

SUPPLEMENTAL MATERIAL

Table S1. Definitions of covariates

Diagnosis	ICD-10-CM code and definition	Diagnostic definition
Atrial fibrillation	I480-484, I489	Admission or outpatient department≥1
EHRA type 2 valvular heart disease		
Mitral valve disease	I340-I342	
Aortic valve disease	I350-I352, I060-I062	Admission≥1
Tricuspid valve disease	I360-I362, I070-I072	
Pulmonary valve disease	I370-I372	
EHRA type 1 valvular heart disease		
Rheumatic mitral stenosis	I050, I052, I059	Admission or outpatient department≥1
Prosthetic heart valves	Z952-Z954	
Pulmonary embolism	I26	Admission≥1
Deep vein thrombosis	I802	Admission≥1
Received joint replacement operation	N0711, N1711, N1721, N2070, N3710, N3721, N3717, N3720, N2072, N2077, N3722, N3727	Admission≥1
End stage renal disease	N185, Z49	Dialysis≥2
Ischemic stroke	I63, I64	Admission≥1 and brain imaging (CT or MRI) ≥1
Intracranial hemorrhage	I60-62	Admission≥1 or RBC transfusion≥1
Hospitalization for GI bleeding	K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K92.0, K92.1, K92.2	Admission≥1 and RBC transfusion≥1

Hypertension	I10-I13, I15; and minimum 1 prescription of anti-hypertensive drug (thiazide, loop diuretics, aldosterone antagonist, alpha-/beta-blocker, calcium-channel blocker, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker).	Admission≥1 or outpatient department≥2
Diabetes mellitus	E11-E14; and minimum 1 prescription of anti-diabetic drugs (sulfonylureas, metformin, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, α-glucosidase inhibitors, and insulin).	Admission≥1 or outpatient department≥2
Dyslipidemia	E78	Admission or outpatient department≥1
Heart failure	I50	Admission or outpatient department≥1
Vascular disease		
Prior MI	I21, I22	Admission or outpatient department≥1
PAD	I70, I73	Admission or outpatient department≥2
Chronic kidney disease	N18	Admission or outpatient department≥1
Chronic hepatitis	B15-19	Admission or outpatient department≥1
Liver cirrhosis	K70-77	Admission or outpatient department≥1
COPD	J41-44	Admission or outpatient department≥1

Abbreviation: COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; MI, myocardial infarction; PAD, peripheral artery disease.

Table S2. Definitions of clinical outcomes

Clinical outcomes	ICD-10-CM code and definition	Diagnostic definition
Ischemic stroke	I63, I64	Admission $\geq$ 1 and brain imaging (CT or MRI) $\geq$ 1
Intracranial hemorrhage	I60-62	Admission $\geq$ 1 or RBC transfusion $\geq$ 1
Hospitalization for GI bleeding	K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K92.0, K92.1, K92.2	Admission $\geq$ 1 and RBC transfusion $\geq$ 1
Hospitalization for major bleeding	Intracranial hemorrhage or gastrointestinal bleeding	ICH, admission $\geq$ 1 or RBC transfusion $\geq$ 1 GI bleeding, admission $\geq$ 1 and RBC transfusion $\geq$ 1
Composite outcome	Ischemic stroke, intracranial hemorrhage, gastrointestinal bleeding or all-cause death	Ischemic stroke, Admission $\geq$ 1 and brain imaging (CT or MRI) $\geq$ 1 ICH, admission $\geq$ 1 or RBC transfusion $\geq$ 1 GI bleeding, admission $\geq$ 1 and RBC transfusion $\geq$ 1

Abbreviation: GI, gastrointestinal; ICH, intracranial hemorrhage.

Table S3. The logistic regression model used to calculate the propensity score

	Coefficient	SE	OR (95% CI)	P value
Age (per year)	0.060	0.003	1.061 (1.057-1.066)	<0.001
Sex (male)	-0.113	0.032	0.645 (0.601-0.693)	<0.001
CHA₂DS₂-VASc score (per point)	-0.044	0.031	0.850 (0.824-0.876)	0.149
Hypertension	0.012	0.034	1.031 (0.964-1.103)	0.731
Diabetes mellitus	-0.016	0.039	1.079 (0.996-1.169)	0.675
Dyslipidemia	-0.050	0.029	1.129 (1.061-1.201)	0.089
Congestive heart failure	0.070	0.033	0.742 (0.692-0.796)	0.034
Prior MI	0.185	0.073	0.764 (0.656-0.889)	0.011
COPD	0.062	0.032	0.863 (0.805-0.926)	0.056
PAD	-0.028	0.041	1.265 (1.164-1.375)	0.490

Abbreviation: CI, confidence interval; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; OR, odds ratio; PAD, peripheral artery disease; SE, standard error of coefficient.

