Treatment of atrial fibrillation with concomitant coronary or peripheral artery disease: Results from the outcomes registry for better informed treatment of atrial fibrillation II

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Background Treatment patterns and outcomes of individuals with vascular disease who have new-onset atrial fibrillation (AF) are not well characterized.

Methods Among patients with new-onset AF, we analyzed treatment and outcomes in those with or without vascular disease in the ORBIT-AF II registry. Vascular disease was defined as coronary disease with or without myocardial infarction (MI) or revascularization, or peripheral artery disease. The primary outcomes included major adverse cardiovascular or neurological events (MACNE) and major bleeding. Cox proportional hazard models were used to adjust the difference in patient characteristics.

Results Overall 1920 of 6203 (31.0%) of new-onset AF had vascular disease. In patients with vascular disease, 62.2% of those were treated with direct oral anticoagulants (DOACs) and 23.4% with warfarin. Dual therapy and triple therapy were used in 36.9% and 4.9%, respectively. Vascular disease patients had increased risk of MACNE (adjusted hazard ratio [aHR] 1.83 [95%CIs 1.32–2.55]), but not major bleeding (aHR 1.24 [0.95–1.63]). Among patients with vascular disease, relative to those on warfarin, those treated with DOACs had similar risk for MACNE (aHR 1.20 [0.77–1.87]) but lower risks for bleeding, although it did not reach statistical significance (aHR 0.70 [0.43–1.15]). Concomitant antiplatelet therapy was associated with higher bleeding (aHR 2.27 [1.38–3.73]) with no apparent reduction in MACNE (aHR 1.50 [1.00–2.25]).

Conclusions Most patients with AF and vascular disease were managed with oral anticoagulation. About half of them were also treated with concomitant antiplatelet therapy, which was associated with increased risk of bleeding, without evidence of improved cardiovascular outcomes. (Am Heart J 2019;213:81-90.)

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Patients with atrial fibrillation (AF) frequently have vascular disease,[1-3] including coronary artery disease (CAD) and peripheral artery disease (PAD), and the presence of concomitant vascular disease is included in the guideline-recommended risk stratification scheme for utilization of oral anticoagulation for AF, the CHA_2DS_2-VASc score.[4] As a result, many patients with AF and vascular disease are eligible for anticoagulant therapy.

The availability of direct oral anticoagulants (DOACs) with lower rates of intracranial hemorrhage compared with warfarin has lowered the threshold for the use of oral anticoagulation for the prevention of ischemic stroke. Current European guidelines recommend oral anti coagulation in patients with AF and only one stroke risk factor (CHA_2DS_2-VASc score of one in men and two in women) with class IIa.[5] In the US guideline, oral anticoagulation for such patients is a recommended option (class IIb), but no

antithrombotic as well as aspirin mono-therapy may also be considered.[6]

The presence of vascular disease complicates antithrombotic therapy in patients with AF. Although the current guidelines universally recommend shorter duration of triple therapy (OAC + dual antiplatelet therapy [DAPT]) in AF patients with myocardial infarction (MI) and/or after percutaneous coronary intervention (PCI), there has been an ongoing debate about whether concomitant antiplatelet agent has additional clinical benefit for managing stable patients with AF and vascular disease, especially in the DOAC era.[5-8] The scant data and lack of consensus increases the complexity of treatment decision in this specific population, resulting in a multiplicity of treatment combinations in clinical practice. However, these treatment patterns in patients with AF and vascular disease in usual clinical care are not well characterized nor are their impact on clinical outcomes well-understood.

The aims of this study were to compare patient characteristics, treatment patterns, and clinical outcomes between AF patients with and without concomitant vascular disease. In addition, in patients with concomitant AF and vascular disease, we sought to evaluate the association of DOACs compared with warfarin on ischemic and bleeding events.

Methods

Data source and study population

The cohort analyzed in this study was derived from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II (ORBIT-AF II) registry. The rationale, design, and methods of the ORBIT-AF II registry have been published previously.[9] Briefly, ORBIT-AF II is a prospective, multicenter nationwide registry of patients with AF. Patients were enrolled at 244 sites by a diversegroup of healthcare professionals including internists, cardiologists, and electrophysiologists. ORBIT-AF II enrolled only patients who either have a new diagnosis of AF within the previous 6 months or were started on DOACs for AF within the previous 3 months. Eligible patients were required to be 21 years of age and older with electrographically-documented AF. Moreover, eligible patients had to be able to adhere to local follow-up every 6 months. Patients with AF due to a reversible cause (e.g. pulmonary embolism, acute thyrotoxicosis, or post-operative status), solitary atrial flutter without AF, or a life expectancy of less than 6 months were excluded. A web-based case report form was used to collect information on patient demographics, medical and surgical history, medications, vital signs, laboratory data, and imaging and electrocardiographic parameters. Changes in pharmacotherapy, cardiac rhythm, and subsequent cardiovascular events and procedures were identified during follow-up.

