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ORIGINAL RESEARCH

Pharmacotherapy for Atrial Fibrillation in Patients With Chronic Kidney Disease: Insights From ORBIT-AF

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***Background*—**Chronic kidney disease (CKD) is a common comorbidity in patients with atrial fibrillation. The presence of CKD complicates drug selection for stroke prevention and rhythm control.

***Methods and Results*—**Patients enrolled in ORBIT AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) with baseline renal function and follow-up data were included (N=9019). CKD was defined as an estimated creatinine clearance <60 mL/min. Patient characteristics were compared by CKD status, and Cox proportional hazards modeling was used to examine the association between oral anticoagulant (OAC) use and outcomes and antiarrhythmic drug use and outcomes stratified by CKD stages. At enrollment, 3490 (39%) patients had an estimated creatinine clearance <60 mL/min. Patients with CKD were older and had higher CHA_2DS_2VASc and Anticoagulant and Risk Factors in Atrial Fibrillation (ATRIA) scores. A rhythm control strategy was selected less frequently in patients with CKD, while OAC use was lower among Stage IV and V CKD patients. After adjustment, no significant interaction was noted for OAC and CKD on all-cause mortality (P=0.5442) or cardiovascular death (P=0.1233), although a trend for increased major bleeding (P=0.0608) and stroke, systemic embolism or transient ischemic attack (P=0.0671) was observed. No interaction was noted for antiarrhythmic drug use and CKD status on all-cause mortality (P=0.9706), or stroke, systemic embolism or transient ischemic attack (P=0.4218).

***Conclusions*—**Patients with atrial fibrillation and CKD are less likely to be treated with rhythm control. Patients with advanced CKD are less likely to receive OAC. Finally, outcomes with OAC in patients with advanced CKD may be materially different with higher rates of both bleeding and stroke. **(*J Am Heart Assoc*. 2018;7:e008928. DOI: 10.1161/JAHA.118.008928.)**

Key Words: antiarrhythmic • anticoagulation • atrial fibrillation • chronic kidney disease

Chronic kidney disease (CKD) is a frequently encountered comorbidity in patients with atrial fibrillation (AF). Contemporary data show that 30% of patients with AF have Stage III, IV, or V CKD.[1] While pharmacotherapy strategies including rhythm control and antithrombotic therapy for stroke prevention are commonly prescribed for AF patients, the presence of CKD has the potential to complicate drug selection in each of these treatment decisions. Recent large clinical trials evaluating non-vitamin K oral anticoagulants (NOAC) for stroke prevention in AF excluded most patients with Stage IV and V CKD, thus limiting the evidence base for clinicians to make antithrombotic treatment decisions in this high-risk population.[2–5] In addition, previous randomized trials comparing a rate control and rhythm control strategy in patients with AF provide little insight into usage and subsequent outcomes of antiarrhythmic drug therapy (AAD) in individuals with CKD.[6,7]

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Accompanying Tables S1 and S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.008928

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Clinical Perspective

What Is New?

- In this analysis of patients enrolled in ORBIT AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation), patients with chronic kidney disease (CKD) were less likely to receive an antiarrhythmic agent and those with advanced CKD were less likely to receive an oral anticoagulant.
- While no interaction was observed for antiarrhythmic use and CKD status on mortality and thrombotic outcomes, trends for increased bleeding and stroke were observed in patients with advanced CKD who received an oral anticoagulant.

What Are the Clinical Implications?

- Given the limited evidence to date on the outcomes associated with antiarrhythmic drug therapy in atrial fibrillation patients with CKD, the lack of an interaction in this analysis between antiarrhythmic therapy and CKD status provides some reassurance for use of these agents in patients with CKD provide appropriate drug selection, dosing, and monitoring is ensured.
- In addition, this analysis provides additional evidence to highlight the high-risk nature of atrial fibrillation patients with advanced CKD with respect to both bleeding and thrombotic and further highlights the need for a randomized trial of antithrombotic therapy in this population.

The objectives of this analysis were to describe the use antithrombotic medications and AADs in patients with AF complicated by CKD. Additionally, we sought to compare outcomes according to use of these therapies in patients with AF across the spectrum of CKD among patients enrolled in a contemporary outpatient AF registry.

Methods

Study Population and Data Source

ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) is a prospective, nationwide, outpatient registry of patients with incident and prevalent AF. Overall, 10 137 patients were enrolled at 176 sites between June 2010 and August 2011. The rationale and design of the ORBIT-AF registry have previously been reported.[8] In brief, to be eligible for enrollment, patients were required to be aged ≥18 years, have electrocardiographic AF, able to provide consent, and able to adhere with local follow-up. Patients were excluded if they had a life expectancy of <6 months, solitary atrial flutter in isolation without AF, or AF secondary to a reversible condition (eg, pulmonary embolism or postoperative AF). Patients were recruited from participating clinics and the clinic visit at the time of enrollment marked the baseline visit. Patients were followed up at 6-month intervals for up to a maximum of 3 years. Data were collected by abstracting from clinical charts and entering into a web-based case report form that included data on age, sex, race/ethnicity, insurance status, education level, medical history, type of AF, AF treatment strategy (rhythm control versus rate control), medical procedure history, vital signs, laboratory data, and current medication use. The Duke Institutional Review Board approved the ORBIT-AF registry, and all participating sites have obtained institutional review board approval pursuant to local requirements. All subjects provided written, informed consent. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Definitions and Outcomes

For the purpose of this analysis, CKD was defined at baseline as an estimated creatinine clearance (eCrCl) <60 mL/min with the following stages: (1) Stage III—eCrCl 30 to 59 mL/min; (2) Stage IV—eCrCl 15 to 29 mL/min; and (3) Stage V—eCrCl <15 mL/min or hemodialysis. The most recent serum creatinine measurement was abstracted from the patient's medical record at their baseline visit. eCrCl was calculated by the Cockroft-Gault equation. Outcomes assessed included all-cause mortality, cardiovascular death, all-cause hospitalization, cardiovascular hospitalization, stroke, non-central nervous system (CNS) systemic embolization or transient ischemic attack (TIA), new onset heart failure, and International Society on Thrombosis and Haemostasis major bleeding. For patients having an event, time to event was defined as time from the baseline visit date to the event date. For patients not having an event, time to event was defined as time from the baseline visit date to last follow-up visit date or death date depending on whether the patient died or not.

