

SUPPLEMENTARY MATERIALS

Title:

Thromboembolic risks with concurrent direct oral anticoagulant and antiseizure medications: A population-based analysis

Journal Name:

CNS drugs

Authors:

Bonaventure Ip¹, MD*; Ho Ko^{1,2}, PhD*; LH Wong^{1,3}, MD; CF Yip^{1,3}, PhD; HS Lau¹, MD; Alexander Lau¹, MD; Xinyi Leng¹, PhD; Howan Leung¹, MD; Howard Chan¹, PhD; Helen Chan¹, BSc; Vincent Mok¹, MD; Yannie Soo¹, MD; Thomas Leung¹, MD[†]

Affiliations:

¹Department of Medicine and Therapeutics, Faculty of Medicine, The Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong

²Li Ka Shing Institute of Health Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong

³Medical Data Analytic Centre, The Chinese University of Hong Kong, Hong Kong

Corresponding Author:

Thomas Leung

drtleung@cuhk.edu.hk

Table S1. Annual incidence rates of ischemic stroke per drug combination (primary analysis)

Drug combination	Sample size	Median FU (months)	Annual incidence rate
PHT-API	476	11	8.3%
PHT-DAB	339	20	5.8%
PHT-RIV	304	20	5.2%
VPA-API	489	10	4.2%
VPA-DAB	340	20	5.8%
VPA-RIV	276	20	5.7%
LEV-API	275	8	5.4%
LEV-DAB	179	21	6.5%
LEV-RIV	152	15	6.0%
NEU-API	2345	11	3.9%
NEU-DAB	1440	19	3.3%
NEU-RIV	1445	19	3.9%

ABBREVIATIONS: Antiseizure medications: LEV: levetiracetam; NEU: P-glycoprotein and cytochrome P450 neutral antiseizure medications; PHT: phenytoin; VPA: valproate Direct oral anticoagulants: API: apixaban; DAB: dabigatran; RIV: rivaroxaban

N.B.: Annual incidences were estimated by the Fine-Gray method, drug combinations with sample size less than 50 were not included

Table S2. Imputed patient characteristics after balancing with the inverse probability of treatment weighting method (epilepsy subgroup)

	CYP/P-gp neutral ASMs	CYP/P-gp modulating ASMs	AMSD	Phenytoin	AMSD	Valproate	AMSD	Levetiracetam	AMSD
n	300	1873		756		609		417	
Daily dosage(mg) mean(sd)	GBP: 604.6(376.9) PGB: 171.5(177.1) Clobazam: 20.1(4.2)	Phenytoin: 144.4(91.7) Valproate: 613.5(265.3) Levetiracetam: 1079.2(605.2) Carbamazepine: 476(131.6) Phenobarbital: 94(45.7)		144.4(91.7)		613.5(265.3)		1079.2(605.2)	
Demographics									
Age mean(sd)	71.9(13.2)	73.2(13.4)	0.015	75(12.3)	0.080	73.5(13.4)	0.047	71.1(13.9)	0.046
Female n(%)	146(48.7)	1003(53.6)	0.044	396(52.4)	0.043	321(52.7)	0.042	246(59.0)	0.062
Smoker n(%)	1(0.3)	23(1.2)	0.009	11(1.5)	0.010	5(0.8)	0.004	6(1.4)	0.011
Drinker n(%)	0(0.0)	41(2.2)	0.020	15(2.0)	0.016	11(1.8)	0.015	12(2.9)	0.026
Medical Co-morbidities									
CHF n(%)	76(25.3)	492(26.3)	0.002	218(28.8)	0.014	168(27.6)	0.009	95(22.8)	0.023
IHD n(%)	65(21.7)	438(23.4)	0.005	181(23.9)	0.007	138(22.7)	0.000	105(25.2)	0.023
PVD n(%)	17(5.7)	1298(69.3)	0.001	47(6.2)	0.000	34(5.6)	0.000	22(5.3)	0.000
IS n(%)	202(67.3)	17(0.9)	0.003	562(74.3)	0.027	441(72.4)	0.036	265(63.5)	0.032
ATE n(%)	5(1.7)	356(19.0)	0.011	4(0.5)	0.008	7(1.1)	0.005	6(1.4)	0.000
VTE n(%)	61(20.3)	588(31.4)	0.012	153(20.2)	0.016	85(14.0)	0.046	88(21.1)	0.012
DM n(%)	93(31.0)	1167(62.3)	0.003	240(31.7)	0.001	194(31.9)	0.006	139(33.3)	0.013
Hypertension n(%)	181(60.3)	108(5.8)	0.002	482(63.8)	0.002	392(64.4)	0.022	249(59.7)	0.006
Hyperlipidemia n(%)	92(30.7)	618(33.0)	0.008	258(34.1)	0.001	201(33.0)	0.001	142(34.1)	0.001
AF n(%)	199(66.3)	1359(72.6)	0.011	556(73.5)	0.025	465(76.4)	0.066	290(69.5)	0.021
Major bleeding n(%)	13(4.3)	1873(100.0)	0.001	29(3.8)	0.001	27(4.4)	0.001	22(5.3)	0.007
CLD n(%)	1(0.3)	82(4.4)	0.003	7(0.9)	0.004	1(0.2)	0.002	3(0.7)	0.003
CKD n(%)	11(3.7)	13(0.7)	0.002	36(4.8)	0.004	27(4.4)	0.006	16(3.8)	0.000
CHADS2Vasc mean(sd)	4.5(2.1)	81(4.3)	0.002	4.9(2.0)	NA	4.7(2.0)	NA	4.3(2.2)	NA
HASBLED mean(sd)	3.4(1.3)	4.6(2.1)	0.005	3.6(1.3)	NA	3.6(1.2)	NA	3.3(1.4)	NA
Background Medications									
Apixaban n(%)	143(47.7)	731(39.0)	0.019	369(48.8)	0.002	297(48.8)	0.002	210(50.4)	0.017