For the purpose of this study, we only included patients with new-onset AF to compare the effectiveness and safety of DOACs relative to warfarin in order to minimize bias in comparison and differences associated with length of AF history. The study was approved by the institutional review board at Duke University (the coordinating center) and each participating center obtained local institutional review board approval. Informed consent was obtained from each participant.

Definitions

"Vascular disease" was defined as any the presence of any of the following: 1) CAD, 2) MI, 3) PCI, 4) coronary artery bypass grafting, 5) PAD, or 6) ischemic cardiomyopathy. Single antiplatelet therapy (SAPT) was defined as the current use of any one of the following: aspirin, clopidogrel, prasugrel, or ticagrelor. DAPT was defined as the current use of Aggrenox, or aspirin plus either clopidogrel, ticlopidine, prasugrel, or ticagrelor. Based upon consensus recommendations from the European Society of Cardiology, in those who were on OAC, the duration of DAPT was considered as "appropriate" if patients met any of the following criteria: 1) most recent MI was within 6 months of enrollment, 2) most recent PCI was within 1 month of enrollment, among those with high bleeding score (HASBLED score $\geq$ 3), or 3) most recent PCI was within 6 months of enrollment, among those with low bleeding score (HASBLED score$<$ 3).[8] All patients who did not have a history of MI and/or PCI but were on DAPT were deemed as "inappropriate".

Primary outcomes of interest included major adverse cardiovascular and neurological events (MACNE) and major bleeding. MACNE was defined as the occurrence of cardiovascular death, myocardial infarction, stroke/non-central nervous system systemic embolism or transient ischemic attack. Major bleeding was defined by the International Society of Thrombosis and Hemostasis criteria: fatal bleeding, and/or symptomatic bleeding in a critical area or organ, and/or bleeding causing a fall in hemoglobin level of 2 g/dL or more, or leading to transfusion of two or more units of whole blood or red cells.[10] The occurrence of stroke or systemic embolism was independently reviewed and adjudicated by the coordinating center using source documentation. As secondary outcomes, individual components of MACNE and hospitalization related to bleeding events were also evaluated in the analysis.

Statistical analysis

We stratified the study population by presence vs. absence of concomitant vascular disease and compared baseline characteristics, treatment patterns, and clinical outcomes. Categorical variables were presented as counts and frequencies, and continuous variables were presented as median values with interquartile ranges (IQRs). Differences between groups were appropriately assessed using

the chi-squared test for categorical and the Wilcoxon rank sum test for continuous variables. Trend in treatment patterns were also assessed by the year of patient enrollment using the Cochran-Armitage test. For outcome comparison, Cox proportional hazard models were performed, testing both the unadjusted and adjusted association between vascular disease and each outcome. Covariates for adjustment were previously identified using a backward selection process with an alpha for inclusion of 0.05 (**eAppendix 1 in the Supplement**). A robust covariance estimate was included in each model in order to account for the correlation within site. As a subgroup analysis, baseline characteristics, treatment patterns, and clinical outcomes were compared in patients with vs. without concomitant PAD. All candidate variables had less than 1% of missingness except for QRS duration (2%), level of education (4%), estimated glomerular filtration rate (8%), hematocrit (11%), left ventricular ejection fraction (13%), and left atrial diameter (17%). Data missing in the multivariable models were addressed using multiple imputations. All continuous variables were tested for linearity, and appropriate non-linear relationships were accounted for using linear splines.

Subsequently, to evaluate the impact of DOACs compared with warfarin on ischemic and bleeding event rates, we confined the analysis cohort to AF patients with concomitant vascular disease who were on OAC at the time of enrollment. Unadjusted Cox proportional hazards models with a robust covariance estimate were performed, testing the association between the use of DOACs vs. warfarin and outcomes. Additionally, a second model was performed with overlap propensity weighting. Compared with inverse propensity weighting, overlap weighting more heavily weights those with a greater chance of receiving either treatment (propensity score close to 0.5).[11] More extreme propensities, those more likely to receive a specific treatment, are not weighted as heavily. Covariates included in the propensity score were listed in the **eAppendix 2 (Supplement)**. Similarly, the impact of antiplatelet therapy on ischemic and bleeding events was also tested using the same method. Only the first result from multiple imputation was used in the propensity-weighted models. The deidentified, aggregate data were analyzed by the Duke Clinical Research Institute using SAS software (version 9.3; SAS Institute).

Results

The ORBIT-AF II registry enrolled 13,394 patients with AF from February 2013 to July 2016 at 244 sites within the United States. Among them, 6475 patients had new-onset AF at the time of enrollment. After excluding patients with moderate to severe mitral stenosis (N = 32), the presence of a mechanical valve (N = 36), and missing follow-up information (N = 204), the remaining 6203 patients from 229 sites were analyzed in this study. Median follow period was 361 (IQR 360–549) days.

