Journal of the American Heart Association

ORIGINAL RESEARCH

Direct Oral Anticoagulants Versus Warfarin in Patients With Atrial Fibrillation and Valve Replacement or Repair

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BACKGROUND: We sought to examine outcomes of direct oral anticoagulants (DOACs) versus warfarin in atrial fibrillation with valve repair/replacement.

METHODS AND RESULTS: Two atrial fibrillation cohorts from Medicare were identified from 2015 to 2019. They comprised patients who underwent surgical or transcatheter mitral valve repair (MV repair cohort) and surgical aortic or mitral bioprosthetic or transcatheter aortic valve replacement (bioprosthetic cohort). Each cohort was divided into warfarin and DOACs (apixaban, rivaroxaban, and dabigatran) groups. Study outcomes included mortality, stroke, and major bleeding. Inverse probability weighting was used for adjustment between the 2 groups in each cohort. The MV repair cohort included 1178 patients. After a median of 468 days, DOACs were associated with lower risk of mortality (hazard ratio [HR], 0.67 [95% CI, 0.55–0.82], $P<0.001$), ischemic stroke (HR, 0.72 [95% CI, 0.52–1.00], $P=0.05$) and bleeding (HR, 0.79 [95% CI, 0.63–0.99], $P=0.04$) compared with warfarin. The bioprosthetic cohort included 8089 patients. After a median follow-up of 413 days, DOACs were associated with similar risk of mortality (adjusted HR, 0.93 [95% CI, 0.86–1.01], $P=0.08$), higher risk of ischemic stroke (adjusted HR, 1.27 [95% CI, 1.13–1.43], $P<0.001$), and lower risk of bleeding (adjusted HR, 0.86 [95% CI, 0.80–0.93], $P<0.001$) compared with warfarin.

CONCLUSIONS: In patients with atrial fibrillation, DOACs are associated with similar mortality, lower bleeding, but higher stroke with bioprosthetic valve replacement and lower risk of all 3 outcomes with MV repair compared with warfarin.

Key Words: apixaban ■ atrial fibrillation ■ brain ischemia ■ dabigatran ■ mitral valve ■ rivaroxaban ■ warfarin

Direct oral anticoagulants (DOACs) have become the preferred therapy to prevent thromboembolism in patients with nonvalvular atrial fibrillation (AF).[1] The prevalence of AF with valvular heart disease is increasing, and the coexistence of both diseases is associated with increased risk of thromboembolism. The landmark trials that evaluated DOACs versus warfarin in patients with AF have included only a small number of patients with valvular AF, and those with prior bioprosthetic valve replacement and/or repair were excluded from the primary analyses.[2–4] Secondary analyses from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, and the RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy) trial, as well as recent observational data have demonstrated potential safety and efficacy of DOACs in patients with valvular AF.[5–7] Importantly, similar outcomes were not reproduced in patients with bioprosthetic valve replacement/repair in a post hoc analysis of the ARISTOTLE trial.[8] Use of DOACs in patients with bioprosthetic valve replacement/repair have been uptrending.[9,10] Furthermore, during the COVID-19 pandemic, there have been reports about switching patients, both with valvular and nonvalvular AF, from

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.026666

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In Medicare patients with atrial fibrillation and surgical or transcatheter mitral valve repair, direct oral anticoagulants are associated with lower risk of all-cause mortality, ischemic stroke, and major bleeding compared with warfarin.
- In Medicare patients with atrial fibrillation and surgical or transcatheter bioprosthetic valve replacement, direct oral anticoagulants are associated with similar risk of all-cause mortality, lower risk of major bleeding, and higher risk of ischemic stroke compared with warfarin.

What Are the Clinical Implications?

- Future randomized controlled trials are needed to replicate the better safety and efficacy of direct oral anticoagulants compared with warfarin in patients with mitral valve repair.

Nonstandard Abbreviations and Acronyms

CHA_2DS_2-VASc	Congestive heart failure, Hypertension, Age 75 years or older, Diabetes mellitus, previous Stroke/TIA, Vascular disease, Age 65–74 years, Sex category
DOAC	direct oral anticoagulants
MVr	surgical mitral valve repair
MV-TEER	mitral valve transcatheter edge-to-edge repair
TAVR	transcatheter aortic valve replacement

warfarin to DOACs to reduce the need for therapeutic monitoring and hence unload the health care systems, and limit exposure of patients to health care personnel, however with concerns about the safety and efficacy of such actions because of scarcity of data about DOACs in patients with bioprosthetic valve replacement. The current study sought to examine the safety and efficacy of DOACs versus warfarin in patients with AF and bioprosthetic valve replacement and valve repair using a nationwide database.

METHODS

Data used for the study are covered under a data use agreement with the Centers for Medicare & Medicaid Services and are not available for distribution by the authors but may be obtained from Centers for Medicare & Medicaid Services with an approved data use agreement.