Statistical Analysis

For this analysis, we excluded patients without creatinine clearance data (n=810) and patients without follow-up data (patients who had a baseline visit but did not return for any other visits) (n=308) for a final study population of 9019 patients from 172 sites. Additionally, for the factors associated with AAD use and the association of AAD use and outcomes stratified by CKD status analyses, patients with permanent AF were excluded (n=2553).

Baseline characteristics, antithrombotic strategy and AAD use are presented by CKD status. Categorical variables are presented as frequencies, and percentages and differences between the groups were assessed by the chi-square test.

Continuous variables are presented as median (Q1-Q3) and differences between the groups were assessed by the Kruskal–Wallis test for >2 groups. Figures displaying unadjusted event rates per 100 patient years by antithrombotic treatment and CKD status for International Society on Thrombosis and Haemostasis major bleeding and stroke, systemic embolism or TIA are presented with 95% confidence intervals.

To identify factors associated with AAD use at baseline, a multivariable hierarchal logistic regression model including site as a random effect for the binary outcome AAD use at baseline versus no AAD use at baseline was fit using all the clinical and demographic characteristics listed in the master candidate variable list (see Table S1). Backward selection with an inclusion criterion of 0.05 was used to build the model. All continuous variables were evaluated for non-linearity with the outcome and those not meeting the linear relationship criteria ($P<0.05$) were accounted for using linear splines. CKD was added to the final model to evaluate the impact CKD has on AAD selection after adjustment.

To evaluate the association of AAD use at baseline with outcomes according to CKD status, Cox proportional hazards modeling with robust standard errors to account for within site clustering was used. The association of AAD use with outcomes was adjusted with inverse propensity weighting of the propensity to receive AAD. The propensity score model was adjusted for (1) those variables known to influence treatment selection in clinical practice, (2) all statistically significant covariates, previously identified by backward selection with stay criteria of 0.05, as being associated with any of the outcomes under evaluation (see Table S2), and (3) and the interaction between CKD status (yes/no) and these variables. All continuous variables were evaluated for non-linearity with AAD use at baseline and non-linear variables were fit with restricted cubic splines. All subjects with extreme propensity scores (ie, no overlap between treatment groups for the propensity score distributions) were excluded from the analysis. An interaction term between AAD use and CKD status was added to each outcome model. Hazard ratio (HR) with corresponding 95% confidence interval and *P*-value are presented along with the event rates per 100 patient years. The same analysis strategy was repeated for testing the association between oral anticoagulant (OAC) use at baseline and outcomes stratified by CKD status (none/stage III/stage IV–V). All candidate variables had <2% missing, except for level of education (5%), hematocrit (4%), LVEF (9%), and left atrial diameter (13%). Missing data were handled with single imputation and imputed values were obtained by Markov Chain Monte Carlo or regression methods.[9] Statistical analyses were performed using SAS software (version 9.4, SAS Institute, Cary, NC), and 2-tailed $P<0.05$ was considered significant for all statistical tests.

Results

The final cohort for this analysis included 9019. At baseline, 3490 (38.7%) patients had CKD, defined as an eCrCl <60 mL/min. Among those with CKD, 2930 patients had Stage III and 560 patients had Stage IV or V CKD. A total of 124 patients received dialysis at the time of enrollment. The median follow-up time was 960 days (Q1, Q3: 672, 1090 days) and was observed to be shorter with increasing CKD severity; No CKD: 1013 days (701, 1095 days), Stage III CKD: 862 days (642, 1083 days), and CKD Stage IV or V: 722.5 days (390.5, 1036.5 days).

A comparison of baseline characteristics according to the CKD severity is shown in Table 1. Significant differences in demographics and comorbid medical conditions were observed across the 3 groups (no CKD, Stage III CKD, Stage IV or V CKD). Increasing age was observed with worsening renal function ($P<0.0001$). Patients with CKD were more likely to be female and have a lower body weight ($P<0.0001$ for each). Additionally, significant differences were also noted across the groups for comorbid illness, including hypertension, heart failure, coronary artery disease, prior stroke or TIA, and gastrointestinal bleeding ($P<0.0001$ for each). Patients with CKD were also observed to have a higher median CHA_2DS_2VASc score (3.0 versus 5.0 versus 5.0; $P<0.0001$) (Figure 1) and a higher median ATRIA score (2.0 versus 3.0 versus 6.0; $P<0.0001$).

OAC Use and Outcomes

The choice of antithrombotic therapy for stroke prevention according to renal function is shown in Table 2. Warfarin therapy across strata of renal function demonstrated significant variation, ($P=0.0003$). Dabigatran use was less frequent in patients with impaired renal function with rates ranging from 5.9% in patients with no CKD to 1.9% in patients with Stage IV CKD. No patients with Stage V CKD received dabigatran. Among aspirin users, those without CKD were most likely to be receiving daily doses ≥100 mg. Lastly, the proportion of patients receiving concomitant oral anticoagulant and antiplatelet therapy was more common in patients without CKD ($P=0.0031$).