Baseline characteristics

Among the study cohort, 1920 (31.0%) had concomitant vascular disease with AF. Of these, 83.0% of patients had CAD, 33.1% had MI, and 25.9% had PAD. The baseline characteristics according to concomitant presence of vascular disease are shown in Table I. Patients with vascular disease were older and more likely to be male and smoke, and have atherosclerotic comorbidities, such as hypertension, hyperlipidemia, diabetes, heart failure, and prior stroke. In addition, patients with vascular disease were more likely to have a lower left ventricular ejection fraction and larger left atrial diameter as compared with those without vascular disease. Patients with vascular disease had higher CHA_2DS_2-VASc scores, ATRIA bleeding scores, and ORBIT bleeding scores.

Treatment patterns

Treatment patterns in the entire study population are shown in Table II stratified by presence vs. absence of concomitant vascular disease. Overall, nearly 84% of patients were receiving OAC. The prescription rate of OAC was modestly higher in patients with concomitant vascular disease than those without, and DOACs were far more frequently prescribed than warfarin regardless of vascular disease status. Antiplatelet therapy was also more frequently used in patients with vascular disease, including SAPT in 44.7% and DAPT in 8.5% compared with 27.6% and 0.4% in those without vascular disease. In patients treated with OAC (N = 5195), the temporal trend of treatment patterns was assessed by the year of patient enrollment (Figure 1). In both groups, the prescription rate of DOACs increased in parallel with decreasing rates of warfarin over time. This trend was consistent regardless of vascular disease status and concomitant use of antiplatelet therapy. Time from most recent MI or PCI until enrolment is summarized in Table III. A total of 101 (1.6%) patients were receiving DAPT in addition to OAC ("triple therapy"), and of these, 39 (38.6%) were taking DAPT for >6 months and 16 (15.8%) did not have a history of MI and/or PCI. As a result, the use of DAPT was considered as inappropriate in 58 out of 101 (58.0%) patients receiving DAPT and OAC.

Concomitant vascular disease and clinical outcomes

Clinical outcomes were compared between patients with and without concomitant vascular disease (Table IV). The rates of MACNE and its individual components were higher in patients with vascular disease than those without except for thromboembolic events. Cox proportional hazard models revealed that concomitant vascular disease was significantly associated with MACNE even after accounting for baseline differences (HR 1.83, 95% CIs 1.32–2.55, $P < .001$). The association was consistent for cardiovascular death and MI, and the main driver of the difference between groups was MI. By contrast, concomitant vascular disease was associated with increased risks of

Table I. Comparison of baseline characteristics between patients with and without vascular disease.