Dabigatran n(%)	100(33.3)	570(30.4)	0.027	232(30.7)	0.025	192(31.5)	0.022	130(31.2)	0.015
Edoxaban n(%)	10(3.3)	76(4.1)	0.017	28(3.7)	0.008	28(4.6)	0.016	19(4.6)	0.011
Rivaroxaban n(%)	87(29.0)	478(25.5)	0.018	229(30.3)	0.014	176(28.9)	0.007	114(27.3)	0.008
Aspirin n(%)	96(32.0)	618(33.0)	0.007	248(32.8)	0.001	211(34.6)	0.027	140(33.6)	0.015
Cilostazol n(%)	1(0.3)	2(0.1)	0.009	0(0.0)	0.002	2(0.3)	0.000	0(0.0)	0.002
Clopidogrel n(%)	23(7.7)	105(5.6)	0.001	39(5.2)	0.015	35(5.7)	0.022	28(6.7)	0.008
Ticagrelor n(%)	1(0.3)	4(0.2)	0.000	2(0.3)	0.000	0(0.0)	0.000	2(0.5)	0.001
Simvastatin n(%)	130(43.3)	799(42.7)	0.041	333(44.0)	0.008	287(47.1)	0.024	158(37.9)	0.040
Rosuvastatin n(%)	10(3.3)	0(0.0)	0.010	21(2.8)	0.006	13(2.1)	0.011	17(4.1)	0.003
Amiodarone n(%)	9(3.0)	52(2.8)	0.002	23(3.0)	0.003	18(3.0)	0.003	13(3.1)	0.001
Dronedarone n(%)	0(0.0)	54(2.9)	0.003	2(0.3)	0.003	3(0.5)	0.005	0(0.0)	NA
Rifampicin n(%)	0(0.0)	5(0.3)	0.002	2(0.3)	0.002	0(0.0)	NA	2(0.5)	0.004
NSAID/COX2i n(%)	10(3.3)	4(0.2)	0.003	14(1.9)	0.007	17(2.8)	0.002	14(3.4)	0.002
Laboratory Parameters									
APTT(s) median(iqr)	34.3(8.5)	32.0(8.3)	NA	33.5(7.4)	NA	33.4(7.7)	NA	33.7(7.3)	NA
PT(s) median(iqr)	24.2(5.5)	22.6(5.8)	NA	23.9(5.2)	NA	23.8(5.0)	NA	24.2(5.0)	NA
Hemoglobin(g/dL) mean(sd)	12.3(1.9)	12.3(1.8)	0.061	12.3(1.8)	0.024	12.4(1.8)	0.024	12.3(1.9)	0.000
Platelet(10 ⁹ /L) mean(sd)	235.3(84.5)	224.6(79.5)	0.011	227.5(77.7)	0.028	218.1(75.3)	0.106	227.3(84.2)	0.076
Creatinine(umol/L) mean(sd)	89.9(46.2)	91.0(50.1)	0.042	93.5(62.0)	0.048	90.5(36.4)	0.009	91.2(46.5)	0.020
ALT(IU/L) mean(sd)	31.5(22.2)	34.4(35.0)	0.114	34(37.4)	0.039	29.8(28.1)	0.010	41.3(39.5)	0.132
HbA1c(%) mean(sd)	6.2(1.1)	6.1(1.0)	0.017	6.2(1.0)	0.013	6.1(1.1)	0.035	6.1(0.9)	0.020
HDL-C(mmol/L) mean(sd)	1.3(0.4)	1.3(0.4)	0.021	1.3(0.4)	0.022	1.3(0.4)	0.056	1.3(0.4)	0.030
LDL-C(mmol/L) mean(sd)	2.2(0.8)	2.1(0.8)	0.005	2.2(0.8)	0.005	2.1(0.8)	0.014	2.1(0.8)	0.032
TC(mmol/L) mean(sd)	4.1(1.0)	4.0(0.9)	0.030	4.1(0.9)	0.006	3.9(0.9)	0.052	3.9(0.9)	0.047
Triglyceride(mmol/L) mean(sd)	1.4(0.7)	1.3(0.7)	0.010	1.3(0.8)	0.014	1.3(0.6)	0.045	1.3(0.7)	0.019
Annual Incidence Rate of Outcomes (%)									
IS	8.8%	8.4%	NA	8.1%	NA	8.7%	NA	7.7%	NA
VTE	5.2%	5.3%	NA	4.6%	NA	3.9%	NA	6.0%	NA
Mortality	13.2%	18.8%	NA	18.1%	NA	19.8%	NA	16.0%	NA