The observed event rates for cardiovascular outcomes according to anticoagulant/antiplatelet treatment and CKD class are shown in Figures 2 and 3. Observed rates of International Society on Thrombosis and Haemostasis major bleeding increased with increasing antithrombotic intensity (observed bleeding rates highest for those patients receiving an OAC plus an antiplatelet agent) and with worsening renal function (Figure 2). In patients receiving an OAC, the observed rates of major bleeding ranged from 2.7% in patients with no CKD, to 7.1% for those with Stage IV or V CKD. Figure 3

Table 1. Baseline Characteristics Stratified by CKD Stage

Characteristic	No CKD (n=5529)	Stage III CKD (n=2930)	Stage IV or V CKD (n=560)	*P* Value
Age, y	70 (63–76)	81 (77–85)	84 (78–88)	<0.0001
Female	33.6%	54.8%	62.3%	<0.0001
Race/ethnicity				
White	89.6%	91.2%	87.7%	0.047
Black/African American	5.0%	3.6%	6.3%	
Hispanic	3.9%	3.8%	4.3%	
Weight, kg	95.3 (83.0–111.0)	73.0 (63.6–84.0)	66.4 (55.5–79.1)	<0.0001
Heart rate	70 (62–80)	70 (63–80)	72 (64–79)	0.181
Type of atrial fibrillation				
New onset	4.8%	3.0%	3.0%	<0.0001
Paroxysmal	51.2%	49.7%	50.7%	
Persistent	17.6%	15.7%	16.1%	
Permanent	26.4%	31.6%	30.2%	
CHA_2DS_2-VASc Score	3.0 (2.0–5.0)	5.0 (4.0–6.0)	5.0 (4.0–6.0)	<0.0001
ATRIA score	2.0 (1.0–4.0)	3.0 (3.0–6.0)	6.0 (4.0–7.0)	<0.0001
Prior stroke/TIA	12.5%	19.8%	21.1%	<0.0001
Hypertension	81.6%	86.7%	87.9%	<0.0001
Diabetes mellitus	30.3%	28.4%	31.1%	0.136
Congestive heart failure	29.2%	38.9%	53.6%	<0.0001
Coronary artery disease	33.1%	43.0%	45%	<0.0001
Prior GI bleed	7.1%	12.7%	15.9%	<0.0001
AF management strategy				
Rate control	64.8%	73.0%	73.4%	<0.0001
Rhythm control	34.9%	26.8%	26.1%	
Baseline OAC				
Warfarin	70.8%	73.9%	66.6%	0.0003
Dabigatran	5.9%	3.9%	1.4%	<0.0001
No OAC	23.4%	22.3%	32.0%	<0.0001

AF indicates atrial fibrillation; CKD, chronic kidney disease; GI, gastrointestinal; OAC, oral anticoagulant; TIA, transient ischemic attack.

illustrates the rates of stroke or TIA according to antithrombotic treatment and CKD class. Stroke or TIA events generally occurred more frequently in patients receiving OAC with Stage IV or V CKD, compared with those without CKD.

The outcomes associated with OAC use versus no OAC across renal function are shown in Table 3. After adjustment, no significant interactions were observed for OAC use and renal function on outcomes including all-cause death ($P_{interaction}$=0.5442) or cardiovascular death ($P_{interaction}$=0.1233), While the confidence intervals for these hazard ratios all overlapped across renal function strata, there were observed trends towards increased bleeding ($P_{interaction}$=0.0608) and increased all-cause stroke, systemic embolism, or TIA ($P_{interaction}$=0.0671) in those with eCrCl<30 mL/min treated with an OAC.

AAD Use and Outcomes

A rhythm control strategy was selected more often in patients without CKD (*P*<0.0001), although, after adjustment for clinical and demographic variables known to impact the selection of a rhythm control strategy, the presence of CKD was not significantly associated with the likelihood of prescribing AAD therapy (odds ratio: 1.13; 95% confidence interval: [0.98–1.31]) (Table S2). Significant differences were noted in the use of individual antiarrhythmic medications

