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Contemporary trends and barriers to oral anticoagulation therapy in Non-valvular atrial fibrillation during DOAC predominant era

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ABSTRACT

There is a need to reassess contemporary oral anticoagulation (OAC) trends and barriers against guideline directed therapy in the United States. Most previous studies were performed before major guideline changes recommended direct oral anticoagulant (DOAC) use over warfarin or have otherwise lacked patient level data. Data on overuse of OAC in low-risk group is also limited. To address these knowledge gaps, we performed a nationwide analysis to analyze current trends. This is a retrospective cohort study assessing non-valvular AF identified using a large United States de-identified administrative claims database, including commercial and Medicare Advantage enrollees. Prescription fills were assessed within a 90-day follow-up from the patient's index AF encounter between January 1, 2016, and December 31, 2020. Among the 339,197 AF patients, 4.4%, 8.0%, and 87.6% were in the low-, moderate-, and high-risk groups (according to CHA_2DS_2-VASc score). An over (29.6%) and under (52.2%) utilization of OAC was reported in low- and high-risk AF patients. A considerably high frequency for warfarin use was also noted among high-risk group patients taking OAC (33.1%). The results suggest that anticoagulation use for stroke prevention in the United States is still comparable to the pre-DOAC era studies. About half of newly diagnosed high-risk non-valvular AF patients remain unprotected against stroke risk. Several predictors of OAC and DOAC use were also identified. Our findings may identify a population at risk of complications due to under- or over-treatment and highlight the need for future quality improvement efforts.

1. Introduction

In patients with atrial fibrillation, the net benefit of OAC therapy is almost unequivocal except for very low stroke risk patients. Even a high bleeding risk score (such as HAS-BLED score) should generally not preclude OAC therapy but rather be used to identify and treat bleeding risk factors.[3] However, despite a strong evidence of benefit, underuse of OAC therapy in real-world setting is common [4] and efforts to improve guideline-adherence need to be prioritized especially considering the rising incidence of cardioembolic strokes.[5] Since the approval of first Direct Oral Anticoagulant (DOAC) in 2011 the oral anticoagulation (OAC) trends have been changing steadily across countries as providers continue to gain confidence with the newer drugs and as evidence/guidelines for use became clearer.[1,2] DOACs offer predictable pharmacokinetics and ease of use by eliminating frequent invasive monitoring requirements and superior outcomes in reducing

Abbreviations: AOR, Adjusted odds ratio; CAD, Coronary arterial disease; CKD, Chronic kidney disease; DOAC, Direct oral anticoagulant; HCM, Hypertrophic cardiomyopathy; NVAF, Non-valvular atrial fibrillation; OAC, Oral anticoagulants; OLDW, OptumLabs Data Warehouse; PAD, Peripheral arterial disease; VKA, Vitamin K antagonist.

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stroke or systemic emboli when compared to warfarin. The first major guideline to reflect a preference for DOAC over warfarin was the 2016 ESC guidance statement (Class 1, Level A recommendation).[3,6] Most prior studies assessing OAC rates were performed before this time, [7–10] when there were several perceived reasons to choose DOAC over warfarin such as lack of provider confidence with newer drugs, less clear guidelines and evidence, lack of specific reversal drugs for DOAC. In United States, the few recent studies have otherwise lacked patient-level data to select for non-valvular atrial fibrillation (NVAF) patients or address factors influencing management decisions. Periodic assessment of OAC trends is critical to establish real-world feedback in various healthcare systems and to identify barriers to appropriate stroke prevention. Therefore, in the present study, we have assessed 1) Trends in OAC dispensing for newly diagnosed NVAF patients during a guideline based, DOAC preferred era (2016–2020) within the United States, especially focusing on low-risk and high-risk groups as stratified by CHA_2DS_2-VASc score. 2) Factors associated with OAC use, and 3) Factors associated with DOAC use over warfarin.

2. Methods

The study design was retrospective, population-based cohort analysis. For this we used de-identified administrative claims data from the Optum Labs Data Warehouse (OLDW), which includes medical and pharmacy claims, laboratory results, and enrollment records for commercial and Medicare Advantage (MA) enrollees. The database contains longitudinal health information for over 200 million enrollees and patients, representing a mixture of ages and geographical regions across the United States.[11] Since the data was de-identified, in compliance with the Health Insurance Portability and Accountability Act and

