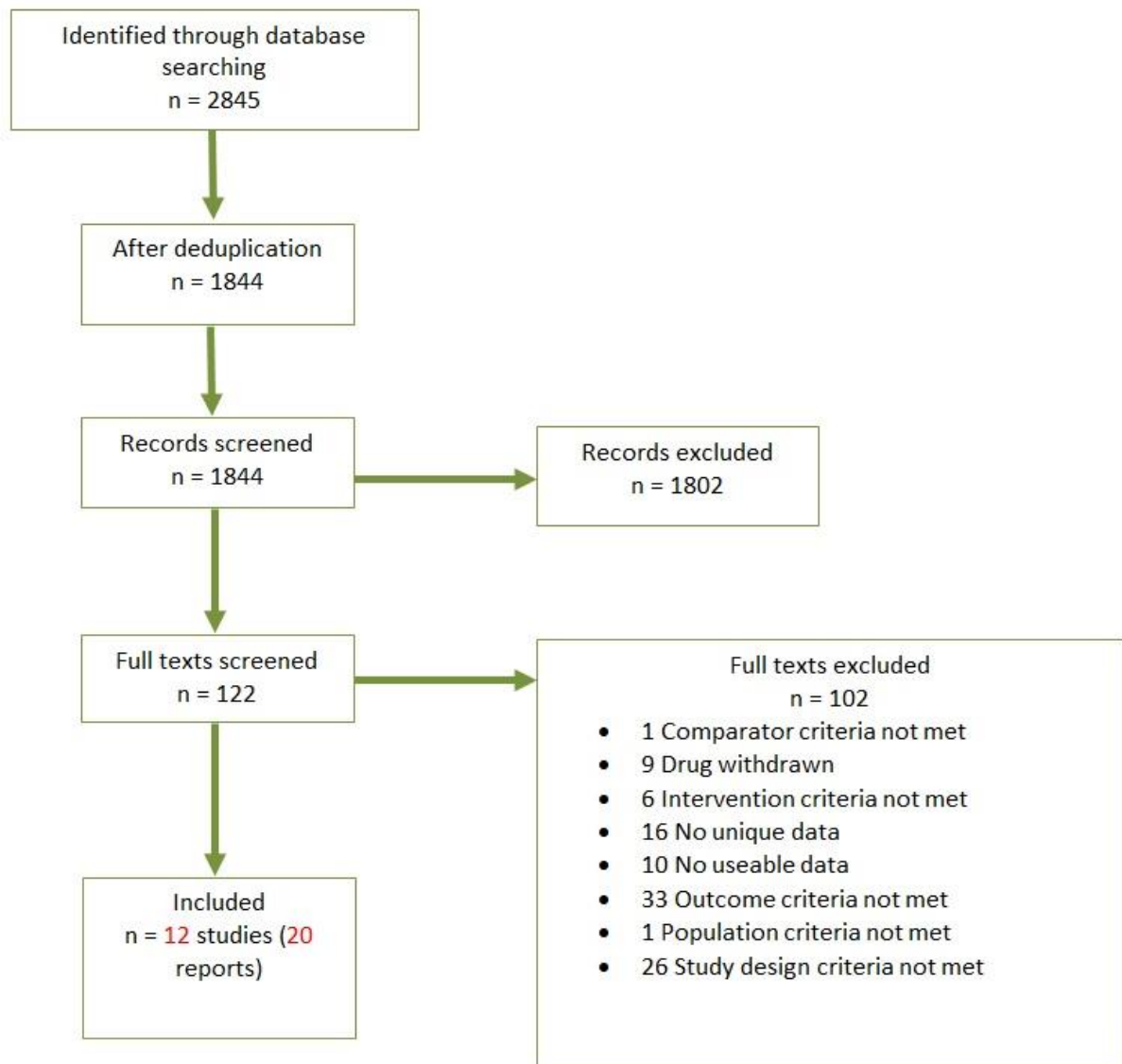


Supplementary Appendix Figures

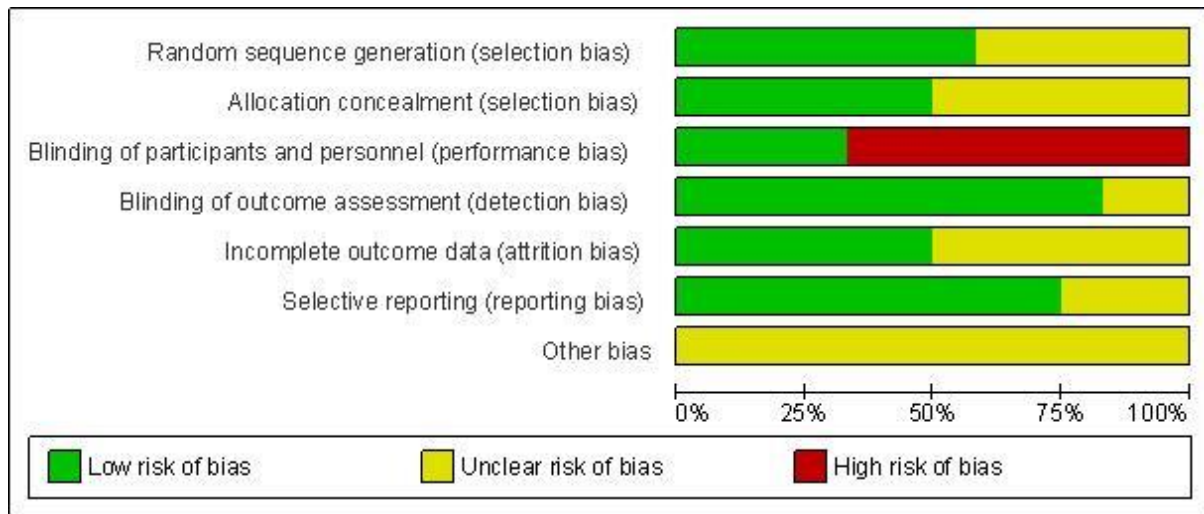
Supplementary Appendix Figure 1 Study flow diagram