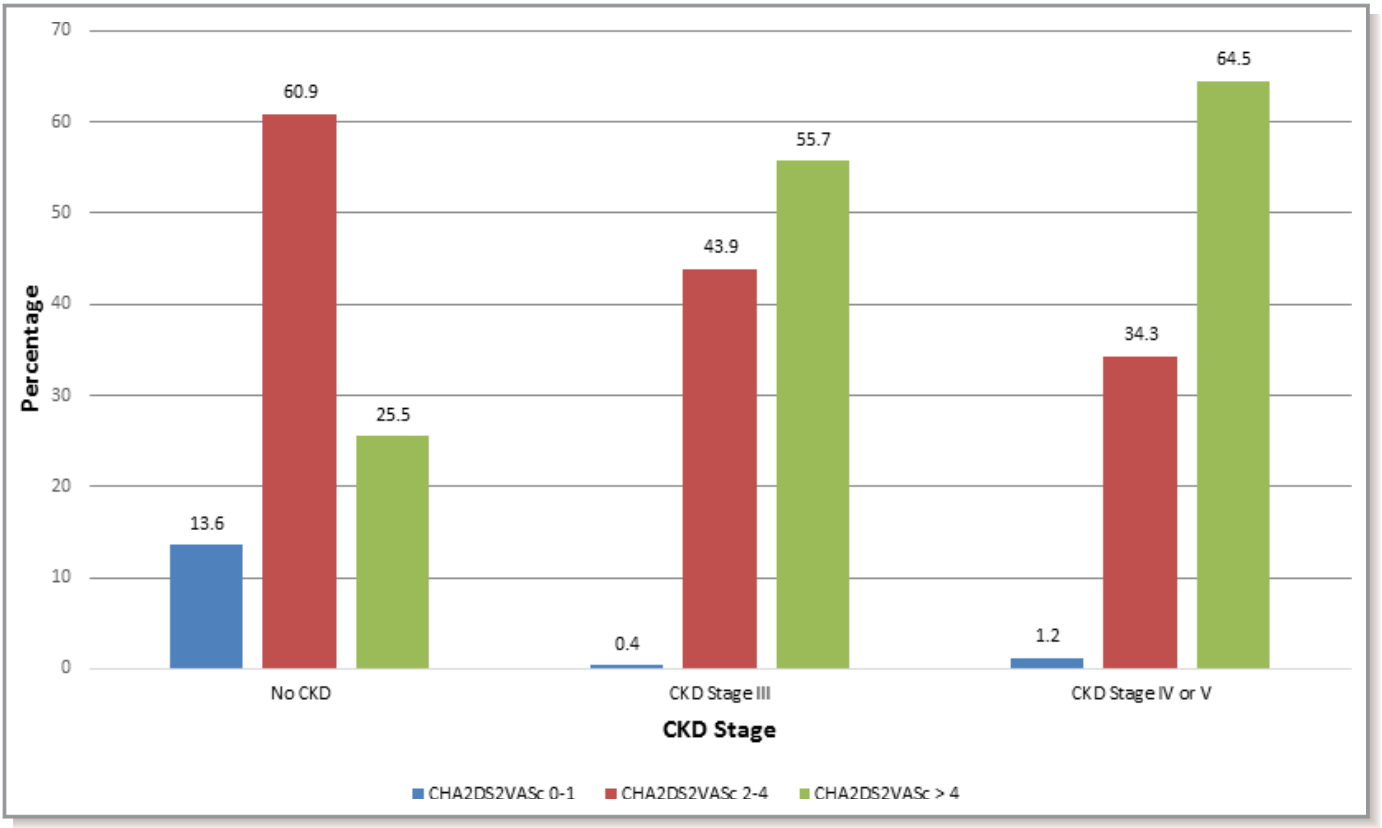

Figure 1. CHA_2DS_2VASc scores according to CKD Status. CKD indicates chronic kidney disease.

across CKD stages (Table 4). The proportion of patients on antiarrhythmic therapy receiving amiodarone increased with worsening renal function ($P<0.0001$) while the proportion receiving sotalol ($P=0.0005$) and dofetilide ($P=0.0015$) was lower in those with CKD. Similarly, the proportion of patients with CKD receiving other frequently prescribed AADs including flecainide and propafenone was lower when compared with patients without CKD. Fifteen patients with Stage IV or V

Table 2. Antithrombotic Strategy Stratified by CKD Stage

	No CKD (n=5529)	Stage III CKD (n=2930)	Stage IV or V CKD (n=560)	*P* Value
Antiplatelet therapy				
Any antiplatelet therapy	48.5%	46.2%	49.1%	0.1085
Aspirin	45.7%	42.6%	43.9%	0.0231
Dose ≥100 mg/day (among aspirin patients)	24.6%	16.3%	16.3%	<0.0001
Clopidogrel	6.3%	8.5%	12.0%	<0.0001
Prasugrel	0.1%	0.1%	0.0%	0.6034
Dipyridamole/aspirin	0.1%	0.2%	0.4%	0.2573
Oral anticoagulation				
Any OAC (Dabigatran or Warfarin)	76.6%	77.7%	68.0%	<0.0001
Dabigatran	5.9%	3.9%	1.4%	<0.0001
Warfarin	70.8%	73.9%	66.6%	0.0003
Combination therapy				
Any anticoagulant and antiplatelet	30.3%	28.9%	23.6%	0.0031
Dabigatran and antiplatelet	2.0%	1.4%	0.4%	0.0028
Warfarin and antiplatelet	28.3%	27.6%	23.2%	0.0381

CKD indicates chronic kidney disease; OAC, oral anticoagulant.

