Online Supplement

Original Research

Comparison of Bleeding Risks and All-Cause Death Between Warfarin and Direct Oral Anticoagulants in Patients With Atrial Fibrillation and Chronic Obstructive Pulmonary Disease: A Multicenter Retrospective Cohort Study

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Supplemental Table 1. List of 12 multi-center hospitals

Number	Institutes	Investigators	City
1	Shanxi Bethune Hospital	Ruijuan Li	Taiyuan
2	First Affiliated Hospital of Xi'an Jiaotong University	Qiaowei Zheng	Xi'an
3	People's Hospital of He'nan University of Chinese Medicine	Xiumei Liu	Zhengzhou
4	Affiliated Fuzhou First Hospital of Fujian Medical University	Hengfen Dai	Fuzhou
5	Pingtan County General Laboratory Area Hospital	Xiangsheng Lin	Fuzhou
6	Huaihe Hospital of Henan University, kaifeng	Yuxin Liu	Kaifeng
7	Department of Pharmacy, the First Affiliated Hospital of Bengbu Medical College	Jun Su	Bengbu
8	Department of Pharmacy, Fujian Maternity and Child Health Hospital	Jinhua Zhang	Fuzhou
9	Affiliated Hospital of Guilin Medical University	Xiaomin Dong	Guilin
10	Ningde Municipal Hospital Affiliated to Ningde Normal University	Cuifang You	Ningde
11	Wuhan Hospital of Traditional Chinese and Western Medicine	Shuzheng Jiang	Wuhan
12	Minzu Hospital of Guangxi Zhuang Autonomous Region	Yanxian Lan	Nanning

Supplementary Table 2. Baseline characteristics of atrial fibrillation patients with and without COPD (unweighted)

Characteristic	AF-only(N=10818)	AF+COPD(N=314)	P-value	SMD
sex,male(%)	6292 (58.2)	234 (74.5)	<0.001	0.352
age,median[IQR]	67.00 [59.00, 75.00]	76.00 [70.00, 82.00]	<0.001	0.873
BMI,median[IQR]	24.22 [21.88, 26.37]	23.22 [21.48, 24.84]	<0.001	0.254
smoking(%)	4094 (37.8)	134 (42.7)	0.093	0.099
drinking(%)	2641 (24.4)	89 (28.3)	0.126	0.089
hypertension(%)	7277 (67.3)	180 (57.3)	<0.001	0.206
diabetes(%)	2558 (23.6)	82 (26.1)	0.344	0.057
HF(%)	2708 (25.0)	170 (54.1)	<0.001	0.623
gout(%)	354 (3.3)	23 (7.3)	<0.001	0.182
stroke(%)	1644 (15.2)	64 (20.4)	0.015	0.136
CHD(%)	2219 (20.5)	148 (47.1)	<0.001	0.586
TIA(%)	386 (3.6)	18 (5.7)	0.062	0.103
hepatic insufficiency(%)	327 (3.0)	9 (2.9)	1.000	0.009
renal insufficiency(%)	1043 (9.6)	37 (11.8)	0.243	0.069
TBil,median[IQR]	15.40 [10.62, 17.90]	13.40 [8.72, 19.45]	0.006	0.037
albumin,median[IQR]	38.50 [36.40, 40.80]	37.85 [33.62, 40.50]	<0.001	0.204
ALT,median[IQR]	22.00 [14.00, 29.40]	19.00 [13.00, 28.98]	0.002	0.059
AST,median[IQR]	28.00 [20.00, 40.10]	24.50 [19.00, 33.98]	<0.001	0.010
ALP,median[IQR]	82.00 [65.00, 89.00]	78.00 [63.10, 90.97]	0.416	0.017
creatinine,median[IQR]	85.00 [69.00, 94.00]	89.50 [75.00, 115.00]	<0.001	0.319
PLT,median[IQR]	199.15 [157.00, 226.67]	195.50 [158.00, 240.00]	0.387	0.134
Hb,median[IQR]	131.60 [122.00, 143.00]	128.00 [115.00, 140.00]	<0.001	0.269
antiplatelet(%)	3359 (31.1)	103 (32.8)	0.549	0.038
anticoagulation(%)	6063 (56.0)	46 (14.6)	<0.001	0.961
NSAIDs(%)	783 (7.2)	40 (12.7)	<0.001	0.184
PPI(%)	6582 (60.8)	150 (47.8)	<0.001	0.265
statins(%)	5930 (54.8)	180 (57.3)	0.410	0.051
ARB(%)	3011 (27.8)	94 (29.9)	0.450	0.046
β-blocker(%)	6883 (63.6)	162 (51.6)	<0.001	0.245
CCB(%)	3053 (28.2)	62 (19.7)	0.001	0.200
Digoxin(%)	1644 (15.2)	81 (25.8)	<0.001	0.265
Has-Bled,median[IQR]	1 [1, 2]	2 [1, 2]	<0.001	0.317
CHA2DS2-VASC,median[IQR]	3 [1, 4]	4 [3, 5]	<0.001	0.792

