

Supplemental Online Content

Schaefer JK, Errickson J, Li Y, et al. Adverse events associated with the addition of aspirin to direct oral anticoagulant therapy without a clear indication. *JAMA Intern Med*. Published online April 19, 2021. doi:10.1001/jamainternmed.2021.1197

eTable 1. Rates of Gastrointestinal Bleeding (per 100 patient years) for DOAC versus DOAC+ASA

eTable 2. Outcomes of DOAC versus DOAC+ASA (rates per 100 patient years) for Patients Without Any History of MI, CAD, PAD, PCI/CABG

eTable 3. Outcomes of DOAC versus DOAC+ASA (rates per 100 patient years) for Patients Continuously on ASA or Not on ASA Throughout Follow-up

eTable 4. Outcomes of DOAC versus DOAC+ASA (rates per 100 patient years) Not Matching on DOAC Dose

eFigure 1. Standardized Difference Plot

eFigure 2. Study Schema

eFigure 3. Percent of Patients Without Recent Myocardial Infarction or Valve Replacement on Aspirin and DOACs by Year

This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Rates of Gastrointestinal Bleeding (per 100 patient years) for DOAC versus DOAC+ASA^a

# per 100 patient years (95% CI)		DOAC n=1047	DOAC+ASA n=1047	p-value
Major bleed	GI	1.60 (1.36, 1.87)	2.23 (1.95, 2.54)	0.22
	Other location	0.50 (0.37, 0.66)	1.03 (0.84, 1.25)	0.10
Minor bleed	GI	3.04 (2.71, 3.40)	4.57 (4.16, 5.01)	0.03
	Other location	16.75 (15.96, 17.57)	19.49 (18.63, 20.37)	0.11

Abbreviations: ASA, acetylsalicylic acid or aspirin; DOAC, direct oral anticoagulant; GI; gastrointestinal.

^aNumber of events per 100 patient years

eTable 2. Outcomes of DOAC versus DOAC+ASA (rates per 100 patient years) for Patients Without Any History of MI, CAD, PAD, PCI/CABG^a

# per 100 patient years (95% CI)	DOAC n=516	DOAC+ASA n=516	p-value
New Thrombosis	2.21 (1.93, 2.52)	2.17 (1.89, 2.48)	0.79
Ischemic/Embolic Stroke	1.10 (0.90, 1.33)	0.57 (0.43, 0.74)	0.18
TIA	0.00	0.23 (0.15, 0.35)	-
PE	0.11 (0.05, 0.20)	0.23 (0.15, 0.35)	0.55
DVT	0.22 (0.14, 0.33)	0.57 (0.43, 0.74)	0.34
MI	0.00	0.11 (0.05, 0.20)	-
New Bleed	25.51 (24.53, 26.52)	28.34 (27.31, 29.40)	0.23
Major	3.75 (3.35, 4.12)	3.20 (2.86, 3.57)	0.52
-Fatal	0.11 (0.05, 0.20)	0.00	-
-Intracranial or intraspinal	0.55 (0.41, 0.72)	0.23 (0.15, 0.35)	0.27
-Life Threatening	1.33 (1.22, 1.58)	0.57 (0.43, 0.74)	0.09
Non-major	20.65 (19.77, 21.56)	24.69 (23.73, 25.68)	0.07
ER Visit	11.90 (11.23, 12.60)	9.60 (9.00, 10.23)	0.10
For bleeding	10.60 (9.97, 11.26)	8.91 (8.33, 9.51)	0.26
For clotting	1.44 (1.21, 1.70)	0.80 (0.63, 1.00)	0.18
Hospitalization	6.29 (5.81, 6.80)	6.74 (6.24, 7.27)	0.92
For bleeding	4.97 (4.54, 5.43)	5.83 (5.37, 6.32)	0.60
For clotting	1.33 (1.11, 1.58)	0.91 (0.73, 1.12)	0.36
Death	3.75 (3.38, 4.15)	3.31 (2.96, 3.69)	0.61

Abbreviations: ASA, acetylsalicylic acid or aspirin; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ER, emergency room; MI, myocardial infarction; PE, pulmonary embolism; TIA, transient ischemic attack.

^aNumber of events per 100 patient years

eTable 3. Outcomes of DOAC versus DOAC+ASA (rates per 100 patient years) for Patients Continuously on ASA or Not on ASA Throughout Follow-up^a