Abbreviations: ASM: antiseizure medications; AF: atrial fibrillation; ALT: alanine aminotransferase; AMSD: absolute mean standardized difference; APTT: activated partial thromboplastin time; ATE: non-ischemic stroke arterial thromboembolism; CHF: congestive heart failure; CKD: chronic kidney disease; CLD: chronic liver disease; COX2i: cyclo-oxygenase 2 inhibitor; CYP/P-gp: cytochrome P450/P-glycoprotein; DM: diabetes mellitus; GBP: gabapentin; HbA1c: glycated hemoglobin A1c; HDL-C: high density lipoprotein cholesterol; ICH: intracranial hemorrhage; IHD: ischemic heart disease; IS: ischemic stroke; LDL-C: low density lipoprotein cholesterol; NA: not applicable; NSAID: non-steroidal anti-inflammatory drugs; PGB: pregabalin; PT: prothrombin time; PVD: peripheral vascular disease; TC: total cholesterol; VTE: venous thromboembolism

N.B.: CYP/P-gp modulating ASMs collectively included phenytoin (n=756), valproate (n=609), levetiracetam (n=417), carbamazepine (n=63) and phenobarbital (n=28).

Table S3. Annual incidence rates of ischemic stroke per drug combination – epilepsy subgroup

Drug combination	Sample size	Median FU (months)	Annual incidence rate
PHT-API	297	12	8.4%
PHT-DAB	229	27	7.1%
PHT-RIV	202	23	6.3%
VPA-API	240	11	9.7%
VPA-DAB	191	23	7.8%
VPA-RIV	150	20	6.8%
LEV-API	167	10	9.0%
LEV-DAB	127	25	5.6%
LEV-RIV	104	16	9.8%
NEU-API	116	16	8.2%
NEU-DAB	82	24	8.1%
NEU-RIV	92	19	9.0%

ABBREVIATIONS: Antiseizure medications: LEV: levetiracetam; NEU: P-glycoprotein and cytochrome P450 neutral antiseizure medications; PHT: phenytoin; VPA: valproate
Direct oral anticoagulants: API: apixaban; DAB: dabigatran; RIV: rivaroxaban

N.B.: Annual incidences were estimated by the Fine-Gray method, drug combinations with sample size less than 50 were not included

Table S4. Imputed patient characteristics after balancing with the inverse probability of treatment weighting method (AF subgroup)

	CYP/P-gp neutral ASMs	CYP/P-gp modulating ASMs	AMSD	Phenytoin	AMSD	Valproate	AMSD	Levetiracetam	AMSD
n	3789	2142		817		816		394	
Daily dosage(mg) mean(sd)	GBP: 509(346) PGB: 100(85.3) Clobazam: 20.1(4.0)	Phenytoin: 150(103) Valproate: 558(242) Levetiracetam: 1002(571) Carbamazepine: 485(162) Phenobarbital: 102(54)		150(103)		558(242)		1002(571)	
Demographics									
Age mean(sd)	78(9.7)	76.5(10.5)	0.013	77.5(10.2)	0.025	76.4(10.9)	0.076	75.1(10.5)	0.045
Female n(%)	1681(44.4)	1139(53.2)	0.032	425(52.0)	0.031	427(52.3)	0.077	236(59.9)	0.037
Smoker n(%)	63(1.7)	31(1.4)	0.001	15(1.8)	0.007	8(1.0)	0.007	7(1.8)	0.009
Drinker n(%)	57(1.5)	40(1.9)	0.004	15(1.8)	0.003	14(1.7)	0.001	9(2.3)	0.013
Medical Co-morbidities									
CHF n(%)	1603(42.3)	708(33.1)	0.013	284(34.8)	0.059	268(32.8)	0.093	123(31.2)	0.000
IHD n(%)	1174(31.0)	595(27.8)	0.032	236(28.9)	0.017	213(26.1)	0.041	114(28.9)	0.005
IS n(%)	1467(38.7)	1470(68.6)	0.001	600(73.4)	0.084	559(68.5)	0.161	270(68.5)	0.050
ATE n(%)	69(1.8)	22(1.0)	0.004	4(0.5)	0.013	14(1.7)	0.002	4(1.0)	0.005
VTE n(%)	145(3.8)	110(5.1)	0.029	44(5.4)	0.007	36(4.4)	0.005	26(6.6)	0.009
DM n(%)	1273(33.6)	762(35.6)	0.009	304(37.2)	0.054	283(34.7)	0.009	146(37.1)	0.014
Hypertension n(%)	2570(67.8)	1487(69.4)	0.049	576(70.5)	0.025	560(68.6)	0.003	269(68.3)	0.028
PVD n(%)	201(5.3)	131(6.1)	0.005	49(6.0)	0.009	53(6.5)	0.002	25(6.3)	0.005
Hyperlipidemia n(%)	1261(33.3)	795(37.1)	0.003	313(38.3)	0.001	291(35.7)	0.011	156(39.6)	0.032
Epilepsy n(%)	199(5.3)	2142(100.0)	0.021	556(68.1)	0.087	465(57.0)	0.161	290(73.6)	0.178
Major bleeding n(%)	248(6.5)	1359(63.4)	0.013	34(4.2)	0.003	33(4.0)	0.023	22(5.6)	0.006
CLD n(%)	28(0.7)	91(4.2)	0.011	9(1.1)	0.000	1(0.1)	0.006	7(1.8)	0.004
CKD n(%)	257(6.8)	19(0.9)	0.006	46(5.6)	0.018	47(5.8)	0.008	20(5.1)	0.004
CHADS2Vasc mean(sd)	4.7(1.8)	117(5.5)	0.072	5.2(1.7)	NA	5(1.8)	NA	4.9(1.8)	NA
HASBLED mean(sd)	3(1.3)	5.0(1.8)	0.011	3.7(1.2)	NA	3.5(1.2)	NA	3.6(1.3)	NA
Background Medications									
Apixaban n(%)	1620(42.8)	918(42.9)	0.006	349(42.7)	0.034	360(44.1)	0.045	170(43.1)	0.038
Dabigatran n(%)	1181(31.2)	666(31.1)	0.012	226(27.7)	0.039	231(28.3)	0.016	113(28.7)	0.025