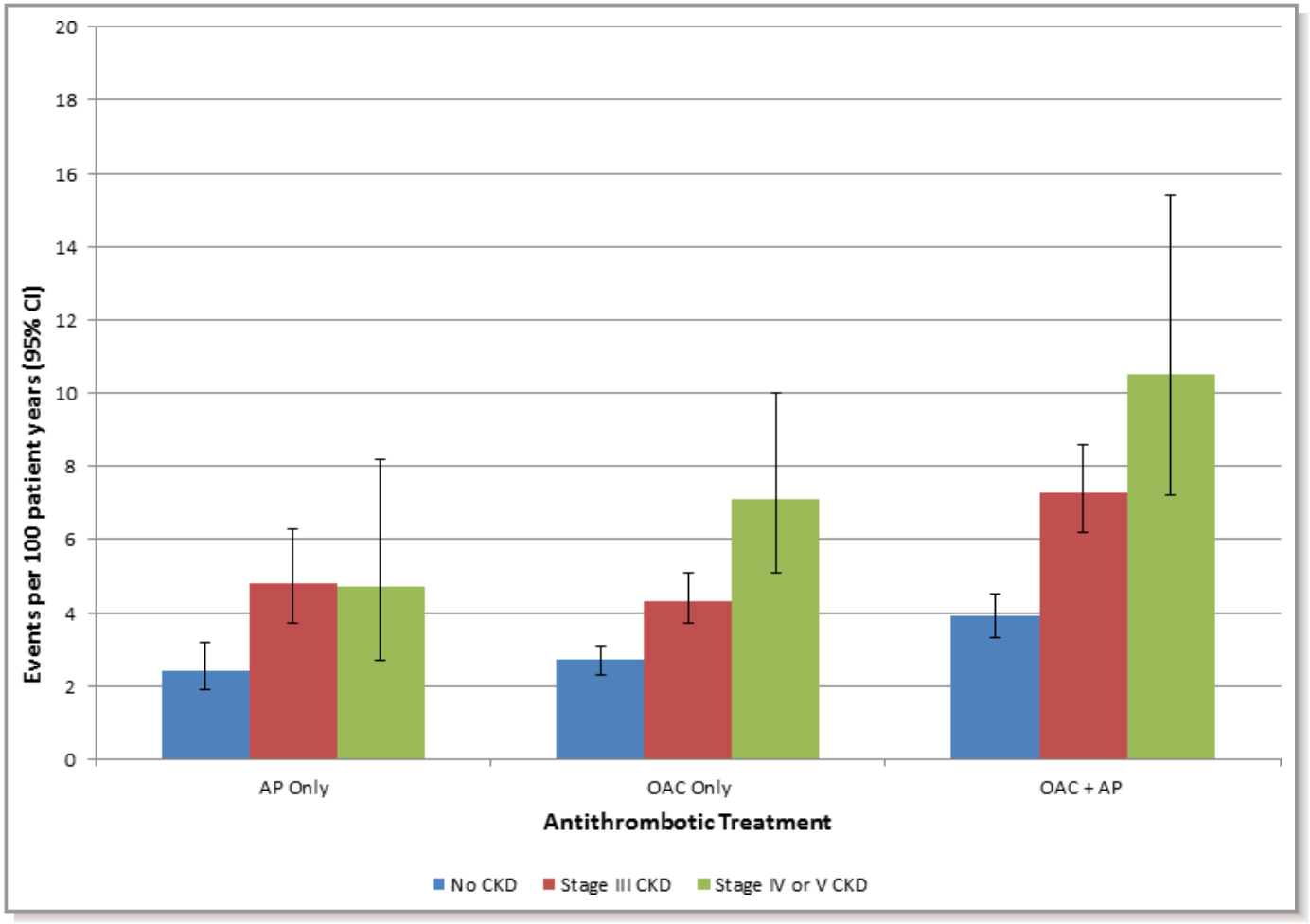

Figure 2. ISTH major bleeding events according to antithrombotic treatment and CKD status. AP indicates antiplatelet; CKD, chronic kidney disease; ISTH, International Society on Thrombosis and Haemostasis; OAC, oral anticoagulant.

CKD were receiving sotalol and one patient with Stage V CKD was receiving dofetilide.

The outcomes associated with AAD therapy versus no AAD therapy in those with CKD (Stage III, IV, or V) and in patients without CKD are shown in Table 5. After inverse propensity weighting, no interaction was observed between AAD use and CKD status on outcomes including all-cause death ($P_{interaction}$=0.9706), cardiovascular death ($P_{interaction}$=0.8881), first cardiovascular hospitalization ($P_{interaction}$=0.0797) or the composite of all-cause death, stroke, systemic embolism or TIA ($P_{interaction}$=0.8407). An interaction was observed between AAD and CKD on the composite outcome of cardiovascular hospitalization or death ($P_{interaction}$=0.0116). Lastly, no interaction was observed for AAD use and CKD status for the safety outcome of first major bleeding event ($P_{interaction}$=0.9669).

Discussion

In this analysis of the ORBIT AF registry, we report observations on the use of antithrombotic and antiarrhythmic agents as well as the outcomes associated with their use in AF patients according to the severity of CKD. There are several major findings in this analysis. First, significant differences were observed in the proportion of patients with CKD receiving a rhythm control strategy and, as expected, variations were noted in the use of individual agents based on the degree of renal impairment. Second, in spite of significantly higher baseline risk for stroke and thromboembolic events, patients with Stage IV or V CKD received OAC less often than those without CKD. Third, the association of AAD and individual outcomes including all-cause stroke were not significantly affected by stage of CKD. Last, the observed rates of both bleeding and thromboembolic events were higher in patients with advanced CKD compared with those patients without CKD.

CKD is common in patients with AF, affecting as many as 4 in 10 patients. Despite the frequency of CKD in patients with AF, randomized studies comparing rhythm and rate control strategies have provided little insight into the proportion of patients with CKD that were enrolled as well as the clinical