	Overall	***No vascular disease***	***Vascular disease***	
Characteristics	***N = 6203***	***N = 4283***	***N = 1920***	***P***
Vascular disease				
History of CAD	1593 (25.68%)	NA	1593 (82.97%)	NA
Prior MI	635 (10.24%)	NA	635 (33.07%)	NA
Prior CABG	525 (8.46%)	NA	525 (27.37%)	NA
Prior PCI	806 (12.99%)	NA	806 (41.98%)	NA
PAD	497 (8.01%)	NA	497 (25.89%)	NA
Ischemic cardiomyopathy	419 (6.75%)	NA	419 (21.82%)	NA
Demographics				
Age, y	71.00 (63.00, 78.00)	69.00 (62.00, 77.00)	74.00 (67.00, 81.00)	<.0001
Sex (Female)	2594 (41.82%)	1957 (45.69%)	637 (33.18%)	<.0001
Race				0.0345
White	5315 (85.68%)	3661 (85.48%)	1654 (86.15%)	
African American	330 (5.32%)	238 (5.56%)	92 (4.79%)	
BMI, kg/m^2	30.02 (26.03, 35.35)	30.19 (26.17, 35.57)	29.67 (25.86, 34.72)	0.0021
Medical history				
Smoking				<.0001
Recent or former	2560 (41.27%)	1592 (37.17%)	968 (50.42%)	
Current	487 (7.85%)	319 (7.45%)	168 (8.75%)	
Hypertension	4927 (79.43%)	3213 (75.02%)	1714 (89.27%)	<.0001
Hyperlipidemia	3905 (62.95%)	2311 (53.96%)	1594 (83.02%)	<.0001
Diabetes	1684 (27.15%)	969 (22.62%)	715 (37.24%)	<.0001
OSAS	1001 (16.14%)	649 (15.15%)	352 (18.33%)	<.0001
CHF	1313 (21.17%)	664 (15.50%)	649 (33.80%)	<.0001
Functional status				<.0001
No CHF	4890 (78.83%)	3619 (84.50%)	1271 (66.20%)	
NYHA Class I	434 (7.00%)	240 (5.60%)	194 (10.10%)	
NYHA Class II	607 (9.79%)	290 (6.77%)	317 (16.51%)	
NYHA Class III/IV	258 (4.16%)	124 (2.90%)	134 (6.98%)	
Stroke/TIA	576 (9.29%)	341 (7.96%)	235 (12.24%)	<.0001
COPD	686 (11.06%)	362 (8.45%)	324 (16.88%)	<.0001
Liver disease	125 (2.02%)	86 (2.01%)	39 (2.03%)	0.9518
Alcohol abuse	254 (4.09%)	178 (4.16%)	76 (3.96%)	0.7165
Drug abuse	80 (1.29%)	46 (1.05%)	34 (1.86%)	0.0062
Gastrointestinal bleed	231 (3.72%)	116 (2.71%)	115 (5.99%)	<.0001
SND	265 (4.27%)	143 (3.34%)	122 (6.35%)	<.0001
Implanted device	519 (8.37%)	232 (5.42%)	287 (14.95%)	<.0001
Prior cardioversions	1012 (16.31%)	715 (16.69%)	297 (15.47%)	0.2273
Catheter ablation of AF	78 (1.26%)	62 (1.45%)	16 (0.83%)	0.0447
AVN/HIS bundle ablation	4 (0.06%)	2 (0.05%)	2 (0.10%)	0.4098
Echocardiographic findings				
LVEF, %	56.00 (50.00, 61.00)	59.00 (51.00, 62.00)	55.00 (45.00, 60.00)	<.0001
LVEF category				<.0001
Missing	800 (12.90%)	625 (14.59%)	175 (9.11%)	
LVEF ≥50%	4244 (68.42%)	3017 (70.44%)	1227 (63.91%)	
LVEF 41–49%	354 (5.71%)	200 (4.67%)	154 (8.02%)	
LVEF 30–40%	529 (8.53%)	287 (6.70%)	242 (12.60%)	
LVEF <30%	276 (4.45%)	154 (3.60%)	122 (6.35%)	
LAD, cm	4.20 (3.70, 4.70)	4.20 (3.70, 4.60)	4.30 (3.90, 4.71)	<.0001
LAD category				<.0001
Missing	1038 (16.73%)	774 (18.07%)	264 (13.75%)	
Normal	1902 (30.66%)	1395 (32.57%)	507 (26.41%)	
Mild enlargement	1583 (25.52%)	1017 (23.75%)	566 (29.48%)	
Moderate enlargement	997 (16.07%)	636 (14.85%)	361 (18.80%)	
Severe enlargement	683 (11.01%)	461 (10.76%)	222 (11.56%)	
Laboratory data				
eGFR	73.43 (58.19, 88.41)	75.58 (61.97, 89.72)	68.12 (52.40, 84.77)	<.0001
Risk scores				
CHA_2DS_2-VASc score				<.0001
Score 0–1	931 (15.01%)	910 (21.25%)	21 (1.09%)	
Score 2–3	2473 (39.87%)	2014 (47.02%)	459 (23.91%)	
Score ≥4	2799 (45.12%)	1359 (31.73%)	1440 (75.00%)	

Table I (*continued*)

Characteristics	Overall N = 6203	No vascular disease N = 4283	Vascular disease N = 1920	P
ATRIA bleeding score				<.0001
Score 0–3	4540 (73.19%)	3376 (78.82%)	1164 (60.63%)	
Score 4	689 (11.11%)	396 (9.25%)	293 (15.26%)	
Score 5 or more	974 (15.70%)	511 (11.93%)	463 (24.11%)	
ORBIT score				<.0001
Low: 0–2	3979 (64.15%)	3013 (70.35%)	966 (50.31%)	
Medium: 3	887 (14.30%)	538 (12.56%)	349 (18.18%)	
High: ≥4	867 (13.98%)	378 (8.83%)	489 (25.47%)	

Continuous variables are presented as medians with interquartile ranges or means with standard deviations, and categorical variables are reported as counts and percentages. Abbreviations: CAD, coronary artery disease; MI, myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; BMI, body mass index; OSAS, obstructive sleep apnea syndrome; CHF, chronic heart failure; NYHA, New York Heart Association; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; PAD, peripheral artery disease; SND, sinus node dysfunction; AF, atrial fibrillation; AVN, atrial-ventricular node; LVEF, left ventricular ejection fraction; LAD, left atrium diameter; eGFR, estimated glomerular filtration rate.

major bleeding and bleeding hospitalization in unadjusted analysis; however, their relationships were no longer significant after the adjustment for the measured confounders (major bleeding: HR 1.24, 95% CIs 0.95–1.63, $P = .11$; bleeding hospitalization: HR 1.15, 95% CIs 0.87–1.52, $P = .33$). Sub-group analysis in patients with peripheral artery produced similar findings as the main analysis (Table V).