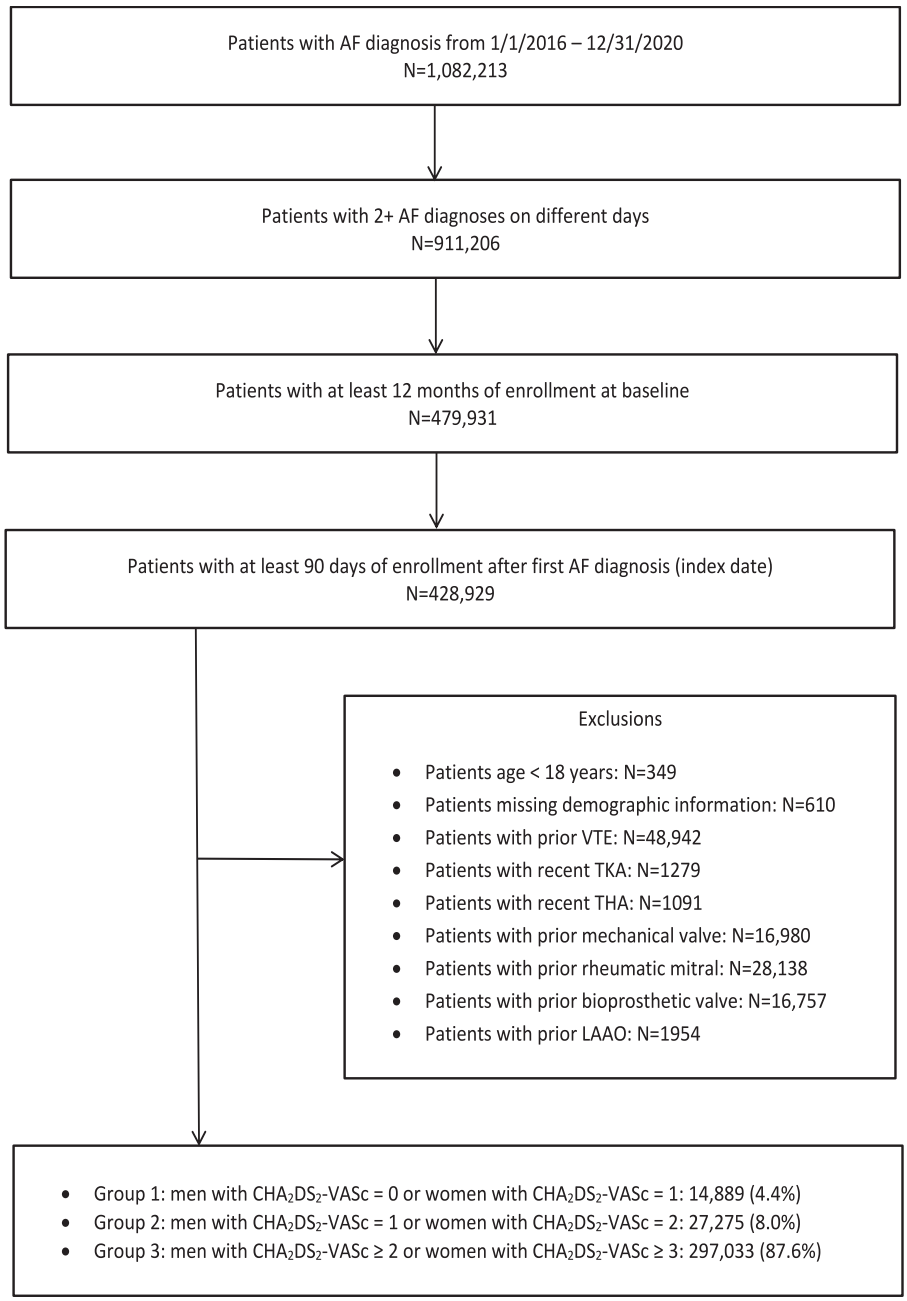

Fig. 1. Flow diagram depicting stepwise exclusion criteria as applied to the initial cohort. **Abbreviations:** AF (atrial fibrillation), VTE, TKA (total knee arthroplasty), THA (total hip arthroplasty), LAAO.

customer requirements, Institutional Review Board approval or waiver of authorization was not required. This study conforms with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies.[12].

The study population included adult patients (≥18 years) with at least two diagnoses of AF between January 1, 2016, and December 31, 2020, on two different days. Outcome event was defined as OAC use within a 90-day follow-up window from the index AF encounter date. In addition, patients were required to have at least 12 months of continuous medical and pharmacy coverage (baseline period) before the first AF diagnosis (index date). Patients with independent valvular indications for warfarin, including mechanical or bioprosthetic valve placement and rheumatic mitral valve stenosis or left atrial appendage occlusion, were excluded. Patients with other independent OAC indications unrelated to AF, such as prior venous thromboembolism or recent (within two weeks) total knee or hip replacement, were also excluded (Fig. 1). These criteria were chosen to primarily include a NVAF population that is newly eligible to receive OAC therapy for AF diagnosis. The specific codes used for inclusion/exclusion criteria are provided in supplementary material (**Table S1-S2**). In a sensitivity analysis, patients with prior history of cardioversion, catheter ablation or surgical ablation/MAZE procedure were further excluded from the cohort with all other criteria kept identical to remove the transient OAC indication.

The remaining cohort was divided mainly into two groups: (1) Low-risk group (CHA_2DS_2-VASc 0 in men or 1 in women), (2) High-risk group (CHA_2DS_2-VASc $\geq$ 2 in men or $\geq$ 3 in women). We also stratified antithrombotic use across a continuous CHA_2DS_2-VASc scores (0–9). These groups were further stratified according to treatment allocation (i) OAC vs no OAC and (ii) DOAC vs warfarin and assessed for association with various baseline patient characteristics.

Covariates included patient demographics (such as age, gender, and region) and type of health plan (commercial or Medicare Advantage). Comorbidities were ascertained using primary and secondary diagnostic codes from all medical claims during 12 months before the index date. Comorbidities assessed included CHA_2DS_2-VASc components, HAS-BLED components [hypertension, chronic kidney disease (CKD), liver disease, stroke, anemia/major bleed, age > 65, alcohol use, antiplatelet/NSAIDs use]. Labile international normalized ratio values were not available in the database, so it was excluded from the HAS-BLED score in our study. Specific codes used to calculate HAS-BLED score in this study are provided in supplementary material (**Table S3-S4**). Other comorbidities included falls, catheter/surgical ablation, hypertrophic cardiomyopathy, cardioversion, implanted device, and obesity. Relevant concurrent medication use, healthcare utilization rates, events (including ischemic stroke, systemic embolism, major or intracranial bleeding) within the previous 3-month and 12-month period were assessed as these can potentially influence OAC utilization.

Baseline patient characteristics were reported as proportion for categorical data and as mean with standard deviation (SD) for continuous variables. Means were compared using paired *t*-test and the proportions were compared using Pearson's chi-squared test. The analysis focused on the low and high-risk subgroups, where the guideline recommendations are relatively clear to allow interpretation. Lastly, the multivariable logistic regression model examined baseline characteristics associated with OAC use and DOAC use. Throughout present study, we have only assessed the drug dispensing rates (prescription fills) which may not reflect physician prescribing rates or actual use of the drug by patients which further depends upon compliance. Model covariates included those discussed previously. All analyses were conducted using SAS Enterprise Guide 7.1 (SAS Institute, Cary NC). X.Y. had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

3. Results

A total of 339,197 AF patients met the study criteria during the period of January 2016 to December 2020. (Fig. 1). Of the health plans examined, 88.6% of the claims were from the Medicare advantage plan, and the rest were from a commercial health plan. Distribution of cohort when risk stratified into low-, moderate-, and high-risk groups according to CHA_2DS_2-VASc score was 4.4%, 8.0%, and 87.6%, respectively. The mean age (SD) in these sub-groups was 51.2 (10.5), 59.9 (9.4), and 75.1 (8.8) years, respectively.