Supplementary Appendix Figure 2. Base line characteristics

Study ID, setting, trial registration no.	Intervention drug & dosage	Participants			Outcomes
	Warfarin	Number randomised (% male)	Age, years mean (SD)	CHADS ₂ score ≥ 3 (n, %)	
Factor Xa Phase III trials					
ARISTOTLE (Granger 2011 + other secondary reports) 39 countries; NCT00412984	Apixaban 5mg x 2/day	9210 (65%)	*70 (63-76)	2758 (30%)	Primary: stroke, systemic embolism, major bleeding Secondary: all-cause mortality, MI, any bleeding, liver function abnormalities, other AEs
	2mg target INR 2.0-3.0	9081 (65%)	* 70 (63-76)	2744 (30%)	
ENGAGE AF-TIMI 48 Giugliano 2013 46 countries; NCT00781391	Edoxaban 60mg Edoxaban 30mg Dose halved in both groups for pts < 60kg or creatinine clearance of 30-50ml per minute or use of verapamil/quinidine	4366 (62.1%) 4304 (61.2%)	*72 (64-78) *72 (64-78)	Mean (SD) 2.8 (1) Mean (SD) 2.8 (1)	Primary: stroke, systemic embolism, major bleeding Secondary: MI, all-cause mortality
	Target INR 2.0-3.0	4395 (62.5%)	*72 (64-78)	Mean (SD) 2.8 (1)	
Rocket-AF Patel 2011 45 countries; NCT00403767	Rivaroxaban20mg (15mg in patients with creatinine clearance of 30-49ml per minute)	7131 (61%)	*73 (65-78)	6205 (87%)	Primary: Stroke or systemic embolism Secondary: Ischaemic stroke, intracranial haemorrhage, major bleeding, gastrointestinal bleeding, MI, all-cause mortality
	Target INR 2-3	7133 (60%)	*73 (65-78)	6197 (87%)	
J-Rocket AF Hori 2012 Japan; NCT00494871	Rivaroxaban 15mg	639 (83%)	**71.0 (34-89)	542 84.8%	Primary: Stroke or systemic embolic event Secondary: Ischaemic stroke, haemorrhagic stroke, systemic embolism, vascular death, mortality, myocardial infarction, major bleeding, gastrointestinal bleeding, clinically relevant non-major bleeding
	Target INR 2-3 (1.6-2.6 if ≥ 70 years)	639 (78%)	**71.2 (43-90)	524 82.0%	
Factor IIa Phase III trials					
RE-LY Connolly 2009 + 5 secondary reports; 44 countries; NCT00262600	Dabigatran 110mg x 2/day Dabigatran 150mg x 2/day	6015 6075	71.4 (8.6) 71.5 (8.8)	1968 (33%) 1981 (33%)	Primary: Stroke or systemic embolism Secondary: haemorrhagic stroke, all-cause mortality
	1, 3 or 5mg, target INR 2.0-3.0	6022	71.6 (8.6)	1933 (32%)	
Factor Xa Phase II trials					
ARISTOTLE-J Ogawa 2011 Japan; NCT00787150	Apixaban 2.5mg x 2/day Apixaban 5mg x 2/day	74 (85%) 74 (82%)	*69.3 70.0	17 (23%) 23 (31%)	Primary: Composite of major bleeding and clinically relevant non-major bleeding Secondary: Ischaemic stroke, systemic embolism, MI, all-cause mortality
	Target INR 2.0-3.0 (1.6-2.6 if ≥ 70 years)	74 (81%)	71.7	21 (28%)	
Edoxaban Asia Chung 2011 Taiwan, Singapore, Hong Kong, South Korea; NCT00504556	Edoxaban 30mg x 4/day Edoxaban 60mg x 4/day	79 (65%) 80 (69%)	64.9 (9.1) 65.9 (7.7)	22 (27.8%) 22 (27.5%)	Primary: Major or clinically relevant, but non-major bleeding Secondary: Ischaemic stroke, systemic embolism, MI, all-cause mortality
	Target INR 2.0	75 (62%)	64.5 (9.5)	17 (22.7%)	
Edoxaban Japan Yamashita 2012 Japan; No clinical trial registration identified. No reply from authors.	Edoxaban 30mg Edoxaban 45mg Edoxaban 60mg	110 (84.0%) 109 (81.3%) 107 (81.7%)	69.4 69.5 68.4	mean/median 1.9/2 mean/median 2.1/2 mean/median 2.1/2	Primary: all bleeding Secondary: thromboembolic events
	Target INR 2.0-3.0	107 (82.9%)	68.8	mean/median 2.2/2	
Edoxaban US/Europe Weitz 2010 USA, eastern Europe; NCT00504556	Edoxaban 30mg Edoxaban 30mg x 2/day Edoxaban 60mg Edoxaban 60mg x 2/day	235 (60%) 245 (61%) 23 (66%) 180 (63%)	65.2 (8.3) 64.8 (8.8) 64.9 (8.8) 64.7 (9.0)	87 88 87 67	Primary: Major or clinically relevant, but non-major bleeding Secondary: Ischaemic stroke, haemorrhagic stroke, systemic embolism, MI, all-cause mortality
	Target INR 2-0	251 (60%)	66.0 (8.5)	90	
Explore-Xa (Connolly 2013 + other secondary reports) USA, Canada, Germany; NCT00742859	Betrixaban 40mg Betrixaban 60mg Betrixaban 80mg	127 (62%) 127 (64%) 127 (70%)	73.3 (8.50) 73.8 (8.35) 72.0 (7.65)	47 (37.0) 46 (36.2) 29 (23%)	Primary: Major or clinically relevant, but non-major bleeding Secondary: Ischaemic stroke, haemorrhagic stroke, systemic embolism, MI, all-cause mortality.
	Target INR 2-0	127 (70%)	72.7 (8.75)	48 (38%)	
Turpie 2010 OPAL-1 Japan, Singapore, Malaysia, Taiwan, Korea, Hong Kong, New Zealand, Thailand, South Africa; NCT00448214	YM150 30mg YM150 60mg YM150 120mg YM150 240mg	90 (86%) 93 (76%) 93 (80%) 78 (77%)	69.3 (8.4) 68.4 (9.4) 67.0 (9.6) 67.4 (9.0)	21 (23.3%) 19 (20.4%) 24 (25.8%) 18 (23.1%)	Primary: Major or clinically relevant, but non-major bleeding Secondary: Ischaemic stroke, haemorrhagic stroke, systemic embolism, MI, all-cause mortality
	Target INR 2-0 1, 3 or 5mg, target INR 2.0-3.0	94 (77%) 6022	67.0 (9.4) 71.6 (8.6)	17 (18.1%) 1933 (32%)	
Factor IIa Phase II trials					
Lip 2009; Austria, Denmark, Hungary, Ireland Norway, Poland, Russia, Sweden, UK; NCT00684307	AZD0837 150mg once daily AZD0837 300mg once daily AZD0837 450mg once daily AZD0837 200mg twice daily	166 (71%) 152 (69%) 157 (69%) 161 (67%)	**69.9 (43-93) **69.8 (45-92) **69.3 (45-88) **67.8 (34-88)	NR	Primary: Major or clinically relevant, but non-major bleeding Secondary: Ischaemic stroke, haemorrhagic stroke, systemic embolism, MI, all-cause mortality
	Target INR 2-0	319 (68%)	**68.3 (33-87)	NR	