Table S4. The proportion of patients with low income

	Before IPTW			After IPTW with 5% trimming		
	Warfarin	NOACs	ASD	Warfarin	NOACs	ASD
Low income (%)	25.6	25.3	0.008	24.6	24.8	0.003

Abbreviation: ASD, absolute standardized difference; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant.

Table S5. Hazard ratios of 6 clinical outcomes for NOAC versus warfarin after additional adjusting for low income

NOAC vs. Warfarin	HR (95% CI)	p-value
Ischemic stroke	0.712 (0.527-0.962)	0.026
Intracranial hemorrhage	0.842 (0.535-1.326)	0.459
Hospitalization for GI bleeding	0.503 (0.351-0.722)	<0.001
Hospitalization for major bleeding	0.605 (0.454-0.807)	<0.001
All-cause death	0.725 (0.595-0.883)	0.001
Composite outcome	0.683 (0.584-0.798)	<0.001

Abbreviation: CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant.

Table S6. The proportion of patients with CKD, liver disease, and antiplatelets

	After IPTW with 5% trimming		
	Warfarin (n=2,371)	NOACs (n=2,792)	ASD
CKD (%)	163 (6.9%)	124 (4.4%)	0.155
Chronic hepatitis (%)	180 (7.6%)	221 (7.9%)	0.026
Liver cirrhosis (%)	41 (1.7%)	38 (1.4%)	0.009
Antiplatelets (%)	1802 (76.0%)	2201 (78.9%)	0.056

Abbreviation: ASD, absolute standardized difference; CKD, chronic kidney disease; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant.

Table S7. Hazard ratios of 6 clinical outcomes for NOAC versus warfarin after additional adjusting for CKD, liver disease, and antiplatelets

NOAC vs. Warfarin	CKD and liver disease		Antiplatelets		CKD, liver disease, and antiplatelets	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Ischemic stroke	0.743 (0.550-1.005)	0.054	0.709 (0.525-0.957)	0.025	0.741 (0.548-1.002)	0.052
Intracranial hemorrhage	0.901 (0.570-1.423)	0.654	0.842 (0.535-1.326)	0.459	0.901 (0.570-1.423)	0.654
Hospitalization for GI bleeding	0.544 (0.379-0.782)	0.001	0.503 (0.351-0.722)	<0.001	0.545 (0.379-0.783)	0.001
Hospitalization for major bleeding	0.649 (0.486-0.867)	0.004	0.605 (0.454-0.807)	0.001	0.650 (0.487-0.868)	0.004
All-cause death	0.761 (0.624-0.928)	0.007	0.724 (0.594-0.882)	0.001	0.760 (0.623-0.927)	0.007
Composite outcome	0.717 (0.613-0.839)	<0.001	0.680 (0.582-0.796)	<0.001	0.716 (0.612-0.838)	<0.001

Abbreviation: CI, confidence interval; CKD, chronic kidney disease; GI, gastrointestinal; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant.

Table S8. Sensitivity analysis restricting the follow-up period to 6-month or 1-year

NOAC vs. Warfarin	HR (95% CI)	P-value
6-month follow-up		
Ischemic stroke	0.690 (0.462-1.030)	0.069
Intracranial hemorrhage	0.614 (0.316-1.192)	0.149
Hospitalization for GI bleeding	0.718 (0.456-1.132)	0.153
Hospitalization for major bleeding	0.726 (0.496-1.062)	0.098
All-cause death	0.692 (0.527-0.911)	0.008
Composite outcome	0.710 (0.576-0.875)	0.001
1-year follow-up		
Ischemic stroke	0.716 (0.513-0.999)	0.049
Intracranial hemorrhage	0.826 (0.504-1.353)	0.447
Hospitalization for GI bleeding	0.524 (0.354-0.777)	0.001
Hospitalization for major bleeding	0.653 (0.478-0.892)	0.007
All-cause death	0.720 (0.578-0.897)	0.003
Composite outcome	0.696 (0.586-0.826)	<0.001

Abbreviation: CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant.

Table S9. Sensitivity analysis: Hazard ratios of 6 clinical outcomes for pooled NOAC versus warfarin by on-treatment analysis

NOAC vs. Warfarin	HR (95% CI)	P-value
Ischemic stroke	0.625 (0.443-0.882)	0.007
Intracranial hemorrhage	0.773 (0.468-1.277)	0.314
Hospitalization for GI bleeding	0.497 (0.330-0.748)	<0.001
Hospitalization for major bleeding	0.582 (0.422-0.803)	0.001
All-cause death	0.705 (0.544-0.912)	0.007
Composite outcome	0.669 (0.555-0.807)	<0.001

Abbreviation: CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant.