# per 100 patient years (95% CI)	DOAC n=621	DOAC+ASA n=621	p-value
New Thrombosis	1.46 (1.23, 1.72)	2.72 (2.41, 3.06)	0.09
Ischemic/Embolic Stroke	0.45 (0.33, 0.60)	0.82 (0.65, 1.02)	0.34
TIA	0.11 (0.05, 0.20)	0.12 (0.06, 0.21)	0.99
PE	0.00	0.12 (0.06, 0.21)	-
DVT	0.34 (0.24, 0.48)	0.83 (0.66, 1.03)	0.21
MI	0.00	0.12 (0.06, 0.21)	-
New Bleed	25.78 (24.79, 26.79)	28.49 (27.45, 29.56)	0.56
Major	4.26 (3.87, 4.68)	5.67 (5.21, 6.16)	0.25
-Fatal	0.34 (0.24, 0.48)	0.12 (0.06, 0.21)	0.36
-Intracranial or intraspinal	0.34 (0.24, 0.48)	0.59 (0.45, 0.76)	0.35
-Life Threatening	0.56 (0.42, 0.73)	1.42 (1.2, 1.67)	0.24
Non-major	20.96 (20.07, 21.88)	22.1 (21.19, 23.04)	0.97
ER Visit	11.21 (10.56, 11.89)	14.54 (13.80, 15.31)	0.11
For bleeding	10.31 (9.69, 10.96)	14.07 (13.34, 14.82)	0.04
For clotting	1.12 (0.92, 1.35)	0.47 (0.35, 0.63)	0.23
Hospitalization	7.06 (6.55, 7.60)	10.28 (9.66, 10.93)	0.08
For bleeding	5.83 (5.37, 6.32)	9.57 (8.97, 10.20)	0.02
For clotting	1.23 (1.02, 1.47)	0.71 (0.55, 0.90)	0.28
Death	4.93 (4.50, 5.39)	4.96 (4.53, 5.42)	0.77

Abbreviations: ASA, acetylsalicylic acid or aspirin; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ER, emergency room; MI, myocardial infarction; PE, pulmonary embolism; TIA, transient ischemic attack.

^aNumber of events per 100 patient years

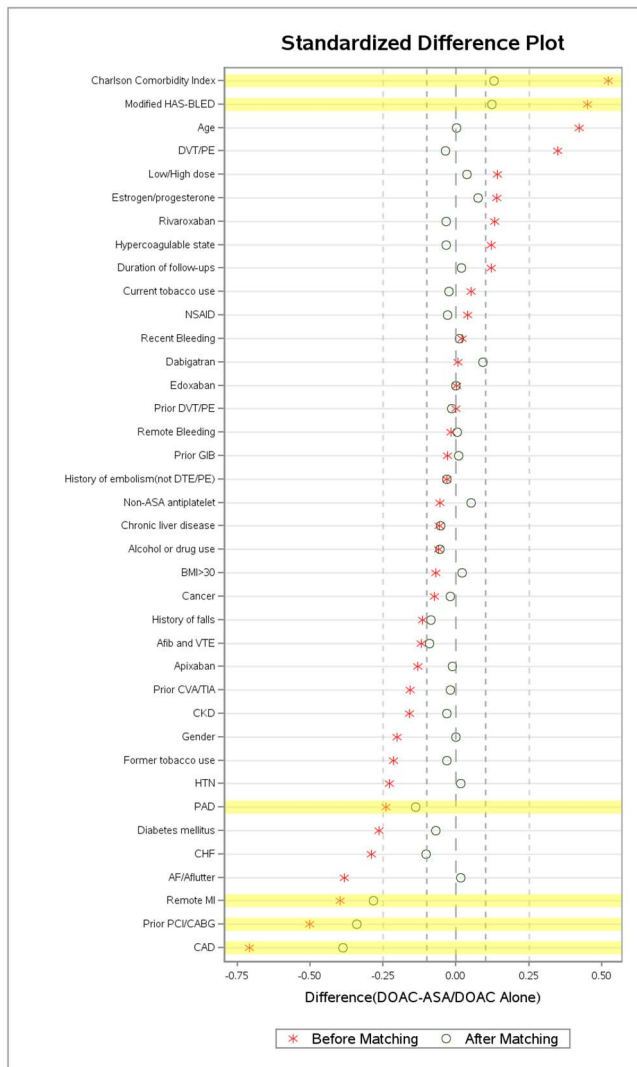
eTable 4. Outcomes of DOAC versus DOAC+ASA (rates per 100 patient years), Not Matching on DOAC Dose^a

# per 100 patient years (95% CI)	DOAC n=1047	DOAC+ASA n=1047	p-value
New Thrombosis	2.51 (2.21, 2.84)	2.50 (2.20, 2.83)	0.83
Ischemic/Embolic Stroke	0.93 (0.75, 1.14)	0.71 (0.55, 0.90)	0.24
TIA	0.22 (0.14, 0.33)	0.11 (0.05, 0.20)	0.39
PE	0.22 (0.14, 0.33)	0.16 (0.09, 0.26)	0.69
DVT	0.66 (0.51, 0.84)	0.87 (0.70, 1.07)	0.43
MI	0.11 (0.05, 0.20)	0.05 (0.02, 0.12)	0.51
New Bleed	26.94 (25.93, 27.98)	31.63 (30.54, 32.75)	0.01
Major	3.77 (3.40, 4.17)	4.95 (4.52, 5.41)	0.16
-Fatal	0.11 (0.05, 0.20)	0.05 (0.02, 0.12)	0.54
-Intracranial or intraspinal	0.38 (0.27, 0.52)	0.33 (0.23, 0.46)	0.76
-Life Threatening	0.93 (0.75, 1.14)	1.42 (1.20, 1.67)	0.21
Non-major	21.41 (20.51, 22.34)	26.13 (25.14, 27.15)	0.01
ER Visit	12.23 (11.55, 12.94)	13.77 (13.05, 14.52)	0.48
For bleeding	10.92 (10.28, 11.59)	13.01 (12.31, 13.74)	0.20
For clotting	1.47 (1.24, 1.73)	0.82 (0.65, 1.02)	0.04
Hospitalization	7.05 (6.54, 7.59)	9.09 (8.51, 9.70)	0.10
For bleeding	5.73 (5.27, 6.22)	8.17 (7.62, 8.75)	0.02
For clotting	1.31 (1.10, 1.55)	0.93 (0.75, 1.14)	0.21
Death	3.50 (3.14, 3.89)	3.76 (3.39, 4.16)	0.97

