascular disease); cognitive impairment; liver disease (medical history of/first detected); and rheumatic heart disease.

For each patient a comorbidity score was calculated from the sum of each individual comorbidity present of the 16 comorbidities categories. For the purpose of this analysis, the cohort was stratified into patients with 0 to 2 comorbidities (low morbidity burden), those with 3 to 5 (moderate morbidity burden), and those with ≥6 comorbidities (high morbidity burden). Multimorbidity was defined as ≥3 comorbidities at admission These cutoffs were based on a similar prior analysis.[17]

For patients not prescribed OAC therapy, we assessed documented reasons for not providing OAC therapy by multimorbidity groups and by age group, which are prospectively captured in GWTG-AFIB.

Outcomes

The primary outcome of interest was OAC prescription at discharge (both OAC on discharge medication and new prescriptions) among patients in the 3 multimorbidity groups. Secondary outcomes of interest included novel oral anticoagulants (NOACs) prescription vitamin K antagonist (VKA) prescription among those prescribed OACs at discharge.

Statistical Analysis

Baseline patient and hospital characteristics in patients with AF are described by multimorbidity groups. Counts with proportions and medians with interquartile ranges (IQRs) are reported for categorical and continuous variables, respectively. The Pearson's chi-square test was used to compare binary or nominal categorical variables, and the Kruskal–Wallis test was used to compare continuous variables or ordinal categorical variables. Percent standardized differences (standardized differences×100) between the 2 higher morbidity burden groups versus the lowest morbidity burden group were calculated. A (percent) standardized difference >10% indicates a significant difference that requires attention. The distribution of comorbidity score was presented using histograms and descriptive tables. We also plotted the prevalence of moderate and high morbidity burden including 95% CIs in patients with AF by year from 2013 to 2019. *P* value for trends were calculated using Cochran-Armitage trend tests from 2013 to 2019. The unadjusted and adjusted associations between OAC description and morbidity burden were fitted using logistic regression models with generalized estimating equations, to account for within-hospital clustering of patients and derive robust variance estimation. The adjusted models included the following covariates: age (continuous age and indicator for age ≥80), sex, race/ethnicity, insurance status, type of AF, prior antiarrhythmics, body mass index, blood pressure, heart rate, admission year, control strategy, hospital region, teaching hospital, number of beds, rural location, and adult cardiac electrophysiology site. We conducted several subgroup analyses. Among those prescribed OAC at discharge, the association between multimorbidity burden and OAC type (ie, NOAC and VKA) was analyzed. A second analysis was conducted to examine the association between multimorbidity and first-time admission for AF versus preexisting AF. A third analysis was conducted excluding patients on OAC therapy at admission. Interaction terms were tested between multimorbidity groups with age (≥80, <80), sex, and calendar year. Multiple imputations were used to handle missing data. Patient characteristics with <25% missing were imputed using multiple imputation with 10 data sets before entering the models. Very few covariates had more than 10% missingness: body mass index (15.7%), ejection fraction (13.5%) and adult cardiac electrophysiological site (13.7%). Hospital characteristics were not imputed (complete case analysis only).

All tests were 2-tailed and statistical significance was declared when $P<0.05$. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics

A total of 34 174 patients with AF aged ≥65 years met our entry criteria. A flowchart for the patient population is shown in Figure 1. Overall, the median age (IQR) was 76 years (71–83), 19 356 (56.6%) were women, 30 063 (88.0%) were Caucasian, and 7083 (20.7%) had first detected AF. At admission 14 324 (41.9%) were on anticoagulation therapy. A total of 13 194 (38.6%) had 0 to