Proportion of patients that had OAC prescription fills within a 90-day follow up window of the index diagnosis date was 29.6% (low-risk group), 40.6% (moderate-risk group) and 52.2% (high-risk group). Of the patients on OAC, warfarin use was 10.7% (low-risk group) and 33.1% (high-risk group), while the rest utilized one of the DOAC drugs.

On a continuous scale (CHA_2DS_2-VASc score: 0–9), DOAC and warfarin use had a slightly decreasing and increasing trend respectively (Fig. 2). DOAC use was highest (37.1%) and lowest (20.1%) for CHA_2DS_2-VASc score 3 and 9 respectively. Warfarin use was highest with CHA_2DS_2-VASc scores > 4. Overall OAC use within the high-risk group showed a lack of variation across the CHA_2DS_2-VASc score. (Fig. 2).

A comparison of baseline characteristics for OAC use vs no OAC, stratified into low-, and high-risk groups is shown in Tables 1 and 2. Most of the patient population was Caucasian (~75%) with about 75% from South or Midwest regions of the United States. Only modest differences according to region were discernible among the two groups.

The mean CHA_2DS_2-VASc and HAS-BLED scores were marginally higher for patients without an OAC prescription fill. Among the individual CHA_2DS_2-VASc score components in the high-risk group, patients with coronary and peripheral vascular disease were less likely to use OAC (61.4% vs 57.3%; P <.001). Among the HAS-BLED score components, history of CKD, stroke, anemia, major bleeding history, alcoholism, liver disease, thienopyridine and NSAID use were all negatively associated with OAC use (P <.001).

Most other comorbidities were also negatively associated with OAC use in the high-risk group including myocardial infarction, falls, gastrointestinal lesions, extracranial bleeding, smoking, chronic obstructive pulmonary disease, end-stage renal and liver disease (P <.001). Whereas obesity, hyperlipidemia and obstructive sleep apnea were positively associated with OAC use (P <.001).

Concurrent medications use including amiodarone (8.5% vs 7.5%), other antiarrhythmic drugs (10.7% vs 8.3%), calcium channel blockers (18.3% vs 15.2%) and digitalis (11.3% vs 7.8%) were all associated with OAC use in the high-risk subgroup (P <.001). Furthermore, patients on OAC were also more likely to have utilized other cardiac-related interventions such as catheter and surgical ablations, cardioversion, permanent pacemaker/defibrillator devices, prior percutaneous coronary intervention or coronary artery bypass graft (P <.001).

The number of all-cause hospital days and non-AF-related emergency room visits or hospitalizations in the last 12 months were slightly higher in the non-OAC group in high-risk patients (P <.001). Also, within the previous 3 months of the index date, patients in the non-OAC group had a slightly higher number of patients with ischemic stroke/systemic embolism, major bleeding, and intracranial bleeding episodes.

Results from the multivariable logistic regression model for low and high-risk groups are detailed in Table 3 and 4. In terms of insurance coverage, Medicare advantage plan was a negative predictor of OAC and DOAC compared to commercial plan in both low and high-risk groups.

In the low-risk group, older men were more likely to be on OAC therapy. Among comorbidities when adjusted for other variables, anemia/major bleeding was a negative predictor for OAC and DOAC therapy. Among comorbidities when adjusted for other variables, anemia/major bleeding was a negative predictor for OAC and DOAC therapy. Liver disease and alcoholism were negative predictors of OAC but were not associated with DOAC. Falls were a negative predictor of OAC use

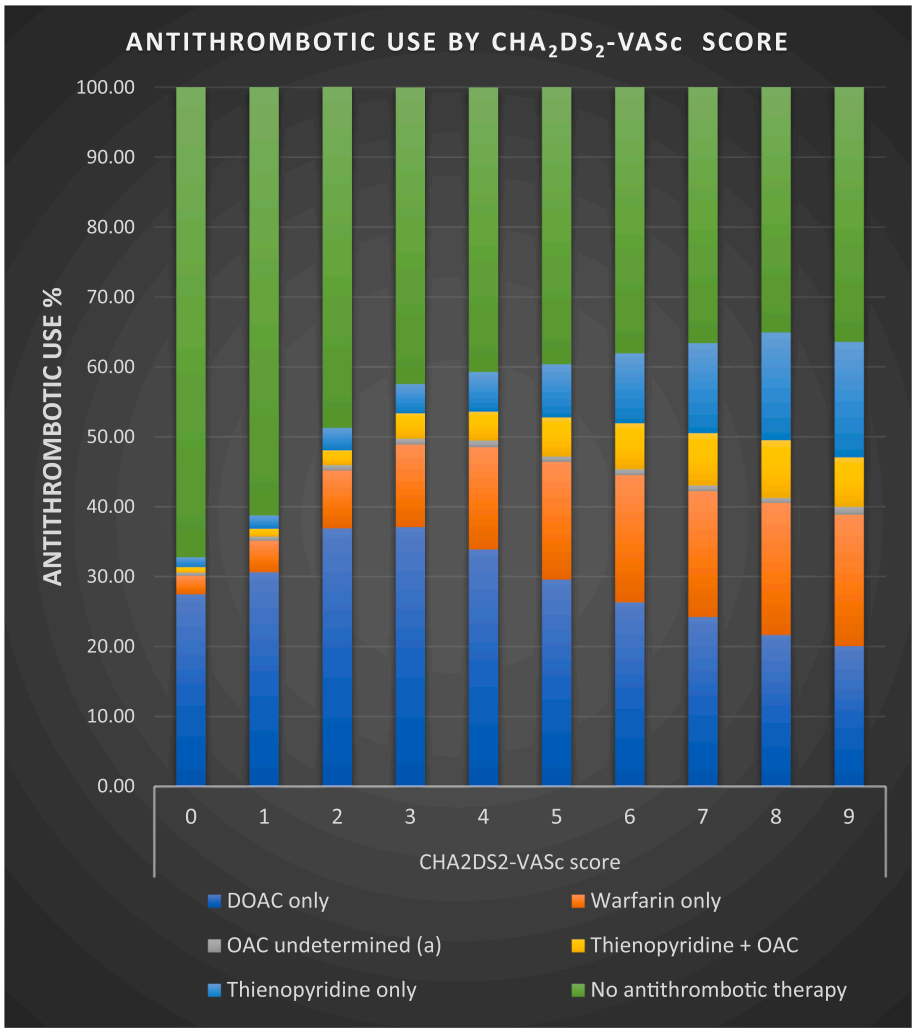

Fig. 2. Graphical representation of antithrombotic therapy utilization stratified by CHA_2DS_2-VASc score. (a) In a small proportion (n = 20) both DOAC (direct oral anticoagulant) and warfarin prescriptions were present likely due to a switch within the study window or a reporting error. (DOACs included apixaban, dabigatran, rivaroxaban and edoxaban; thienopyridines included anagrelide, cilostazol, clopidogrel, dipyridamole, prasugrel, ticagrelor, ticlopidine and vorapazar) **Abbreviations:** OAC (oral anticoagulant), DOAC (direct oral anticoagulant).