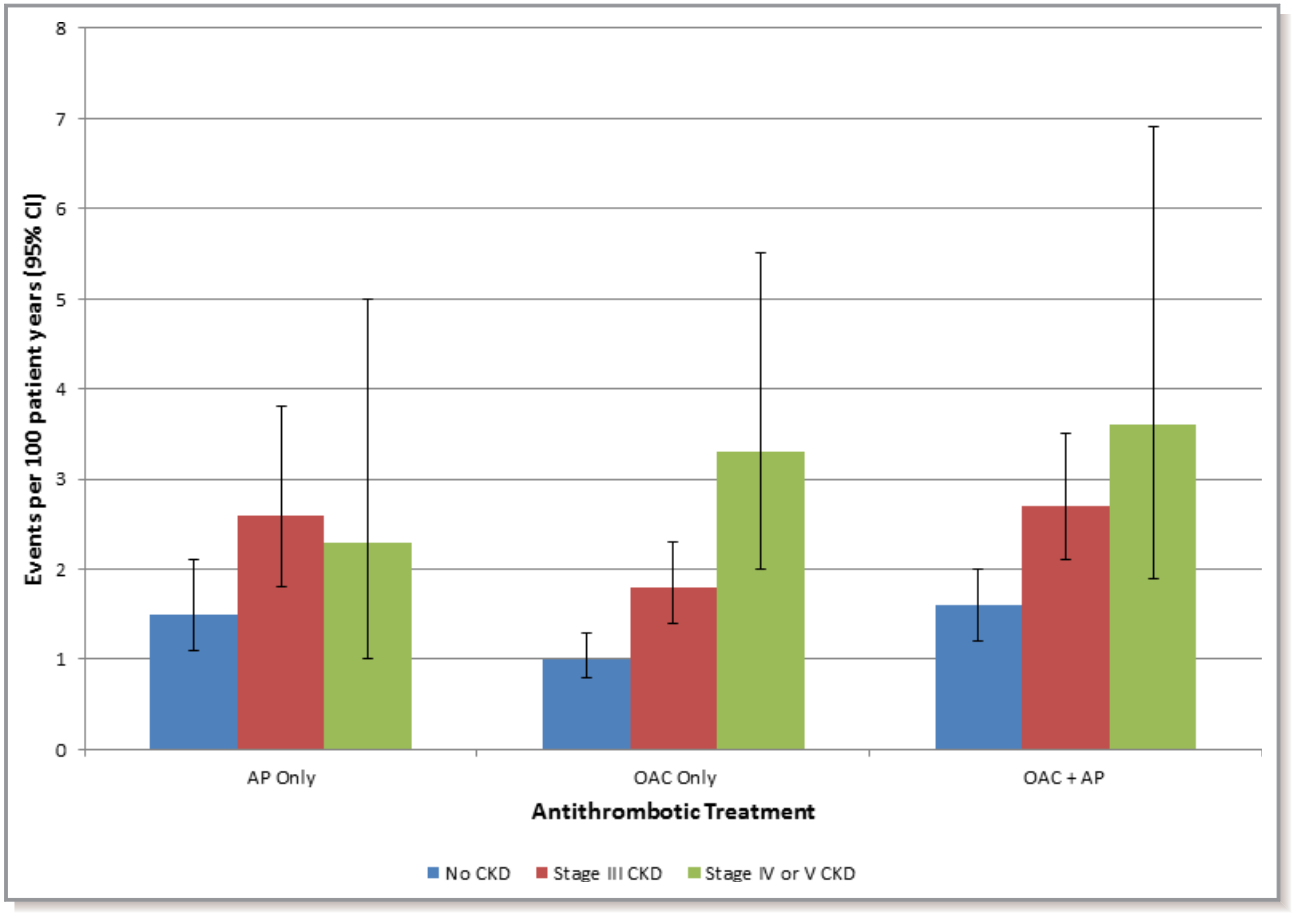

Figure 3. Stroke, systemic embolism, or transient ischemic attack according to antithrombotic treatment and CKD status. AP indicates antiplatelet; CKD, chronic kidney disease; OAC, oral anticoagulant.

outcomes for each treatment strategy in patients with CKD.[6,7] The lack of outcomes data combined with the labeled dose modifications/contraindications for several commonly used AADs based on the degree of renal impairment make clinical decisions challenging for these patients.

In this nationwide, observational cohort, patients with CKD were less likely to be managed with a rhythm control strategy when compared with patients without CKD. This difference in management is likely multifactorial and due, at least in part, to the higher proportion of patients with permanent/long-standing persistent AF among patients with CKD as compared with those without CKD. When a rhythm control strategy was selected for a patient with CKD, significant differences were noted in the rates of individual AAD use. These differences in prescribing patterns can be partially attributed to labeled recommendations for dose adjustment of agents such as flecainide in patients with CKD and contraindications to the use of sotalol in patients with a eCrCl <40 mL/min and dofetilide when eCrCl <20 mL/min. Notably, we did observe sotalol use in 15 patients with Stage IV or V CKD, highlighting the opportunity for prescriber education with this agent in CKD patients with AF. In spite of significant differences in the rates of use of individual agents in CKD patients versus those without CKD, no interaction was observed between AAD use and CKD status with respect to individual cardiovascular outcomes. The absence of an interaction suggests that similar outcomes can be expected with appropriate antiarrhythmic therapy in patients with CKD. We did observe an association with AAD therapy and lower risk for the composite outcome of cardiovascular hospitalization or death as well as a trend towards increased cardiovascular hospitalization with AAD therapy in patients with CKD. These hypothesis generating observations require further investigation. However, as previously published data have shown, AAD use has been observed more frequently in patients who have a greater burden of AF symptoms.[10] While these data do not establish different treatment effects of AAD therapy in AF patients with CKD, they do provide some initial evidence for decisions on AAD use in this high-risk population.

Previously published observational data have shown a higher degree of comorbid medical conditions in AF patients with CKD compared with those without CKD.[1] Similarly, this

Table 3. Oral Anticoagulation and Outcomes According to CKD Status

Outcome	No CKD		Stage III CKD		Stage IV or V CKD		Interaction *P* Value
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	
All-cause death	0.73 (0.57–0.93)	0.0124	0.84 (0.67–1.06)	0.1419	0.89 (0.58–1.38)	0.6080	0.5442
Cardiovascular death	0.71 (0.47–1.05)	0.0894	0.79 (0.56–1.11)	0.1744	1.74 (0.85–3.52)	0.1273	0.1233
First cardiovascular hospitalization	0.94 (0.81–1.07)	0.3453	1.03 (0.86–1.24)	0.7355	1.08 (0.72–1.63)	0.7120	0.6435
Cardiovascular hospitalization or death	0.91 (0.81–1.03)	0.1544	1.01 (0.86–1.20)	0.8666	0.95 (0.67–1.35)	0.7803	0.6339
First stroke, systemic embolism or TIA	0.67 (0.45–0.99)	0.0425	0.91 (0.56–1.47)	0.6946	2.71 (0.76–9.63)	0.1230	0.0671
Composite of death, stroke, systemic embolism, and TIA	0.70 (0.57–0.87)	0.0012	0.89 (0.71–1.10)	0.2771	0.96 (0.63–1.47)	0.8501	0.1544
New-onset heart failure	0.93 (0.51–1.72)	0.8249	1.16 (0.65–2.04)	0.6206	1.14 (0.38–3.36)	0.8171	0.8786
First ISTH major bleeding event	0.91 (0.67–1.24)	0.5575	1.15 (0.81–1.63)	0.4415	2.32 (1.12–4.81)	0.0239	0.0608