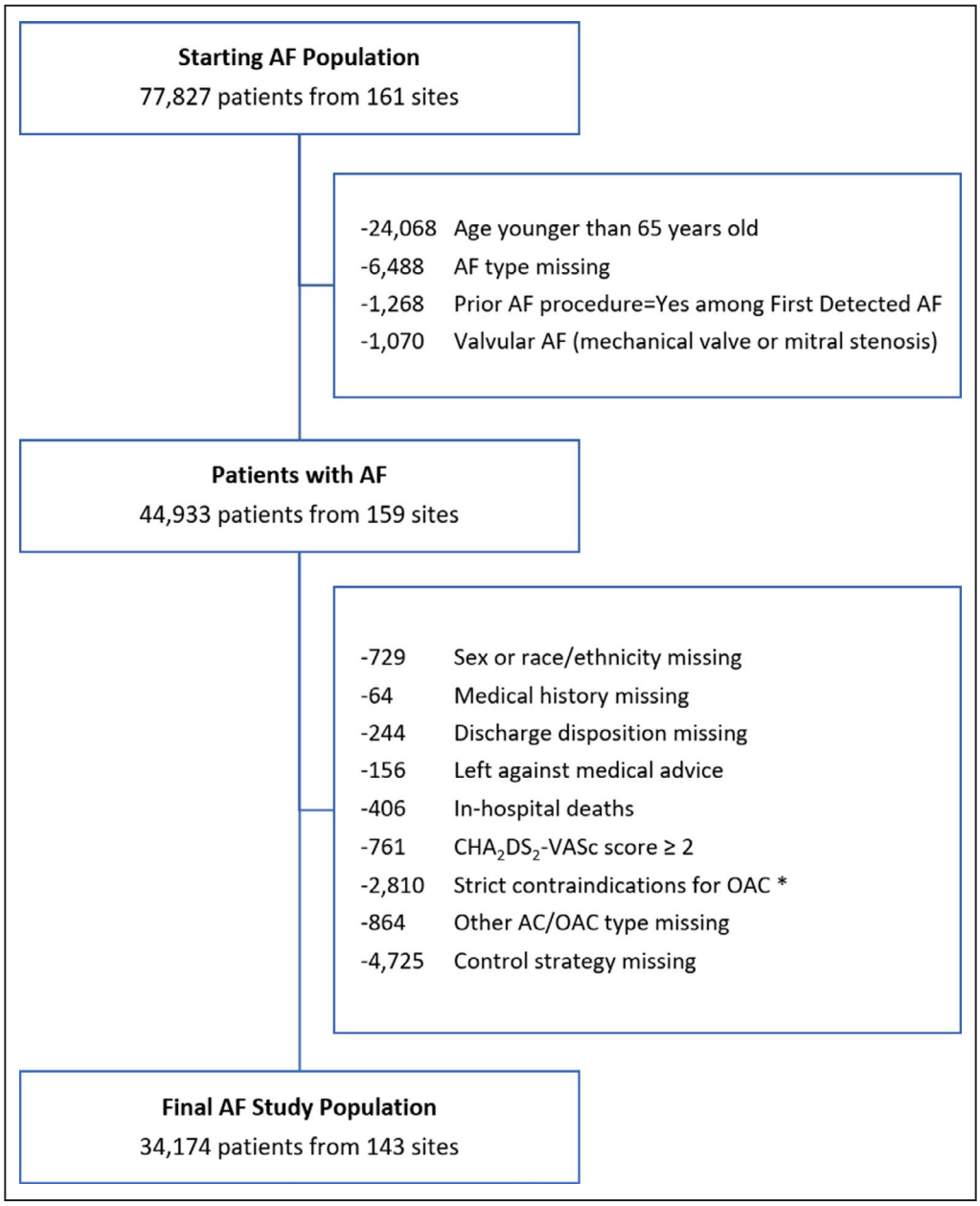

Figure 1. Flowchart of the study inclusion.
*Strict contraindications for OAC therapy were prior bleeding events, prior intracranial hemorrhage, allergy, recent operation, or severe comorbid illness (eg, severe renal or liver disease). AC indicates anticoagulation; AF, atrial fibrillation; and OAC, oral anticoagulant.

2 comorbidities, 17 331 (50.7%) had 3 to 5 comorbidities, and 3649 (10.7%) had ≥6 comorbidities.

The median age was relatively similar across the comorbidity groups. However, compared to those with 0 to 2 comorbidities, those with higher comorbidity burden were less likely to be Caucasian and more likely to be men and to have persistent or permanent AF. The renal function declined in estimated glomerular filtration rate (median [IQR]) across the comorbidity groups (66 [53–81] versus 60 [45–74] versus 50 [35–67]) and those with higher comorbidity burden had increasing (median [IQR]) CHA_2DS_2-VASc (3 [3–4] versus 5 [4–6] versus 6 [5–7]) and HAS-BLED scores (2 [2–3] versus 3 [2–3] versus 4 [3–4]), for those with 0 to 2 comorbidities, 3 to 5 comorbidities, and ≥6 comorbidities, respectively (Table 1).

Comorbidities and Multimorbidity

The most prevalent comorbidity was hypertension (81.6%), followed by heart failure (37.8%), coronary artery disease (36.7%), and diabetes mellitus (28.2%) (Table 2). The distribution of multimorbidity is shown

Table 1. Baseline Characteristics by Comorbidity Score

Variable	Overall	Low Comorbidity Burden (0–2)	Moderate Comorbidity Burden (3–5)	High Comorbidity Burden (≥6)	*P* Value	SD: 3–5 vs 0–2	SD: ≥6 vs 0–2
	N=34 174	N=13 194	N=17 331	N=3649			
Demographics							
Age, y*	76 (71–83)	76 (70–82)	77 (71–83)	76 (71–82)	<0.0001	10.0	2.4
Sex: female	19 356 (56.6)	7798 (59.1)	9559 (55.2)	1999 (54.8)	<0.0001	8.0	8.7
Race/Ethnicity					<0.0001	7.4	16.8
White	30 063 (88.0)	11 737 (89.0)	15 204 (87.7)	3122 (85.6)			
Black	1435 (4.2)	426 (3.2)	778 (4.5)	231 (6.3)			
Hispanic (any race)	1507 (4.4)	538 (4.1)	780 (4.5)	189 (5.2)			
Asian	376 (1.1)	171 (1.3)	180 (1.0)	25 (0.7)			
Other	793 (2.3)	322 (2.4)	389 (2.2)	82 (2.2)			
Type of atrial fibrillation					<0.0001	22.2	39.8
Permanent/longstanding persistent atrial fibrillation	3296 (9.6)	864 (6.5)	1871 (10.8)	561 (15.4)			
Persistent atrial fibrillation	7507 (22.0)	2676 (20.3)	3997 (23.1)	834 (22.9)			
Paroxysmal atrial fibrillation	16 288 (47.7)	6254 (47.4)	8269 (47.7)	1765 (48.4)			
First detected atrial fibrillation	7083 (20.7)	3400 (25.8)	3194 (18.4)	489 (13.4)			
Measures							
Body mass index*					<0.0001	19.1	38.8
Median (IQR)	28.4 (24.5–33.1)	27.4 (23.9–31.6)	28.8 (24.7–33.7)	30.3 (25.9–35.8)			
Missing, %	5381 (15.7)	2309 (17.5)	2612 (15.1)	460 (12.6)			
Estimated glomerular filtration rate, mL/min per 1.73 m^2*					<0.0001	26.7	64.1
Median (IQR)	61 (47–77)	66 (53–81)	60 (45–74)	50 (35–67)			
Missing, %	1119 (3.3)	507 (3.8)	527 (3.0)	85 (2.3)			
Risk Scores							
CHA_2DS_2-VASc Score*					<0.0001	116.2	217.1
Median (IQR)	4 (3–5)	3 (3–4)	5 (4–6)	6 (5–7)			
HAS-BLED Score*					<0.0001	75.2	154.0
Median (IQR)	3 (2–3)	2 (2–3)	3 (2–3)	4 (3–4)			
Missing, %	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)			
Prior AF procedure							
Cardioversion	7912 (23.2)	2868 (21.7)	4199 (24.2)	845 (23.2)	<0.0001	5.9	3.4

(*Continues*)