Edoxaban n(%)	132(3.5)	57(2.7)	0.007	16(2.0)	0.023	24(2.9)	0.009	15(3.8)	0.010
Rivaroxaban n(%)	856(22.6)	483(22.5)	0.021	226(27.7)	0.023	201(24.6)	0.007	96(24.4)	0.002
Aspirin n(%)	1145(30.2)	780(36.4)	0.020	305(37.3)	0.059	293(35.9)	0.034	149(37.8)	0.068
Cilostazol n(%)	17(0.4)	2(0.1)	0.011	0(0.0)	0.004	2(0.2)	0.003	0(0.0)	0.001
Clopidogrel n(%)	278(7.3)	132(6.2)	0.003	55(6.7)	0.017	49(6.0)	0.016	24(6.1)	0.004
Ticagrelor n(%)	15(0.4)	4(0.2)	0.001	2(0.2)	0.001	0(0.0)	0.003	2(0.5)	0.002
Simvastatin n(%)	1603(42.3)	990(46.2)	0.003	402(49.2)	0.072	391(47.9)	0.003	157(39.8)	0.056
Atorvastatin n(%)	0(0.0)	0(0.0)	0.007	0(0.0)	NA	0(0.0)	NA	0(0.0)	NA
Rosuvastatin n(%)	163(4.3)	73(3.4)	0.003	29(3.5)	0.008	22(2.7)	0.014	18(4.6)	0.003
Amiodarone n(%)	126(3.3)	91(4.2)	0.003	37(4.5)	0.003	31(3.8)	0.006	21(5.3)	0.018
Dronedarone n(%)	52(1.4)	9(0.4)	0.000	2(0.2)	0.012	4(0.5)	0.005	1(0.3)	0.003
Rifampicin n(%)	2(0.1)	4(0.2)	0.015	2(0.2)	0.000	0(0.0)	0.000	2(0.5)	0.004
NSAID/COX2i n(%)	218(5.8)	47(2.2)	0.020	13(1.6)	0.027	23(2.8)	0.026	6(1.5)	0.023
Laboratory Parameters									
APTT(s) median(iqr)	34.7(8.0)	32.1(8.0)	NA	33.1(7.0)	NA	34(7.8)	NA	33.9(7.4)	NA
PT(s) median (iqr)	24.6(5.3)	22.7(5.5)	NA	23.7(4.9)	NA	24.2(5.1)	NA	24.4(5.0)	NA
Hemoglobin(g/dL) mean(sd)	12.2(1.8)	12.3(1.8)	0.010	12.2(1.8)	0.07	12.5(1.8)	0.089	12.3(1.9)	0.061
Platelet(10⁹/L) mean(sd)	224(70.5)	218.8(70.9)	0.035	225.5(72.3)	0.023	214(69.8)	0.120	215.3(71.0)	0.024
Creatinine(umol/L) mean(sd)	98(48.9)	96.0(54.1)	0.014	96(53.1)	0.023	96.2(51.1)	0.005	99.2(66.3)	0.024
ALT(IU/L) mean(sd)	31.5(40.5)	33.9(40.6)	0.009	34.8(46.0)	0.019	30(34.1)	0.042	41.1(44.4)	0.184
HbA1c(%) mean(sd)	6.4(1.1)	6.2(1.0)	0.035	6.2(1.0)	0.003	6.2(1.1)	0.048	6.2(1.0)	0.019
HDL-C(mmol/L) mean(sd)	1.3(0.4)	1.3(0.4)	0.011	1.3(0.4)	0.015	1.2(0.4)	0.119	1.3(0.4)	0.046
LDL-C(mmol/L) mean(sd)	2(0.7)	2.1(0.7)	0.004	2.1(0.7)	0.018	2.1(0.8)	0.021	2(0.7)	0.037
TC(mmol/L) mean(sd)	3.9(0.9)	3.9(0.9)	0.012	4(0.9)	0.014	3.9(0.9)	0.028	3.8(0.8)	0.012
Triglyceride(mmol/L) mean(sd)	1.3(0.7)	1.3(0.7)	0.016	1.3(0.8)	0.034	1.3(0.6)	0.006	1.3(0.7)	0.049
Annual Incidence Rate of Outcome (%)									
IS	5.0%	7.9%	NA	9.5%	NA	6.3%	NA	8.5%	NA
VTE	0.2%	1.0%	NA	1.7%	NA	0.2%	NA	1.4%	NA
Mortality	12.7%	22.5%	NA	23.9%	NA	21%	NA	18.4%	NA