Treatment Effect of DOACs vs. warfarin and antiplatelet therapy in patients with vascular disease

In AF patients with concomitant vascular disease who were treated with OAC (n = 1645), clinical outcomes were compared according to the type of OAC (DOACs vs. warfarin) and status (presence or absence) of antiplatelet therapy (Table VI **and eTable 1 in the Supplement**). The risk of MACNE was not significantly different between DOACs and warfarin. The rate of major bleeding was numerically lower in patients treated with DOACs than those treated with warfarin, and this trend was consistent even after the adjustment, although they did not reach statistical significance (major bleeding: HR 0.70, 95% CIs 0.43–1.15, $P = .16$). The rate of MACNE was not different between presence and absence of antiplatelet therapy, whereas the use of antiplatelet therapy was associated with increased risks of bleeding events (HR 2.27, 95% CIs 1.38–3.73, $P = .001$). Similarly, in patients without vascular disease who were on OAC, the rate of MACNE was similar regardless of antiplatelet therapy. However, contrary to findings in patients with vascular disease, the rate of major bleeding was not different between patients who were on concomitant antiplatelet agent and those who were not (P for interaction = 0.027; **eTable 1 in the Supplement**). Furthermore, among 58 patients who were receiving "inappropriate" triple therapy [DAPT plus OAC], 5 (8.6%) experienced major bleeding during follow-up.

Discussion

We examined outcomes of new-onset AF in patients with concomitant vascular disease in a large, contemporary nationwide registry. Overall, about 30% of patients in this new-onset AF cohort had vascular disease. There are several major findings from this analysis. First, overall use of OAC was high, 84%, and modestly but significantly higher among patients with vascular disease, consistent with their higher CHA2DS2-VASc score. Yet, concomitant antiplatelet therapy was frequently inconsistent with consensus recommendations in terms of indication and duration of DAPT. Second, the use of DOACs increased over time in parallel with decreased warfarin use regardless of vascular disease status and concomitant antiplatelet therapy. Third, patients with vascular disease had increased risks of mortality and MI compared with those without vascular disease but similar risks of bleeding events. Fourth, relative to those on warfarin, those treated with DOACs had similar risk for MACNE but lower risks for bleeding, although it did not reach statistical significance. Finally, in new-onset AF patients with vascular disease, the concomitant use of antiplatelet therapy was associated with increased risk of bleeding, without definitive evidence of improved cardiovascular outcomes.

Treatment patterns of antithrombotic regimen

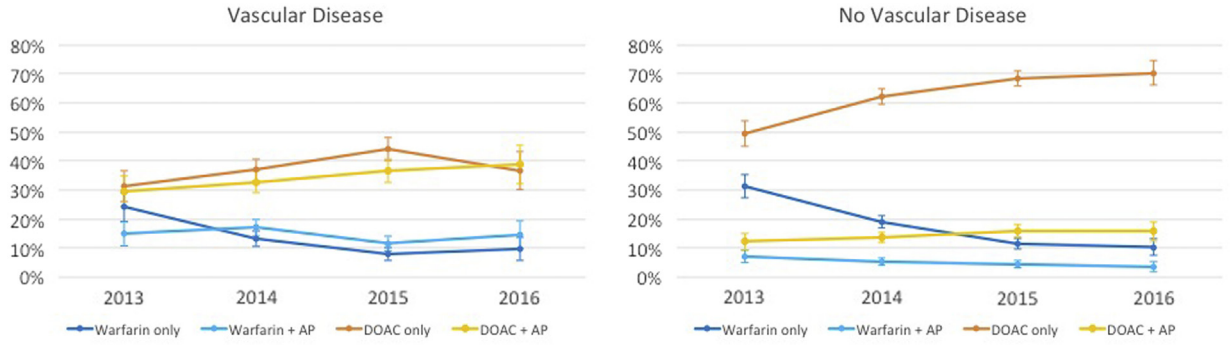
Similar to previous reports, the use of DOACs increased over time in parallel with the decrease in warfarin therapy in our study cohort.[12-14] This trend was consistent regardless of the concomitant use of antiplatelet therapy, which is congruent with the 2017 European Society of Cardiology guideline on DAPT recommending DOACs over warfarin when the concomitant use of antiplatelet therapy is required in patients with AF.[8] We also found that, approximately 2% of patients treated with OAC used concomitant DAPT (triple therapy); furthermore, of these, about half of triple therapy was continued for >6 months and considered to be inappropriate by European consensus recommendations.

Table II. Treatment patterns by vascular disease status.