Table 1. Continued

Variable	Overall N=34 174	Low Comorbidity Burden (0–2) N=13 194	Moderate Comorbidity Burden (3–5) N=17 331	High Comorbidity Burden (≥6) N=3649	*P* Value	SD: 3–5 vs 0–2	SD: ≥6 vs 0–2
Ablation	3572 (10.5)	1348 (10.2)	1859 (10.7)	365 (10.0)	0.2253	1.7	0.7
AF surgery (surgical maze)	265 (0.8)	54 (0.4)	164 (0.9)	47 (1.3)	<0.0001	6.6	9.6
Medications used prior to admission							
Aspirin	13 503 (39.5)	4316 (32.7)	7395 (42.7)	1792 (49.1)	<0.0001	20.7	33.9
Antiplatelet agent	2666 (7.8)	451 (3.4)	1652 (9.5)	563 (15.4)	<0.0001	25.0	42.0
Anticoagulation therapy					<0.0001	19.5	33.4
Vitamin K antagonist	7323 (21.4)	2177 (16.5)	4074 (23.5)	1072 (29.4)			
Novel OAC	12 334 (36.1)	4743 (36.0)	6315 (36.5)	1276 (35.0)			
No OAC	14 324 (41.9)	6203 (47.0)	6846 (39.5)	1275 (35.0)			
Antiarrhythmic—any					0.5978	0.4	1.5
Yes, %	6635 (19.4)	2563 (19.4)	3342 (19.3)	730 (20.0)			
Missing, %	16 (0.0)	6 (0.0)	7 (0.0)	3 (0.1)			
Triple therapy (OAC and antiplatelet) at admission					<0.0001	8.7	15.6
Yes, %	399 (1.2)	71 (0.5)	240 (1.4)	88 (2.4)			
Missing, %	16 (0.0)	6 (0.0)	7 (0.0)	3 (0.1)			

AF indicates atrial fibrillation; HAS-BLED, hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol; and OAC, oral anticoagulant.
*Continuous variables reported as median with interquartile range.

Table 2. Comorbidity Score

Variable	Overall N=34 174	Low Comorbidity Burden (0–2) N=13 194	Moderate Comorbidity Burden (3–5) N=17 331	High Comorbidity Burden (≥6) N=3649
Morbidities				
Hypertension	27 870 (81.6)	8975 (68.0)	15 435 (89.1)	3460 (94.8)
Heart failure/ cardiomyopathy/cardiac transplant, first detected heart failure	12 907 (37.8)	2019 (15.3)	8065 (46.5)	2823 (77.4)
CAD (medical history of CAD, prior MI, PCI. first detected CAD, MI. procedure in this hospital PCI)	12 530 (36.7)	1744 (13.2)	8040 (46.4)	2746 (75.3)
Diabetes mellitus (medical history or first detected)	9654 (28.2)	1112 (8.4)	6155 (35.5)	2387 (65.4)
Hypo- or hyperthyroidism	7452 (21.8)	1357 (10.3)	4564 (26.3)	1531 (42.0)
Obstructive sleep apnea	5398 (15.8)	670 (5.1)	3248 (18.7)	1480 (40.6)
Chronic obstructive pulmonary disease	6051 (17.7)	669 (5.1)	3636 (21.0)	1746 (47.8)
Cancer	6727 (19.7)	1243 (9.4)	4100 (23.7)	1384 (37.9)
Cerebrovascular disease (medical history of carotid disease, TIA, stroke, ICH, first detected stroke/TIA/ ICH)	6181 (18.1)	779 (5.9)	3753 (21.7)	1649 (45.2)
Depression	4618 (13.5)	548 (4.2)	2679 (15.5)	1391 (38.1)
Anemia (Hgb <10 mg/dL)	3920 (11.5)	306 (2.3)	2169 (12.5)	1445 (39.6)
Renal disease (medical history or dialysis)	2005 (5.9)	106 (0.8)	1091 (6.3)	808 (22.1)
Peripheral vascular disease (medical history or first detected atherosclerotic vascular disease)	2460 (7.2)	136 (1.0)	1361 (7.9)	963 (26.4)
Cognitive impairment	1476 (4.3)	188 (1.4)	889 (5.1)	399 (10.9)
Liver disease (medical history or first detected)	278 (0.8)	21 (0.2)	145 (0.8)	112 (3.1)
Rheumatic heart disease	119 (0.3)	14 (0.1)	75 (0.4)	30 (0.8)

CAD indicates coronary artery disease; ICH, intracranial cerebral hemorrhage; MI, myocardial infarction; PCI, percutaneous coronary intervention; and TIA, transient ischemic attack.

in Figure 2. The median (IQR) number of comorbidities was 3 (2–4) and the mean (SD) was 3.21 (1.76). The number of patients with AF and multimorbidity (≥3 comorbidities) increased from 59.7% in 2014 to 64.3% in 2019 (*P* trend=0.002). A similar increase was observed in the number of patients with high morbidity burden (≥6 comorbidities), which increased from 9.2% in 2014 to 11.9% in 2019 (*P* trend <0.001) (Figure 3).

In-Hospital Treatment

The overall OAC prescription rate at discharge was 85.6%. The rate of discharged with VKA increased with increasing morbidity burden, 23.9% in the low comorbidity burden (0–2 comorbidities) versus 39.2% in the high comorbidity group (≥6 comorbidities). Conversely, the rate of apixaban and rivaroxaban decreased with increasing morbidity burden. However, those with a high morbidity had higher rates of dose reduction of both apixaban and rivaroxaban. Very few patients were discharged with edoxaban (n=36), and dabigatran had similar discharge rates across morbidity groups. Moreover, patients with high multimorbidity burden were more likely to be treated with antiplatelet therapy (3.5% in the low comorbidity group versus 14.0% in the high comorbidity group) and beta blockers (60.3% in the low comorbidity group versus 76.0% in the high comorbidity group) and were less likely to undergo ablation (15.4% in the low comorbidity group versus 9.8% in the high comorbidity group) and cardioversion (34.0% in the low comorbidity group versus 29.4% in the high comorbidity group). Left atrial appendage occlusion devices were more common in the high comorbidity group (6.1%) than those in the low comorbidity group (2.6%). Those with multimorbidity more often had a rate control strategy planned (51.1%) compared to those with low multimorbidity (40.5%) and fewer with high multimorbidity had planned a rhythm control (48.9%) as compared with those with low multimorbidity burden (59.5%) (Table 3).