Study Cohort

The Medicare Provider Analysis and Review (MedPAR) 100% File was used to identify 2 cohorts of Medicare beneficiaries from 2015 to 2019. The first cohort (Repair) included patients who underwent surgical mitral valve repair (MVr), or mitral valve transcatheter edge-to-edge repair (MV-TEER) with Mitral Clip system. The second cohort (Bioprosthetic) included patients who underwent surgical bioprosthetic valve replacement (in mitral and/or aortic position) or transcatheter aortic valve replacement (TAVR). The *International Classification of Diseases, Ninth and Tenth Revisions (ICD-9; ICD-10)* procedure codes used to identify study cohort are presented in Table S1. Among these 2 cohorts, patients with AF, either preexisting or new onset, were identified. The study start date was the date of valve intervention in patients with preexisting AF or the date of AF diagnosis in patients with new onset AF after valve intervention.

We excluded patients who were not enrolled in Medicare part D for drugs coverage, and patients who were not included in the Medicare 5% enhanced sample files. We also excluded patients who had <1 year coverage of Medicare Fee-for-Service before the study start date. Patient's demographics including age, sex, and race, and dates of enrollment were extracted from Medicare Beneficiary Summary Files. Patient comorbidities were ascertained using all *ICD* codes submitted in the 1 year preceding the study start date using Elixhauser's method.[11] For each patient, the CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age 75 years or older, Diabetes mellitus, previous Stroke/TIA, Vascular disease, Age 65–74 years, Sex category) score and an *ICD*-based "Hospital Frailty Risk Score" validated in patients with valvular intervention were calculated.[12] The Institutional Review Board at the Cleveland Clinic approved the study with waiver of informed consent.

Exposure of Interest and Study Outcomes

Each cohort was divided based on the anticoagulant agent prescribed at the study start date into 2 groups: the vitamin K antagonist group included warfarin, and the DOACs group included apixaban, rivaroxaban, or dabigatran. Edoxaban was excluded because of the very small number of patients treated with it. All pharmacy claims for the study participants were extracted from Medicare Part D Event Files, with details on the prescribed drug name, filling date, dose strength, number of pills supplied, and number of days covered. For each participant, continuous exposure to the drug of interest was confirmed by tracking the prescription fills,

and if a patient filled a medication prematurely, number of extra pills was added to the exposure period. If a patient had a gap of >60 days with no new refills, the patient was determined to have stopped the drug and was censored. By this study design, proportion of days covered is >90% for all study participants. Patients were followed until the drug was stopped, the patient switched to a different anticoagulant (crossed to the other group), had an event, or until the study end date. The study primary outcome was all-cause mortality in follow-up. The study secondary outcomes included ischemic stroke and major bleeding in follow-up. Major bleeding definition was consistent with prior studies.[13]

Statistical Analysis

Continuous patient variables are presented as mean and SD and compared using Student *t* test or as median and interquartile range and compared using the Mann–Whitney test. Categorical patient variables are presented as percentages and compared using χ^2 or Fisher exact test. To adjust for measured confounders and to limit confounding by indication, inverse probability treatment weighting method was utilized with estimation of the average treatment effects.[14] First, a nonparsimonious logistic regression model was performed with the dependent variable receipt of DOAC, and the following independent variables: age, sex, anemia, liver disease, kidney disease, lung disease, prior bleeding, tumor, and prior *ICD* placement, CHA_2DS_2-VASc score, location of valve, and the frailty score (which includes >100 clinical variables, Table S2), to generate patients' propensity scores (PSs). Then the unstabilized inverse probability weights of receiving DOAC for the whole cohort were derived from the PSs. Multivariable survival models were created using the inverse probability weights to determine the adjusted effect of DOAC use on the primary and secondary outcomes. To account for competing risk of death, Fine–Gray models were performed for the study secondary outcomes, and subdistribution hazards ratios (HRs) are presented.[15] The validity of the proportional hazards assumption was evaluated by inspecting the log (–log [survival] plot against log [time]). If the assumption was violated, *P* values were reported from restricted mean survival time nonparametric method.[16] The inverse probability treatment weighting procedure including estimating PSs was performed on each cohort separately. We also tested whether there is a difference in the association of DOAC with the study outcomes by the valve location (aortic versus mitral) by performing an interaction analysis between the OAC group and the location of the valve. If the interaction is significant, subgroup analysis was further performed for the study outcomes in mitral and aortic positions separately. In each subgroup analysis, the estimation of PSs for the 2 groups was recalculated with logistic regression. To test the robustness of our results, sensitivity analyses were performed using the PS matching method. Using PSs generated and described in the first step, the 2 groups in each cohort were matched with a greedy approach and a caliper of 0.05 with up to 3 cases of warfarin matched to 1 case of DOAC. Standardized differences were calculated between the groups after PS matching, and a difference <0.1 was considered not significant. To account for competing risk of death, cumulative incidence curves for the study outcomes are presented in the PS matched cohort.

The analysis was performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC), R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria), and GraphPad Prism version 8.0 (GraphPad Software, Inc., San Diego, CA).

RESULTS

Valve Repair Cohort

The study cohort included 1178 patients with AF and valve repair (MV-TEER n=541, surgical MVr n=637) and AF, 687 patients (58.3%) of whom were on warfarin, and 491 (41.7%) on DOACs (Figure S1). Table 1 shows the baseline characteristics of the patients. DOAC patients were older (mean age 77.5±9.2 versus 75.0±8.7, *P*<0.001). Patients in the DOAC group had similar CHA_2DS_2-VASc score (median 5 [4–6] versus 5 [4–6], *P*=0.1) and frailty score (7.1 [3.0–13.5] versus 6.7 [3.5–11.7], *P*=0.2) compared with patients in the warfarin group. There was no difference between the 2 groups in prevalence of most comorbidities.