	Overall	No vascular disease	Vascular disease	
	N = 6203	N = 4283	N = 1920	*P*
Anticoagulant therapy				
OAC type	5195 (83.75%)	3550 (82.89%)	1645 (85.68%)	0.0059
Warfarin	1232 (19.86%)	782 (18.26%)	450 (23.44%)	<.0001
DOACs	3963 (63.89%)	2768 (64.63%)	1195 (62.24%)	
Dabigatran	291 (4.69%)	209 (4.88%)	82 (4.27%)	0.2944
Rivaroxaban	1967 (31.71%)	1400 (32.69%)	567 (29.53%)	0.0135
Apixaban	1663 (26.81%)	1128 (26.34%)	535 (27.86%)	0.2092
Edoxaban	42 (0.68%)	31 (0.72%)	11 (0.57%)	0.5029
Antiplatelet therapy				
Number of antiplatelet agents				<.0001
None	3978 (64.13%)	3081 (71.94%)	897 (46.72%)	
SAPT	2043 (32.94%)	1184 (27.64%)	859 (44.74%)	
DAPT	182 (2.93%)	18 (0.42%)	164 (8.54%)	
Type of antiplatelet agent				
Aspirin	2084 (33.60%)	1169 (27.29%)	915 (47.66%)	<.0001
Clopidogrel	282 (4.55%)	41 (0.96%)	241 (12.55%)	<.0001
Prasugrel	13 (0.21%)	2 (0.05%)	11 (0.57%)	<.0001
Ticagrelor	19 (0.31%)	0 (0.00%)	19 (0.99%)	<.0001
Aggrenox	5 (0.08%)	4 (0.09%)	1 (0.05%)	0.5961
Strategy				<.0001
Antiplatelet therapy alone	728 (11.74%)	507 (11.84%)	221 (11.51%)	
OAC alone	3698 (59.62%)	2855 (66.66%)	843 (43.91%)	
OAC + SAPT	1396 (22.51%)	688 (16.06%)	708 (36.88%)	
OAC + aspirin	1284 (20.70%)	665 (15.53%)	619 (32.24%)	<.0001
OAC + clopidogrel	104 (1.68%)	22 (0.51%)	82 (4.27%)	<.0001
OAC + other antiplatelet agent	8 (0.13%)	1 (0.02%)	7 (0.36%)	0.0005
OAC + DAPT	101 (1.63%)	7 (0.16%)	94 (4.90%)	

Abbreviations: OAC, oral anticoagulation; DOACs, direct oral anticoagulants; SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy.

Figure 1



Temporal Trend of Treatment Patterns in AF Patients With and Without Concomitant Vascular Disease. Temporal trends of treatment patterns in patients who were anticoagulated are shown by presence (a) or absence (b) of vascular disease. Trend tests showed statistical significance in all groups expect for warfarin + AP in patients with vascular disease (P for trend = 0.246). Abbreviations: AP, antiplatelet therapy; DOAC, direct oral anticoagulants.

Vascular disease and clinical outcomes

Vascular disease is included as a risk factor for stroke in patients with AF in guideline-recommended risk stratification schema.[5,6] Although, in our analysis, concomitant vascular disease was associated with increased risk of MACNE, cardiovascular death, and MI, the risk of thromboembolic event was not significantly different according to presence or absence of concomitant vascular disease. Despite its inclusion in the CHA_2DS_2-VASc score, most studies have found no significant effect of vascular disease on the risk of thromboembolic event in AF, particularly once other risk factors were included in the analysis.[15] Our study is

Table III. Time from Most Recent MI or PCI until Enrolment and Appropriateness of Dual Antiplatelet Therapy in Patients Treated With Triple Therapy.

	Overall	Warfarin	DOACs
	N = 101	N = 42	N = 59
Time from most recent MI/PCI until enrollment			
≤ 1 month	32 (31.68%)	13 (30.95%)	19 (32.20%)
1–6 months	14 (13.86%)	6 (14.29%)	8 (13.56%)
6–12 months	5 (4.95%)	2 (4.76%)	3 (5.08%)
> 12 months	34 (33.66%)	13 (30.95%)	21 (35.59%)
No prior MI or PCI	16 (15.84%)	8 (19.05%)	8 (13.56%)
Type of CAD			
Prior MI	54 (53.47%)	24 (57.14%)	30 (50.85%)
Prior PCI	74 (73.27%)	29 (69.05%)	45 (76.27%)
Appropriateness of DAPT			
No	58 (58.00%)	23 (56.10%)	35 (59.32%)
Yes	42 (42.00%)	18 (43.90%)	24 (40.68%)

Patients were deemed "appropriate", if patients met any of the following criteria: 1) most recent MI was within 6 months of enrollment, 2) most recent PCI was within 1 month of enrollment, among those with high bleeding score (HASBLED score ≥ 3), or 3) most recent PCI was within 6 months of enrollment, among those with low bleeding score (HASBLED score< 3).
Abbreviations: DOACs, direct oral anticoagulants; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; DAPT, dual antiplatelet therapy.