Abbreviations: ASM: antiseizure medications; AF: atrial fibrillation; ALT: alanine aminotransferase; AMSD: absolute mean standardized difference; APTT: activated partial thromboplastin time; ATE: non-ischemic stroke arterial thromboembolism; CHF: congestive heart failure; CKD: chronic kidney disease; CLD: chronic liver disease; COX2i: cyclo-oxygenase 2 inhibitor; CYP/P-gp: cytochrome P450/P-glycoprotein; DM: diabetes mellitus; GBP: gabapentin; HbA1c: glycated hemoglobin A1c; HDL-C: high density lipoprotein cholesterol; ICH: intracranial hemorrhage; IHD: ischemic heart disease; IS: ischemic stroke; LDL-C: low density lipoprotein cholesterol; NA: not applicable; NSAID: non-steroidal anti-inflammatory drugs; PGB: pregabalin; PT: prothrombin time; PVD: peripheral vascular disease; TC: total cholesterol; VTE: venous thromboembolism

N.B.: CYP/P-gp modulating ASMs collectively included phenytoin (n=817), valproate (n=816), levetiracetam (n=394), carbamazepine (n=85) and phenobarbital (n=30).

Table S5. Annual incidence rates of ischemic stroke per drug combination – atrial fibrillation subgroup

Drug combination	Sample size	Median FU (months)	Annual incidence rate
PHT-API	349	12	10%
PHT-DAB	255	27	7.1%
PHT-RIV	197	23	6.1%
VPA-API	360	11	6.0%
VPA-DAB	257	23	6.3%
VPA-RIV	174	20	8.7%
LEV-API	170	10	5.2%
LEV-DAB	122	25	8.9%
LEV-RIV	87	16	8.3%
NEU-API	1620	16	4.3%
NEU-DAB	1116	24	4.4%
NEU-RIV	921	19	5.2%

ABBREVIATIONS: Antiseizure medications: LEV: levetiracetam; NEU: P-glycoprotein and cytochrome P450 neutral antiseizure medications; PHT: phenytoin; VPA: valproate
Direct oral anticoagulants: API: apixaban; DAB: dabigatran; RIV: rivaroxaban

N.B.: Annual incidences were estimated by the Fine-Gray method, drug combinations with sample size less than 50 were not included

Table S6. Patient characteristics after balancing with the inverse probability of treatment weighting method (sensitivity analysis)

	Neutral	Phenytoin	AMSD	Valproate	AMSD	Levetiracetam	AMSD
n	5400	948		870		578	
Demographics							
Age mean(sd)	75.9(11.5)	75.4(12.5)	0.053	73.9(13.6)	0.157	70.6(14.0)	0.068
Female n(%)	2366(43.8)	463(48.8)	0.022	433(49.8)	0.050	323(55.9)	0.098
Smoker n(%)	95(1.8)	15(1.6)	0.005	10(1.1)	0.005	10(1.7)	0.011
Drinker n(%)	80(1.5)	17(1.8)	0.002	12(1.4)	0.000	16(2.8)	0.026
Medical Co-morbidities							
CHF n(%)	1856(34.4)	276(29.1)	0.039	250(28.7)	0.049	133(23.0)	0.031
IHD n(%)	1444(26.7)	235(24.8)	0.011	204(23.4)	0.046	131(22.7)	0.063
IS n(%)	1750(32.4)	600(63.3)	0.061	496(57.0)	0.128	316(54.7)	0.112
ATE n(%)	93(1.7)	5(0.5)	0.009	13(1.5)	0.000	6(1.0)	0.017
VTE n(%)	816(15.1)	188(19.8)	0.029	148(17.0)	0.040	143(24.7)	0.097
DM n(%)	1676(31.0)	325(34.3)	0.065	279(32.1)	0.011	174(30.1)	0.033
Hypertension n(%)	3291(60.9)	608(64.1)	0.034	544(62.5)	0.029	323(55.9)	0.005
PVD n(%)	263(4.9)	52(5.5)	0.012	47(5.4)	0.009	27(4.7)	0.003
Hyperlipidemia n(%)	1641(30.4)	318(33.5)	0.001	281(32.3)	0.002	187(32.4)	0.016
AF n(%)	3708(68.7)	671(70.8)	0.001	615(70.7)	0.033	361(62.5)	0.009
Epilepsy n(%)	288(5.3)	615(64.9)	0.073	446(51.3)	0.098	384(66.4)	0.227
Major bleeding n(%)	320(5.9)	39(4.1)	0.001	42(4.8)	0.012	33(5.7)	0.014
CLD n(%)	37(0.7)	9(0.9)	0.002	2(0.2)	0.006	9(1.6)	0.002
CKD n(%)	312(5.8)	42(4.4)	0.009	40(4.6)	0.011	20(3.5)	0.005
CHADS2Vasc mean(sd)	4.2(2.0)	4.7(2.0)	NA	4.5(2.1)	NA	4(2.2)	NA
HASBLED mean(sd)	2.7(1.3)	3.3(1.3)	NA	3.2(1.4)	NA	3.1(1.5)	NA
Background Medications							
Apixaban n(%)	2278(42.2)	378(39.9)	0.023	368(42.3)	0.001	245(42.4)	0.097
Dabigatran n(%)	1482(27.4)	255(26.9)	0.004	226(26.0)	0.005	148(25.6)	0.083
Edoxaban n(%)	333(6.2)	36(3.8)	0.012	34(3.9)	0.012	33(5.7)	0.008
Rivaroxaban n(%)	1307(24.2)	279(29.4)	0.039	242(27.8)	0.018	152(26.3)	0.006
Aspirin n(%)	1515(28.1)	306(32.3)	0.040	292(33.6)	0.045	184(31.8)	0.028
Cilostazol n(%)	22(0.4)	1(0.1)	0.001	2(0.2)	0.004	0(0.0)	0.002

