

Supplementary Online Content

Huang W-Y, Singer DE, Wu Y-L, et al. Association of intracranial hemorrhage risk with non-vitamin K antagonist oral anticoagulant use vs aspirin use: a systematic review and meta-analysis. *JAMA Neurol*. Published online August 13, 2018.

doi:10.1001/jamaneurol.2018.2215

eFigure. Study selection

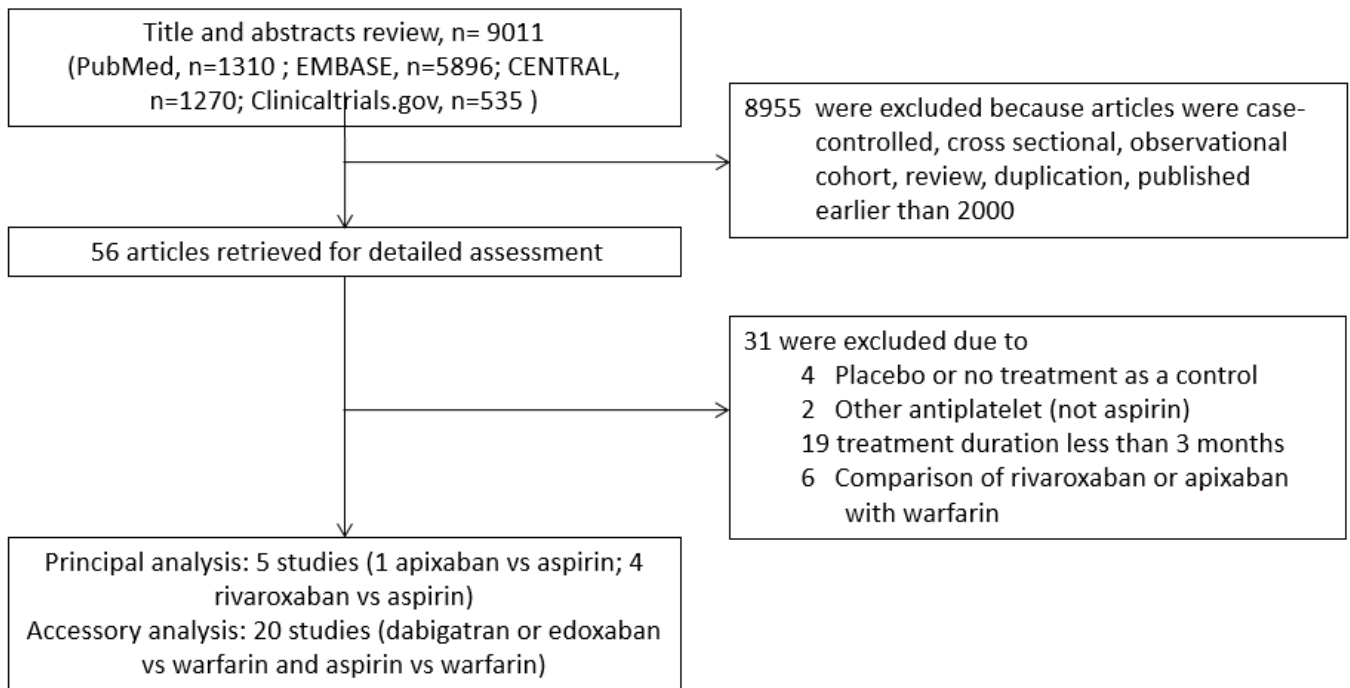
eTable 1. Risk of Bias of Included Trials (New Oral Anticoagulants vs Aspirin)

eTable 2. Characteristics of Included Trials for Accessory Analysis (Dabigatran or Edoxaban vs Warfarin and Aspirin vs Warfarin)

eTable 3. Indirect Comparison of Dabigatran, Edoxaban versus Aspirin in Primary and Secondary Endpoints

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

eFigure



eTable 1

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants / personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Apixaban vs Aspirin						
AVERROES 2011, multi-countries	+	+	+	+	?	+
Rivaroxaban vs Aspirin						
EINSTEIN CHOICE 2017, multi-countries	+	+	+	+	+	+
COMPASS 2017 (stable cardiovascular disease), multi-countries	+	+	+	+	+	+
COMPASS 2017 (Stable peripheral or carotid artery disease), multi-countries	+	+	+	+	+	+
NAVIGATE ESUS 2018 (Embolic strokes of undetermined source), multi-countries	+	+	+	+	+	+

eTable 2. Characteristics of Included Trials for Accessory Analysis (Dabigatran or Edoxaban vs Warfarin and Aspirin vs Warfarin)