and DOAC were preferred in those with a history of fall. HCM and cardioversion were predictors of OAC use but not for a choice of DOAC over warfarin. Implanted device was negatively associated with OAC and DOAC use. Lastly, antiarrhythmic drug use was negatively associated with OAC use.

In the high-risk group, older men with NVAF were more likely to be on OAC but less likely to be on DOAC. Heart failure, Diabetes Mellitus were positive predictors of OAC but negative predictors of DOAC. CAD/PAD was negatively associated with OAC and DOAC use. HAS-BLED components were mostly negative predictors to OAC use. Further, warfarin was preferred with history of CKD, stroke or anemia/major bleeding. DOAC was preferred with history of liver disease, alcoholism, antiplatelet/NSAIDs use. Falls were a negative predictor to OAC use while obesity was associated with both OAC and DOAC use. Lastly, Cardioversion, Implanted device, and antiarrhythmic drug were positively associated with OAC use and negatively with DOAC use.

In the sensitivity analysis, 4,153 (29.5%) patients had OAC use in the low-risk group (N = 14,096) while 141,196 (51.1%) patients had OAC use noted in the high-risk group (N = 276,450). Predictors of OAC use for the sensitivity analysis are detailed in **Table S5 and S6**. Briefly, results for the low-risk group were similar to the main analysis and in the high-risk group, heart failure and amiodarone/other antiarrhythmic drug use were no longer significant predictors of OAC use while falls were noted as significant predictor of DOAC use.

4. Discussion

In this study, using the nationwide data of OLDW, we provide several key insights into the problem of under and over-prescription of OAC. Considerable changes have been made in the guidelines of AF management in the last decade and through this work we highlight the need to strengthen evidence-based care in NVAF patients at the point of care.

Within the low-risk group, a significant proportion (about 30%) of patients had OAC prescription fills. Majority of this group composed of relatively young (mean age 54 years) males (74%). OAC use primarily comprised of NOAC (91%) in this group. In this low-risk NVAF subgroup, independent indications for OAC use such as venous thromboembolism and recent total knee or hip replacement were excluded. Other possible indications for OAC use had low prevalence during previous 12 months such as cardioversion (5%) and catheter ablation (1.7%). Also, in the sensitivity analysis, the OAC utilization rates remained similar to the main analysis. Further, there was minimal AF and non-AF related hospital days and healthcare utilization in this subgroup. Overall, these findings suggest an overutilization of OAC in low-risk CHA_2DS_2-VASc group. As per guidelines, OAC is not recommended in this group due to the unjustifiable incremental increase in major bleeding risk compared to the annual absolute risk reduction for ischemic stroke risk.[3] Among independent predictors of OAC use in low-risk group, antiarrhythmic drugs and implanted device were negatively associated with OAC use and may suggest a better guideline adherence in patients under specialized care.

Table 1
Patient Characteristics (low-risk group).