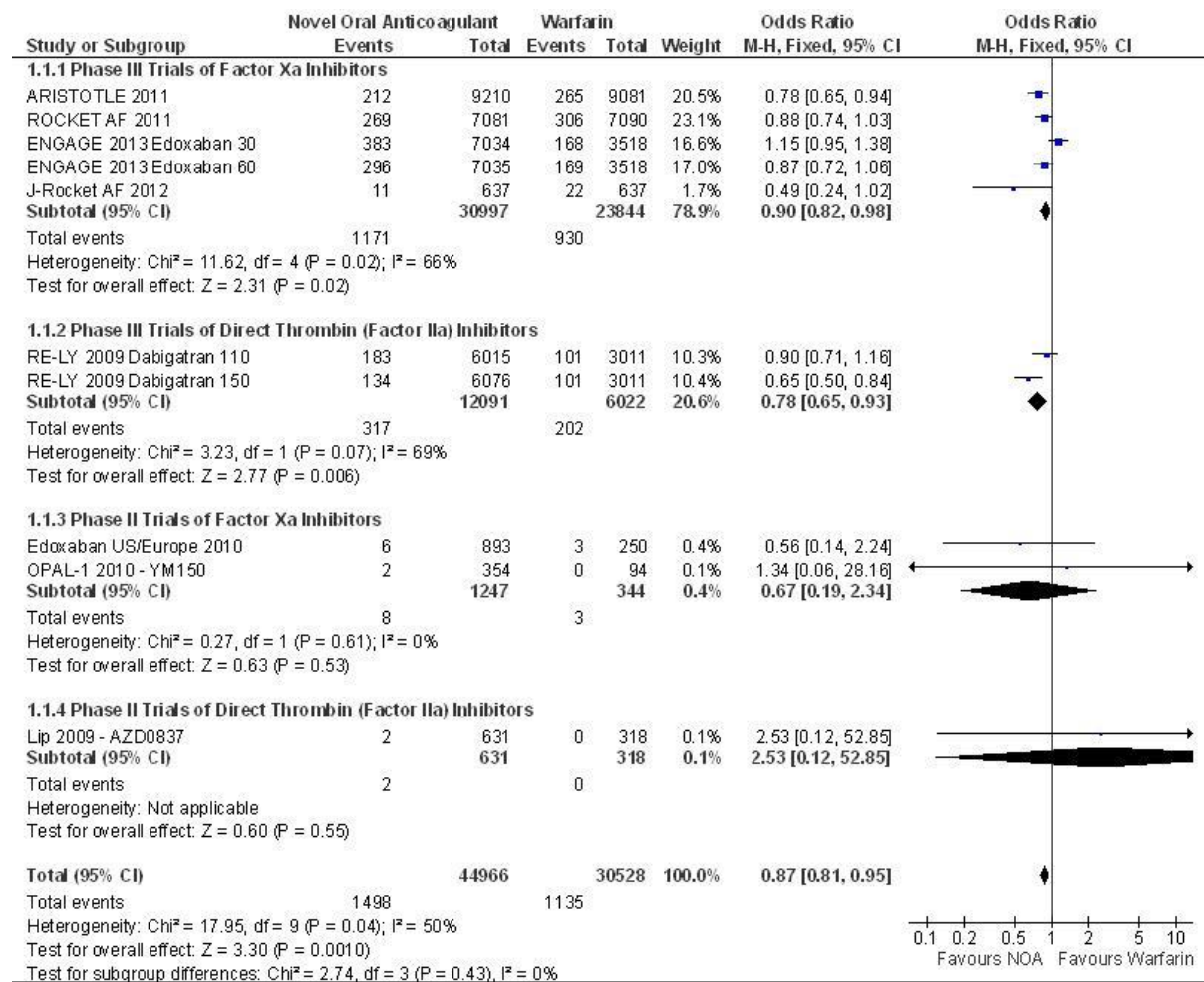
Supplementary Appendix Figure 3 Risk of Bias Summary Table One