Study acronym	Population characteristics	Mean age	Women (%)	Active group		Control group	Years of follow-up	Intracranial hemorrhage		Fatal bleeding		Major bleeding	
				NOACs	Warfarin			NOACs	Warfarin	NOACs	Warfarin	NOACs	Warfarin
Dabigatran													
RE-LY, 2009 ¹	AF	71	36.4	12091 patients Dabigatran 110mg bid (6015) or 150mg bid (6076)	6022 patients Warfarin INR 2-3		2	63	76	na	na	697	397
RE-COVER, 2009 ²	Acute venous thromboembolism	54.7	41.6	1273 patients parenteral anticoagulation For 9 days, followed by Dabigatran 150mg bid	1266 patients parenteral anticoagulation For 9 days, followed by Warfarin INR 2-3		0.5	0	3	1	1	20	24
RE-MEDY & RE-SONATE, 2013 ³	Venous thromboembolism complete at least 3 months treatment	54.9	40	2111 patients Dabigatran 150mg bid	1426 patients Warfarin INR 2-3		0.5-3	na	na	0	1	15	25
Edoxaban													
Chung et al, 2010 ⁴	AF (Asian)	65.1	34.6	159 patients Edoxaban	75 patients Warfarin INR		0.25	0	0	0	1	0	2

				30mg OD (79) or 60mg OD (80)	2-3								
ENGAGE AF-TIMI 48, 2013 ⁵	AF	72	38.1	14069 patients edoxaban 60mg OD (7035) or 30mg OD (7034)	7036 patients Warfarin INR 2-3	2.8	102	132	53	59	672	524	
HOKUSAI-VT E, 2013 ⁶	DVT, pulmonary embolism	55.8	42.8	4118 patients Enoxaparin or Heparin for at least 5 days, followed by Edoxaban 60mg OD or 30mg OD if CrCl 30–50 mL/min or <60 kg	4122 patients Enoxaparin or Heparin for at least 5 days, followed by Warfarin INR 2-3	1	5	18	2	10	56	66	
Aspirin vs Warfarin				Aspirin	Warfarin		Aspirin	Warfarin	Aspirin	Warfarin	Aspirin	Warfarin	
BOA, 2000 ⁷	s/p infrainguinal bypass surgery	69	35.9	1324 patients Aspirin 80mg OD	1326 patients Warfarin INR 3-4.5	1.75	4	18	12	16	56	108	
WARSS, 2001 ⁸	Recent noncardioemboli	63	40.7	1103 patients Aspirin 325mg	1103 patients INR 1.4-2.8	2	na	na	5	7	30	38	

	c stroke			OD								
ASPECT-2, 2002 ⁹	Acute coronary syndromes	61.2	23.4	336 patients Aspirin 80mg OD	325 patients Warfarin INR 3-4	1	0	0	0	0	3	3
WARIS II, 2002 ¹⁰	Myocardial infarction	60.2	23.6	1206 patient Aspirin 160mg OD	1216 patients Warfarin INR 2.8-4.2	4	1	10	0	5	8	38
WASH, 2004 ¹¹	EF <=35%	63.5	24.5	91 patients Aspirin 300mg OD	89 patients Warfarin INR 2-3	2.3	na	na	na	na	1	4
WASID, 2005 ¹²	TIA or stroke with intracranial artery 50-99% stenosis	63.6	38.5	280 patients Aspirin 325-1300mg OD	289 patients Warfarin INR 2-3	1.8	1	3	1	2	9	24
Hu et al, 2006 ¹³	AF	63.3	40.3	369 patients Aspirin 150-160mg OD	335 patients Warfarin INR 2-3 or INR 1.6-2.5 when Age>=75	1.6	0	3	0	2	0	5
HELAS, 2006 ¹⁴	EF<35%, IHD, sinus rhythm	61.6	10.8	61 patients Aspirin 325mg OD	54 patients Warfarin INR 2-3	1.5	na	na	0	0	0	4
Martí-Fàbre gas et al, 2006 ¹⁵	Symptomatic stenosis of MCA	67.4	32	14 patients Aspirin 300mg OD	14 patients Warfarin INR 2-3	1.9	0	1	0	1	0	1
ESPRIT, 2007 ¹⁶	TIA or minor stroke of arterial origin	61.5	31.6	532 patients Aspirin 30-325mg OD	536 patients Warfarin INR 2-3	4.6	9	18	4	11	18	45

BAFTA, 2007 ¹⁷	AF (elderly)	81.5	45.4	485 patient Aspirin 75mg OD	488 patients Warfarin INR 2-3	2.7	6	8	1	1	25	25
WATCH, 2009 ¹⁸	EF ≤35%, sinus rhythm	63	15	523 patients Aspirin 162mg OD	540 patients INR 2-3.5	1.9	3	6	na	na	19	28
Monagle et al, 2011 ¹⁹	After Fontan procedure in children	4.8	36	57 patient Aspirin 5mg/kg OD	54 patients Warfarin INR 2-3	2	1	0	0	0	1	1
WARCEF, 2012 ²⁰	EF ≤35%, sinus rhythm	61	20	1163 patients Aspirin 325mg OD	1142 patients Warfarin INR 2-3.5	3.5	7	5	4	7	31	66

NOACs indicates new oral anticoagulants; AF, atrial fibrillation; VKA, vitamin K antagonist; bid, twice a day; OD, once daily; INR, international normalized ratio; DVT, deep vein thrombosis; CrCl, creatinine clearance; PE, pulmonary embolism; TIA, transient ischemic attack; EF, ejection fraction; IHD, ischemic heart disease; MCA, middle cerebral artery; na, not available.

