Online Supplement

Methods

Only English language articles were included, with no minimum search date through February 28, 2017. A hand search of some systematic reviews and guidelines was performed.
We used the following search terms and their corresponding Medical Subject Heading (MeSH) terms to identify the articles for each PICO.

PICO 1
'stroke' OR 'transient ischemic attack' OR 'TIA' OR 'cerebrovascular accident*' OR 'CVA' OR 'cerebrovascular apoplexy' OR 'cerebrovascular infarct*' OR 'cerebrovascular embolism' OR 'cerebrovascular disorder' OR 'brain ischemia' OR 'brain infarct*' OR 'brain haemorrhage' OR 'wind stroke' OR 'cerebral embolism' OR 'cerebral haemorrhage' OR 'cardioembolic stroke' OR 'intracranial arteriosclerosis' OR 'hemiparesis' OR 'hemiplegia' AND 'atrial fibrillation' OR 'AF' OR 'atrial arrhythmias' OR 'nonvalvular atrial fibrillation' OR 'non-valvular atrial fibrillation' OR 'NVAF' OR 'atrial flutter' AND 'aspirin' OR 'antiplatelet therapy' OR 'dual antiplatelet therapy' OR 'DAPT' OR 'anticoagulant*' OR 'thienopyridine derivatives' OR 'clopidogrel' OR 'ticlopidine' OR 'dipyridamole' OR 'prasugrel' OR 'terutroban' OR 'sarpogrelate' OR 'cilostazol' OR 'vitamin K antagonist*' OR 'VKA' OR 'warfarin' OR 'phenprocoumon' OR 'acenocoumarol' OR 'fluindione' OR 'tecarfarin' OR 'direct oral anticoagulants' OR 'non-vitamin K antagonist oral anticoagulants' OR 'NOAC*' OR 'pradaxa' OR 'apixaban' OR 'dabigatran' OR 'edoxaban' OR 'rivaroxaban' OR 'ximelagatran' OR 'Xa inhibitor*' OR 'terutroban' OR 'triflusal' OR 'platelet aggregation inhibitor*' AND 'randomized controlled trials' OR 'random allocation' OR 'controlled clinical trials' OR 'control groups' OR 'clinical trial*' OR 'double-blind method' OR 'single-blind method' OR 'controlled clinical trial' OR 'random' OR 'RCT*' OR 'controlled trial' OR 'quasi-random*' OR 'quasi random*' OR 'pseudo-random*' OR 'pseudo random*'.

PICO 2A
'stroke' OR 'transient ischemic attack' OR 'TIA' OR 'cerebrovascular accident*' OR 'CVA' OR 'cerebrovascular apoplexy' OR 'cerebrovascular infarct*' OR 'cerebrovascular embolism' OR 'cerebrovascular disorder' OR 'brain ischemia' OR 'brain infarct*' OR 'brain haemorrhage' OR 'wind stroke' OR 'cerebral embolism' OR 'cerebral haemorrhage' OR 'cardioembolic stroke' OR 'intracranial

arteriosclerosis' OR 'hemiparesis' OR 'hemiplegia' AND 'atrial fibrillation' OR 'AF' OR 'atrial arrhythmias' OR 'nonvalvular atrial fibrillation' OR 'non-valvular atrial fibrillation' OR 'NVAF' OR 'atrial flutter' AND 'aspirin' OR 'antiplatelet therapy' OR 'dual antiplatelet therapy' OR 'DAPT' OR 'anticoagulant*' OR 'thienopyridine derivatives' OR 'clopidogrel' OR 'ticlopidine' OR 'dipyridamole' OR 'prasugrel' OR 'terutroban' OR 'sarpogrelate' OR 'cilostazol' OR 'vitamin K antagonist*' OR 'VKA' OR 'warfarin' OR 'phenprocoumon' OR 'acenocoumarol' OR 'fluindione' OR 'tecarfarin' OR 'direct oral anticoagulants' OR 'non-vitamin K antagonist oral anticoagulants' OR 'NOAC*' OR 'pradaxa' OR 'apixaban' OR 'dabigatran' OR 'edoxaban' OR 'rivaroxaban' OR 'ximelagatran' OR 'Xa inhibitor' OR 'terutroban' OR 'triflusal' OR 'platelet aggregation inhibitor' AND 'early' OR 'late' OR 'emergent' OR 'immediate' OR 'delayed' AND 'randomized controlled trial*' OR 'random allocation' OR 'controlled clinical trials' OR 'control groups' OR 'clinical trial*' OR 'double-blind method' OR 'single-blind method' OR 'controlled clinical trial' OR 'random' OR 'RCT*' OR 'controlled trial' OR 'quasi-random*' OR 'quasi random*' OR 'pseudo-random*' OR 'pseudo random*'.