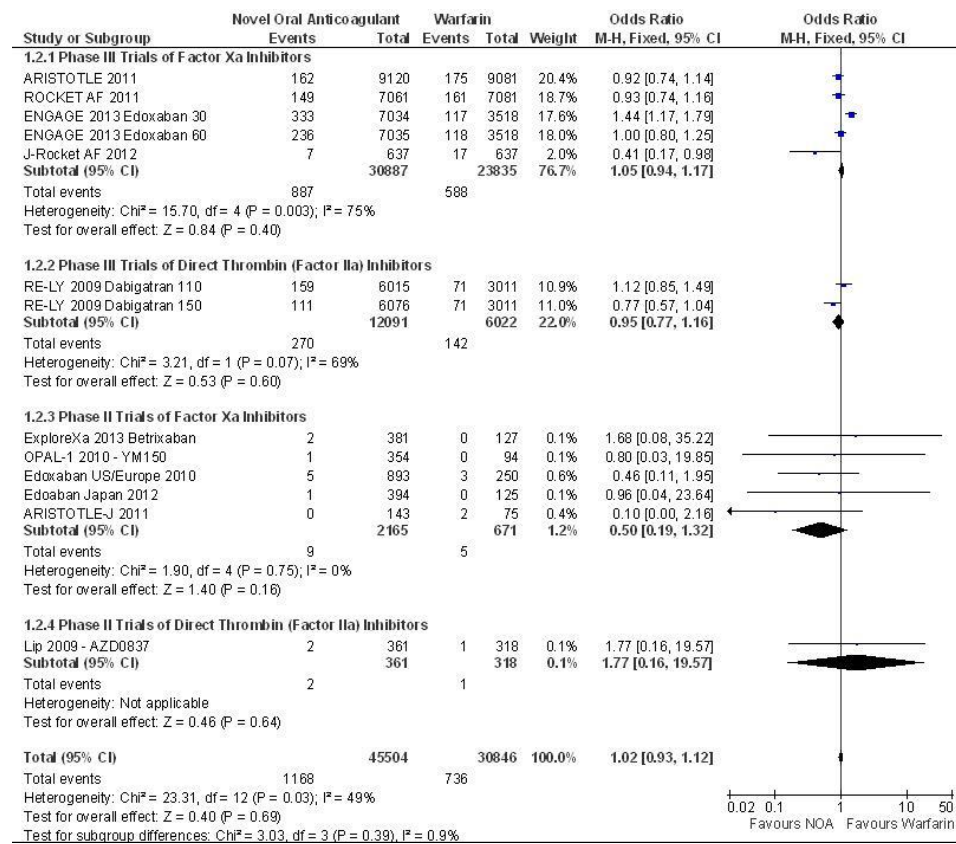
Supplementary Appendix Figure 4 Risk of Bias Summary Table Two

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
ARISTOTLE 2011	+	+	+	+	+	+	?
ARISTOTLE-J 2011	?	?	+	+	?	?	?
Edoxaban Asia 2011	?	?	+	+	+	+	?
Edoxaban Japan 2012	?	?	+	?	?	?	?
Edoxaban US/Europe 2010	+	+	+	+	?	+	?
ENGAGE AF-TIMI 48 2013	+	+	+	+	?	+	?
ExploreXa 2013 Betrixaban	+	?	+	+	+	+	?
J-Rocket AF 2012	?	?	+	+	+	?	?
Lip 2009 - AZD0837	+	+	+	+	?	+	?
OPAL-1 2010 - YM150	?	?	+	?	+	+	?
RE-LY 2009	+	+	+	+	+	+	?
ROCKET AF 2011	+	+	+	+	?	+	?

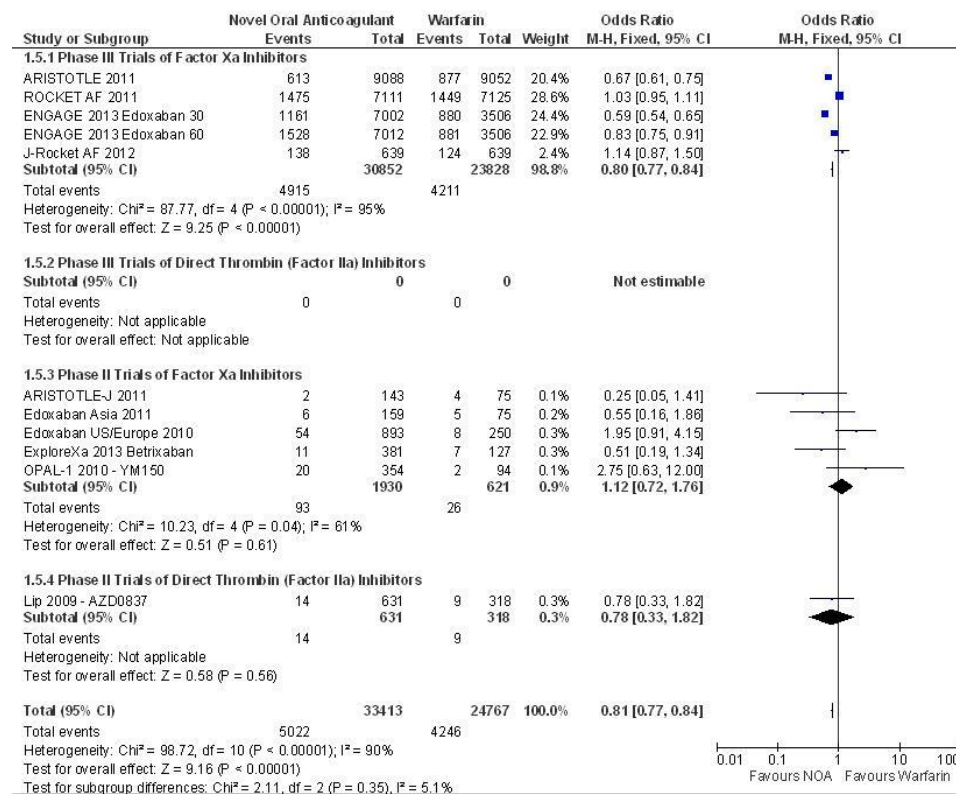
Supplementary Appendix Figure 5 Stroke or Systemic Embolism Fixed Effects Model