After median follow-up of 468 days (interquartile range, 168–1207 days), DOACs were associated with lower risk of mortality compared with warfarin (HR, 0.67 [95% CI, 0.55–0.82], *P*<0.001), with no evidence of interaction between MV-TEER versus surgical MVr ($P_{interaction}$=0.4) (Table 2). DOACs were associated with lower risk of ischemic stroke (HR, 0.72 [95% CI, 0.52–1.00], *P*=0.05) with no interaction between MV-TEER versus surgical MVr ($P_{interaction}$=0.4), as well as lower risk of major bleeding (HR, 0.79 [95% CI, 0.63–0.99], *P*=0.04) but with evidence of interaction with MV-TEER versus surgical MVr ($P_{interaction}$<0.001). In subgroup analysis, DOAC was associated with lower risk of major bleeding only with surgical MVr (HR, 0.58 [95% CI, 0.43–0.77], *P*<0.001), but not with MV-TEER (HR, 1.26 [95% CI, 0.86–1.85], *P*=0.2).

Table 3 shows baseline characteristics of the 2 groups after PS matching. Both groups were well balanced in all variables. Upon PS matching, DOACs were associated with similar risk of mortality (HR, 0.82 [95% CI, 0.60–1.10], *P*=0.09), ischemic stroke (HR, 0.76 [95% CI, 0.44–1.31], *P*=0.3), and lower risk of major bleeding

Table 1. Baseline Characteristics of the Study Cohort

Bioprosthetic valve cohort			
	DOAC N=3093	Warfarin N=4996	*P* value
Age, y	78.0±8.1	76.4±8.1	<0.001
Female sex	42.4	44.6	0.06
White race	92.1	90.9	0.1
Black race	3.6	4.6	
Hypertension	93	90.3	<0.001
Diabetes	40.9	36.8	<0.001
Heart failure	68.4	65.1	0.002
Chronic kidney disease	25.4	24.8	0.5
Coronary artery disease	76.4	74.4	0.045
Stroke	15.9	16.4	0.5
Lung disease	34.8	32.8	0.07
Liver disease	4	3.7	0.5
Drug abuse	1.1	1.3	0.6
Anemia	33.5	33.3	0.9
Peripheral vascular disease	30.7	30.6	0.9
CHA_2DS_2-VASc, mean±SD	5 (4–6)	5 (4–6)	0.3
Frailty score, median (IQR)	7.3 (3.4–13.1)	7.1 (3.7–12.4)	0.8
Bioprosthetic mitral	9.1	19.4	<0.001
Bioprosthetic aortic	36.7	44.1	
TAVR	51.8	29.8	
Bioprosthetic mitral and aortic	2.5	6.7	
Apixaban	70.7	NA	
Rivaroxaban	23.7		
Dabigatran	5.6		
Mitral valve repair cohort			
	DOAC N=491	Warfarin N=687	
Age, y	77.5±9.2	75.0±8.7	<0.001
Female sex	49.5	47.0	0.4
White race	88	90.5	0.3
Black race	7.1	5.0	
Hypertension	87.6	85.0	0.2
Diabetes	25.3	27.8	0.3
Heart failure	76.6	71.2	0.04
Chronic kidney disease	27.9	25.3	0.3
Coronary artery disease	68.2	64.3	0.2
Stroke	9.4	8.2	0.5
Lung disease	34.2	32.9	0.6
Liver disease	3.3	3.6	0.7
Anemia	34.8	30.4	0.1
Peripheral vascular disease	19.1	18.1	0.6
CHA_2DS_2-VASc, mean±SD	5 (4–6)	5 (4–6)	0.1
Frailty score, median (IQR)	7.1 (3.0–13.5)	6.7 (3.5–11.7)	0.2
Mitral clip	61.9	34.5	<0.001
Surgical mitral valve repair	38.1	65.5	

(*Continued*)

Table 1. Continued

Mitral valve repair cohort			
	DOAC N=491	Warfarin N=687	
Apixaban	67.2	NA	
Rivaroxaban	26.1		
Dabigatran	6.7		

CHA_2DS_2-VASc indicates Congestive heart failure, Hypertension, Age 75 years or older, Diabetes mellitus, previous Stroke/TIA, Vascular disease, Age 65–74 years, Sex category; DOAC, direct oral anticoagulants; IQR, interquartile range; NA; not applicable and TAVR, transcatheter aortic valve replacement.

by restricted mean survival time (mean difference −6.8 [95% CI, 5.9–7.7 months], *P*=0.04) compared with warfarin (Figures 1A through 1C).

Bioprosthetic Group

The study included 8089 patients with AF and bioprosthetic valve (mitral N=1250, surgical aortic N=3338, TAVR N=3090, and both mitral and aortic N=411), 4996 (61.7%) of whom were on warfarin and 3093 (38.3%) on DOACs (apixaban n=2186, rivaroxaban n=734, and dabigatran n=173). Patients on DOACs were older (mean age 78.0±8.1 versus 76.4±8.1, *P*<0.001), and had a higher prevalence of diabetes, heart failure, and hypertension compared with patients on warfarin (Table 1). There was no difference between the 2 groups in prevalence of anemia, liver or kidney disease, or in $CHADS_2$VASc or frailty scores.