PICO 2B

'stroke' OR 'transient ischemic attack' OR 'TIA' OR 'cerebrovascular accident*' OR 'CVA' OR 'cerebrovascular apoplexy' OR 'cerebrovascular infarct*' OR 'cerebrovascular embolism' OR 'cerebrovascular disorder' OR 'brain ischemia' OR 'brain infarct*' OR 'brain haemorrhage' OR 'wind stroke' OR 'cerebral embolism' OR 'cerebral haemorrhage' OR 'cardioembolic stroke' OR 'intracranial arteriosclerosis' OR 'hemiparesis' OR 'hemiplegia' AND 'atrial fibrillation' OR 'AF' OR 'atrial arrhythmias' OR 'nonvalvular Atrial fibrillation' OR 'non-valvular atrial fibrillation' OR 'NVAF' OR 'atrial flutter' AND 'heparin' OR 'Low-Molecular-Weight Heparin' OR 'LMWH' OR 'heparinoid*' OR 'enoxaparin*' OR 'glycosaminoglycan*' OR 'nadroparin*' OR 'mesoglycan*' OR 'tedelparin*' OR 'certoparin' or 'tinzaparin' OR 'parnaparin' OR 'dalteparin' OR 'reviparin' OR 'fraxiparin* OR 'danaparoid' OR 'lomoparan' OR 'org 10172' OR 'pentosan polysulfate' AND 'randomized controlled trial*' OR 'random allocation' OR 'controlled clinical trials' OR 'control groups' OR 'clinical trial*' OR 'double-blind method' OR 'single-blind method' OR 'controlled clinical trial' OR 'random' OR 'RCT*' OR 'controlled trial' OR 'quasi-random*' OR 'quasi random*' OR 'pseudo-random*' OR 'pseudo random*'.

PICO 3

'left atrial appendage*' OR 'left atrium appendage*' OR 'left auricular appendage*' AND 'excis*' OR 'excision*' OR 'occlude*' OR 'occlusion*' OR 'closure*' OR 'destruction' OR 'obliterat*' OR 'ligation*' OR

'ligat*' OR 'sutur*' OR 'exclusion*' OR 'exclud*' OR 'appendectom*' OR 'thoracoscop*' OR 'minithoracotom*' OR 'mini-thoracotom*' OR 'stapling' OR 'stapled' OR 'stapler*' OR 'sew' OR 'sewn' OR 'oversew*' OR 'clamp*' OR 'clip*' OR 'atriclip' OR 'Gillinov-Cosgrove LAA system' OR 'ligature' OR 'amputat*' OR 'resect*' OR 'removal' OR 'remove*' OR 'surger*' OR 'surgical' OR 'CABG' OR 'coronary artery bypass graft' OR 'MAZE' OR 'AVR' OR 'sternotom*' OR 'percutaneous*' OR 'Watchman' OR 'Watchman device' OR 'Lariat' OR 'PLAATO' OR 'Amplatzer' OR 'Coherex FlatStent' OR 'Lambre' OR 'minimal surgical' OR 'endovascular closure' OR 'Percutaneous Left Atrial appendage transcatheter occlusion' AND 'stroke' OR 'transient ischemic attack' OR 'TIA' OR 'cerebrovascular accident*' OR 'CVA' OR 'cerebrovascular apoplexy' OR 'cerebrovascular infarct*' OR 'cerebrovascular embolism' OR 'cerebrovascular disorder' OR 'brain ischemia' OR 'brain infarct*' OR 'brain haemorrhage' OR 'wind stroke' OR 'cerebral embolism' OR 'cerebral haemorrhage' OR 'cardioembolic stroke' OR 'intracranial arteriosclerosis' OR 'hemiparesis' OR 'hemiplegia' AND 'atrial fibrillation' OR 'AF' OR 'atrial arrhythmias' OR 'nonvalvular atrial fibrillation' OR 'non-valvular atrial fibrillation' OR 'NVAF' OR 'atrial flutter' AND 'vitamin K antagonist*' OR 'VKA' OR 'warfarin' OR 'phenprocoumon' OR 'acenocoumarol' OR 'fluindione' OR 'tecarfarin' OR 'direct oral anticoagulants' OR 'non-vitamin K antagonist oral anticoagulants' OR 'NOAC*' OR 'pradaxa' OR 'apixaban' OR 'dabigatran' OR 'edoxaban' OR 'rivaroxaban' OR 'ximelagatran' OR 'Xa inhibitor*' OR 'terutroban' OR 'triflusal' AND 'randomized controlled trial*' OR 'random allocation' OR 'controlled clinical trials' OR 'control groups' OR 'clinical trial*' OR 'double-blind method' OR 'single-blind method' OR 'controlled clinical trial' OR 'random' OR 'RCT*' OR 'controlled trial' OR 'quasi-random*' OR 'quasi random*' OR 'pseudo-random*' OR 'pseudo random*'.