Footnotes：Values are median (interquartile range) except as noted

COPD: Chronic obstructive pulmonary disease, BMI: Body mass index, HF: Heart failure, CHD: coronary heart disease, TIA: Transient ischemic attack, DOACs: Direct oral anticoagulants, TBil: total bilirubin, ALT: Alanine transaminase, AST: Aspartate transaminase , ALP: Alkaline phosphatase, PLT: Platelet count, Hb: Hemoglobin, NSAIDs: Nonsteroidal antiinflammatory drugs, PPI: Proton pump inhibitor, ARB: Angiotensin receptor blockers, CCB: Calcium entry blockers

Supplementary Table 3. Event Counts by Treatment and Outcome for Patients with AF and AF with COPD

Outcomes	AF-only(N=10818)[a]		AF+COPD(N=314)[b]	
	Warfarin (N=1189)	DOACs[c] (N=9629)	Warfarin (N=43)	DOACs (N=271)
Total Bleeding	85(7.15)	893(9.27)	6(13.95)	21(7.75)
Major Bleeding	18(1.51)	262(2.72)	1(2.33)	9（3.32）
Minor Bleeding	69(5.80)	631(6.55)	5(11.63)	12(4.43)
All-cause death	128(10.77)	629(6.53)	6(13.95)	33(12.18)
thromboembolic events[d]	28(2.35)	246(2.55)	0(0)	7(2.58)
NACE[e]	44(3.70)	408(4.24)	1(2.33)	16(5.90)

Footnotes：Values are n (%), where % is the column percentage within each treatment group.Counts shown here are unweighted; overlap-weighted effective counts and absolute risks are provided in Supplementary table.

a. AF-only denotes atrial fibrillation without COPD.

b. AF-only denotes atrial fibrillation without COPD.

c. DOACs include dabigatran, apixaban, rivaroxaban, and edoxaban.

d. thromboembolic events indicates thromboembolism (ischemic stroke or systemic embolism).

e. NACE (net adverse clinical events) : thromboembolic events or major bleeding (composite).

Supplementary Table 4. Overlap-weighted event counts and absolute risks by treatment arm, shown separately for AF-only and AF+COPD[a]

Outcomes	OACs	AF-only			AF+COPD		
		Non-events	Events	Rate(%)[b]	Non-events	Events	Rate(%)
Total bleeding	Warfarin	10446.09	685.91	6.16	9438.34	1693.66	15.21
	DOAC	10170.67	961.33	8.64	10230.51	901.49	8.10
Major bleeding	Warfarin	10894.18	237.82	2.14	10694.27	437.73	3.93
	DOAC	10703.70	428.30	3.85	10745.68	386.32	3.47
Minor bleeding	Warfarin	10653.58	478.42	4.30	9703.47	1428.53	12.83
	DOAC	10598.10	533.90	4.80	10598.52	533.48	4.79
All cause death	Warfarin	9453.89	1678.11	15.07	9425.53	1706.47	15.33
	DOAC	9951.82	1180.18	10.60	9822.35	1309.65	11.76
NACE[c]	Warfarin	10764.26	367.74	3.30	10693.64	438.36	3.94
	DOAC	10500.55	631.45	5.67	10441.40	690.60	6.20

Footnotes:

a. Non-events and Events are weighted effective counts.

b. Rate (%): 100 × (events) / [(events) + (non-events)] within each treatment arm.

c. NACE (net adverse clinical events) : thromboembolic events or major bleeding (composite).