Clopidogrel n(%)	400(7.4)	62(6.5)	0.004	46(5.3)	0.021	34(5.9)	0.031
Ticagrelor n(%)	30(0.6)	2(0.2)	0.003	1(0.1)	0.006	2(0.3)	0.000
Simvastatin n(%)	2063(38.2)	427(45.0)	0.057	371(42.6)	0.009	204(35.3)	0.050
Atorvastatin n(%)	0(0.0)	0(0.0)	NA	0(0.0)	NA	0(0.0)	NA
Rosuvastatin n(%)	226(4.2)	27(2.8)	0.009	24(2.8)	0.000	21(3.6)	0.010
Amiodarone n(%)	146(2.7)	29(3.1)	0.003	27(3.1)	0.007	25(4.3)	0.004
Dronedarone n(%)	56(1.0)	2(0.2)	0.009	4(0.5)	0.007	1(0.2)	0.003
Rifampicin n(%)	6(0.1)	2(0.2)	0.000	1(0.1)	0.001	4(0.7)	0.002
NSAID/COX2i n(%)	359(6.6)	22(2.3)	0.030	30(3.4)	0.022	23(4.0)	0.014
Laboratory Parameters							
APTT(s) median(iqr)	34.3(7.8)	33.1(7.0)	NA	33.7(7.7)	NA	33.4(7.4)	NA
PT(s) median (iqr)	24.4(5.1)	23.6(4.8)	NA	24(4.9)	NA	24(5.1)	NA
Hemoglobin(g/dL) mean(sd)	12(1.9)	12.1(1.8)	0.019	12.2(1.8)	0.037	12.1(1.9)	0.015
Platelet(10 ⁹ /L) mean(sd)	232.9(79.1)	230.4(79.8)	0.007	221.7(77.5)	0.034	230.8(84.8)	0.167
Creatinine(umol/L) mean(sd)	95.7(53.0)	91.6(51.7)	0.014	91.9(53.8)	0.004	90.7(60.1)	0.221
ALT(IU/L) mean(sd)	32.8(43.6)	36.4(50.7)	0.012	29.7(32.1)	0.034	43.9(46.0)	0.083
HbA1c(%) mean(sd)	6.3(1.1)	6.3(1.1)	0.004	6.2(1.1)	0.028	6.2(1.0)	0.022
HDL-C(mmol/L) mean(sd)	1.3(0.4)	1.3(0.4)	0.035	1.3(0.4)	0.046	1.2(0.4)	0.083
LDL-C(mmol/L) mean(sd)	2.1(0.8)	2.2(0.8)	0.032	2.1(0.8)	0.151	2.1(0.8)	0.005
TC(mmol/L) mean(sd)	3.9(0.9)	4.1(0.9)	0.017	4(1.0)	0.124	4(1.0)	0.005
Triglyceride(mmol/L) mean(sd)	1.3(0.7)	1.3(0.8)	0.043	1.3(0.7)	0.024	1.3(0.8)	0.103
Clinical Events							
IS event n(%)	288(5.3)	107(11.3)	NA	91(10.5)	NA	68(11.8)	NA
VTE event n(%)	190(3.5)	63(6.6)	NA	47(5.4)	NA	64(11.1)	NA
Mortality n(%)	1681(31.1)	435(45.9)	NA	373(42.9)	NA	215(37.2)	NA