After a median follow-up of 413 days (interquartile range, 164–1015 days), with inverse probability treatment weighting adjustment, DOACs were associated with similar risk of mortality (HR 0.93, 95% CI 0.86–1.01, *P*=0.08) compared with warfarin, with no interaction with location of valve ($P_{interaction}$=0.2) (Table 2). However, DOACs were associated with a higher risk of ischemic stroke (HR, 1.27 [95% CI, 1.13–1.43], *P*<0.001) and lower risk of major bleeding (HR, 0.86 [95% CI, 0.80–0.93], *P*<0.001) with no interaction with location of valve ($P_{interaction}$>0.1) in both outcomes. For instance, DOAC was associated with higher risk of ischemic stroke in surgical aortic valve replacement (HR, 1.24 [95% CI, 1.05–1.45]), TAVR (HR, 1.22 [95% CI, 0.99–1.50]), and MVR (HR, 1.70 [95% CI, 1.29–2.24]) ($P_{interaction}$=0.2).

Table 3 shows baseline characteristics of the 2 groups after PS matching. Both groups were well balanced in all variables. Upon PS matching, there was evidence of violation of proportional hazards assumption for the mortality outcome. Using the restricted mean survival time method, DOAC was associated with lower mortality compared with warfarin (mean difference in survival +2.8 [95% +2.3 to +3.4 months, *P*=0.049] [Figure 2A]). For the study secondary outcomes, results remained similar with DOAC associated with higher risk of ischemic stroke (HR, 1.27 [95% CI, 1.07–1.51], *P*=0.007), and lower risk of major bleeding (HR, 0.86 [95% CI, 0.76–0.97], *P*=0.01) (Figure 2B and 2C).

DISCUSSION

In this study examining the use of DOACs versus warfarin in patients with valve repair/replacement and AF in the United States, important findings were observed. First, the off-label use of DOACs in these elderly patients in the United States is common, reaching ≈42% with valve repair. Second, midterm outcomes with DOACs versus warfarin varied among different groups of patients with AF and valve repair/replacement. In patients with AF and valve repair, DOACs were associated with reduced risk of mortality compared with warfarin, driven by reduction in both ischemic stroke and major bleeding. Furthermore, in patients with AF and bioprosthetic valve replacement, DOACs were associated with similar mortality compared with warfarin, likely because of counterbalance of increased risk of ischemic stroke and reduced risk of major bleeding.

DOACs Versus Warfarin in AF and Mitral Valve Repair

There is an increase in the trends of utilization of DOACs in patients with AF and mitral valve repair,[10] despite lack of supportive literature. Few observational studies examined different antithrombotic therapies (aspirin, rivaroxaban, and warfarin) after surgical mitral valve repair in absence of another indication for OAC.[17,18] In patients after valve repair and other indication for OAC, the recent European

Table 2. Adjusted Long-Term Outcomes With Direct Oral Anticoagulants Versus Warfarin in Both Study Cohorts

Outcome	Hazards ratio	95% CI	*P* value
Mitral valve repair cohort			
All-cause mortality	0.67	0.55–0.82	<0.001
Ischemic stroke	0.72	0.52–1.00	0.05
Major bleeding	0.79	0.63–0.99	0.04
Bioprosthetic valve replacement cohort			
All-cause mortality	0.93	0.86–1.01	0.08
Ischemic stroke	1.27	1.13–1.43	<0.001
Major bleeding	0.86	0.80–0.93	<0.001

Table 3. Baseline Characteristics of the Study Cohort After Propensity Score Matching

Biological valve comparison			
	DOAC N=2940	Warfarin N=4360	Standardized differences
Age, y	77.76 (8.00)	77.87 (8.30)	−0.01
Male sex	0.59 (0.49)	0.56 (0.50)	0.06
CHA_2DS_2-VASc score	5.12 (1.51)	5.18 (1.50)	−0.03
Frailty score	9.38 (8.56)	9.63 (8.21)	−0.03
Prior ICD	0.03 (0.17)	0.03 (0.17)	−0.01
Anemias	0.32 (0.47)	0.35 (0.48)	−0.06
Liver disease	0.04 (0.20)	0.04 (0.19)	0.01
Chronic pulmonary disease	0.34 (0.47)	0.34 (0.48)	0
Chronic kidney disease	0.24 (0.43)	0.26 (0.44)	−0.06
Hypertension	0.93 (0.26)	0.92 (0.27)	0.04
Diabetes	0.41 (0.49)	0.39 (0.49)	0.03
Congestive heart failure	0.68 (0.47)	0.68 (0.47)	−0.02
Coronary artery disease	0.76 (0.43)	0.76 (0.43)	0
Stroke	0.15 (0.36)	0.17 (0.37)	−0.04
Drug abuse	0.01 (0.11)	0.01 (0.10)	0.01
Peripheral vascular disease	0.31 (0.46)	0.33 (0.47)	−0.05
Location of bioprosthetic valve	2.45 (0.70)	2.45 (0.70)	0
Mitral valve repair comparison			
	DOAC N=403	Warfarin N=596	
Age, y	76.37 (9.38)	76.91 (8.42)	−0.06
Male sex	0.52 (0.50)	0.51 (0.50)	0.02
CHA_2DS_2-VASc score	4.72 (1.61)	4.75 (1.58)	−0.01
Frailty	8.68 (7.66)	9.32 (7.81)	−0.08
Prior ICD	0.10 (0.30)	0.10 (0.30)	0
Deficiency anemias	0.33 (0.47)	0.36 (0.48)	−0.06
Liver disease	0.03 (0.18)	0.03 (0.17)	0.01
Chronic pulmonary disease	0.33 (0.47)	0.32 (0.47)	0.03
Hypertension	0.86 (0.35)	0.86 (0.35)	0.01
Diabetes	0.26 (0.44)	0.26 (0.44)	−0.02
Congestive heart failure	0.71 (0.45)	0.73 (0.44)	−0.04
Chronic kidney disease	0.27 (0.44)	0.30 (0.46)	−0.08
Coronary artery disease	0.68 (0.47)	0.66 (0.47)	0.04
Stroke	0.10 (0.30)	0.09 (0.28)	0.04
Drug abuse	0.01 (0.11)	0.02 (0.14)	−0.06
Peripheral vascular disease	0.19 (0.40)	0.19 (0.39)	0.01
Mitral clip	0.54 (0.50)	0.54 (0.50)	0
Surgical MV repair	0.46 (0.50)	0.46 (0.50)	0