Table IV. Clinical outcomes by vascular disease status.

	Vascular disease		Unadjusted		Adjusted	
	No (N = 4283)	Yes (N = 1920)	HR (95% CI)	P	HR (95% CI)	*P*
MACNE	108 (2.04)	132 (5.55)	2.73 (1.99–3.73)	<.0001	1.83 (1.32–2.55)	0.0003
CV Death	38 (0.71)	68 (2.83)	3.99 (2.86–5.58)	<.0001	2.16 (1.44–3.25)	0.0002
MI	20 (0.37)	40 (1.66)	4.45 (2.58–7.68)	<.0001	3.50 (2.01–6.10)	<.0001
Stroke, non-CNS embolism, or TIA	57 (1.07)	42 (1.75)	1.63 (0.95–2.81)	0.0787	1.22 (0.65–2.27)	0.5378
Major bleeding	131 (2.49)	101 (4.29)	1.73 (1.34–2.23)	<.0001	1.24 (0.95–1.63)	0.1139
Bleeding hospitalization	122 (2.32)	96 (4.08)	1.76 (1.36–2.29)	<.0001	1.15 (0.87–1.52)	0.3260

Cells present the number of events (rate per 100-patient years).
Abbreviations: HR, hazard ration; MACNE, major adverse cardiovascular and neurological event; CV, cardiovascular; MI, myocardial infarction; CNS, central nerve system; TIA, transient ischemic attack.

consistent with these prior works and expands that vascular disease may not contribute to stratify patients at risk for ischemic stroke in the DOAC era. In our study, vascular disease was not associated with increased risk of major bleeding. The secondary analysis from the ROCKET-AF trial reported that the association between vascular disease and major bleeding was dependent on the severity of vascular disease.[16] The limited proportion of patients who had both coronary and peripheral artery diseases in our study population may have resulted in non-significant difference in major bleeding between those with and without vascular disease.

Concomitant use of antiplatelet agent in patients with AF and vascular disease

Prior data from the nationwide Danish registry demonstrated that combined therapy of antiplatelet agent and warfarin in patients with AF and stable coronary artery was associated with increased risk of bleeding compared with warfarin mono-therapy, with no incremental benefit in terms of reduction in thromboembolic or cardiovascular events.[17] Our results confirm and extend these findings in the more contemporary DOAC era.[18] Due to the findings from 3 recent randomized controlled trials supporting dual therapy over triple therapy in terms of reduction in bleeding events with similar efficacy, the consensus recommendations from the European Society of Cardiology recommend a shorter duration of triple therapy (no longer than 6 months).[8,19-21] Although ACC/AHA guidelines admit individualized approach to triple therapy, a recent white paper from the US by Angiolillo et al. for antithrombotic therapy in patients with AF undergoing PCI recommends dual therapy of clopidogrel and DOAC as a default therapy after PCI, and triple therapy is not recommended more than 1 month even in patients with low bleeding risk.[6,7,22] Based upon our data from US clinical practice, 58.0% of triple therapy was not optimal nor consistent with European consensus recommendations, resulting in high incidence of major bleeding in these population (8.6% in patients receiving triple

therapy against consensus recommendations vs. 2.4% in those receiving OAC mono-therapy). There are a few clinical scenarios where the prolonged triple therapy could be justified, such as recurrent ACS or stent thrombosis, but otherwise, triple therapy should be administered as shortly as possible.

DOACs vs. warfarin in patients with AF and vascular disease

To date, there is no randomized clinical trial comparing the effectiveness efficacy and safety of DOACs relative to warfarin in patient with AF and vascular disease. However, the findings from studies in patients with AF who had undergone PCI may be helpful. The PIONEER AF-PCI study, which randomized patients with AF who had undergone PCI into 3 regimens (rivaroxaban [15 mg once daily] plus a P2Y12 inhibitor vs. low-dose rivaroxaban [2.5 mg twice daily] plus DAPT vs. standard therapy with a dose-adjusted warfarin plus DAPT) showed the rates of clinically significant bleeding were lower in the two regimens including DOACs than in the regimen including warfarin, with similar efficacy.[20] In addition, the recent observational study from the Danish registry demonstrated that, in AF patients with MI and/or after PCI, DOAC in combination of DAPT was associated with a significantly decreased risk of bleeding with similar efficacy compared with warfarin in combination with DAPT.[23] Despite the insignificant difference after the adjustment, our result of lower bleeding rates in DOACs than in warfarin is consistent with the previous findings in patients with AF who had undergone PCI and suggests that they could be applied in managing patients with AF and vascular disease.