Abbreviations: AF: atrial fibrillation; ALT: alanine aminotransferase; AMSD: absolute mean standardized difference; APTT: activated partial thromboplastin time; ATE: non-ischemic stroke arterial thromboembolism; CHF: congestive heart failure; CKD: chronic kidney disease; CLD: chronic liver disease; COX2i: cyclo-oxygenase 2 inhibitor; DM: diabetes mellitus; HbA1c: glycated hemoglobin A1c; HDL-C: high density lipoprotein cholesterol; ICH: intracranial hemorrhage; IHD: ischemic heart disease; IS: ischemic stroke; LDL-C: low density lipoprotein cholesterol; NA: not applicable; NSAID: non-steroidal anti-inflammatory drugs; PT: prothrombin time; PVD: peripheral vascular disease; TC: total cholesterol; VTE: venous thromboembolism

Table S7. Patient characteristics after balancing with the inverse probability of treatment weighting method (epilepsy subgroup – sensitivity analysis)

	Neutral	Phenytoin	AMSD	Valproate	AMSD	Levetiracetam	AMSD
n	288	615		446		384	
Demographics							
Age mean(sd)	72.3(12.8)	75.5(12.4)	0.084	73.9(13.7)	0.110	71.5(13.8)	0.045
Female n(%)	142(49.3)	316(51.4)	0.029	226(50.7)	0.005	224(58.3)	0.077
Smoker n(%)	1(0.3)	8(1.3)	0.010	3(0.7)	0.002	6(1.6)	0.013
Drinker n(%)	0(0.0)	10(1.6)	0.013	6(1.3)	0.008	11(2.9)	0.019
Medical Co-morbidities							
CHF n(%)	76(26.4)	183(29.8)	0.007	133(29.8)	0.040	91(23.7)	0.034
IHD n(%)	65(22.6)	147(23.9)	0.003	108(24.2)	0.003	102(26.6)	0.035
IS n(%)	196(68.1)	456(74.1)	0.034	316(70.9)	0.028	245(63.8)	0.042
ATE n(%)	5(1.7)	3(0.5)	0.009	5(1.1)	0.003	6(1.6)	0.002
VTE n(%)	59(20.5)	123(20.0)	0.017	67(15.0)	0.035	85(22.1)	0.018
DM n(%)	90(31.3)	199(32.4)	0.009	147(33.0)	0.003	130(33.9)	0.033
Hypertension n(%)	178(61.8)	406(66.0)	0.009	295(66.1)	0.021	233(60.7)	0.003
AF n(%)	194(67.4)	455(74.0)	0.029	337(75.6)	0.050	267(69.5)	0.022
Epilepsy n(%)	288(100.0)	615(100.0)	NA	446(100.0)	NA	384(100.0)	NA
Major bleeding n(%)	13(4.5)	22(3.6)	0.001	21(4.7)	0.006	22(5.7)	0.010
CLD n(%)	1(0.3)	7(1.1)	0.007	1(0.2)	0.003	3(0.8)	0.003
CKD n(%)	11(3.8)	26(4.2)	0.004	17(3.8)	0.008	14(3.6)	0.002
Background Medications							
Apixaban n(%)	111(38.5)	243(39.5)	0.007	175(39.2)	0.009	153(39.8)	0.011
Dabigatran n(%)	84(29.2)	166(27.0)	0.016	117(26.2)	0.013	108(28.1)	0.007
Edoxaban n(%)	9(3.1)	21(3.4)	0.010	15(3.4)	0.003	16(4.2)	0.011
Rivaroxaban n(%)	84(29.2)	185(30.1)	0.001	139(31.2)	0.007	107(27.9)	0.015
Aspirin n(%)	94(32.6)	193(31.4)	0.012	157(35.2)	0.042	134(34.9)	0.019
Cilostazol n(%)	1(0.3)	0(0.0)	0.003	2(0.4)	0.002	0(0.0)	0.004
Clopidogrel n(%)	22(7.6)	31(5.0)	0.016	25(5.6)	0.027	27(7.0)	0.009
Ticagrelor n(%)	1(0.3)	1(0.2)	0.002	0(0.0)	NA	1(0.3)	0.001
Simvastatin n(%)	126(43.8)	274(44.6)	0.005	209(46.9)	0.003	149(38.8)	0.040
Atorvastatin n(%)	0(0.0)	0(0.0)	NA	0(0.0)	NA	0(0.0)	NA
Rosuvastatin n(%)	10(3.5)	16(2.6)	0.004	9(2.0)	0.016	15(3.9)	0.002
Amiodarone n(%)	9(3.1)	18(2.9)	0.004	13(2.9)	0.010	12(3.1)	0.001