Table S10. Number of events, crude event rates according to various subgroups in patients with EHRA type 2 VHD

Subgroup category	Treatment group	Total number	Ischemic stroke		ICH		Hospitalization for GI bleeding		Hospitalization for major bleeding		All-cause death		Composite outcome*	
			Events	IR [†]	Events	IR [†]	Events	IR [†]	Events	IR [†]	Events	IR [†]	Events	IR [†]
Age (years)														
<65	Warfarin	1052	24	1.2	11	0.5	26	1.3	36	1.8	39	1.9	79	4.0
	NOACs	457	11	2.8	6	1.5	0	0	6	1.5	5	1.2	18	4.6
65-74	Warfarin	813	44	2.9	22	1.4	29	1.9	51	3.3	99	6.3	157	10.6
	NOACs	1042	24	2.5	10	1.1	11	1.1	20	2.1	37	3.9	66	7.0
≥75	Warfarin	806	73	5.2	26	1.8	63	4.5	81	5.8	198	13.4	286	21.6
	NOACs	1559	50	3.7	20	1.4	46	3.4	62	4.5	189	13.6	257	19.3
Sex														
Male	Warfarin	1382	83	3.3	39	1.5	71	2.8	104	4.1	185	7.1	298	12.2
	NOACs	1884	59	3.5	27	1.6	39	2.3	61	3.6	147	8.6	227	13.7
Female	Warfarin	1289	58	2.4	20	0.8	47	1.9	64	2.7	151	6.1	224	9.5
	NOACs	1174	26	2.5	9	0.9	18	1.7	27	2.6	84	8.1	114	11.3
CHA ₂ DS ₂ -VASc														
0-2	Warfarin	840	16	1.1	8	0.5	12	0.8	19	1.3	34	2.3	59	4.0
	NOACs	492	7	1.8	3	0.7	2	0.5	5	1.2	7	1.7	19	4.8
≥3	Warfarin	1831	125	3.6	51	1.4	106	3.0	149	4.3	302	8.3	463	13.9
	NOACs	2566	78	3.4	33	1.4	55	2.4	83	3.6	224	9.5	322	14.1

Type of valvular heart disease														
MR	Warfarin	1134	60	2.8	26	1.2	44	2.0	65	3.0	141	6.4	215	10.4
	NOACs	1278	30	2.6	14	1.2	19	1.6	28	2.4	82	6.9	119	10.4
Others[‡]	Warfarin	1537	81	2.9	33	1.2	74	2.6	103	3.7	195	6.7	307	11.4
	NOACs	1780	55	3.6	22	1.4	38	2.4	60	3.9	149	9.5	222	14.7

*Composite outcome, ischemic stroke + ICH + hospitalization for GI bleeding + all-cause death

[†]Incidence rate, per 100 person-years

[‡]Other valvular disease included AS, AR, TS, TR, PS, and PR.

Abbreviation: AR, aortic regurgitation; AS, aortic stenosis; GI, gastrointestinal; ICH, intracranial hemorrhage; MR, mitral regurgitation; NOAC, non-vitamin K antagonist oral anticoagulant; PR, pulmonary regurgitation; PS, pulmonary stenosis; TR, tricuspid regurgitation; TS, tricuspid stenosis.

Table S11. Baseline characteristics of patients with EHRA type 1 VHD

	Warfarin (n=366)	NOACs (n=245)	P value
Age, years	67.2±12.4	74.5±9.0	< 0.001
<65	34.7	10.6	
65-74	33.3	33.1	
≥75	32.0	56.3	
Men	47.0	55.1	0.050
CHA₂DS₂-VASc score	3.7±1.9	4.4±1.6	< 0.001
0-2	27.1	10.6	
≥3	73.0	89.4	
Hypertension	73.8	77.1	0.345
Diabetes mellitus	21.6	22.9	0.710
Dyslipidemia	47.5	58.8	0.006
Heart failure	56.3	49.0	0.076
Prior MI	11.2	13.5	0.400
PAD	12.3	17.1	0.093
COPD	27.3	26.1	0.743
NOAC dose[†]			
Regular dose	-	28.2	-
Reduced dose	-	71.8	-

Values are mean ± standard deviation or %.