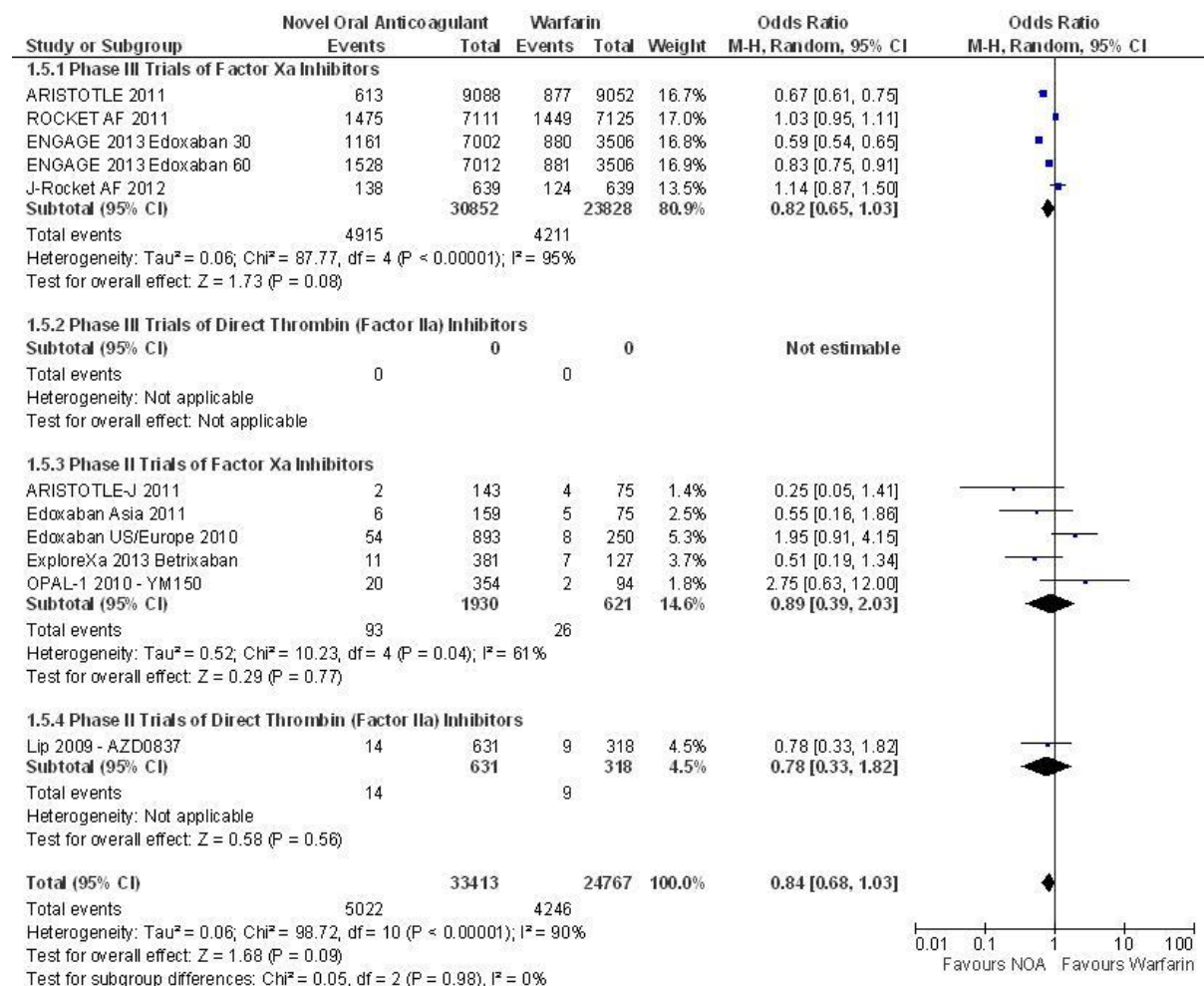
Supplementary Appendix Figure 6 Ischaemic Stroke Fixed Effects Model