PICO 4

'intracerebral haemorrhage' OR 'brain haemorrhage' OR 'cerebral haemorrhage' OR 'brain ischemia' OR 'hemorrhagic stroke' AND 'atrial fibrillation' OR 'AF' OR 'atrial arrhythmias' OR 'nonvalvular atrial fibrillation' OR 'non-valvular atrial fibrillation' OR 'NVAF' OR 'atrial flutter' AND 'vitamin K antagonist*' OR 'VKA' OR 'warfarin' OR 'phenprocoumon' OR 'acenocoumarol' OR 'fluindione' OR 'tecarfarin' OR 'direct oral anticoagulants' OR 'non-vitamin K antagonist oral anticoagulants' OR 'NOAC*' OR 'pradaxa' OR 'apixaban' OR 'dabigatran' OR 'edoxaban' OR 'rivaroxaban' OR 'ximelagatran' OR 'Xa inhibitor' OR 'terutroban' OR 'triflusal'.

PICO 5A

'cognitive deficits' OR 'cognitive impairment' OR 'dementia' AND 'stroke' OR 'transient ischemic attack' OR 'TIA' OR 'cerebrovascular accident*' OR 'CVA' OR 'cerebrovascular apoplexy' OR 'cerebrovascular infarct*' OR 'cerebrovascular embolism' OR 'cerebrovascular disorder' OR 'brain ischemia' OR 'brain infarct*' OR 'brain haemorrhage' OR 'wind stroke' OR 'cerebral embolism' OR 'cerebral haemorrhage' OR 'cardioembolic stroke' OR 'intracranial arteriosclerosis' OR 'hemiparesis' OR 'hemiplegia' AND 'atrial fibrillation' OR 'AF' OR 'atrial arrhythmias' OR 'nonvalvular atrial fibrillation' OR 'non-valvular atrial fibrillation' OR 'NVAF' OR 'atrial flutter' AND 'aspirin' OR 'antiplatelet' OR 'dual antiplatelet therapy' OR 'DAPT' OR 'anticoagula*' OR 'thienopyridine derivatives' OR 'clopidogrel' OR 'ticlopidine' OR 'dipyridamole' OR 'prasugrel' OR 'terutroban' OR 'sarpogrelate' OR 'cilostazol' OR 'vitamin K antagonist*' OR 'VKA' OR 'warfarin' OR 'phenprocoumon' OR 'acenocoumarol' OR 'fluindione' OR 'tecarfarin' OR 'direct oral anticoagulants' OR 'non-vitamin K antagonist oral anticoagulants' OR 'NOAC*' OR 'pradaxa' OR 'apixaban' OR 'dabigatran' OR 'edoxaban' OR 'rivaroxaban' OR 'ximelagatran' OR 'Xa inhibitor' OR 'terutroban' OR 'triflusal' OR 'platelet aggregation inhibitor'.