RE-LY indicates Randomized Evaluation of Long-Term Anticoagulation Therapy; RE-COVER, Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism; RE-MEDY & RE-SONATE, Secondary Prevention of Venous Thromboembolism & Twice-daily Oral Direct Thrombin Inhibitor Dabigatran Etxilate in the Long-term Prevention of Recurrent Symptomatic Proximal Venous Thromboembolism in Patients With Symptomatic Deep-vein Thrombosis or Pulmonary Embolism; ENGAGE AF-TIMI 48, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48; HOKUSAI-VTE, (LMW) Heparin/Edoxaban Versus (LMW) Heparin/Warfarin in Subjects With Symptomatic Deep-Vein Thrombosis (DVT) and or Pulmonary Embolism (PE); BOA, Dutch Bypass Oral anticoagulants or Aspirin; WARSS, Warfarin-Aspirin Recurrent Stroke Study; ASPECT-2, Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2; WARIS II, Warfarin-Aspirin Reinfarction Study II; WASH, the Warfarin/Aspirin Study in Heart failure; WASID, the Warfarin-Aspirin Symptomatic Intracranial Disease; HELAS, Heart failure Long-term Antithrombotic Study; ESPRIT, the European/Australasian Stroke Prevention in Reversible Ischemia Trial; BAFTA, the Birmingham Atrial Fibrillation Treatment of the Aged Study; WATCH, the Warfarin and Antiplatelet Therapy in Chronic Heart Failure; WARCEF, the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction.

eTable 3. Indirect Comparison of Dabigatran, Edoxaban versus Aspirin in Primary and Secondary Endpoints

	Dabigatran vs ASA	Edoxaban vs ASA
	Odds ratio (95% CI)	Odds ratio (95% CI)
Intracranial hemorrhage	0.72 (0.42-1.23)	0.75 (0.46-1.24)
Fatal bleeding	1.08 (0.13-9.22)	0.73 (0.41-1.31)
Major bleeding	1.64 (1.32-2.03)	1.24 (1.00-1.52)

REFERENCES

1. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151.
2. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361(24):2342-2352.
3. Schulman S, Kearon C, Kakkar AK, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med*. 2013;368(8):709-718.
4. Chung N, Jeon HK, Lien LM, et al. Safety of edoxaban, an oral factor Xa inhibitor, in Asian patients with non-valvular atrial fibrillation. *Thromb Haemost*. 2011;105(3):535-544.
5. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093-2104.
6. Hokusai VTEI, Buller HR, Decousus H, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369(15):1406-1415.
7. Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch Bypass Oral Anticoagulants or Aspirin Study): a randomised trial. *Lancet*. 2000;355(9201):346-351.
8. Mohr JP, Thompson JL, Lazar RM, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med*. 2001;345(20):1444-1451.
9. van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE, Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2 Research G. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. *Lancet*. 2002;360(9327):109-113.
10. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med*. 2002;347(13):969-974.
11. Cleland JG, Findlay I, Jafri S, et al. The Warfarin/Aspirin Study in Heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. *Am Heart J*. 2004;148(1):157-164.
12. Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med*. 2005;352(13):1305-1316.
13. Hu TY, Chang HP, Sun YH, Chiang LC. Warfarin and aspirin for prevention of thromboembolism in patients with non-valvular atrial fibrillation: a randomized controlled study. *Chin J Cardiol*. 2006;34(4):295-298.
14. Cokkinos DV, Haralabopoulos GC, Kostis JB, Toutouzas PK, investigators H. Efficacy of antithrombotic therapy in chronic heart failure: the HELAS study. *Eur J Heart Fail*. 2006;8(4):428-432.
15. Marti-Fabregas J, Cocho D, Marti-Vilalta JL, et al. Aspirin or anticoagulants in stenosis of the middle cerebral artery: A randomized trial. *Cerebrovasc Dis*. 2006;22(2-3):162-169.
16. Group ES, Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised

controlled trial. *Lancet Neurol.* 2007;6(2):115-124.

17. Mant J, Hobbs FD, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet.* 2007;370(9586):493-503.
18. Massie BM, Collins JF, Ammon SE, et al. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. *Circulation.* 2009;119(12):1616-1624.
19. Monagle P, Cochrane A, Roberts R, et al. A multicenter, randomized trial comparing heparin/warfarin and acetylsalicylic acid as primary thromboprophylaxis for 2 years after the Fontan procedure in children. *J Am Coll Cardiol.* 2011;58(6):645-651.
20. Homma S, Thompson JL, Pullicino PM, et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. *N Engl J Med.* 2012;366(20):1859-1869.