CHA_2DS_2-VASc indicates Congestive heart failure, Hypertension, Age 75 years or older, Diabetes mellitus, previous Stroke/TIA, Vascular disease, Age 65–74 years, Sex category; DOACs, direct oral anticoagulants; ICD, implantable cardioverter defibrillator; and MV, mitral valve.

Society of Cardiology guidelines do not specify the preferred agent because of lack of data.[19] Similarly, the recent American College of Cardiology/American Heart Association guidelines do not comment on antithrombotic therapy after valve repair.[20] To our knowledge, the current study is the first to examine DOACs versus warfarin in nearly 1200 patients with AF and valve repair, >40% of whom were on DOACs. Importantly, DOACs were associated with lower rates in all 3 outcomes: mortality, ischemic stroke, and major bleeding. It is possible that the combination of lower risk of thromboembolism with valve repair compared with bioprosthetic valve replacement, as well as the easier-to-maintain therapeutic level with DOACs versus warfarin, have contributed to the lower stroke risk with DOACs, which in addition to the known lower bleeding risk resulted in lower risk of mortality.

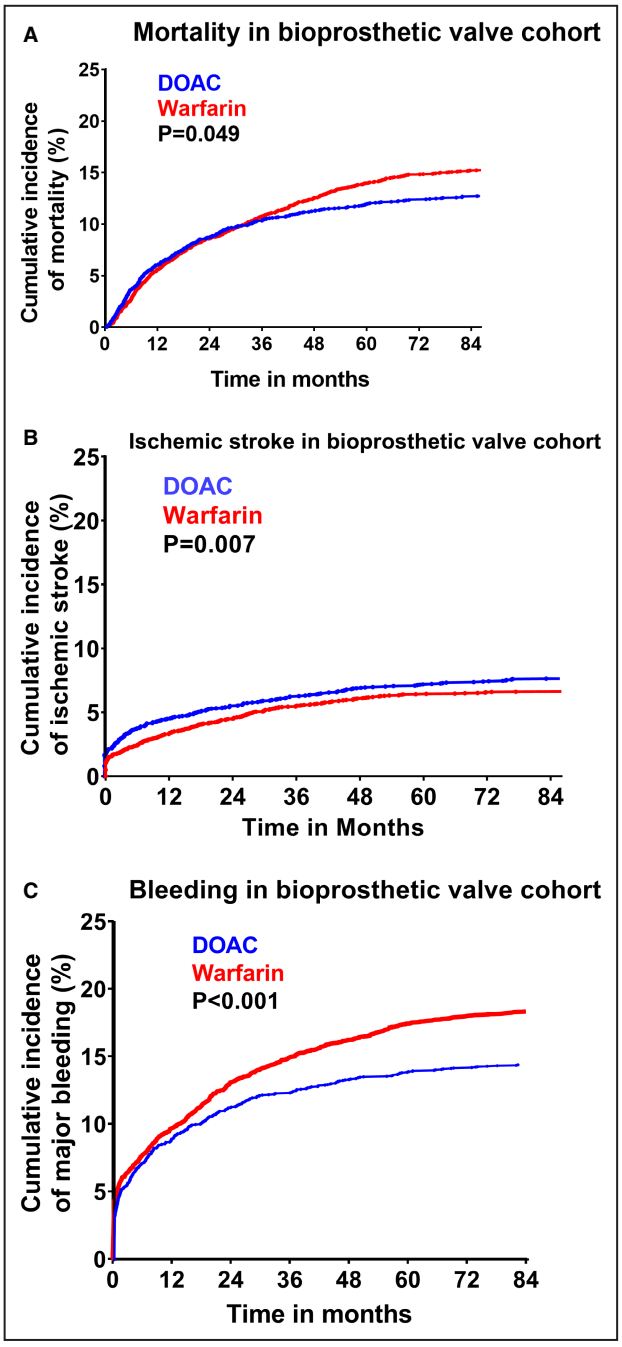

Figure 1. Cumulative incidence of study end points in patients with atrial fibrillation and mitral valve repair cohort. Cumulative incidence of (**A**) all-cause mortality, (**B**) ischemic stroke, and (**C**) major bleeding in patients with atrial fibrillation and mitral valve repair. DOAC indicates direct oral anticoagulants.