Patient Characteristics	No OAC (N = 10,484)	OAC (N = 4405)	Total (N = 14,889)	p value
OAC use				
Warfarin	0 (0.0%)	473 (10.7%)	473 (3.2%)	<0.0001
NOAC	0 (0.0%)	4000 (90.8%)	4000 (26.9%)	<0.0001
Age (years)				<0.0001
Mean (SD)	50.1 (11.0)	54.0 (8.9)	51.2 (10.5)	
Median	53	56	54	
Q1, Q3	43.0, 59.0	50.0, 61.0	45.0, 60.0	
Range	(18.0–64.0)	(18.0–64.0)	(18.0–64.0)	
Gender				<0.0001
Female	3396 (32.4%)	1164 (26.4%)	4560 (30.6%)	
Male	7088 (67.6%)	3241 (73.6%)	10329 (69.4%)	
Region				0.0029
Midwest	3338 (31.8%)	1526 (34.6%)	4864 (32.7%)	
Northeast	1009 (9.6%)	425 (9.6%)	1434 (9.6%)	
South	4029 (38.4%)	1649 (37.4%)	5678 (38.1%)	
Unknown	81 (0.8%)	21 (0.5%)	102 (0.7%)	
West	2027 (19.3%)	784 (17.8%)	2811 (18.9%)	
Health plan				0.0112
Commercial	9904 (94.5%)	4206 (95.5%)	14110 (94.8%)	
Medicare Advantage	580 (5.5%)	199 (4.5%)	779 (5.2%)	
HAS-BLED				<0.0001
Mean (SD)	0.4 (0.7)	0.3 (0.6)	0.4 (0.6)	
Median	0	0	0	
Q1, Q3	0.0, 1.0	0.0, 1.0	0.0, 1.0	
Range	(0.0–4.0)	(0.0–4.0)	(0.0–4.0)	
HAS-BLED components				
Age > 65 years	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
CKD	61 (0.6%)	19 (0.4%)	80 (0.5%)	0.2515
Stroke	29 (0.3%)	0 (0.0%)	29 (0.2%)	0.0005
Ischemic stroke	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
TIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Anemia/Major bleed	2204 (21.0%)	732 (16.6%)	2936 (19.7%)	<0.0001
Anemia	1361 (13.0%)	457 (10.4%)	1818 (12.2%)	<0.0001
Major bleed	1133 (10.8%)	354 (8.0%)	1487 (10.0%)	<0.0001
Liver disease	777 (7.4%)	258 (5.9%)	1035 (7.0%)	0.0007
Alcoholism	447 (4.3%)	133 (3.0%)	580 (3.9%)	0.0003
Thienopyridine /NSAIDs	784 (7.5%)	294 (6.7%)	1078 (7.2%)	0.0841
Thienopyridine	*	*	16 (0.1%)	0.1341
NSAIDs	*	*	1064 (7.1%)	0.1288
Other comorbidities				
Myocardial infarction	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Falls	558 (5.3%)	184 (4.2%)	742 (5.0%)	0.0034
Hyperlipidemia	3405 (32.5%)	1373 (31.2%)	4778 (32.1%)	0.1184
Hypertrophic cardiomyopathy	44 (0.4%)	33 (0.7%)	77 (0.5%)	0.0105
Smoking	1940 (18.5%)	795 (18.0%)	2735 (18.4%)	0.5113
Obesity	1632 (15.6%)	842 (19.1%)	2474 (16.6%)	<0.0001
COPD	260 (2.5%)	98 (2.2%)	358 (2.4%)	0.3535
Obstructive sleep apnea	1303 (12.4%)	503 (11.4%)	1806 (12.1%)	0.0850
Skilled nursing facility	135 (1.3%)	51 (1.2%)	186 (1.2%)	0.5148
Extracranial bleeding	1093 (10.4%)	350 (7.9%)	1443 (9.7%)	<0.0001
ESRD requiring dialysis	*	*	*	0.1123
Gastrointestinal lesions	277 (2.6%)	89 (2.0%)	366 (2.5%)	0.0254
End stage liver disease	40 (0.4%)	12 (0.3%)	52 (0.3%)	0.3030
Interventions				
Catheter ablation	215 (2.1%)	76 (1.7%)	291 (2.0%)	0.1904
Cardioversion	404 (3.9%)	216 (4.9%)	620 (4.2%)	0.0034
Surgical ablation/ MAZE	*	*	*	0.8869
Implanted device				0.0467
None	10185 (97.1%)	4315 (98.0%)	14500 (97.4%)	
CRT defibrillator	*	*	*	
ICD	85 (0.8%)	25 (0.6%)	110 (0.7%)	
CRT pacemaker	65 (0.6%)	17 (0.4%)	82 (0.6%)	
Dual chamber pacemaker	112 (1.1%)	33 (0.7%)	145 (1.0%)	
Single chamber pacemaker	*	*	*	
CABG	*	*	*	0.4877
PCI	*	*	*	0.2057
Healthcare Utilization				
Number of AF hospitalizations	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)	0.8231
Number of non-AF hospitalizations	0.1 (0.3)	0.0 (0.2)	0.1 (0.3)	<0.0001
All-cause hospital days	7.3 (9.9)	4.5 (3.7)	6.6 (8.9)	0.0011
Events within past 3 months				
Ischemic stroke or systemic embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Major bleed	*	*	*	0.0407
Intracranial bleed	*	*	*	0.1472
Number of events within past 12 months, mean (SD)				
Ischemic stroke or systemic embolism	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	–
Major bleed	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.7664
Intracranial bleed	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.1123

Baseline comparison of patient characteristics stratified according to oral anticoagulant use within the low-risk group. (*Cell size less than 11 are suppressed to protect patient confidentiality.).

Abbreviations: Oral anticoagulant (OAC); Direct oral anticoagulant (DOAC); coronary artery disease (CAD); peripheral artery disease (PAD); chronic kidney disease (CKD); transient ischemic attack; non-steroidal anti-inflammatory drug (NSAID); chronic obstructive pulmonary disease (COPD); end-stage renal disease (ESRD); implantable cardioverter-defibrillator (ICD); coronary artery bypass graft (CABG); percutaneous coronary intervention (PCI).

Among the high-risk group, only about half the patients (52%) had OAC prescription fills. Further, 33% of OAC use in this group was warfarin instead of DOAC. These results reflect a high proportion of patients that are still left unprotected from stroke risk or are otherwise not on guideline directed OAC therapy. Here we did not consider the adherence and persistence rates [13] for OAC therapy which are further likely to reduce the number of AF patients left unprotected against stroke. Although not directly comparable, these numbers seem comparable to the pre-DOAC era studies in the United States that were predominantly comprised of patients using VKA.[7,9,14] In comparison, some other high-income countries during the post-DOAC era have reported considerably higher OAC rates in the high-risk group approaching 84.3% in a large prospective Belgian cohort.[15] Among the independent predictors older men, patients with heart failure, diabetes mellitus, CAD/PAD, CKD, stroke/thromboembolism, anemia/major bleeding were more likely to receive warfarin instead of DOAC. This may suggest a relative avoidance of DOAC by clinicians in patients with

Table 2
Patient Characteristics (high-risk group).