CI indicates confidence interval; CKD, chronic kidney disease; ISTH, International Society on Thrombosis and Haemostasis; TIA, transient ischemic attack.

analysis observed a higher comorbid medical burden in patients with CKD as evidenced by significantly higher prognostic risk scores including CHA_2DS_2-VASc and ATRIA scores. In light of these higher prognostic scores in patients with CKD, we observed significantly lower rates of OAC use with moderate to severe renal dysfunction. The lower rates of anticoagulation likely reflect the uncertainty about risks and benefits of OAC therapy in those with Stage IV-V CKD, given the exclusion of these patients from randomized trials comparing NOACs to warfarin for stroke prevention.[2–5] Moreover, the use of warfarin in these patients has not always been associated with lower risk of stroke. The observation of a trend towards increased stroke risk of OAC in those with eCrCl $\leq$30 mL/min in predominantly warfarin-treated populations may explain the lower rates of stroke prevention therapy in these patients.[11]

Table 4. Antiarrhythmic Drug use stratified by Renal Function*

Medication	No CKD (n=1749)	Stage III CKD (n=748)	Stage IV or V CKD (n=137)	*P* Value
Amiodarone	28.8%	42.9%	68.6%	<0.0001
Sotalol	23.2%	18.9%	10.9%	0.0005
Dronedarone	16.4%	16.4%	8.8%	0.0603
Flecainide	12.4%	5.7%	3.6%	<0.0001
Propafenone	9.0%	6.3%	3.6%	0.0121
Dofetilide	7.8%	4.9%	1.5%	0.0015
Disopyramide	0.4%	0.3%	2.2%	0.0075
Ranolazine	1.0%	1.6%	1.5%	0.4014
Other AAD	2.2%	4.3%	2.2%	0.0162

*Specific antiarrhythmic drug (AAD) use is among patients taking any antiarrhythmic drug.

Data from previous observational analyses have shown variable results with respect to the use of warfarin and risk for bleeding or embolic stroke risk in AF patients receiving dialysis. Three analyses identified an association between warfarin use and increased risk for bleeding and embolic stroke,[11–13] while the fourth analysis associated warfarin use with an increased risk of bleeding and a decreased risk of stroke or systemic embolism.[14] In the present analysis, a trend towards increased bleeding as well as all-cause stroke, systemic embolism, or TIA was observed in patients with Stage IV or V CKD treated with an OAC compared with patients without CKD that received an OAC. These data highlight the risk of bleeding as well as stroke in patients with CKD and the need for continued focus on this high-risk subgroup of patients in randomized trials to help define optimal stroke prevention strategies. Given the risks of bleeding in these patients, it is possible that they may benefit the most from non-pharmacologic approaches to stroke prevention such as left atrial appendage occlusion.

Limitations

Several limitations should be noted when considering these data. First, the use of AADs as well as antithrombotic agents was at the discretion of the treatment provider and was not randomized. Next, while the propensity scoring used a large number of covariates to adjust for potential confounding, residual or unmeasured confounding may impact the observed associations. Third, the dose of AADs was not available thus limiting our ability to assess if the appropriate dose was used in instances when renal dose adjustment was required. Fourth, a relatively small number of patients in this analysis had Stage IV or V CKD at enrollment thereby limiting the power to detect significant differences in outcomes in this group. In addition, a

Table 5. Antiarrhythmic Drug Therapy and Outcomes According to CKD Status

Outcome	No CKD		CKD		Interaction *P*Value
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	
All-cause death	0.80 (0.61–1.04)	0.0995	0.80 (0.66–0.96)	0.0153	0.9706
Cardiovascular death	0.97 (0.61–1.55)	0.9040	0.95 (0.70–1.29)	0.7363	0.8881
First cardiovascular hospitalization	1.44 (1.27–1.64)	<0.0001	1.23 (1.05–1.44)	0.0121	0.0797
Cardiovascular hospitalization or death	1.35 (1.19–1.52)	<0.0001	1.09 (0.95–1.25)	0.2200	0.0116
First stroke, systemic embolism or TIA	0.74 (0.48–1.13)	0.1599	0.94 (0.60–1.48)	0.7971	0.4218
Composite of death, stroke, systemic embolism, and TIA	0.82 (0.65–1.05)	0.1131	0.85 (0.71–1.02)	0.0804	0.8407
New-onset heart failure	1.22 (0.72–2.05)	0.4547	1.03 (0.60–1.77)	0.9146	0.6432
First ISTH major bleeding event	0.92 (0.72–1.19)	0.5230	0.93 (0.70–1.22)	0.5882	0.9669

CI indicates confidence interval; CKD, chronic kidney disease; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; TIA, transient ischemic attack.

relatively small proportion of patients in this cohort were receiving dabigatran and no patients were receiving other NOAC agents, thus limiting our ability to assess outcomes associated with these medications. Last, by using only the creatinine clearance at enrollment, it is possible that patients with changing or worsening renal function over the course of follow-up were not appropriately categorized at the time certain clinical events occurred.

Conclusions

Approximately 2 in 5 patients with AF have CKD. Patients with AF and CKD have a higher burden of comorbidities, and consequently higher risk for bleeding and thromboembolic events. CKD patients are less likely to receive a rhythm control strategy and patients with Stage IV or V CKD are less likely to receive anticoagulation. Reassuringly, antiarrhythmic therapy was not associated with worse outcomes in patients with CKD. Overall, patients with CKD had higher observed rates of bleeding and thromboembolic events compared with those without CKD. These nationwide registry data highlight the high-risk features of AF patients with CKD and further support the need for randomized controlled trials in this population to provide evidence on the treatment effect of medication regimens.