Odds of OAC Prescription

The odds of receiving an OAC decreased across increasing number of comorbidities. Compared with patients with low comorbidity burden (0–2 comorbidities), the adjusted odds ratio (OR) for receiving OAC therapy in those with 3 to 5 comorbidities was 0.93 (95% CI, 0.82–1.05) and for those with ≥6 comorbidities the adjusted OR was 0.72 (95% CI, 0.60–0.86).

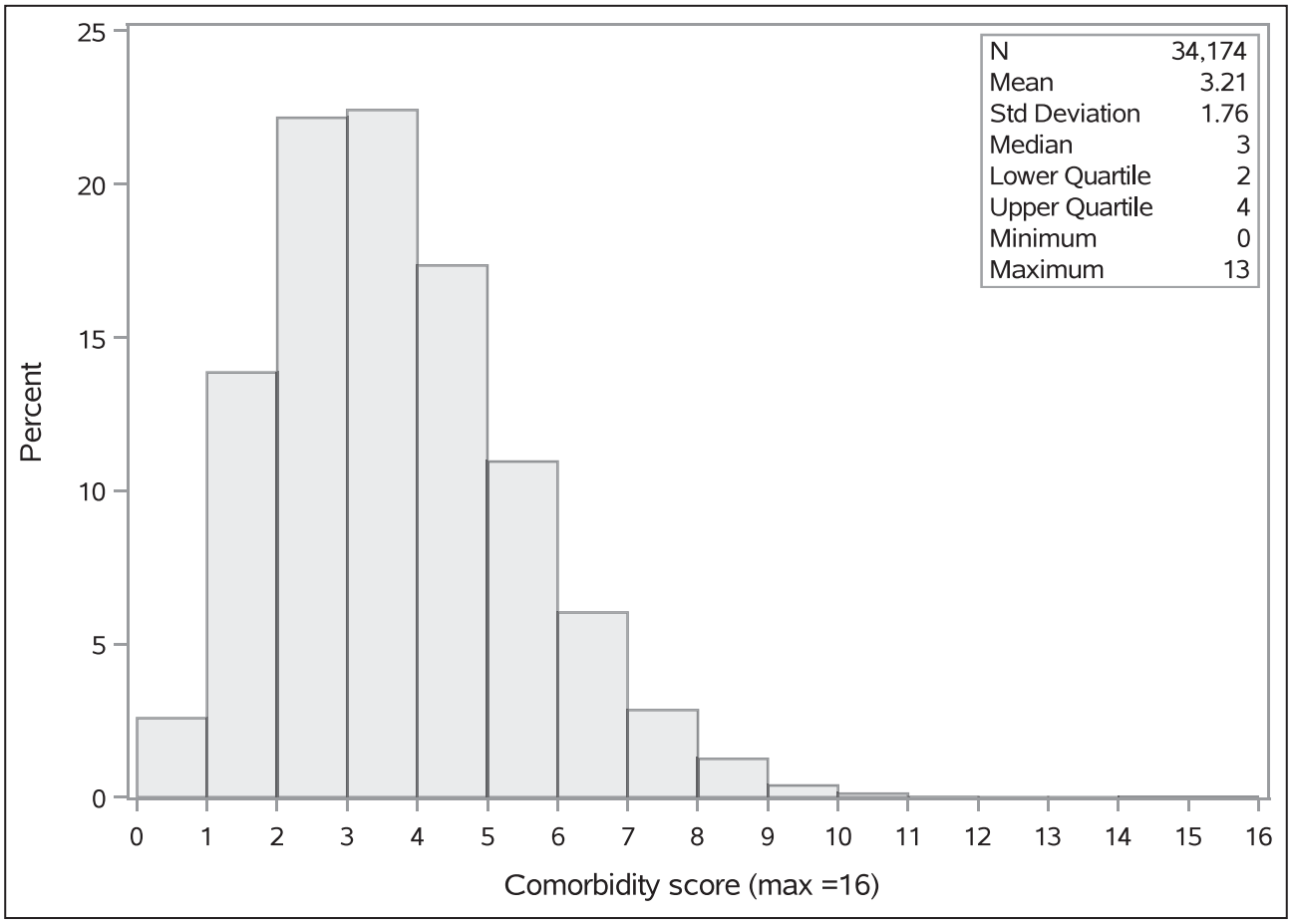

Figure 2. Distribution of comorbidity scores.
Histogram of the comorbidity score distribution with mean, SD, median, lower (25%) quartile, upper (75%) quartile, minimum and maximum.

For those prescribed OAC at discharge, compared to low comorbidity burden (0–2), the odds of receiving NOAC decreased by increasing comorbidity burden. The adjusted OR for receiving NOAC therapy in those with 3 to 5 comorbidities was 0.72 (95% CI, 0.67–0.78) and for those with ≥6 comorbidities the odds were 0.59 (95% CI, 0.50–0.69). Similar association of lower odds of OAC prescription at discharge among those with high multimorbidity was found for both those without prior existing AF and in those with prior existing AF. For those patients naïve to OAC therapy and compared to low comorbidity burden (0–2), the odds of receiving OAC decreased by increasing comorbidity burden. The adjusted odds ratio for receiving NOAC therapy in those with 3 to 5 comorbidities was 0.72 (95% CI, 0.67–0.78) and for those with ≥6 comorbidities the odds were 0.59 (95% CI, 0.50–0.69) (Table 4).

The major difference in documented reasons of nonprescription of OAC at discharge in those with high morbidity burden compared to low morbidity burden was frequent falls/frailty (24.5% versus 31.0%) and high bleeding risk (14.2% versus 24.6%). Conversely, physician preference for nonprescription was more common in those with low comorbidity burden (15.1% versus 11.1%) as was patient refusal (17.5% versus 11.9%) (Table 5). A major difference in nonprescription by age was frequent falls/frailty (42.2% for those aged >80 years versus 13.0% for those aged between 65 and 80) (Table S1).

There was no interaction between morbidity burden and age (*P* interaction=0.358) or sex (*P* interaction=0.244) In analyses evaluating the odds of receiving an OAC in the low versus high morbidity groups by year, we found no significant interaction, indicating that these odds did not vary by year.