Patient Characteristics	No OAC (N = 141,966)	OAC (N = 155,067)	Total (N = 297,033)	p value
OAC use				
Warfarin	0 (0.0%)	51309 (33.1%)	51309 (17.3%)	<0.0001
NOAC	0 (0.0%)	106619 (68.8%)	106619 (35.9%)	<0.0001
Age (years)				<0.0001
Mean (SD)	75.1 (9.2)	75.2 (8.4)	75.1 (8.8)	
Median	76	76	76	
Q1, Q3	70.0, 84.0	70.0, 82.0	70.0, 83.0	
Range	(18.0–88.0)	(19.0–88.0)	(18.0–88.0)	
Gender				<0.0001
Female	67456 (47.5%)	71900 (46.4%)	139356 (46.9%)	
Male	74510 (52.5%)	83167 (53.6%)	157677 (53.1%)	
Region				<0.0001
Midwest	39164 (27.6%)	48865 (31.5%)	88029 (29.6%)	
Northeast	22623 (15.9%)	25699 (16.6%)	48322 (16.3%)	
South	67265 (47.4%)	67132 (43.3%)	134397 (45.2%)	
Unknown	113 (0.1%)	57 (0.0%)	170 (0.1%)	
West	12801 (9.0%)	13314 (8.6%)	26115 (8.8%)	
Health plan				0.9244
Commercial	16112 (11.3%)	17616 (11.4%)	33728 (11.4%)	
Medicare Advantage	125854 (88.7%)	137451 (88.6%)	263305 (88.6%)	
CHA_2DS_2-VASc				<0.0001
Mean (SD)	4.7 (1.7)	4.6 (1.6)	4.7 (1.7)	
Median	5	4	4	
Q1, Q3	3.0, 6.0	3.0, 6.0	3.0, 6.0	
Range	(2.0–9.0)	(2.0–9.0)	(2.0–9.0)	
CHA_2DS_2-VASc components				
Heart failure	48527 (34.2%)	52162 (33.6%)	100689 (33.9%)	0.0018
Systolic	18381 (12.9%)	20895 (13.5%)	39276 (13.2%)	<0.0001
Diastolic	20834 (14.7%)	22886 (14.8%)	43720 (14.7%)	0.5214
Hypertension	133413 (94.0%)	146510 (94.5%)	279923 (94.2%)	<0.0001
Diabetes mellitus	60388 (42.5%)	66523 (42.9%)	126911 (42.7%)	0.0460
Thromboembolism	30743 (21.7%)	32548 (21.0%)	63291 (21.3%)	<0.0001
CAD or PAD	87189 (61.4%)	88846 (57.3%)	176035 (59.3%)	<0.0001
CAD	80241 (56.5%)	82123 (53.0%)	162364 (54.7%)	<0.0001
PAD	26123 (18.4%)	24068 (15.5%)	50191 (16.9%)	<0.0001
HAS-BLED				<0.0001
Mean (SD)	3.2 (1.2)	3.1 (1.1)	3.1 (1.2)	
Median	3	3	3	
Q1, Q3	2.0, 4.0	2.0, 4.0	2.0, 4.0	
Range	(0.0–8.0)	(0.0–8.0)	(0.0–8.0)	
HAS-BLED components				
Age > 65 years	80874 (57.0%)	88680 (57.2%)	169554 (57.1%)	–
CKD	31797 (22.4%)	30878 (19.9%)	62675 (21.1%)	<0.0001
Stroke	22570 (15.9%)	23719 (15.3%)	46289 (15.6%)	<0.0001
Ischemic stroke	21488 (15.1%)	23134 (14.9%)	44622 (15.0%)	0.0978
TIA	16047 (11.3%)	17291 (11.2%)	33338 (11.2%)	0.1877
Anemia/Major bleed	85694 (60.4%)	84990 (54.8%)	170684 (57.5%)	<0.0001
Anemia	74152 (52.2%)	72003 (46.4%)	146155 (49.2%)	<0.0001
Major bleed	40604 (28.6%)	37543 (24.2%)	78147 (26.3%)	<0.0001
Liver disease	23447 (16.5%)	21781 (14.0%)	45228 (15.2%)	<0.0001
Alcoholism	8547 (6.0%)	7034 (4.5%)	15581 (5.2%)	<0.0001
Thienopyridine/ NSAIDs	29703 (20.9%)	25016 (16.1%)	54719 (18.4%)	<0.0001
Thienopyridine	16818 (11.8%)	11839 (7.6%)	28657 (9.6%)	<0.0001
NSAIDs	14776 (10.4%)	14478 (9.3%)	29254 (9.8%)	<0.0001
Other comorbidities				
Myocardial infarction	27743 (19.5%)	26099 (16.8%)	53842 (18.1%)	<0.0001
Falls	36265 (25.5%)	30623 (19.7%)	66888 (22.5%)	<0.0001
Hyperlipidemia	122022 (86.0%)	136726 (88.2%)	258748 (87.1%)	<0.0001
Hypertrophic cardiomyopathy	1265 (0.9%)	1846 (1.2%)	3111 (1.0%)	<0.0001
Smoking	54472 (38.4%)	54776 (35.3%)	109248 (36.8%)	<0.0001
Obesity	44904 (31.6%)	56340 (36.3%)	101244 (34.1%)	<0.0001
COPD	23179 (16.3%)	21896 (14.1%)	45075 (15.2%)	<0.0001
Obstructive sleep apnea	27754 (19.5%)	35534 (22.9%)	63288 (21.3%)	<0.0001
Skilled nursing facility	42456 (29.9%)	33149 (21.4%)	75605 (25.5%)	<0.0001
Extracranial bleeding	37334 (26.3%)	35418 (22.8%)	72752 (24.5%)	<0.0001
ESRD requiring dialysis	2256 (1.6%)	1493 (1.0%)	3749 (1.3%)	<0.0001
Gastrointestinal lesions	9868 (7.0%)	8716 (5.6%)	18584 (6.3%)	<0.0001
End stage liver disease	2371 (1.7%)	1357 (0.9%)	3728 (1.3%)	<0.0001
Interventions				
Catheter ablation	1985 (1.4%)	2885 (1.9%)	4870 (1.6%)	<0.0001
Cardioversion	5610 (4.0%)	12718 (8.2%)	18328 (6.2%)	<0.0001
Surgical ablation/ MAZE	74 (0.1%)	110 (0.1%)	184 (0.1%)	0.0396
Implanted device				<0.0001
None	122975 (86.6%)	131864 (85.0%)	254839 (85.8%)	
CRT defibrillator	459 (0.3%)	806 (0.5%)	1265 (0.4%)	
ICD	6880 (4.8%)	8242 (5.3%)	15122 (5.1%)	
CRT pacemaker	1770 (1.2%)	1959 (1.3%)	3729 (1.3%)	
Dual chamber pacemaker	7585 (5.3%)	9274 (6.0%)	16859 (5.7%)	
Single chamber pacemaker	2297 (1.6%)	2922 (1.9%)	5219 (1.8%)	
CABG	16110 (11.3%)	16241 (10.5%)	32351 (10.9%)	<0.0001
PCI	19233 (13.5%)	19174 (12.4%)	38407 (12.9%)	<0.0001
Concurrent medication				
Amiodarone	10616 (7.5%)	13242 (8.5%)	23858 (8.0%)	<0.0001
Other AADs	11833 (8.3%)	16582 (10.7%)	28415 (9.6%)	<0.0001

(*continued on next page*)

Table 2 (*continued*)