Dronedaron n(%)	0(0.0)	2(0.3)	0.003	2(0.4)	0.001	0(0.0)	NA
Rifampicin n(%)	0(0.0)	2(0.3)	0.003	0(0.0)	NA	2(0.5)	0.005
NSAID/COX2i n(%)	9(3.1)	12(2.0)	0.007	10(2.2)	0.010	14(3.6)	0.005
Laboratory Parameters							
APTT(s) median(iqr)	34.4(8.7)	33.7(7.4)	NA	33.5(7.9)	NA	33.7(7.2)	NA
PT(s) median(iqr)	24.2(5.6)	24.1(5.2)	NA	23.9(5.0)	NA	24.2(4.9)	NA
Hemoglobin(g/dL) mean(sd)	12.3(1.9)	12.3(1.8)	0.008	12.4(1.8)	0.031	12.4(1.9)	0.026
Platelet(10 ⁹ /L) mean(sd)	235.5(85.5)	226.4(77.4)	0.032	217.6(75.4)	0.156	227.9(85.3)	0.078
Creatinine(umol/L) mean(sd)	90.6(46.7)	91.3(46.6)	0.024	89.1(31.6)	0.054	90.8(46.7)	0.002
ALT(IU/L) mean(sd)	31.4(22.5)	33.4(39.3)	0.086	28.9(27.1)	0.134	41.7(40.6)	0.196
HbA1c(%) mean(sd)	6.2(1.0)	6.2(1.1)	0.009	6.1(1.1)	0.113	6.1(1.0)	0.090
HDL-C(mmol/L) mean(sd)	1.3(0.4)	1.3(0.4)	0.028	1.3(0.4)	0.015	1.3(0.4)	0.052
LDL-C(mmol/L) mean(sd)	2.2(0.8)	2.2(0.8)	0.015	2.1(0.8)	0.063	2.1(0.8)	0.108
TC(mmol/L) mean(sd)	4.1(1.0)	4.1(0.9)	0.029	4(0.9)	0.111	3.9(0.9)	0.169
Triglyceride(mmol/L) mean(sd)	1.4(0.7)	1.3(0.8)	0.014	1.3(0.7)	0.180	1.3(0.7)	0.090
CHADS2Vasc mean(sd)	4.6(2.1)	4.9(2.0)	NA	4.8(2.1)	NA	4.4(2.2)	NA
HASBLED mean(sd)	3.4(1.3)	3.6(1.3)	NA	3.5(1.3)	NA	3.4(1.4)	NA
Clinical Events							
IS event n(%)	41(14.2)	73(11.9)	NA	65(14.6)	NA	57(14.8)	NA
VTE event n(%)	25(8.7)	39(6.3)	NA	26(5.8)	NA	37(9.6)	NA
Mortality n(%)	94(32.6)	281(45.7)	NA	204(45.7)	NA	135(35.2)	NA

Abbreviations: AF: atrial fibrillation; ALT: alanine aminotransferase; AMSD: absolute mean standardized difference; APTT: activated partial thromboplastin time; ATE: non-ischemic stroke arterial thromboembolism; CHF: congestive heart failure; CKD: chronic kidney disease; CLD: chronic liver disease; COX2i: cyclo-oxygenase 2 inhibitor; DM: diabetes mellitus; HbA1c: glycated hemoglobin A1c; HDL-C: high density lipoprotein cholesterol; ICH: intracranial hemorrhage; IHD: ischemic heart disease; IS: ischemic stroke; LDL-C: low density lipoprotein cholesterol; NA: not applicable; NSAID: non-steroidal anti-inflammatory drugs; PT: prothrombin time; PVD: peripheral vascular disease; TC: total cholesterol; VTE: venous thromboembolism

Table S8. Outcome comparison among ASMs (sensitivity analysis)

	Primary Analysis (n=7796)			Epilepsy Subgroup (n=1733)		
	Median follow-up (months)	aHR (95% CI)	p-value	Median follow-up (months)	aHR (95% CI)	p-value
Ischemic stroke						
Phenytoin vs Neutral ASM	15	1.51 (1.08 - 2.13)	0.017	15	0.80 (0.55 - 1.18)	0.257
Valproate vs Neutral ASM	14	1.17 (0.81 - 1.69)	0.391	14	0.97 (0.60 - 1.55)	0.892
Levetiracetam vs Neutral ASM	13	1.5 (0.70 - 3.22)	0.300	13	0.92 (0.62 - 1.37)	0.685
Venous thromboembolism						
Phenytoin vs Neutral ASM	16	1.61 (1.06 - 2.43)	0.025	16	0.78 (0.47 - 1.32)	0.358
Valproate vs Neutral ASM	15	1.72 (1.09 - 2.70)	0.020	15	0.73 (0.37 - 1.43)	0.358
Levetiracetam vs Neutral ASM	14	2.69 (0.93 - 7.76)	0.060	14	0.93 (0.56 - 1.54)	0.777
Death						
Phenytoin vs Neutral ASM	18	1.50 (1.27 - 1.76)	<0.001	18	1.34 (1.06 - 1.70)	0.014
Valproate vs Neutral ASM	17	1.30 (1.10 - 1.54)	0.002	17	1.42 (1.07 - 1.89)	0.014
Levetiracetam vs Neutral ASM	16	0.96 (0.59 - 1.57)	0.87	16	0.90 (0.69 - 1.17)	0.432

Abbreviations: ASM: antiseizure medications; aHR: adjusted hazard ratio; CI: confidence interval