DISCUSSION

In a contemporary quality improvement database of patients with AF aged ≥65 years and indicated for OAC therapy, we found that (1) multimorbidity was present in more than two thirds of the patients, and high morbidity

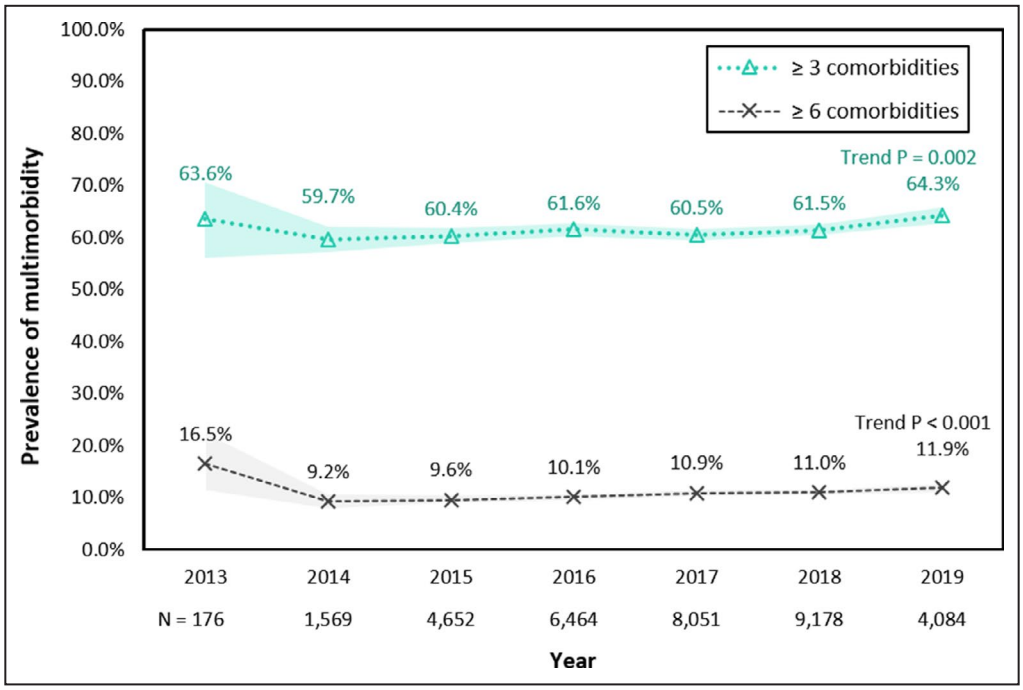

Figure 3. Prevalence of multimorbidity burden of ≥3 and ≥6 (y-axis) by calendar year (x-axis). Prevalence of multimorbidity by calendar year is shown for all patients with ≥3 comorbidities and ≥6 comorbidities, including 95% CI and *P* test for trend.

burden was present in more than 1 in 10 patients; (2) multimorbidity burden increased in prevalence from 2014 to 2019; and (3) the overall prescription rates of OACs were high (85.6%), but a high morbidity burden was associated with lower odds of being prescribed OAC therapy at discharge, particularly because of concerns over fall risk.

Owing largely to an aging population, the overall burden of multimorbidity is increasing. In a quality-of-care inpatient database with contemporary patients with AF, the burden of multimorbidity is high and has increased from 59.7% in 2014 to 64.3% in 2019 (not counting the prevalence of comorbidity in 2013, as we only included 173 patients that year). This stresses the importance of adequate treatment in this population. In other registries of patients with AF, such as GARFIELD-AF (Global Anticoagulant Registry in the Field-Atrial Fibrillation) and the UK Biobank, the presence of comorbidity is high and has been associated with an increased risk of all-cause mortality, stroke, and major bleeding.[18,19]

In older patients with AF, the risk of stroke and the risk of OAC-associated bleeding are increased. Multimorbidity further increases the risks of stroke and bleeding. Thus, the choice to anticoagulate is usually determined by weighing the risk of stroke against the risk of bleeding. Studies have repeatedly shown that the risk of stroke is higher than the risk of major bleeding, even in the most frail and older population, and lower risk of bleeding has been observed with NOAC use, in particular apixaban.[20] These facts along with our finding of decreased OAC use with increased morbidity burden are concerning.

OAC Prescription

Prior results from the GWTG-AFIB registry have reported higher OAC prescription rates of 93.5% in the whole registry and 94.9% among patients with AF and heart failure.[16,21] The discrepancies between prior studies and our study are most likely related to the inclusion of only patients with nonvalvular AF and patients aged ≥65 years. Most studies on the odds of OAC prescription in older patients with AF have primarily addressed patients with frailty. A meta-analysis of patients with AF and frailty and OAC treatment has found no association between frailty and OAC prescription at hospital discharge (pooled adjusted OR 0.40 [95% CI, 0.13–1.23]).[22] In a single-center study of admitted patients with AF (n=550) assessing the relationship between OAC prescription, frailty, and Charlson comorbidity score showed that the odds of OAC prescriptions were lower for every point increase in Charlson Comorbidity Index but they found no association with frailty status.[23] A similar analysis of older patients with AF conducted in the Danish nationwide registries also found a significant decreased odds of OAC prescription by morbidity burden.[24] Our results show that high morbidity burden conferred lower odds of OAC prescription and a treatment strategy favoring VKA over NOACs. This