DOAC Versus Warfarin in AF and Bioprosthetic Valve

The utilization of DOACs rather than warfarin in patients with AF and bioprosthetic valves is increasing, reaching 6% of patients in 2017.[9] In a recent large retrospective cohort, DOACs were used in up to 16% of those patients.[21] The relatively lower risk of thromboembolism with bioprosthetic valves compared with mechanical valves is likely to encourage physicians to consider discontinuing giving patients warfarin, given its known limitations including narrow therapeutic range, need for frequent monitoring, and potential noncompliance. Few studies have demonstrated the overall safety and efficacy of using DOACs versus warfarin in patients with AF and bioprosthetic aortic or mitral valves. In the study by Duan et al that included 2672 patients with AF and bioprosthetic heart valve, DOACs were associated with fewer bleeding events, and similar mortality compared with warfarin.[21] Although DOACs were associated with numerically higher thromboembolic events compared with warfarin, this did not reach statistical significance.[21] In Brazilian patients with AF and mitral bioprosthetic valve, the RIVER (Rivaroxaban for Valvular Heart Disease and Atrial Fibrillation) trial demonstrated the noninferiority of rivaroxaban in the time to composite outcome of mortality, major cardiovascular events, and bleeding compared with warfarin, but with a higher rate of the secondary outcome of ischemic stroke.[22]

In patients with TAVR, results are less consistent in the literature. In the randomized ATLANTIS (Anti-Thrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis) trial,[23] the use of apixaban 5 mg twice daily in patients with an indication for anticoagulation was associated with similar primary outcome of time to death, thromboembolic or major bleeding events compared with warfarin.[24] In the 4D computed tomography subset cohort from the same study, apixaban was associated with a statistically nonsignificant increase in the primary outcome of ≥1 prosthetic leaflet with reduced leaflet motion grade 3/4 or hypoattenuated leaflet thrombosis grade 3/4 at 90 days.[24] Four observational studies further added to the debate. In a Danish nationwide study with a total of 735 patients, there was no difference in the risk of arterial thromboembolism, bleeding, or mortality between DOACs and warfarin.[25] In the OCEAN-TAVI (Optimized Transcatheter Valvular Intervention) registry, DOACs were associated with less mortality, but similar rates of stroke and bleeding compared with warfarin.[26] In the Registry of Aortic Valve Bioprostheses Established by Catheter, the risk of both mortality and bleeding was lower with DOAC, with similar rates of stroke, compared with warfarin.[27] In contrast, a study that included 962 patients from 4 European tertiary centers demonstrated higher rates of composite outcome of mortality, bleeding, and stroke compared with warfarin, driven by increase in the rates of stroke.[28] An important limitation to some of these registry studies is that therapy was assigned in the beginning of the study, and patients were assumed to have continued the same therapy during the study follow-up period,

