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Patients with atrial fibrillation (AF) commonly have impaired renal function. The safety and efficacy of direct oral anticoagulants (DOACs) in patients with chronic kidney disease (CKD) and end-stage renal disease has not been fully elucidated. This study evaluated and compared the safety outcomes of DOACs versus warfarin in patients with nonvalvular AF and concomitant CKD. Patients in our health system with AF prescribed oral anticoagulants during 2010 to 2017 were identified. All-cause mortality, bleeding and hemorrhagic, and ischemic stroke were evaluated based on degree of renal impairment and method of anticoagulation. There were 21,733 patients with a CHA₂DS₂-VASc score of ≥ 2 included in this analysis. Compared with warfarin, DOAC use in patients with impaired renal function was associated with lower risk of mortality with a hazard ratio (HR): 0.76 (95% confidence interval [CI] 0.70 to 0.84, p value <0.001) in patients with eGFR >60 , HR 0.74 (95% CI 0.68 to 0.81, p value <0.001) in patients with eGFR >30 to 60, and HR 0.76 (95% CI 0.63 to 0.92, p value <0.001) in patients with eGFR ≤ 30 or on dialysis. Bleeding requiring hospitalization was also less in the DOAC group with a HR 0.93 (95% CI 0.82 to 1.04, p value 0.209) in patients with eGFR >60 , HR 0.83 (95% CI 0.74 to 0.94, p value 0.003) in patients with eGFR >30 to 60, and HR 0.69 (95% CI 0.50 to 0.93, p value 0.017) in patients with eGFR ≤ 30 or on dialysis. In conclusion, in comparison to warfarin, DOACs appear to be safe and effective with a lower risk of all-cause mortality and lower bleeding across all levels of CKD. © 2019 Elsevier Inc. All rights reserved. (Am J Cardiol 2020;125:210–214)

Table 1
Baseline demographics and characteristics stratified by anticoagulation strategy

Variable	Total	DOAC	Warfarin	p Value
# Of patients	21,733	10,794	10,939	
Age (years)	75.7 ± 9.96	75.0 ± 9.97	76.4 ± 9.91	<0.001
Female	10,862 (50.0%)	5,472 (50.7%)	5,390 (49.3%)	0.036
Race				<0.001
White	20,493 (94.3%)	10,229 (94.8%)	10,264 (93.8%)	
Black	981 (4.5%)	419 (3.9%)	562 (5.1%)	
Other	259 (1.2%)	146 (1.4%)	113 (1.0%)	
Body Mass Index (Kg/M ²)	30.4 ± 7.23	30.7 ± 7.34	30.2 ± 7.11	<0.001
Estimated glomerular filtration rate	62.3 ± 25.7	64.9 ± 23.3	59.7 ± 27.7	<0.001
Obesity*	14,525 (66.8%)	7,642 (70.8%)	6,883 (62.9%)	<0.001
Cancer	3,514 (16.2%)	1,839 (17.0%)	1,675 (15.3%)	<0.001
Lung cancer	231 (1.1%)	120 (1.1%)	111 (1.0%)	0.486
Dialysis	181 (0.8%)	34 (0.3%)	147 (1.3%)	<0.001
Major bleeding	2,807 (12.9%)	1,512 (14.0%)	1,295 (11.8%)	<0.001
Pulmonary hypertension	1,086 (5.0%)	430 (4.0%)	656 (6.0%)	<0.001
Chronic obstructive pulmonary disease	3,252 (15.0%)	1,590 (14.7%)	1,662 (15.2%)	0.339
Congestive heart failure	6,000 (27.6%)	2,473 (22.9%)	3,527 (32.2%)	<0.001
Diabetes mellitus	7,047 (32.4%)	3,340 (30.9%)	3,707 (33.9%)	<0.001
Coronary artery disease	6,792 (31.3%)	3,202 (29.7%)	3,590 (32.8%)	<0.001
Hypertension*	16,395 (75.4%)	8,362 (77.5%)	8,033 (73.4%)	<0.001
Hyperlipidemia*	13,697 (63.0%)	7,042 (65.2%)	6,655 (60.8%)	<0.001
Stroke	3,360 (15.5%)	1,720 (15.9%)	1,640 (15.0%)	0.055
Hemorrhagic stroke	176 (0.8%)	78 (0.7%)	98 (0.9%)	0.154
Vascular disease	1,262 (5.8%)	625 (5.8%)	637 (5.8%)	0.917
Deep venous thrombosis	682 (3.1%)	268 (2.5%)	414 (3.8%)	<0.001
Pulmonary embolism	731 (3.4%)	244 (2.3%)	487 (4.5%)	<0.001
CKD group				<0.001
EGFR ≤30 (ml/min) or dialysis	1,525 (7.0%)	475 (4.4%)	1,050 (9.6%)	
EGFR >30-60 (ml/min)	9,118 (42.0%)	4,273 (39.6%)	4,845 (44.3%)	
EGFR >60 (ml/min)	11,090 (51.0%)	6,046 (56.0%)	5,044 (46.1%)	
Medications:				<0.001
Apixaban	4,952 (22.8%)	4,952 (45.9%)	0 (0.0%)	
Dabigatran	1,507 (6.9%)	1,507 (14.0%)	0 (0.0%)	
Edoxaban	11 (0.1%)	11 (0.1%)	0 (0.0%)	
Rivaroxaban	4,324 (19.9%)	4,324 (40.1%)	0 (0.0%)	
Warfarin	10,939 (50.3%)	0 (0.0%)	10,939 (100%)	