Patient Characteristics	No OAC (N = 141,966)	OAC (N = 155,067)	Total (N = 297,033)	p value
Calcium channel blockers as rate control drugs	21622 (15.2%)	28342 (18.3%)	49964 (16.8%)	<0.0001
Aspirin	2923 (2.1%)	2719 (1.8%)	5642 (1.9%)	<0.0001
Digitalis	11011 (7.8%)	17521 (11.3%)	28532 (9.6%)	<0.0001
Baseline (years), mean (SD)	4.2 (3.1)	4.1 (3.1)	4.2 (3.1)	<0.0001
Follow-up (years), mean (SD)	2.3 (1.5)	2.6 (1.6)	2.5 (1.5)	<0.0001
Health utilization within past 12 months, mean (SD)				
Number of AF emergency room visits	0.0 (0.1)	0.0 (0.2)	0.0 (0.2)	<0.0001
Number of non-AF emergency room visits	0.6 (1.4)	0.5 (1.0)	0.5 (1.2)	<0.0001
Number of AF hospitalizations	0.0 (0.1)	0.0 (0.2)	0.0 (0.1)	<0.0001
Number of non-AF hospitalizations	0.4 (0.9)	0.3 (0.7)	0.4 (0.8)	<0.0001
All-cause hospital days	9.9 (12.8)	8.3 (9.9)	9.2 (11.6)	<0.0001
Patients with Events within past 3 months				
Ischemic stroke or systemic embolism	1868 (1.3%)	1850 (1.2%)	3718 (1.3%)	0.0026
Major bleed	1750 (1.2%)	656 (0.4%)	2406 (0.8%)	<0.0001
Intracranial bleed	535 (0.4%)	125 (0.1%)	660 (0.2%)	<0.0001
Number of events within past 12 months, mean (SD)				
Ischemic stroke or systemic embolism	0.0 (0.2)	0.0 (0.2)	0.0 (0.2)	<0.0001
Major bleed	0.0 (0.2)	0.0 (0.1)	0.0 (0.2)	<0.0001
Intracranial bleed	0.0 (0.1)	0.0 (0.0)	0.0 (0.1)	<0.0001

Baseline comparison of patient characteristics stratified according to oral anticoagulant use within the high-risk group.
Abbreviations: Oral anticoagulant (OAC); Direct oral anticoagulant (DOAC); coronary artery disease (CAD); peripheral artery disease (PAD); chronic kidney disease (CKD); transient ischemic attack; non-steroidal anti-inflammatory drug (NSAID); chronic obstructive pulmonary disease (COPD); end-stage renal disease (ESRD); cardiac resynchronization therapy (CRT); implantable cardioverter-defibrillator (ICD); coronary artery bypass graft (CABG); percutaneous coronary intervention (PCI); antiarrhythmic drug (AAD).

a higher tendency for bleeding and is consistent with findings from a previous study.[16] DOAC use was more likely in patients with liver disease and alcoholism likely reflecting the metabolism of these drugs.

A high proportion of warfarin use suggests that the grade 1 A recommendation [3,17] of DOAC use over warfarin is either under-recognized or inadequately realized. The major clinical settings in which VKA is the agent of choice include: 1) moderate-severe mitral stenosis or bioprosthetic/mechanical heart valve (both excluded from analysis). 2) Severe CKD patients, when physicians usually opt for either VKA or apixaban (note: this group included only 1% of end-stage renal disease patients). 3) When additional patient costs are not justified (e.g., out of pocket payments or lower bracket incomes). By exclusion, underutilization may relate to the direct higher costs associated with DOAC relative to warfarin. Inadequacies of Medicare advantage plan such as high-out of pocket maximum; hassles of prior authorization and referral requirements could have discouraged patients from starting long term OAC treatment.[18] Indeed, Medicare Advantage plan in this study was

Table 3
Predictors of OAC and DOAC use (low-risk group).

Variables	OAC use (vs no OAC)		DOAC use (vs warfarin)	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**
Age group				
18–44 years	ref	ref	ref	ref
45–54 years	1.76 (1.58, 1.97)	<0.0001	0.84 (0.58, 1.22)	0.3678
55 + years	2.74 (2.47, 3.02)	<0.0001	0.72 (0.51, 1.01)	0.0575
Gender				
Female	ref	ref	ref	ref
Male	1.35 (1.24, 1.46)	<0.0001	0.99 (0.78, 1.26)	0.9539
Health plan				
Commercial	ref	ref	ref	ref
Medicare Advantage	0.73 (0.62, 0.87)	0.0003	0.22 (0.16, 0.31)	<0.0001
HAS-BLED components				
Anemia/Major bleed	0.78 (0.70, 0.85)	<0.0001	0.70 (0.53, 0.91)	0.0076
Liver disease	0.84 (0.72, 0.97)	0.0191	1.47 (0.90, 2.39)	0.1246
Alcoholism	0.79 (0.64, 0.97)	0.0221	1.73 (0.84, 3.57)	0.1343
Antiplatelets/NSAIDs	0.91 (0.79, 1.05)	0.1867	1.78 (1.07, 2.95)	0.0273
Other comorbidities				
Falls	0.86 (0.72, 1.02)	0.0908	2.56 (1.27, 5.16)	0.0087
Hypertrophic cardiomyopathy	2.52 (1.56, 4.07)	0.0002	1.03 (0.35, 3.02)	0.9553
Cardioversion	1.45 (1.20, 1.73)	0.0001	1.10 (0.66, 1.84)	0.7141
Implanted device	0.71 (0.55, 0.91)	0.0069	0.24 (0.14, 0.39)	<0.0001
Concurrent medication				
Amiodarone/other AADs	0.70 (0.62, 0.80)	<0.0001	0.78 (0.54, 1.11)	0.1708

Multivariable model assessing the association of clinically relevant variables to oral anticoagulant use within the low-risk group.
Abbreviations: non-steroidal anti-inflammatory drug (NSAID); antiarrhythmic drug (AAD).

a negative predictor of OAC and DOAC use compared to commercial plan. The negative association of Medicare plan for DOAC use relative to private insurance plan has previously been reported.[19].