Supplementary Table 5. Baseline characteristics in the matched cohort vs the excluded patients (PSM 1:1)

Characteristic	Included(N=624)	Excluded(N=10508)	p	SMD
sex,male(%)	467 (74.8)	6059 (57.7)	<0.001	0.369
age,median[IQR]	76.00 [70.00, 83.00]	67.00 [59.00, 74.00]	<0.001	0.893
BMI,median[IQR]	23.44 [21.40, 25.16]	24.22 [21.91, 26.37]	<0.001	0.217
smoking(%)	265 (42.5)	3963 (37.7)	0.020	0.097
drinking(%)	174 (27.9)	2556 (24.3)	0.050	0.081
hypertension(%)	362 (58.0)	7095 (67.5)	<0.001	0.198
diabetes(%)	157 (25.2)	2483 (23.6)	0.409	0.036
HF(%)	324 (51.9)	2554 (24.3)	<0.001	0.593
gout(%)	40 (6.4)	337 (3.2)	<0.001	0.150
stroke(%)	130 (20.8)	1578 (15.0)	<0.001	0.152
CHD(%)	293 (47.0)	2074 (19.7)	<0.001	0.603
TIA(%)	38 (6.1)	366 (3.5)	0.001	0.122
hepatic insufficiency(%)	16 (2.6)	320 (3.0)	0.574	0.029
renal insufficiency(%)	80 (12.8)	1000 (9.5)	0.008	0.105
TBil,median[IQR]	13.60 [9.40, 18.60]	15.50 [10.70, 17.90]	0.002	0.029
albumin,median[IQR]	37.75 [34.20, 40.30]	38.50 [36.50, 40.80]	<0.001	0.229
ALT,median[IQR]	19.00 [12.88, 29.40]	22.00 [14.20, 29.40]	<0.001	0.076
AST,median[IQR]	24.00 [18.00, 35.00]	28.00 [20.00, 40.10]	<0.001	0.056
ALP,median[IQR]	78.00 [63.00, 92.00]	82.00 [65.00, 89.00]	0.288	0.015
creatinine,median[IQR]	89.50 [73.00, 113.00]	85.00 [69.00, 94.00]	<0.001	0.291
PLT,median[IQR]	196.00 [158.00, 240.25]	199.20 [157.00, 226.00]	0.087	0.140
Hb,median[IQR]	129.00 [113.30, 141.00]	131.60 [122.60, 143.20]	<0.001	0.251
antiplateletv	221 (35.4)	3241 (30.8)	0.019	0.097
anticoagulation(%)	82 (13.1)	6027 (57.4)	<0.001	1.044
NSAIDs(%)	91 (14.6)	732 (7.0)	<0.001	0.248
PPI(%)	306 (49.0)	6426 (61.2)	<0.001	0.245
statins(%)	369 (59.1)	5741 (54.6)	0.031	0.091
ARB(%)	206 (33.0)	2899 (27.6)	0.004	0.118
β_blocker(%)	310 (49.7)	6735 (64.1)	<0.001	0.294
CCB(%)	123 (19.7)	2992 (28.5)	<0.001	0.206
Digoxin(%)	151 (24.2)	1574 (15.0)	<0.001	0.234
Has-Bled,median[IQR]	2.00 [1.00, 2.00]	1.00 [1.00, 2.00]	<0.001	0.364
CHA2DS2-VASC,median[IQR]	4.00 [3.00, 6.00]	3.00 [1.00, 4.00]	<0.001	0.784

Footnotes：Values are median (interquartile range) except as noted

COPD: Chronic obstructive pulmonary disease, BMI: Body mass index, HF: Heart failure, CHD: coronary heart disease, TIA: Transient ischemic attack, DOACs: Direct oral anticoagulants, TBil: total bilirubin, ALT: Alanine transaminase, AST: Aspartate transaminase , ALP: Alkaline phosphatase, PLT: Platelet count, Hb: Hemoglobin, NSAIDs: Nonsteroidal antiinflammatory drugs, PPI: Proton pump inhibitor, ARB: Angiotensin receptor blockers, CCB: Calcium entry blockers

Supplementary Table 6. Crude (unadjusted) and propensity-score–matched (1:1) associations of COPD (vs no COPD) with outcomes in the overall atrial fibrillation cohort, stratified by anticoagulant type

Footnotes:

Outcomes	OACs	Crude(unadjusted)[a]			PSM(1:1)[b]		
		OR(95%CI)	RD(95%CI),%[c]	P for interaction	aOR(95%CI)	RD(95%CI),%	P for interaction
Total bleeding	Warfarin	2.11(0.86-5.13)	7.8(-0.8 to 21.0)	0.065	6.18(0.97-39.23)	11.4(-1.0 to 23.8)	0.016
	DOACs	0.82(0.52-1.29)	-1.4(-4.2 to 2.2)		0.58(0.32-1.03)	-5.0(-10.3 to 0.3)	
Major bleeding	Warfarin	1.55(0.20-11.88)	2.2(-1.4 to 13.8)	0.832	NE[d]	4.0(0.4 to 15.9)	-
	DOACs	1.23(0.62-2.41)	0.7(-1.0 to 3.4)		0.66(0.29-1.50)	-1.7(-5.2 to 1.8)	
Minor bleeding	Warfarin	2.14(0.81-5.60)	6.9(-0.9 to 19.8)	0.042	5.02(0.82-30.84)	8.9(-2.6 to 20.7)	0.026
	DOACs	0.66(0.37-1.19)	-2.0(-4.0 to 1.0)		0.56(0.27-1.15)	-3.4(-7.7 to 0.8)	
All-cause death	Warfarin	1.34(0.56-3.25)	4.2(-4.4 to 17.3)	0.426	2.16(0.44-10.66)	6.3(-10.0 to 20.4)	0.494
	DOACs	1.98(1.37-2.88)	5.7(2.2 to 9.9)		1.18(0.69-2.04)	1.5(-3.9 to 7.0)	
NACE[e]	Warfarin	0.62(0.08-4.61)	0.1(-3.8 to 11.4)	0.433	NE	3.6(0.4 to 14.0)	–
	DOACs	1.42(0.85-2.37)	1.8(-0.6 to 5.0)		0.84(0.42-1.68)	-1.1(-5.5 to 3.3)	

a.Crude (unadjusted): within-OAC logistic model with COPD as the only predictor; interaction P from an unadjusted model with COPD×OAC in the overall cohort.

b. PSM (1:1): propensity scores using covariates with |SMD|>0.10; 1:1 nearest-neighbour matching.

c. RD(95%CI), %: absolute risk difference (COPD − no COPD), in percentage points.

d. NE: not estimable due to zero/sparse events or separation.

e. NACE (net adverse clinical events) : thromboembolic events or major bleeding (composite).

Supplementary Table 7. Overlap-weighted event counts and absolute risks by treatment group in patients with AF and COPD[a]

Outcome	Warfarin			DOACs			Min weighted cell[c]
	Non-events	Events	Rate(%)[b]	Non-events	Events	Rate(%)	
Total bleeding	21.79	3.86	15.1	23.83	1.71	6.7	1.71
Major bleeding	25.61	0.04	0.2	25.22	0.32	1.3	0.04
Minor bleeding	21.82	3.83	14.9	24.15	1.39	5.4	1.39
All-cause death	23.39	2.26	8.8	23.05	2.49	9.8	2.26
NACE[d]	25.61	0.04	0.2	24.86	0.67	2.6	0.04

Footnotes：

a. Weighted counts (non-events and events) are effective counts after applying overlap weights (ATO target population) and can be non-integers due to weighting; minor discrepancies may occur because of rounding.

b. Rate (%): 100 × (events) / [(events) + (non-events)] within each treatment arm.

c. Min weighted cell: The minimum of the four overlap-weighted cells in the 2×2 table for that outcome (Warfarin-event, Warfarin-non-event, DOAC-event, DOAC-non-event); used as a small-cell diagnostic.

d. NACE (net adverse clinical events) : thromboembolic events or major bleeding (composite).