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Supplemental Material

Table S1: Factors Associated with Antiarrhythmic Drug use at Baseline (n=6466)

Variable	OR (95% CI)	P-value	Global P-value
Prior cardioversions	2.29 (2.02-2.60)	<.0001	.
Heart rate per 10 bpm increase to 75	0.68 (0.63-0.73)	<.0001	.
AF Type		.	<.0001
New Onset	Reference	.	.
Paroxysmal AF	2.14 (1.64-2.81)	<.0001	.
Persistent AF	0.98 (0.73-1.31)	0.8809	.
Age		.	<.0001
Age per 5 year increase btw 60-80	0.90 (0.86-0.94)	<.0001	.
Age per 5 year increase above 80	0.86 (0.76-0.97)	0.0130	.
EHRA Score		.	<.0001
No symptoms	Reference	.	.
Mild	1.46 (1.28-1.67)	<.0001	.
Severe	1.83 (1.53-2.18)	<.0001	.
Disabling	1.68 (1.14-2.46)	0.0081	.

Variable	OR (95% CI)	P-value	Global P-value
Prior AV Node/HIS Bundle Ablation	0.35 (0.21-0.59)	<.0001	.
Frailty	0.62 (0.47-0.83)	0.0015	.
Hypothyroidism	1.21 (1.05-1.39)	0.0078	.
Hematocrit per 1% increase	0.98 (0.97-1.00)	0.0104	.
Sinus node dysfunction	1.22 (1.05-1.43)	0.0116	.
LAD Type		.	0.0006
Normal	Reference	.	.
Mild enlargement	0.82 (0.71-0.95)	0.0075	.
Moderate enlargement	0.82 (0.70-0.96)	0.0161	.
Severe enlargement	0.70 (0.58-0.83)	<.0001	.
Site Specialty		.	0.0055
Family Practice/Internal Medicine	Reference	.	.
Cardiology	1.42 (1.08-1.86)	0.0107	.
Electrophysiology	1.78 (1.21-2.63)	0.0033	.
CHF		.	0.0226
No CHF	Reference	.	.

Variable	OR (95% CI)	P-value	Global P-value
NYHA Class I	0.75 (0.61-0.92)	0.0055	.
NYHA Class II	0.84 (0.69-1.00)	0.0560	.
NYHA Class III/IV	0.91 (0.70-1.18)	0.4698	.
LVEF Type		.	0.0288
Normal	Reference	.	.
Mild dysfunction	0.88 (0.72-1.08)	0.2325	.
Moderate dysfunction	0.94 (0.76-1.16)	0.5478	.
Severe dysfunction	1.44 (1.07-1.93)	0.0149	.
Race		.	0.0318
White	Reference	.	.
Black	0.66 (0.50-0.89)	0.0064	.
Hispanic	0.77 (0.53-1.13)	0.1814	.
Other	1.06 (0.65-1.72)	0.8268	.

AF, atrial fibrillation; EHRA, European Heart Rhythm Association; LAD, left atrial diameter; CHF, congestive heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction

Table S2: Covariate Adjustment List

Demographics

1. Age, years
2. Gender – Male/Female
3. Level of Education – Some School/High School Graduate/College Graduate/Post Graduate
4. Payor/Insurance – Medicare or Medicaid/Private/Others

Medical History

1. Smoking – Current/Recent or Former/Non-smoker
2. Cancer - Yes/No
3. Hypertension - Yes/No
4. Diabetes – Yes/No
5. GI Bleed – Yes/No
6. Obstructive Sleep Apnea – Yes/No
7. Dialysis – Yes/No
8. Hyperlipidemia – Yes/No
9. Anemia – Yes/No
10. Cognitive Impairment/Dementia – Yes/No
11. Frailty – Yes/No
12. COPD – Yes/No

Cardiovascular History

1. Peripheral Vascular Disease – Yes/No
2. Stroke or TIA – Yes/No
3. Congestive Heart Failure (CHF) – No CHF/NYHA Class I/NYHA Class II/NYHA Class III or NYHA Class IV

4. Significant Valvular Disease – Yes/No
5. Prior Valve Replacement/Repair – Yes/No

Coronary Artery Disease History

1. History of Coronary Artery Disease – Yes/No
2. Prior MI – Yes/No
3. Any PCI – Yes/No

Vital Signs & AF status

1. Height, cm
2. Diastolic Blood Pressure, mmHG
3. Systolic Blood Pressure, mmHG
4. Body Mass Index, kg/m^2

Echocardiographic Assessment (TTE or TEE)

1. LVEF – Normal ($\geq$50%)/Mild dysfunction (>40%, <50%)/Moderate dysfunction ($\geq$30%, $\leq$40%)/Severe dysfunction (<30%)
2. LAD Type – Normal/Mild enlargement/Moderate enlargement/Severe enlargement

Laboratory Data

1. Estimated creatinine clearance eCrCl (Cockroft-Gault), mL/min
2. Hematocrit, %

Atrial Fibrillation Diagnosis

1. Type of AF – First Detected or New Onset/Paroxysmal AF/Persistent AF /Permanent AF
2. AF duration

Functional Status

1. Functional Status – Living independently/Living with assistance or Resides in assisted living facility or Resides in skilled nursing home or Bedbound

Provider or Site

1. Primary Investigator/Site Specialty – Cardiology/Electrophysiology/Family Practice or Internal Medicine
2. Region

GI, gastrointestinal; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; NYHA, New York Heart Association; MI, myocardial infarction; PCI, percutaneous coronary intervention; AF, atrial fibrillation; LVEF, left ventricular ejection fraction; LAD, left atrial diameter;