The OAC utilization within the high-risk group was relatively unaffected by the CHA_2DS_2-VASc score (threshold effect) and is consistent with previous research [7]. This may suggest an influence of other unknown factors on management decision within this group (e.g., risks not well-captured in our dataset, patients/physician preference or cost). Among the CHA_2DS_2-VASc score components, particularly in a high-risk group, all components increased the odds of OAC use except CAD/PAD which might be due to the clinical challenge of balancing benefit versus harm in these patients posed by concurrent dual or triple oral antithrombotic therapy. Most of the HAS-BLED score components were negatively associated with OAC use. Additionally, there was a higher prevalence of most comorbidities in the non-OAC group. Patients in the non-OAC group were more likely to have utilized non-AF-related hospital facilities, such as skilled nursing facilities, higher non-AF emergency room visits, hospitalization, and all-cause hospital days. Thus, it is reasonable to speculate that patients not on OAC represented a sicker population with a higher prevalence of most non-AF related comorbidities, potentially adding to the bleeding risk. From a patient's perspective, these findings may suggest a weariness and an ambivalent nature towards accepting further long-term primary preventive treatments without providing immediate symptomatic benefits or a cure to their ongoing problems. This is similar to some prior studies that have linked polypharmacy and worsening of health outcomes with low adherence to OAC therapy.[13] Thus, we emphasize a need to engage patients in a

Table 4
Predictors of OAC use (high-risk group).

Variables	OAC use (vs no OAC)		DOAC use (vs warfarin)	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**
Age group				
18–64 years	ref	ref	ref	ref
65–74 years	1.41 (1.37, 1.46)	<0.0001	1.06 (1.00, 1.11)	0.0436
75 + years	1.51 (1.46, 1.56)	<0.0001	0.85 (0.81, 0.90)	<0.0001
Gender				
Female	ref	ref	ref	ref
Male	1.03 (1.01, 1.04)	0.0006	0.81 (0.79, 0.83)	<0.0001
Health plan				
Commercial	ref	ref	ref	ref
Medicare Advantage	0.91 (0.89, 0.94)	<0.0001	0.47 (0.44, 0.49)	<0.0001
CHA_2DS_2-VASc components				
Heart failure	1.02 (1.00, 1.04)	0.0184	0.62 (0.60, 0.63)	<0.0001
Diabetes mellitus	1.07 (1.05, 1.08)	<0.0001	0.92 (0.90, 0.94)	<0.0001
Thromboembolism	1.07 (1.04, 1.10)	<0.0001	0.88 (0.84, 0.92)	<0.0001
CAD or PAD	0.87 (0.85, 0.88)	<0.0001	0.84 (0.82, 0.86)	<0.0001
HAS-BLED components				
CKD	0.89 (0.87, 0.91)	<0.0001	0.96 (0.93, 0.98)	0.0015
Stroke	1.03 (1.00, 1.07)	0.0557	0.90 (0.85, 0.94)	<0.0001
Anemia/Major bleed	0.83 (0.82, 0.85)	<0.0001	0.86 (0.84, 0.88)	<0.0001
Liver disease	0.88 (0.86, 0.90)	<0.0001	1.21 (1.17, 1.25)	<0.0001
Alcoholism	0.82 (0.79, 0.84)	<0.0001	1.21 (1.14, 1.28)	<0.0001
Antiplatelets/NSAIDs	0.75 (0.74, 0.77)	<0.0001	1.86 (1.80, 1.93)	<0.0001
Other comorbidities				
Falls	0.74 (0.73, 0.75)	<0.0001	1.02 (0.99, 1.05)	0.2745
Obesity	1.32 (1.30, 1.34)	<0.0001	1.26 (1.23, 1.29)	<0.0001
Intervention				
Catheter ablation/surgical ablation/MAZE	0.89 (0.84, 0.95)	0.0005	1.03 (0.95, 1.12)	0.5133
Cardioversion	2.14 (2.07, 2.22)	<0.0001	0.92 (0.88, 0.96)	0.0001
Implanted device	1.18 (1.15, 1.20)	<0.0001	0.72 (0.69, 0.74)	<0.0001
Concurrent medication				
Amiodarone/other AADs	1.04 (1.02, 1.06)	0.0006	0.67 (0.64, 0.69)	<0.0001

Multivariable model assessing the association of clinically relevant variables to oral anticoagulant use within the high-risk group.
Abbreviations: coronary artery disease (CAD); peripheral artery disease (PAD); chronic kidney disease (CKD); antiarrhythmic drug (AAD).

shared decision-making process and help direct them towards more beneficial treatment options or revisit the decision later.[20] Lastly, patients on OAC were more likely to have utilized other cardiac-related interventions such as catheter/surgical ablations, cardioversion, permanent pacemaker/defibrillator devices, prior percutaneous coronary intervention, or coronary artery bypass graft. These findings suggest that patients under specialty care may have higher rates of OAC utilization.

To our knowledge, this is the only study to have studied exclusively NVAF patients in the US during this time period. Further, limited prior data is available for overutilization of OAC in the low-risk group. Some recent studies have otherwise lacked patient level data to exclude independent indications for OAC therapy or study predictors and barriers to OAC therapy.[21–23].

Potential limitations of this study are as follows. Administrative claims might be subject to misclassification and claims data may be driven by reimbursement concerns. However, the results would still represent the true utilization patterns among patients even if prescription rates by physicians may have been higher than prescription fills. The guidelines recommend OAC prescription based on CHA_2DS_2-VASc score, the actual treatment decisions are individualized for each patient and include patient's preferences, values, and insurance coverage. We have attempted to incorporate some of these possibilities while assessing the inferences of our results. Provider specialty and hospital setting in which AF was diagnosed is not assessed in this study and may be further predictors of OAC use. Some of the independent transient indications for OAC use such as ablation and cardioversion were included in the main analysis but removed in a separate sensitivity analysis. Finally, the study population included patients with commercial health insurance, and Medicare Advantage, and may not generalize to those with no coverage.

5. Conclusions

Despite the added benefits DOAC use over VKA, the guideline based OAC use in AF patients seems comparable to pre-DOAC era studies. Both under and over treatment patterns were notable findings with a significant proportion of high-risk patients still treated with warfarin. Although the nuances of clinical practice that drive individual patient and clinician decisions are not possible to resolve from observational data sources alone, our findings highlight the need for future systematic processes to optimize OAC utilization especially considering the rising incidence of embolic strokes.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Anthony H. Kashou reports financial support was provided by Mayo Clinic Minnesota.].

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2023.101212.

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