Limitations

Our findings should be interpreted in the context of several potential limitations. First, the study population was confined to new-onset AF and generalizability of the result is an issue. However, we chose to limit our analyses to patient with new onset AF in our assessment of the effectiveness and safety of DOACs relative to warfarin, so that we could control for potential biases that may arise in other persistent or chronic AF patients (e.g. patients who died after the initiation of OAC or experienced adverse events related to OAC who then changed antithrombotic regimen prior to enrollment). Second, despite our use of a large number of characteristics to adjust for potential confounding, residual and/or unmeasured confounding may exist in our observational study using registry data. Accordingly, it is important to note that the findings represent associations, do not imply causality, and should be considered hypothesis generating. Third, despite the relatively large sample size, our analysis evaluating the impact of DOACs compared with warfarin on ischemic and bleeding events may have been underpowered based on sample size and event rates. Fourth, "vascular disease" in our study included two types of atherosclerotic disease, coronary and peripheral artery disease. The effectiveness and safety of antithrombotic regimen may differ between atherosclerotic disease types; therefore, our findings need to be cautiously interpreted. That being said, given the similar definition of vascular disease in the recent Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, our approach could be acceptable.[24] Finally, medication adherence in follow-up was not taken into account. When comparing DOACs with warfarin, treatment allocation was determined at the time of patient enrollment and we did not assess its initiation or discontinuation during the follow-up periods. This is analogous to intention-to-treat analysis in clinical trials, which is an accepted methodology for evaluating outcomes by assignment to therapy, such as one drug vs. another.

Conclusions

In this contemporary nationwide new-onset AF cohort, vascular disease was associated with increased risks of MACNE, cardiovascular death, and MI, but not thromboembolic and bleeding events. For managing patients with new-onset AF and vascular disease, DOACs with concomitant use of antiplatelet therapy were increasingly used. The rate of bleeding events appears to be lower in patients treated with DOACs than warfarin but with similar efficacy. The concomitant use of antiplatelet agent, especially DAPT, needs to be reconsidered, given its inappropriate use and the increased risk of bleeding with no apparent clinical benefit. Further studies are required to clarify the optimal management in this specific high-risk population.

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Table V. Clinical outcomes by peripheral artery disease status (sub-group analysis).

	Peripheral artery disease		Unadjusted		Adjusted	
	No (N = 4283)	Yes (N = 497)	HR (95% CI)	P	HR (95% CI)	*P*
MACNE	108 (2.04)	46 (7.35)	3.61 (2.22–5.87)	<.0001	2.14 (1.26–3.63)	0.0049
CV Death	38 (0.71)	23 (3.64)	5.16 (3.05–8.73)	<.0001	2.48 (1.22–5.03)	0.0119
MI	20 (0.37)	12 (1.89)	5.03 (2.29–11.05)	<.0001	4.47 (2.00–9.97)	0.0003
Stroke, non-CNS embolism, or TIA	57 (1.07)	15 (2.37)	2.21 (1.13–4.32)	0.0203	1.57 (0.77–3.19)	0.2174
Major bleeding	131 (2.49)	30 (4.86)	1.99 (1.34–2.94)	0.0006	1.28 (0.84–1.96)	0.2457
Bleeding hospitalization	122 (2.32)	23 (3.71)	1.63 (1.06–2.50)	0.0256	0.95 (0.61–1.49)	0.8196

Cells present the number of events (rate per 100-patient years).
Abbreviations: HR, hazard ration; MACNE, major adverse cardiovascular and neurological event; CV, cardiovascular; MI, myocardial infarction; CNS, central nerve system; TIA, transient ischemic attack.

Table VI. Clinical outcomes by anticoagulant type and antithrombotic strategy in patients with concomitant atrial fibrillation and vascular disease

	No. of pts	MACNE			Major bleeding		
		No. of event	Unadjusted HR	Adjusted HR	No. of event	Unadjusted HR	Adjusted HR
By type of OAC							
Warfarin	450	36 (6.00)	Reference	Reference	33 (5.61)	Reference	Reference
DOAC	1195	74 (5.10)	0.82 (0.55–1.22)	1.20 (0.77–1.87)	52 (3.61)	0.62 (0.40–0.96)	0.70 (0.43–1.15)
By antithrombotic strategy							
OAC alone	843	46 (4.34)	Reference	Reference	28 (2.65)	Reference	Reference
OAC + AP	802	64 (6.45)	1.48 (1.03–2.14)	1.50 (1.00–2.25)	57 (5.87)	2.20 (1.53–3.17)	2.27 (1.38–3.73)

Cells present the number of events (rate per 100-patient years).
Abbreviations: OAC, oral anticoagulant; AP, antiplatelet; HR, hazard ration; DOAC, direct oral anticoagulant; MACNE, major adverse cardiovascular and neurological event; CV, cardiovascular; MI, myocardial infarction; CNS, central nerve system; TIA, transient ischemic attack.

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Appendix. Supplementary data

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