PICO 5B

'small vessel disease' AND 'MRI' OR 'Magnetic Resonance Imaging' OR 'Magnetic Resonance Angiography' OR 'white matter lesions' OR 'micro-bleeds' OR 'cerebral microbleeds' OR 'cerebral small vessel disease' OR 'intracerebral hemorrhage' OR 'microcirculation*' AND 'stroke' OR 'transient ischemic attack' OR 'TIA' OR 'cerebrovascular accident*' OR 'CVA' OR 'cerebrovascular apoplexy' OR 'cerebrovascular infarct*' OR 'cerebrovascular embolism' OR 'cerebrovascular disorder' OR 'brain ischemia' OR 'brain infarct*' OR 'brain haemorrhage' OR 'wind stroke' OR 'cerebral embolism' OR 'cerebral haemorrhage' OR 'cardioembolic stroke' OR 'intracranial arteriosclerosis' OR 'hemiparesis' OR 'hemiplegia' AND 'atrial fibrillation' OR 'AF' OR 'atrial arrhythmias' OR 'nonvalvular atrial fibrillation' OR 'non-valvular atrial fibrillation' OR 'NVAF' OR 'atrial flutter' AND 'aspirin' OR 'antiplatelet' OR 'dual antiplatelet therapy' OR 'DAPT' OR 'anticoagula*' OR 'thienopyridine derivatives' OR 'clopidogrel' OR 'ticlopidine' OR 'dipyridamole' OR 'prasugrel' OR 'terutroban' OR 'sarpogrelate' OR 'cilostazol' OR 'vitamin K antagonist*' OR 'VKA' OR 'warfarin' OR 'phenprocoumon' OR 'acenocoumarol' OR 'fluindione' OR 'tecarfarin' OR 'direct oral anticoagulants' OR 'non-vitamin K antagonist oral anticoagulants' OR 'NOAC*' OR 'pradaxa' OR 'apixaban' OR 'dabigatran' OR 'edoxaban' OR 'rivaroxaban' OR 'ximelagatran' OR 'Xa inhibitor' OR 'terutroban' OR 'triflusal' OR 'platelet aggregation inhibitor'.

PICO 5C

‘atrial fibrillation’ OR ‘AF’ OR ‘atrial arrhythmias’ OR ‘nonvalvular atrial fibrillation’ OR ‘non-valvular atrial fibrillation’ OR ‘NVAF’ OR ‘atrial flutter’ AND ‘dabigatran’ OR ‘rivaroxaban’ OR ‘apixaban’ OR ‘edoxaban’ OR ‘NOACs’ OR ‘non-vitamin K antagonist oral anticoagulants’ OR ‘new oral anticoagulant’ OR ‘oral factor Xa inhibitor’ OR ‘Xa inhibitors’ OR ‘oral thrombin inhibitor’ OR ‘vitamin K antagonists’ OR ‘warfarin’ OR ‘anticoagulants’ AND ‘chronic kidney disease’ OR ‘renal failure’ OR ‘creatinine clearance’ OR ‘kidney function’ OR ‘creatinine’ OR ‘eGFR’ OR ‘renal impairment’ AND ‘random’ OR ‘random allocation’ OR ‘randomized’ OR ‘RCT’ OR ‘controlled trial’ OR ‘randomized controlled trials’.