Table 3. In-Hospital Treatment by Comorbidity Score

Variable	Overall N=34 174	Low Comorbidity Burden (0–2) N=13 194	Moderate Comorbidity Burden (3–5) N=17 331	High Comorbidity Burden (≥6) N=3649	*P* Value	SD: 3–5 vs 0–2	SD: ≥6 vs 0–2
Oral medication during this hospitalization							
None	1102 (3.8)	594 (5.3)	451 (3.0)	57 (1.8)	<0.0001	11.5	19.2
Antiarrhythmics	12 731 (43.4)	4856 (43.5)	6606 (44.2)	1269 (39.6)	<0.0001	1.5	7.9
Oral anticoagulants	22 364 (76.3)	8330 (74.6)	11 500 (77.0)	2534 (79.0)	<0.0001	5.6	10.5
Vitamin-K antagonist	6998 (31.5)	2048 (24.7)	3927 (34.4)	1023 (40.5)	<0.0001	21.2	34.1
Dabigatran	907 (4.1)	359 (4.3)	455 (4.0)	93 (3.7)	0.2599	1.8	3.3
Rivaroxiban	4627 (20.8)	1938 (23.4)	2284 (20.0)	405 (16.0)	<0.0001	8.3	18.6
Apixaban	10 082 (45.4)	4059 (49.0)	4967 (43.5)	1056 (41.8)	<0.0001	11.2	14.6
Edoxaban	29 (0.1)	17 (0.2)	10 (0.1)	2 (0.1)	0.0582	3.1	3.3
Missing, %	139 (0.6)	53 (0.6)	78 (0.7)	8 (0.3)			
Antiplatelets agent	2147 (7.3)	392 (3.5)	1307 (8.7)	448 (14.0)	<0.0001	22.0	37.7
Aspirin	13 064 (44.6)	4197 (37.6)	7049 (47.2)	1818 (56.7)	<0.0001	19.5	39.0
Beta blocker	19 541 (66.7)	6734 (60.3)	10 371 (69.4)	2436 (76.0)	<0.0001	19.2	34.1
Calcium channel blocker	10 948 (37.3)	4098 (36.7)	5593 (37.4)	1257 (39.2)	0.0338	1.5	5.2
Digoxin	3118 (10.6)	967 (8.7)	1721 (11.5)	430 (13.4)	<0.0001	9.5	15.2
In-hospital oral medications, missing, %	4861 (14.2)	2026 (15.4)	2393 (13.8)	442 (12.1)			
Discharge meds							
Anticoagulation therapy	29 239 (85.6)	11 304 (85.7)	14 847 (85.7)	3088 (84.6)	0.2369	0.0	3.0
OAC					<0.0001	18.1	30.9
Vitamin-K antagonist	8759 (25.6)	2701 (20.5)	4848 (28.0)	1210 (33.2)			
Novel OAC	20 480 (59.9)	8603 (65.2)	9999 (57.7)	1878 (51.5)			
No OAC	4935 (14.4)	1890 (14.3)	2484 (14.3)	561 (15.4)			
OAC type					<0.0001	19.7	34.3
Edoxaban	36 (0.1)	19 (0.2)	16 (0.1)	1 (0.0)			
Rivaroxaban	6146 (21.0)	2663 (23.6)	2973 (20.0)	510 (16.5)			
Apixaban	13 157 (45.0)	5455 (48.3)	6448 (43.4)	1254 (40.6)			
Dabigatran	1141 (3.9)	466 (4.1)	562 (3.8)	113 (3.7)			
Vitamin-K antagonist	8759 (30.0)	2701 (23.9)	4848 (32.7)	1210 (39.2)			
Apixaban dose					<0.0001	13.7	23.3
5 mg	9837 (79.7)	4226 (83.2)	4732 (77.9)	879 (73.7)			
2.5 mg	2509 (20.3)	852 (16.8)	1344 (22.1)	313 (26.3)			
Missing, %	810 (6.2)	376 (6.9)	372 (5.8)	62 (4.9)			

(*Continues*)

Table 3. Continued

Variable	Overall N=34 174	Low Comorbidity Burden (0–2) N=13 194	Moderate Comorbidity Burden (3–5) N=17 331	High Comorbidity Burden (≥6) N=3649	*P* Value	SD: 3–5 vs 0–2	SD: ≥6 vs 0–2
Rivaroxaban dose					<0.0001	18.1	46.7
20 mg	4349 (76.9)	1989 (82.2)	2062 (74.9)	298 (62.0)			
15 mg	1244 (22.0)	406 (16.8)	661 (24.0)	177 (36.8)			
10 mg	62 (1.1)	25 (1.0)	31 (1.1)	6 (1.2)			
Missing, %	491 (8.0)	243 (9.1)	219 (7.4)	29 (5.7)			
Dabigatran dose					0.8735	2.6	4.9
150 mg	960 (89.6)	384 (89.1)	480 (89.9)	96 (90.6)			
75 mg	111 (10.4)	47 (10.9)	54 (10.1)	10 (9.4)			
Missing, %	70 (6.1)	35 (7.5)	28 (5.0)	7 (6.2)			
Rhythm control/rate control strategy					<0.0001	7.7	21.5
Rate control strategy planned	14 882 (43.5)	5343 (40.5)	7673 (44.3)	1866 (51.1)			
Rhythm control strategy planned	19 292 (56.5)	7851 (59.5)	9658 (55.7)	1783 (48.9)			
Procedures during this hospitalization							
No procedures	15 548 (48.2)	5887 (47.4)	7863 (47.9)	1798 (52.3)	<0.0001	1.2	9.9
Ablation	4357 (13.5)	1909 (15.4)	2110 (12.9)	338 (9.8)	<0.0001	7.2	16.7
Cardioversion	10 753 (33.3)	4230 (34.0)	5513 (33.6)	1010 (29.4)	<0.0001	0.9	10.0
Cardiac resynchronization therapy with defibrillator/pacemaker	190 (0.6)	41 (0.3)	115 (0.7)	34 (1.0)	<0.0001	5.2	8.2
Implantable cardioverter defibrillator	85 (0.3)	20 (0.2)	49 (0.3)	16 (0.5)	0.0039	2.9	5.5
Left atrial age	1195 (3.7)	321 (2.6)	665 (4.1)	209 (6.1)	<0.0001	8.2	17.3
Pacemaker	1003 (3.1)	349 (2.8)	529 (3.2)	125 (3.6)	0.0215	2.4	4.7
Percutaneous coronary intervention	742 (2.3)	141 (1.1)	476 (2.9)	125 (3.6)	<0.0001	12.6	16.5
Surgical maze	132 (0.4)	47 (0.4)	75 (0.5)	10 (0.3)	0.3006	1.2	1.5
Procedures missing	1908 (5.6)	764 (5.8)	931 (5.4)	213 (5.8)	0.2242	1.8	0.2

OAC indicates oral anticoagulants.