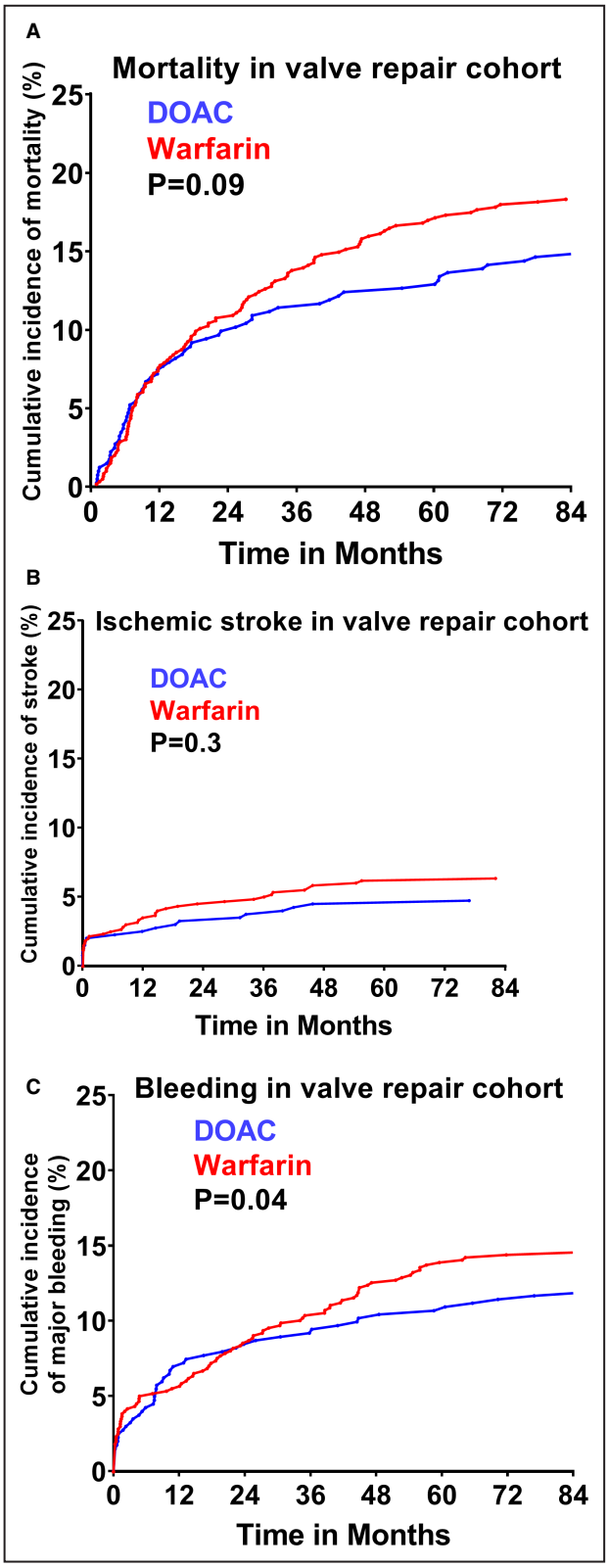

Figure 2. Cumulative incidence of study end points in patients with atrial fibrillation and bioprosthetic valve replacement cohort.
Cumulative incidence of (**A**) all-cause mortality, (**B**) ischemic stroke, and (**C**) major bleeding in patients with atrial fibrillation and bioprosthetic valve replacement. DOAC indicates direct oral anticoagulants.

without systematic assessment for continuation of assigned treatment in follow-up, and hence, potential lack of capture of patients who stopped their treatment or crossed over to the other arm. The recently published ENVISAGE-TAVI AF (Edoxaban versus Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation–Atrial Fibrillation) trial, edoxaban was noninferior to warfarin in patients with prevalent AF undergoing TAVR, but the incidence of major bleeding was higher with edoxaban compared with warfarin.[29]

In the current study, DOACs were utilized in more than one third of patients with AF and bioprosthetic valve and were associated with similar midterm mortality compared with warfarin, without interaction with the valve location. While the risk of ischemic stroke appeared to be higher with DOACs, such an effect was counterbalanced with significant reduction in major bleeding. Although the higher risk of ischemic stroke in patients with bioprosthetic valve replacement is likely attributed to higher rates of valve thrombosis, other unknown factors related to aortic valve disease could play a role. In a recent study from a Danish nationwide registry, DOACs were associated with a higher risk of ischemic stroke compared with warfarin in patients with severe aortic stenosis, without valve replacement.[30]

Our study comes with several limitations. First, because of the observational nature of our study, results may be impacted with residual confounding and bias. For instance, the decision of the physician to proceed with one anticoagulation agent over the other could have been potentially affected by uncaptured patient characteristics. Despite utilizing 2 adjustment methods, namely, inverse probability weighting and PS matching to adjust for measured confounders between both groups, residual selection bias because of unmeasured confounders cannot be entirely excluded. Second, we could not calculate the Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage score for the study cohort because of lack of some variables in the database such as over-the-counter aspirin and nonsteroidal anti-inflammatory drugs, history of labile international normalized ratio, and number of alcohol drinks per week. This may have impacted bleeding outcomes in the current study. Third, we did not have data on important echocardiography variables such as left ventricular ejection fraction or left atrial volume. Fourth, our study included patients enrolled in part D benefits from the Medicare database enhanced 5% sample, so results might not be generalizable to younger patients with private insurance,

or Medicare patients not enrolled in Part D benefits. Lastly, in our study, we used Medicare Part D Event Files to ascertain the study exposure variable, DOAC versus warfarin. Using Part D data comes with some limitations. If the patient is prescribed the drug, but does not fill the prescription, this patient would not be captured in our study cohort, because our study included only patients who filled the prescriptions and thus resulted in the pharmacy submitting a claim to Medicare. Furthermore, if a patient has a secondary insurance (for instance, Veterans Affairs Health insurance), they can get a prescription for their anticoagulation from their secondary insurance, but again, such a patient would not be included in our study. Both limitations would decrease sensitivity but would not affect specificity of exposure ascertainment in our study. Furthermore, any misclassification would be nondifferential and would only bias the results toward the null. The large size cohort allowing for enough power to study clinical outcomes, the consistent longitudinal follow-up of pharmacy claims and refills for all patients to ensure no dropout or cross-over, and finally the novel results in an area of a major gap of knowledge are the main strengths of the current study.

CONCLUSIONS

In patients with AF, DOACs are associated with similar mortality in patients with surgical and transcatheter bioprosthetic valve replacement, and reduced mortality in those with surgical and transcatheter mitral valve repair. Major bleeding was less with DOACs in both bioprosthetic valve replacement and valve repair cohorts. Ischemic stroke was higher with DOACs in patients with bioprosthetic valve replacement, but less in patients with valve repair, compared with warfarin. These rather novel findings call for future randomized controlled trials to determine the best anticoagulation strategy in patients with AF and concomitant valve disease.

ARTICLE INFORMATION

Received May 2, 2022; accepted July 18, 2022.

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Sources of Funding

The current research was partly funded by philanthropic gifts by the Haslam Family, Bailey Family and Khouri family to the Cleveland Clinic for Dr Milind Desai's research.

Disclosures

Dr Desai is a consultant for Medtronic and Bristol Myers Squibb. He is on the executive steering committee of a trial sponsored by Bristol Myers Squibb. The remaining authors report no conflicts of interest.