DOAC = Direct oral anticoagulant; eGFR = estimated glomerular filtration rate.

* These characteristics were based on the ICD-9 and ICD-10 codes, which were identified based on the following criteria. Hypertension was diagnosed based on a blood pressure >149/90 mm Hg. Obesity was defined as a BMI >30 kg/m². Hyperlipidemia was defined as either having a triglyceride level >150 mg/dl or low density lipoprotein >100 mg/dl.

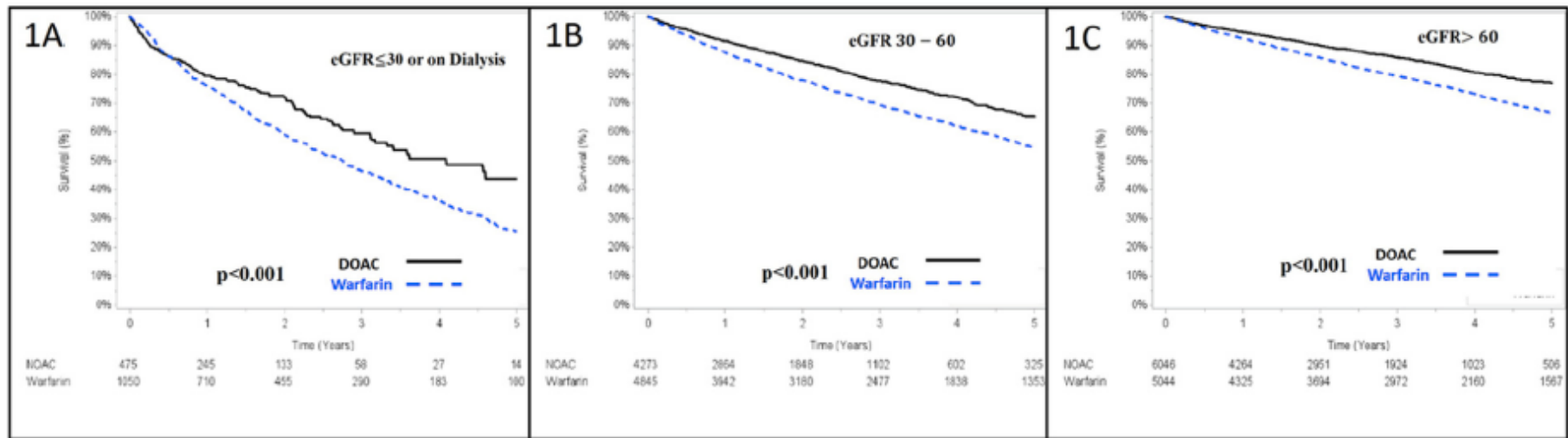


Figure 1. Kaplan-Meier curve of mortality in DOAC- and warfarin-treated patients with eGFR ≤ 30 (A), eGFR of 30–60 (B), and eGFR > 60 (C).