Abbreviations: ASA, acetylsalicylic acid or aspirin; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ER, emergency room; MI, myocardial infarction; PE, pulmonary embolism; TIA, transient ischemic attack.

^aNumber of events per 100 patient years

eFigure 1: Standardized Difference Plot^{a,b,c,d}



Abbreviations: AFib, atrial fibrillation; Aflutter, atrial flutter; ASA, acetylsalicylic acid or aspirin; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CVA, cerebrovascular accident; DVT, deep vein thrombosis; GIB, gastrointestinal bleed; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly; HTN, hypertension; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PE, pulmonary embolism; TIA, transient ischemic attack.

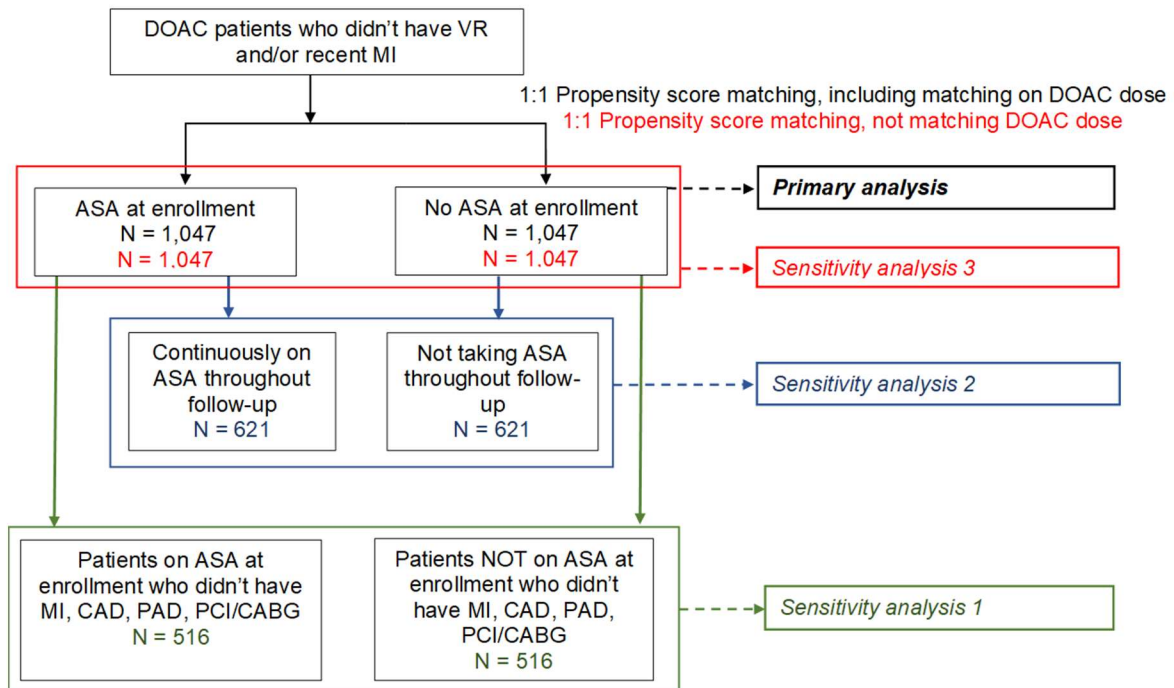
^aAbsolute standardized differences in baseline covariates between patients treated with DOAC+ASA and those treated with DOAC monotherapy for atrial fibrillation or venous thromboembolism, before and after propensity score matching.

^bHighlighted variables indicate those with residual differences after matching that were then included in the Poisson models.

^c Labile INR was excluded when calculating the HAS-BLED score.

^dSpecific DOAC drug types were not used for matching but are shown for reference.

eFigure 2: Study Schema



Abbreviations: ASA, acetylsalicylic acid or aspirin; CABG, coronary artery bypass graft; CAD, coronary artery disease; DOAC, direct oral anticoagulant; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PE, pulmonary embolism; TIA, transient ischemic attack; VR, valve replacement.

eFigure 3: Percent of Patients Using Aspirin+DOAC Without a Clear Indication by Year