[†]Regular dose NOACs are 20 mg rivaroxaban once daily, 150 mg dabigatran twice daily, 5 mg apixaban twice daily, and 60 mg edoxaban once daily. Reduced dose NOACs are 15/10 mg rivaroxaban once daily, 110 mg dabigatran once daily, 2.5 mg apixaban twice daily, and 30 mg edoxaban once daily.

Abbreviation: ASD, absolute standardized difference; COPD, chronic obstructive pulmonary disease; EHRA, Evaluated Heartvalves, Rheumatic or Artificial; MI, myocardial infarction; NOAC, non-vitamin K antagonist oral anticoagulant; PAD, peripheral artery disease; VHD, valvular heart disease.

Figure S1. Distribution of propensity scores in pooled NOAC and warfarin groups before and after weighting

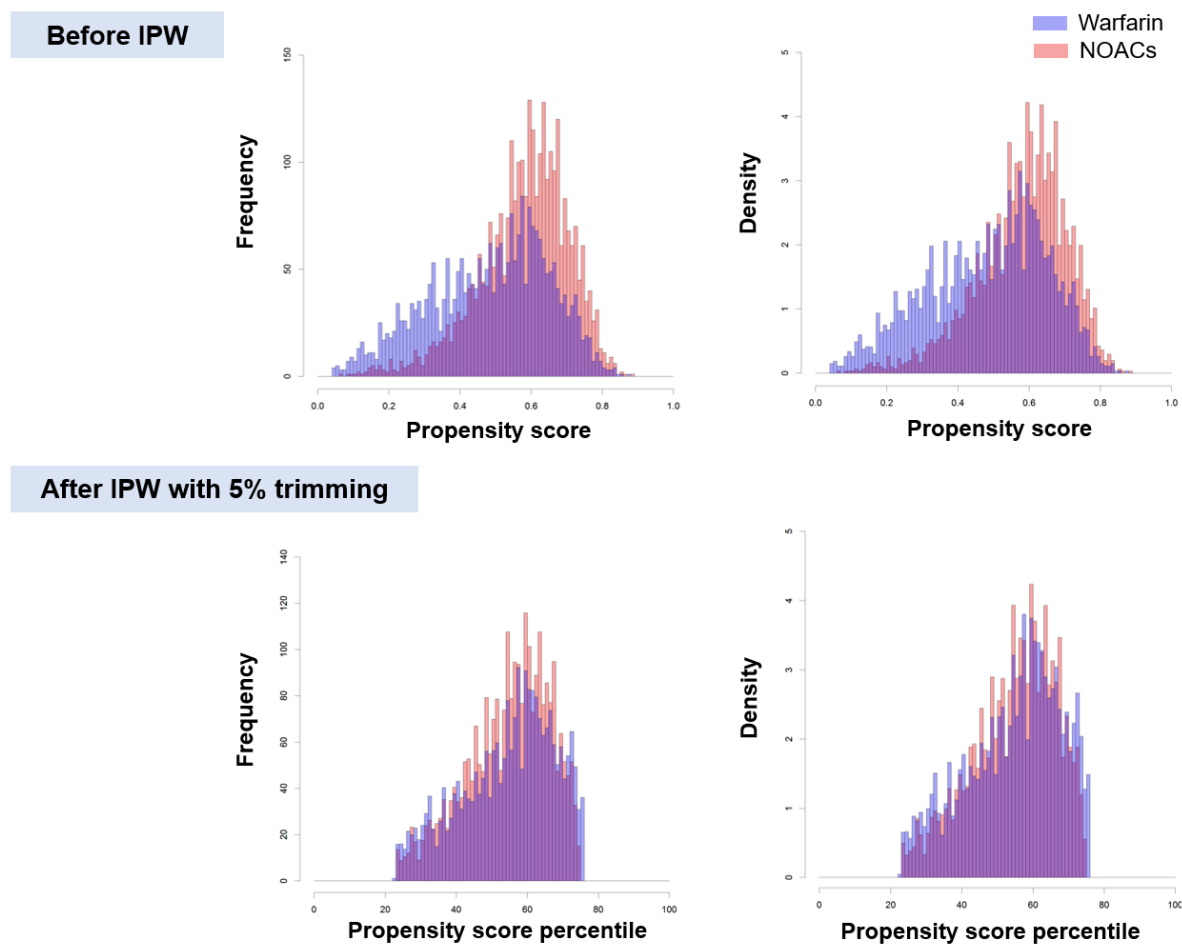


Figure S2. Hazard ratios of six clinical outcomes with pooled NOAC versus warfarin using multivariate Cox regression analysis in patients with EHRA type 2 VHD