Table 2
Risk of clinical outcomes based on renal function and anticoagulation strategy

	EGFR \leq 30 ml/min or on dialysis			EGFR >30-60 ml/min			EGFR >60 ml/min		
	Events/ Incidence*	Adjusted HR (95%CI)	p Value	Events/ Incidence*	Adjusted HR (95%CI)	p Value	Events/ Incidence*	Adjusted HR (95% CI)	p Value
All-cause mortality									
DOAC	133/19.3	0.76 (0.63-0.92)	0.005	748/8.4	0.74 (0.68, 0.81)	<0.001	726/5.3	0.76 (0.70, 0.84)	<0.001
Warfarin	613/26.3	REF	REF	2,041/12.3	REF	REF	1,540/8.1	REF	REF
Bleeding event									
DOAC	51/7.9	0.69 (0.50, 0.93)	0.017	439/5.3	0.83 (0.74, 0.94)	0.003	485/3.8	0.93 (0.82, 1.04)	0.209
Warfarin	216/10.5	REF	REF	871/5.9	REF	REF	699/4.0	REF	REF
Embolic stroke									
DOAC	14/2.1	0.60 (0.34, 1.09)	0.092	204/2.4	0.87 (0.73, 1.04)	0.117	239/1.8	0.86 (0.73, 1.02)	0.087
Warfarin	66/2.9	REF	REF	400/2.5	REF	REF	380/2.1	REF	REF
Hemorrhagic stroke									
DOAC	4/0.6	0.55 (0.19, 1.61)	0.276	30/0.3	0.41 (0.27, 0.61)	<0.001	46/0.3	0.58 (0.40, 0.82)	0.002
Warfarin	23/1.0	REF	REF	127/0.8	REF	REF	114/0.6	REF	REF

* Total number of events/total follow up time (Years)/Incidence per 100 patient years. DOAC = Direct oral anticoagulant.



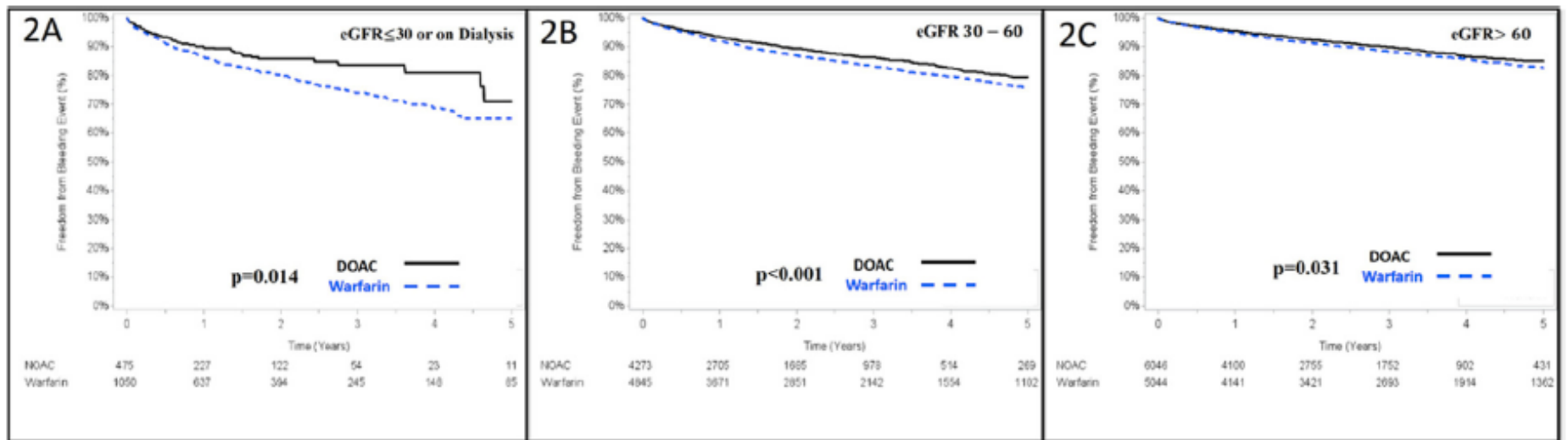


Figure 2. Kaplan-Meier curve of bleeding in DOAC- and warfarin-treated patients with eGFR ≤ 30 (A), eGFR of 30–60 (B), and eGFR >60 (C).

Table 3
Association between bleeding and stroke events with subsequent mortality

	All patients	Alive	Expired	
All patients	No bleed or stroke, %	86.66%	73.06%	p <0.0001
	With bleed or stroke, %	13.34%	26.94%	
eGFR <30 ml/min	No bleed or stroke, %	55.07%	36.22%	p <0.0001
	With bleed or stroke, %	44.93%	63.78%	
eGFR 30-60ml/min	No bleed or stroke, %	72.63%	55.68%	p <0.0001
	With bleed or stroke, %	27.37%	44.32%	
eGFR >60 ml/min	No bleed or stroke, %	82.27%	63.93%	p <0.0001
	With bleed or stroke, %	17.73%	36.07%	

eGFR = estimated glomerular filtration rate.