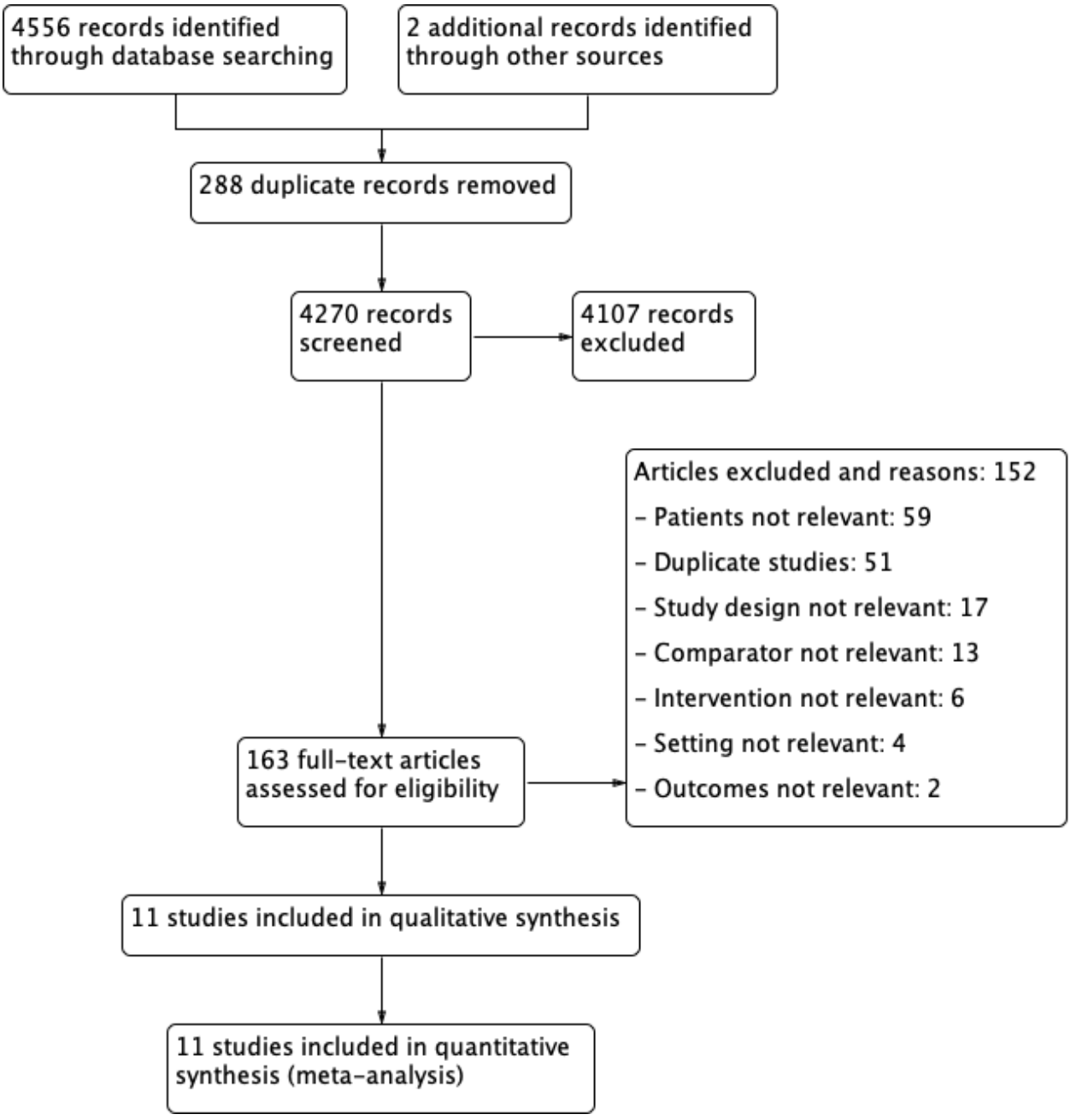
eTable 1. Quality of evidence grading

Grade	Definition	Criteria* Type of evidence	Implication	Symbol
High	Confidence that true effect lies close to estimate	Randomized trial	Further research unlikely to change confidence in the effect estimate	⨁⨁⨁⨁
Moderate	Moderate confidence of the effect estimate		Further research likely to change confidence and may change effect estimate	⨁⨁⨁
Low	Limited confidence; the true effect may be substantially different from the estimate	Observational study	Further research very likely to change confidence and effect estimate	⨁⨁
Very low	Little confidence; true effect is likely to be substantially different than estimate	Other	Any estimate of effect is very uncertain	⨁