Supplementary Table8. Sensitivity Analysis of DOAC vs Warfarin in Patients with AF-COPD: Odds Ratios (OR) and Risk Differences (RD)

	Model 3[a]		Model 4[b]		Model 5[c]	
	OR(95%CI)	RD(95%CI)[d]	aOR(95%CI)	RD(95%CI)	aOR(95%CI)	RD(95%CI)
Total bleeding	0.27(0.08 -0.96)	-6.2(-17.1 to 4.6)	0.21(0.07 -0.61)	-20.4(-44.9 to 4.1)	NE[e]	-17.0(-35.5 to 1.5)
Major bleeding	2.61(0.27 -25.09)	1.0(-4.0 to 6.0)	5.05(0.18 -140.66)	2.4(0.1 to 4.7)	99.652(0.46 -21499.61)[f]	0.5(-0.3 to 1.3)
Minor bleeding	0.18(0.04 -0.85)	-7.2(-17.1 to 2.7)	0.09(0.02 -0.40)	-22.8(-47.3 to 1.7)	NE	-17.5(-36.0 to 1.0)
All-cause death	1.01(0.33 -3.12)	-1.8(-12.9 to 9.3)	2.15(0.58 -7.91)	6.2(-0.3 to 12.8)	0.14(0 -3.79)	2.4(-17.5 to 22.4)
NACE[g]	0.78(0.11 -5.80)	3.6(-1.7 to 8.9)	7.16(0.30 -173.35)	4.8(1.9 to 7.7)	NE	0.7(-0.2 to 1.7)

Footnotes:

a. Model 3 (Unweighted, adjusted): Logistic regression adjusted for prespecified clinical covariates and variables with residual imbalance (|SMD|>0.10).Adjusted covariates:albumin, BMI, CHA2DS2-VASC, creatinine, Has-Bled, PLT, β-blocker, antiplatelet, NSAIDs, PPI, Hb, TBil, ALT, AST, ALP, statins, ARB, CCB, Digoxin, smoking, drinking, hepatic-insufficiency, renal-insufficiency.

b. Model 4 (IPTW, adjusted): Stabilized inverse probability of treatment weighting (ATE), probit propensity score, 1% tail trimming, Logistic regression adjusted for prespecified clinical covariates and variables with residual imbalance (|SMD|> 0.10).Adjusted covariates: age, albumin, BMI, Has-Bled, PLT, β-blocker, CHD, HF

c. Model 5 (Overlap weighting, antiplatelet excluded): Overlap weights from a probit propensity score after excluding patients receiving antiplatelet agents; covariates selected as above.Adjusted covariates:albumin, BMI, CHA2DS2-VASC.

d. RD (95% CI): RD is expressed as absolute risk difference (%) without the percentage symbol，defined as DOAC − warfarin (attributable risk in DOAC minus attributable risk in warfarin), negative values favor DOAC.

e. NE: not estimable due to sparse data (quasi-complete separation): in these instances, one treatment arm had near-zero weighted events, leading the logistic coefficient to diverge.

f. The extremely large OR reflects sparse-data/(quasi-)complete separation after overlap weighting (with antiplatelet exclusion): the (weighted) event count in one arm was ~0, with very small effective sample size (ESS) and minimum weighted cell <5, causing the logit coefficient to diverge and the OR/CI to inflate.

e. NACE (net adverse clinical events) : thromboembolic events or major bleeding (composite).

Supplementary Table 9. Overlap-weighted event counts and absolute risks by renal function: eGFR ≥60 vs <60 mL/min/1.73 m², comparing warfarin with DOACs[a]

Footnotes:

Outcomes	eGFR	Warfarin			DOACs		
		Non-events	Events	Rate(%)[b]	Non-events	Events	Rate(%)
Total bleeding	≥60	16.72	3.07	0.16	16.71	1.36	0.08
	＜60	5.66	1.05	0.16	7.92	0.58	0.07
Major bleeding	≥60	19.79	0	0	17.79	0.27	0.02
	＜60	6.61	0.11	0.02	8.37	0.13	0.02
Minor bleeding	≥60	16.72	3.07	0.16	16.98	1.08	0.06
	＜60	5.77	0.94	0.14	8.05	0.45	0.05
All cause death	≥60	19.15	0.64	0.03	15.69	2.37	0.13
	＜60	4.89	1.82	0.27	8.24	0.26	0.03
NACE[c]	≥60	19.79	0	0	17.61	0.45	0.02
	＜60	6.61	0.11	0.02	8.37	0.13	0.02

a. Weighted counts (non-events and events) are effective counts after applying overlap weights (ATO target population) and can be non-integers due to weighting.

b. Rate (%): 100 × (events) / [(events) + (non-events)] within each treatment arm.

c. NACE (net adverse clinical events) : thromboembolic events or major bleeding (composite).