Table 4. Odds Ratio of Discharge Treatment

Outcomes	Comorbidity Score	Unadjusted Analysis		Adjusted Analysis*	
		OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Total study cohort (n=34 174)					
OACs prescribed at discharge (Yes vs No)			0.4010		0.0119
	0–2	Reference		Reference	
	3–5	1.00 (0.89–1.12)	0.9909	0.93 (0.82–1.05)	0.2587
	≥6	0.92 (0.77–1.09)	0.3457	0.72 (0.60–0.86)	0.0002
OAC type (NOACs vs VKA, among those prescribed OAC)			<0.0001		<0.0001
	0–2	Reference		Reference	
	3–5	0.65 (0.61–0.69)	<0.0001	0.72 (0.67–0.78)	<0.0001
	≥6	0.49 (0.42–0.57)	<0.0001	0.59 (0.50–0.69)	<0.0001
First detected AF (n=7083)					
OACs prescribed (Yes vs No)			0.1768		0.0562
	0–2	Reference		Reference	
	3–5	0.93 (0.81–1.05)	0.2463	0.91 (0.79–1.06)	0.2374
	≥6	0.78 (0.62–0.98)	0.0357	0.65 (0.51–0.83)	0.0004
OAC type (NOACs vs VKA, among those prescribed OAC)			0.0006		0.0076
	0–2	Reference		Reference	
	3–5	0.64 (0.50–0.82)	0.0003	0.68 (0.55–0.84)	0.0005
	≥6	0.53 (0.37–0.75)	0.0003	0.59 (0.42–0.82)	0.0017
Preexisting AF (n=27 091)					
OACs prescribed (Yes vs No)			0.2766		0.0833
	0–2	Reference		Reference	
	3–5	0.96 (0.85–1.08)	0.4933	0.94 (0.82–1.08)	0.3983
	≥6	0.86 (0.71–1.04)	0.1101	0.77 (0.62–0.94)	0.0118
OAC type (NOACs vs VKA, among those prescribed OAC)			<0.0001		<0.0001
	0–2	Reference		Reference	
	3–5	0.69 (0.63–0.75)	<0.0001	0.72 (0.67–0.79)	<0.0001
	≥6	0.53 (0.45–0.62)	<0.0001	0.58 (0.49–0.68)	<0.0001
Patients naïve to OAC (n=14 324)					
OACs prescribed (Yes vs No)			0.0036		0.0027
	0–2	Reference		Reference	
	3–5	0.81 (0.71–0.93)	0.0022	0.84 (0.74–0.96)	0.0117
	≥6	0.64 (0.53–0.77)	<0.0001	0.59 (0.48–0.73)	<0.0001
OAC type (NOACs vs VKA, among those prescribed OAC)			<0.0001		0.0008
	0–2	Reference		Reference	
	3–5	0.64 (0.56–0.74)	<0.0001	0.70 (0.60–0.82)	<0.0001
	≥6	0.46 (0.35–0.59)	<0.0001	0.55 (0.44–0.69)	<0.0001

AF indicates atrial fibrillation; NOACs, novel oral anticoagulants; OAC, oral anticoagulants; and VKA, vitamin K antagonist.

*Model adjusted for age (age×indicator variable for age ≥80), sex, race/ethnicity, insurance status, type of atrial fibrillation, prior antiarrhythmic, body mass index, systolic blood pressure, heart rate, control strategy, admission year, hospital region, teaching status, number of beds, rural location, adult cardiac electrophysiology site.

may be explained by the decline in renal function in those with a high burden of comorbidity. A similar trend toward use of VKA over NOACs in patients with decreased renal function was found in previous studies from GWTG-AFIB.[16,21] This is an interesting finding as a reduced dose of NOACs still can be efficacious in patients with renal dysfunction.[25] Furthermore, in OAC naïve patients, we observed even lower odds of OAC prescription in the presence of high multimorbidity. Lower rates of OAC prescriptions in these

Table 5. Documented Reasons for Those Not Receiving OAC at Discharge, Stratified by Morbidity Burden

Variable	Overall N=4935	Low Comorbidity Burden (0–2) N=1890	Moderate Comorbidity Burden (3–5) N=2484	High Comorbidity Burden (≥6) N=561	*P* Value	SD: 3–5 vs 0–2	SD: ≥6 vs 0–2
OAC relative contraindications							
Any contraindications to anticoagulation therapy	3523 (71.4)	1263 (66.8)	1856 (74.7)	404 (72.0)	<0.0001	17.4	11.3
OAC relative contraindication categories							
Unable to adhere/monitor	157 (3.2)	58 (3.1)	81 (3.3)	18 (3.2)	0.9370	1.1	0.8
Occupational risk	4 (0.1)	2 (0.1)	1 (0.0)	1 (0.2)	0.5200	2.4	1.9
High bleeding risk	941 (19.1)	268 (14.2)	535 (21.5)	138 (24.6)	<0.0001	19.3	26.6
Frequent falls/frailty	1411 (28.6)	463 (24.5)	774 (31.2)	174 (31.0)	<0.0001	14.9	14.6
Patient refusal/preference	862 (17.5)	363 (19.2)	432 (17.4)	67 (11.9)	0.0004	4.7	20.1
Physician preference	744 (15.1)	327 (17.3)	355 (14.3)	62 (11.1)	0.0004	8.3	18.0
Need for dual antiplatelet therapy	54 (1.1)	10 (0.5)	34 (1.4)	10 (1.8)	0.0076	8.7	11.7
Transient or reversible causes of atrial fibrillation	63 (1.3)	28 (1.5)	30 (1.2)	5 (0.9)	0.5007	2.4	5.5
Physician preference only	485 (9.8)	218 (11.5)	230 (9.3)	37 (6.6)	0.0010	7.5	17.3
Moderate contraindications*	1982 (40.2)	697 (36.9)	1056 (42.5)	229 (40.8)	0.0008	11.5	8.1

Not all patients without OAC prescription had a relative contraindication available. Patients could have more than 1 contraindication. OAC indicates oral anticoagulants.