Supplemental Material

Tables S1–S2
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. List of the used ICD-9 and ICD-10 procedure codes used for identifying study cohort

	ICD-9 code	ICD-10 code
Transcatheter aortic valve replacement	35.05, 35.06	02RF37Z, 02RF38Z, 02RF3JZ, 02RF3KZ, 02RF37H, 02RF38H, 02RF3JH, 02RF3KH, X2RF332
Bioprosthetic surgical aortic valve replacement	35.21	02RF07Z, 02RF08Z, 02RF0KZ
Bioprosthetic surgical mitral valve replacement	35.23	02RG07Z, 02RG08Z, 02RG0KZ
Transcatheter mitral valve repair	35.97	02UG3JZ
Surgical mitral valve repair	35.12	02QG0ZZ, 02VG0ZZ

Table S2. Individual components of the claims based hospital frailty score

ICD code	Diagnosis
G81	Hemiplegia
G30	Alzheimer's disease
I69	Sequelae of cerebrovascular disease
R29	Other symptoms and signs involving the nervous and musculoskeletal systems
N39	Other disorders of urinary system
F05	Delirium, not induced by alcohol and other psychoactive substances
W19	Unspecified fall
S00	Superficial injury of head
R31	Unspecified hematuria
B96	Other bacterial agents as the cause of diseases classified to other chapters (secondary code)
R41	Other symptoms and signs involving cognitive functions and awareness
R26	Abnormalities of gait and mobility
I67	Other cerebrovascular diseases
R56	Convulsions, not elsewhere classified
R40	Somnolence, stupor, and coma
T83	Complications of genitourinary prosthetic devices, implants, and grafts
S06	Intracranial injury
S42	Fracture of shoulder and upper arm
E87	Other disorders of fluid, electrolyte, and acid-base balance
M25	Other joint disorders, not elsewhere classified
E86	Volume depletion
R54	Senility
F03	Unspecified dementia
W18	Other fall on same level
Z75	Problems related to medical facilities and other health care
F01	Vascular dementia
S80	Superficial injury of lower leg
L03	Cellulitis
H54	Blindness and low vision
E53	Deficiency of other B group vitamins
Z60	Problems related to social environment
G20	Parkinson's disease
R55	Syncope and collapse
S22	Fracture of rib(s), sternum and thoracic spine
K59	Other functional intestinal disorders
N17	Acute renal failure

L89	Decubitus ulcer
Z22	Carrier of infectious disease
B95	Streptococcus and staphylococcus as the cause of diseases classified to other chapters
L97	Ulcer of lower limb, not elsewhere classified
R44	Other symptoms and signs involving general sensations and perceptions
K26	Duodenal ulcer
I95	Hypotension
N19	Unspecified renal failure
A41	Other septicemia
Z87	Personal history of other diseases and conditions
J96	Respiratory failure, not elsewhere classified
M19	Other arthrosis
G40	Epilepsy
M81	Osteoporosis without pathological fracture
S72	Fracture of femur
S32	Fracture of lumbar spine and pelvis
E16	Other disorders of pancreatic internal secretion
R94	Abnormal results of function studies
N18	Chronic renal failure
R33	Retention of urine
R69	Unknown and unspecified causes of morbidity
N28	Other disorders of kidney and ureter, not elsewhere classified
R32	Unspecified urinary incontinence
G31	Other degenerative diseases of nervous system, not elsewhere classified
Y95	Nosocomial condition
S09	Other and unspecified injuries of head
R45	Symptoms and signs involving emotional state
G45	Transient cerebral ischemic attacks and related syndromes
Z74	Problems related to care-provider dependency
M79	Other soft tissue disorders, not elsewhere classified
W06	Fall involving bed
S01	Open wound of head
A04	Other bacterial intestinal infections
A09	Diarrhea and gastroenteritis of presumed infectious origin
J18	Pneumonia, organism unspecified
J69	Pneumonitis due to solids and liquids
R47	Speech disturbances, not elsewhere classified
E55	Vitamin D deficiency
Z93	Artificial opening status

R63	Symptoms and signs concerning food and fluid intake
H91	Other hearing loss
W10	Fall on and from stairs and steps
W01	Fall on same level from slipping, tripping and stumbling
E05	Thyrotoxicosis [hyperthyroidism]
M41	Scoliosis
R13	Dysphagia
Z99	Dependence on enabling machines and devices
M80	Osteoporosis with pathological fracture
K92	Other diseases of digestive system
I63	Cerebral Infarction
N20	Calculus of kidney and ureter
F10	Mental and behavioral disorders due to use of alcohol
Y84	Other medical procedures as the cause of abnormal reaction of the patient
R00	Abnormalities of heart beat
J22	Unspecified acute lower respiratory infection
Z73	Problems related to life-management difficulty
R79	Other abnormal findings of blood chemistry
Z91	Personal history of risk-factors, not elsewhere classified
S51	Open wound of forearm
F32	Depressive episode
M48	Spinal stenosis (secondary code only)
E83	Disorders of mineral metabolism
M15	Polyarthrosis
D64	Other anemias
L08	Other local infections of skin and subcutaneous tissue
R11	Nausea and vomiting
K52	Other noninfective gastroenteritis and colitis
R50	Fever of unknown origin

Figure S1. Study cohort Flow chart