Supplementary Table 10. Overlap-weighted event counts and absolute risks by DOAC class (Factor Xa inhibitors vs dabigatran)[a]

Outcomes	FXa inhibitors[b]			Dabigatran		
	Non-events	Events	Rate(%)[c]	Non-events	Events	Rate(%)
Total bleeding	13.64	2.27	14.28	14.87	0.89	5.64
Major bleeding	14.28	1.63	10.26	15.75	0.01	0.09
Minor bleeding	15.27	0.64	4.02	14.89	0.87	5.55
All-cause death	13.39	2.52	15.84	13.89	1.88	11.91
NACE[d]	13.80	2.11	13.28	14.21	1.56	9.88

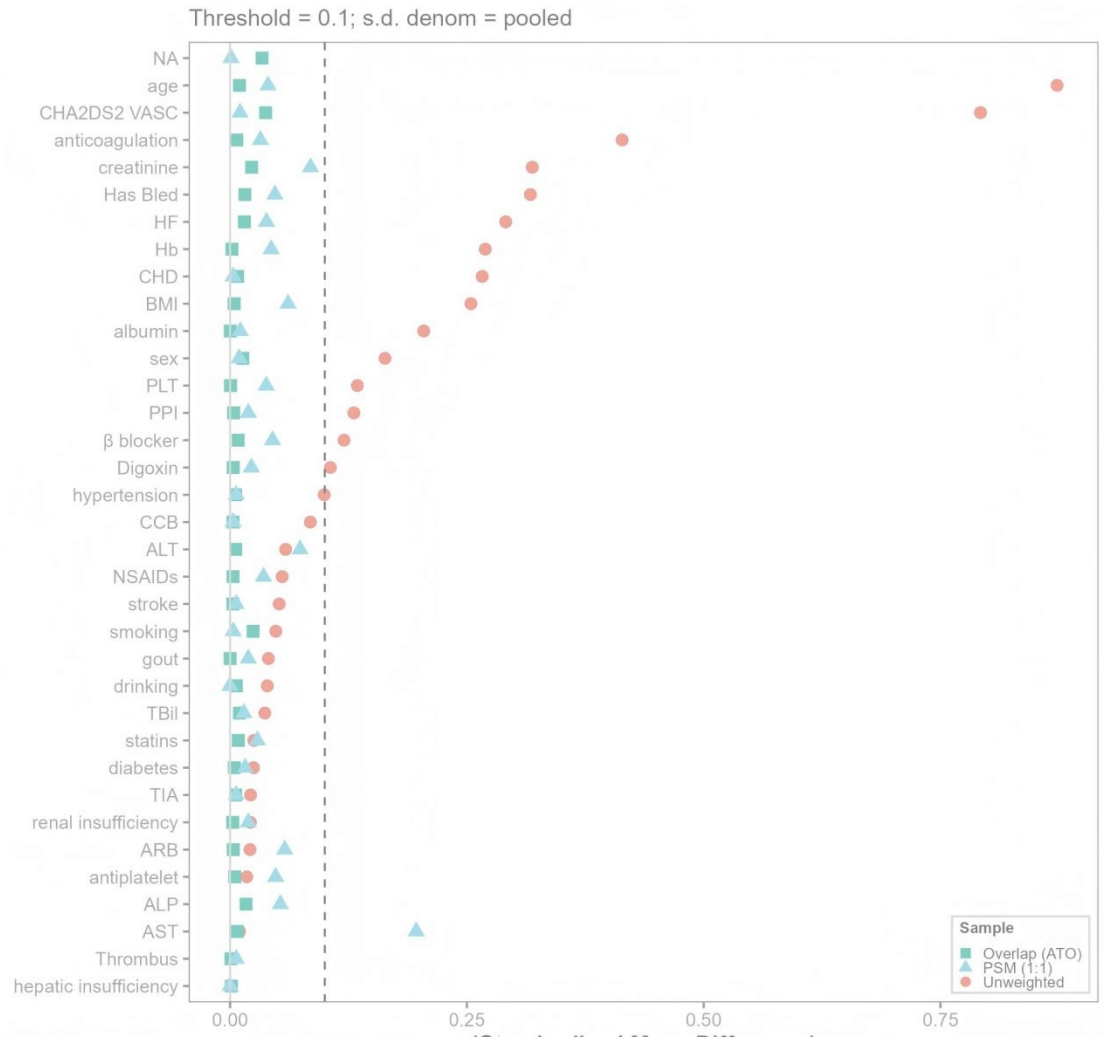
Footnotes:

a. Weighted counts (non-events and events) are effective counts after applying overlap weights (ATO target population) and can be non-integers due to weighting