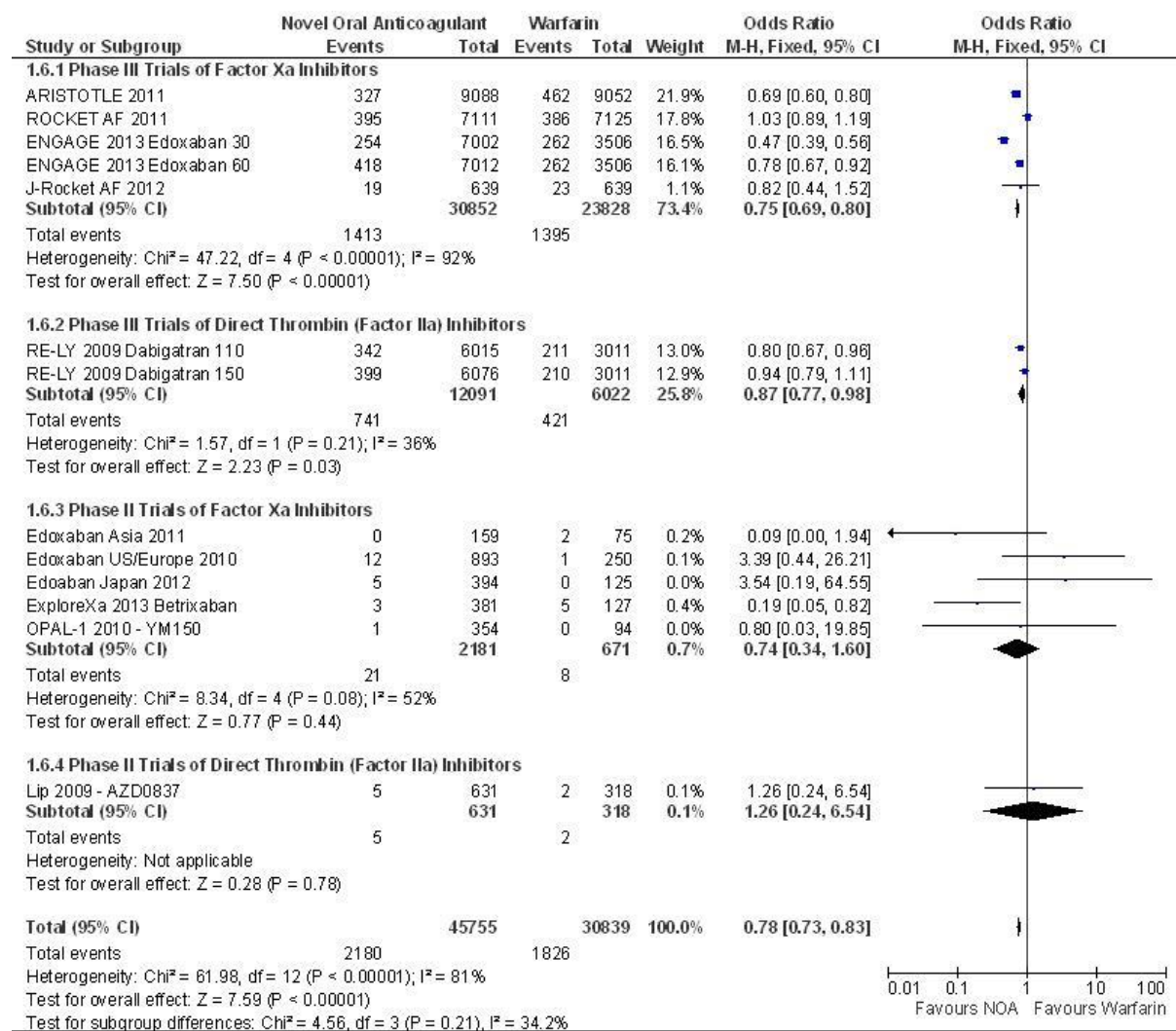
Supplementary Appendix Figure 7



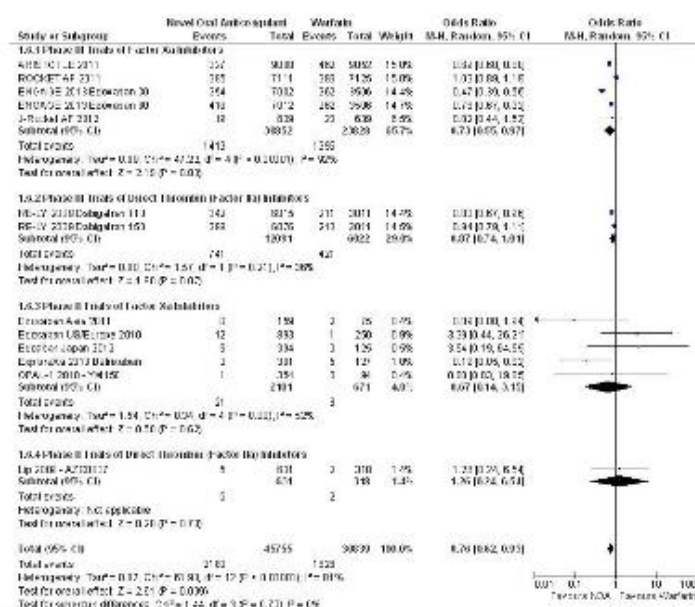
Supplementary Appendix Figure 8 Major or Clinically Relevant Non-Major Bleeding Random Effects Forest Plot