*Moderate contraindications include any relative contraindication except frailty or physician preference.

patients could be explained in part by the contemporary lack of guidelines for patients with AF and multimorbidity, the perceived high bleeding risk, and a possible misconception of the outcomes of OAC when patients fall. We found that many patients with a high multimorbidity burden (1275 patients, 35.0%) were not on OAC therapy, the most common documented reasons being frequent falls, frailty, and high bleeding risk. In the ORBIT AF registry, the most common reasons for no OAC therapy among eligible patients were patient refusal and a history of falls or frailty.[26] Similarly, in a previous study in the GWTG-AFIB registry, of all patients with AF eligible for OAC who were not on one, the most common reasons for no anticoagulation were frequent falls and frailty.[16] Although studies that have evaluated OAC therapy, primarily VKA, in patients with frequent falls have been conflicting, most studies have found that the risk of bleeding is very low unless the patient is falling very frequently at up to 300 times per year. The risk may even be lower when treated with NOACs.[27–31] A high bleeding risk was the other major factor driving nonprescription of OACs. However, there is growing evidence that the net clinical benefit of OAC therapy, in particular in the era of NOACs, outweighs the bleeding risk in most cases with a favorable safety profile even in patients with high HAS-BLED scores, including patients with multimorbidity.[32,33] In patients aged more than 80 years, although most studies have found a positive net clinical benefit of using an OAC, the evidence of benefit is less clear and randomized data are lacking.[9,34,35] A recent post hoc analysis from ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) further substantiated this point. The study found that the benefit of apixaban over warfarin in terms of efficacy and safety was preserved in those with multimorbidity. The study replicated the finding that multimorbidity was associated with worse outcomes of death, stroke, and major bleeding, but also found that those with multimorbidity treated with apixaban had significantly lower rates of bleeding compared to those treated with warfarin.[17]

Our results highlight a gap between current knowledge and clinical misperceptions regarding the benefits and risks of OAC therapy and underscore the need for initiatives that improve the use of OAC therapy in patients with high multimorbidity. One such strategies was recently demonstrated in the IMPACT-AF trial (a multifaceted intervention to improve treatment with oral anticoagulants in atrial fibrillation). The multifaceted intervention included patient and provider education on anticoagulation therapy and showed an increase in guideline-recommended prescription and compliance of anticoagulation therapy.[36]

Limitations

This study has some limitations. We included only patients with nonvalvular AF. Although we excluded patients with strict contraindications to OAC therapy,

some may have had relative contraindications to OAC therapy that were not collected. Because of the lack of data on indications for OACs in GWTG-AF, we were not able to exclude patients who were on an OAC for reasons other than AF. We did not have any frailty assessment available; however, a standard definition for frailty is currently not used across studies, which limits the evaluation of the impact of frailty. We used a cumulative count of comorbidities, which has previously been used as a marker of frailty.[37,38] The cumulative count of comorbidities provides a convenient and reproducible way of assessing functional impairment. As frailty was not collected in the GWTG-AF registry, the cumulative count of comorbidities is the best alternative. One important limitation was that the severity of each comorbidity was not available, and both cardiovascular and noncardiovascular comorbidities contributed equally to the assessment of the morbidity score. Although we treated all comorbidities as having the same weight, the different comorbidities (eg, hypertension, coronary artery disease, cognitive deficit, hypothyroidism, or depression, etc) do not portend the same risk of AF or AF-related complications. However, studies on measuring multimorbidity have concluded that simple measures, such as a simple count of chronic diseases or of prescribed medications, are almost as good at predicting healthcare use as more sophisticated methods.[39,40] For our analysis, we believe that the number of comorbidities, and not just their severity, likely influences clinical decisions regarding oral anticoagulation and subsequent outcomes. Patient selection may have played a role, as these patients were recruited in a quality-of-care inpatient database whose aim was to improve stroke prevention in hospitalized patients with AF, potentially limiting the generalizability of the results. Patients treated in other healthcare settings may have different prescription rates dependent on comorbidity burden.

CONCLUSIONS

In a nationwide US quality improvement database of patients with AF aiming to improve stroke prophylaxis, we found that multimorbidity was highly prevalent; it was present in more than two thirds of patients with nonvalvular AF aged ≥65 years. From 2014 to 2019 the burden of multimorbidity increased. Although we found high prescription rates for OAC therapy (86.5%), a high morbidity burden was associated with lower odds of OAC prescription with frequent falls/frailty being the most common reason for nonuse. These results highlight a gap between current knowledge and clinical practice and the need for educational implementation tools to increase guideline-recommended OAC therapy in patients with AF and multimorbidity.

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Supplementary Material

Table S1

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Supplemental Material

Table S1. Reasons for non-prescription of OAC therapy by age.

Variable	Overall	Age 65-80	Age >80	P Value	SD: 65-80 vs >80
	N=4,935	N=2,293	N=2,642		
Age, median (IQR)	82 (74 - 89)	73 (69 - 77)	88 (84 - 92)	<.0001	331,1
OAC Contraindications					
Any Contraindications to Anticoagulation Therapy	3,523 (71.4)	1,457 (63.5)	2,066 (78.2)	<.0001	32,7
Unable to Adhere/Monitor	157 (3.2)	77 (3.4)	80 (3.0)	0,5100	1,9
Occupational Risk	4 (0.1)	1 (0.0)	3 (0.1)	0,3893	2,5
High Bleeding Risk	941 (19.1)	444 (19.4)	497 (18.8)	0,6227	1,4
Frequent Falls/Frailty	1,411 (28.6)	297 (13.0)	1,114 (42.2)	<.0001	69,2
Patient Refusal/Preference	862 (17.5)	384 (16.7)	478 (18.1)	0,2143	3,5
Physician Preference	744 (15.1)	400 (17.4)	344 (13.0)	<.0001	12,3
Need for Dual Antiplatelet Therapy	54 (1.1)	33 (1.4)	21 (0.8)	0,0300	6,1
Transient or reversible causes of atrial fibrillation	63 (1.3)	36 (1.6)	27 (1.0)	0,0872	4,8
Physician Preference Only	485 (9.8)	308 (13.4)	177 (6.7)	<.0001	22,5
Moderate Contraindications (any contraindication except frailty or physician preference)	1,982 (40.2)	935 (40.8)	1,047 (39.6)	0,4123	2,3

IQR, interquartile range.