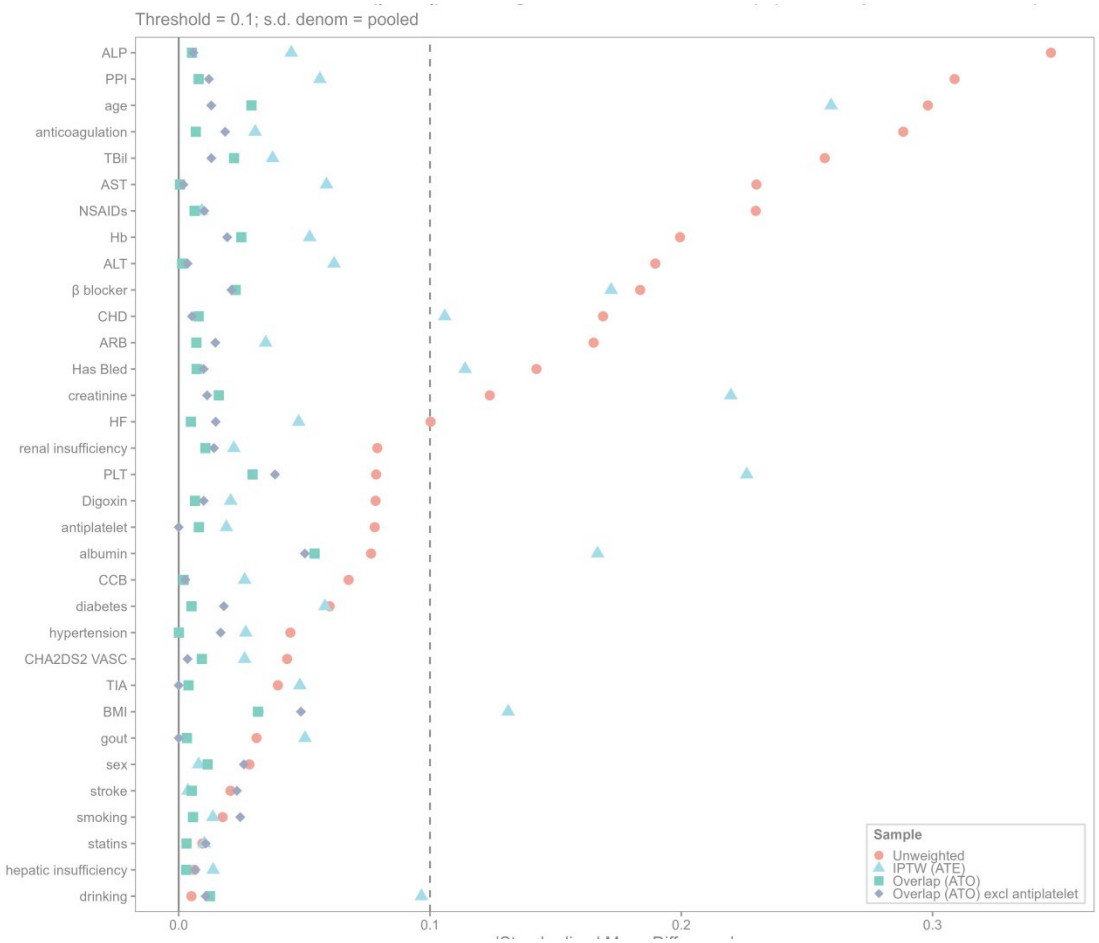
b. FXa inhibitors include apixaban, rivaroxaban, and edoxaban.

c. Rate (%): 100 × (events) / [(events) + (non-events)] within each treatment arm.

d. NACE (net adverse clinical events) : thromboembolic events or major bleeding (composite).



Supplementary figure S1.Supplementary Figure S1. Covariate balance (|SMD|) across analytic methods—Unweighted vs Overlap weighting (ATO) vs 1:1 Propensity Score Matching.



Supplementary Figure S2. Covariate balance (|SMD|) across methods—Unweighted vs IPTW (ATE) vs Overlap weighting (ATO), with and without antiplatelet-user exclusion.