Supplementary Appendix Figure 9 Major Bleeding Fixed Effects Model Forest Plot

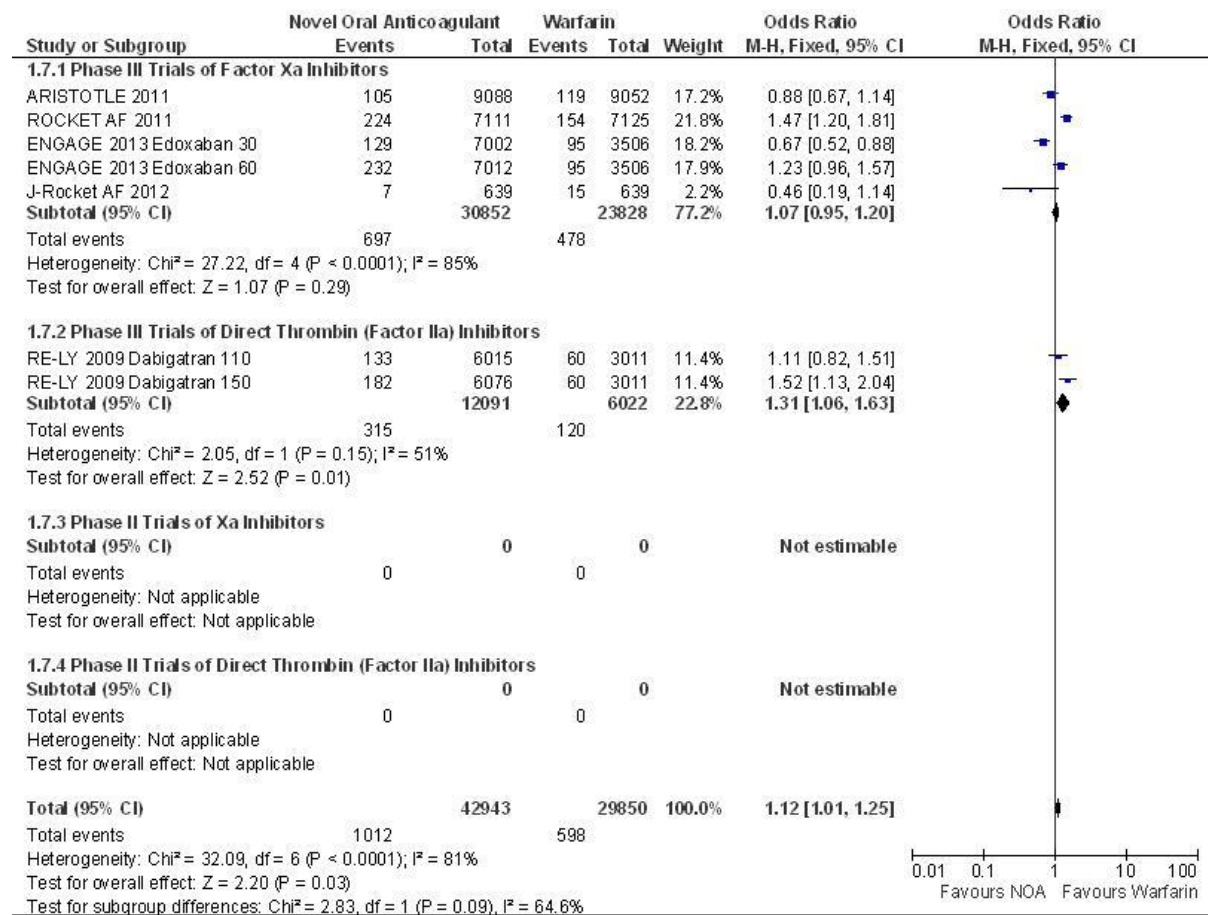


Supplementary Appendix Figure 10 Major Bleeding Random Effects Model

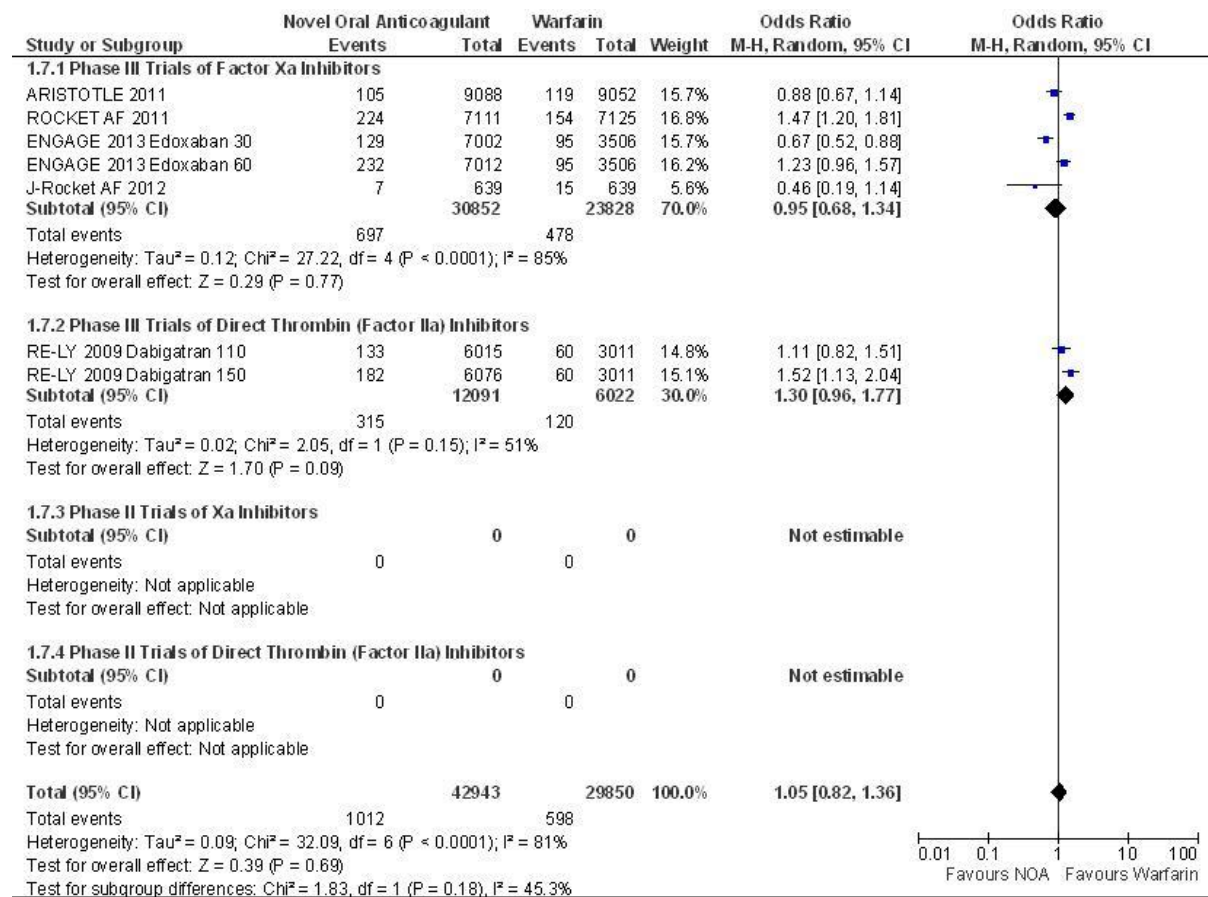


Supplementary Appendix Figure 10 Major Bleeding Random Effects Model

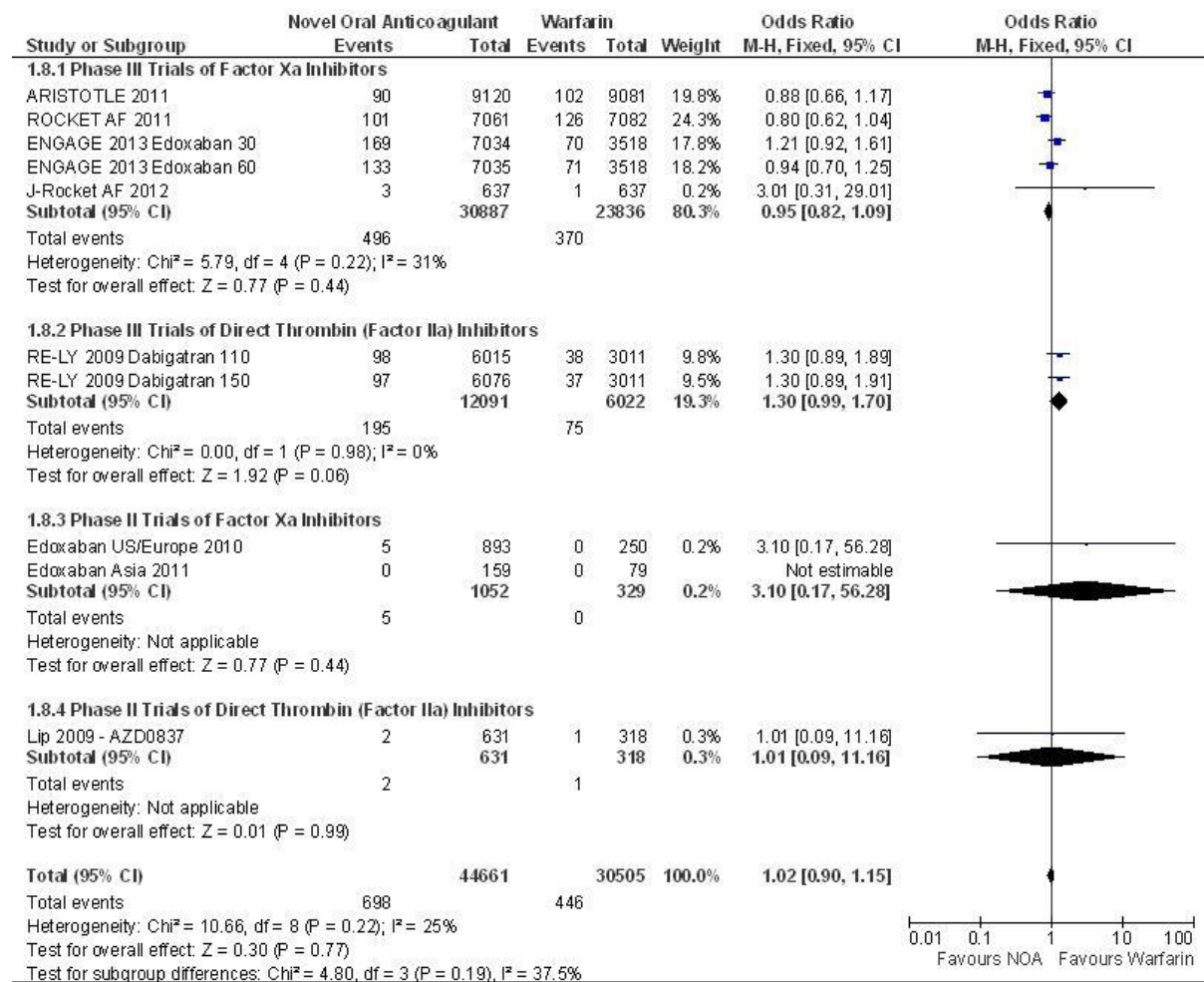
Supplementary Appendix Figure 11 Gastrointestinal Bleeding Fixed Effects Model Forest Plot



Supplementary Appendix Figure 12 Gastrointestinal Bleeding Random Effects Model Forest Plot



Supplementary Appendix Figure 13 Myocardial Infarction Fixed Effects Model Forest Plot



Supplementary Appendix Figure 14 Myocardial Infarction Random Effects Model Forest Plot