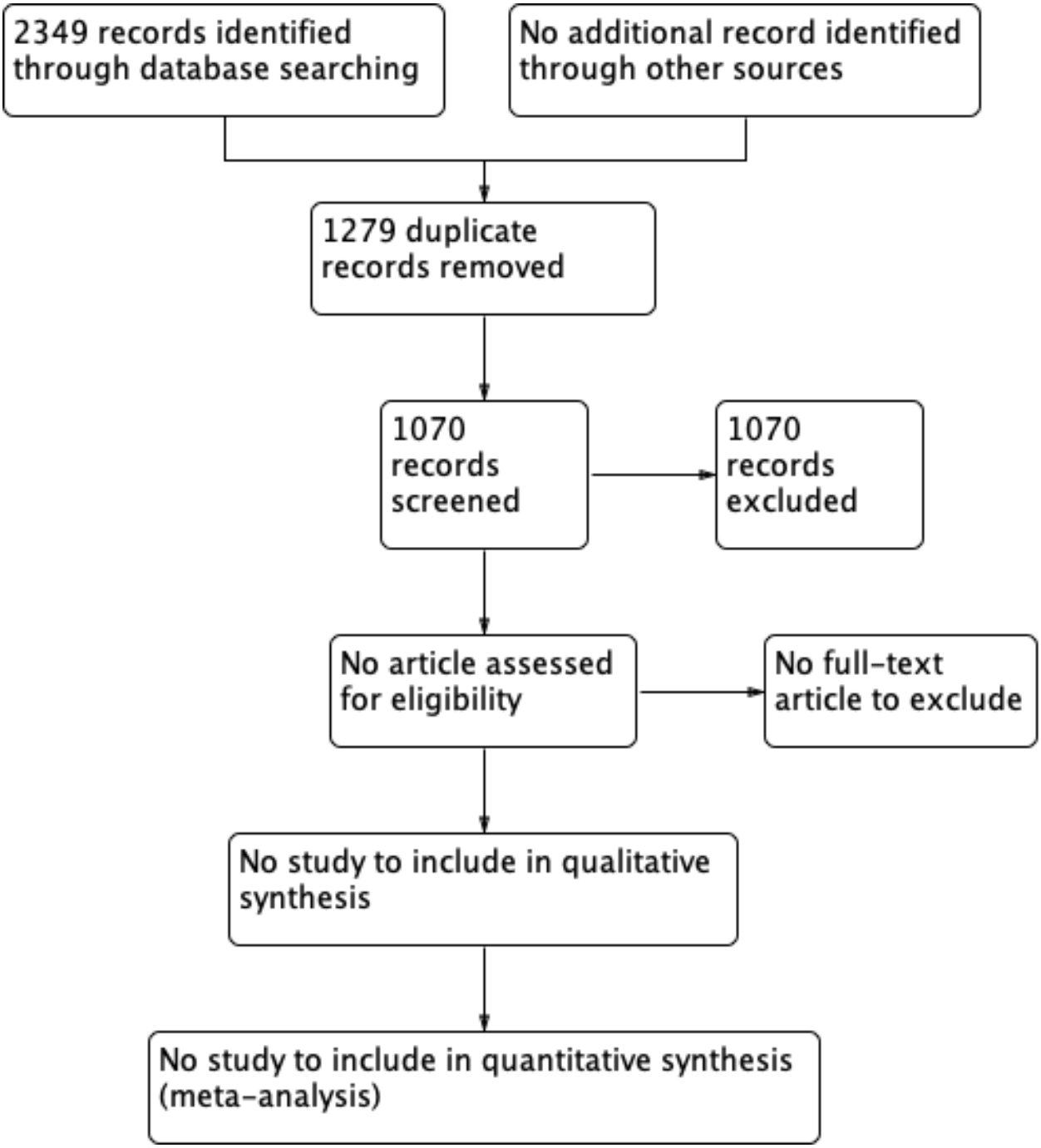
*Decrease grade by one or two levels if limitation in study design or execution, inconsistency of results, indirectness of evidence, imprecise or sparse data, publication bias (asymmetry of a funnel plot of a meta-analysis of ≥ 6 studies/comparison; increase grade if strong evidence of association (relative risk >2, or <0.5) in two or more observational studies with no plausible confounders (1 level), very strong evidence of association (relative risk >5, or <0.2) based on direct evidence with no major threats to validity (2 levels), dose response gradient (1 level), all plausible confounders would have reduced demonstrated effect or increase the effect if no effect was observed (1 level)

Results

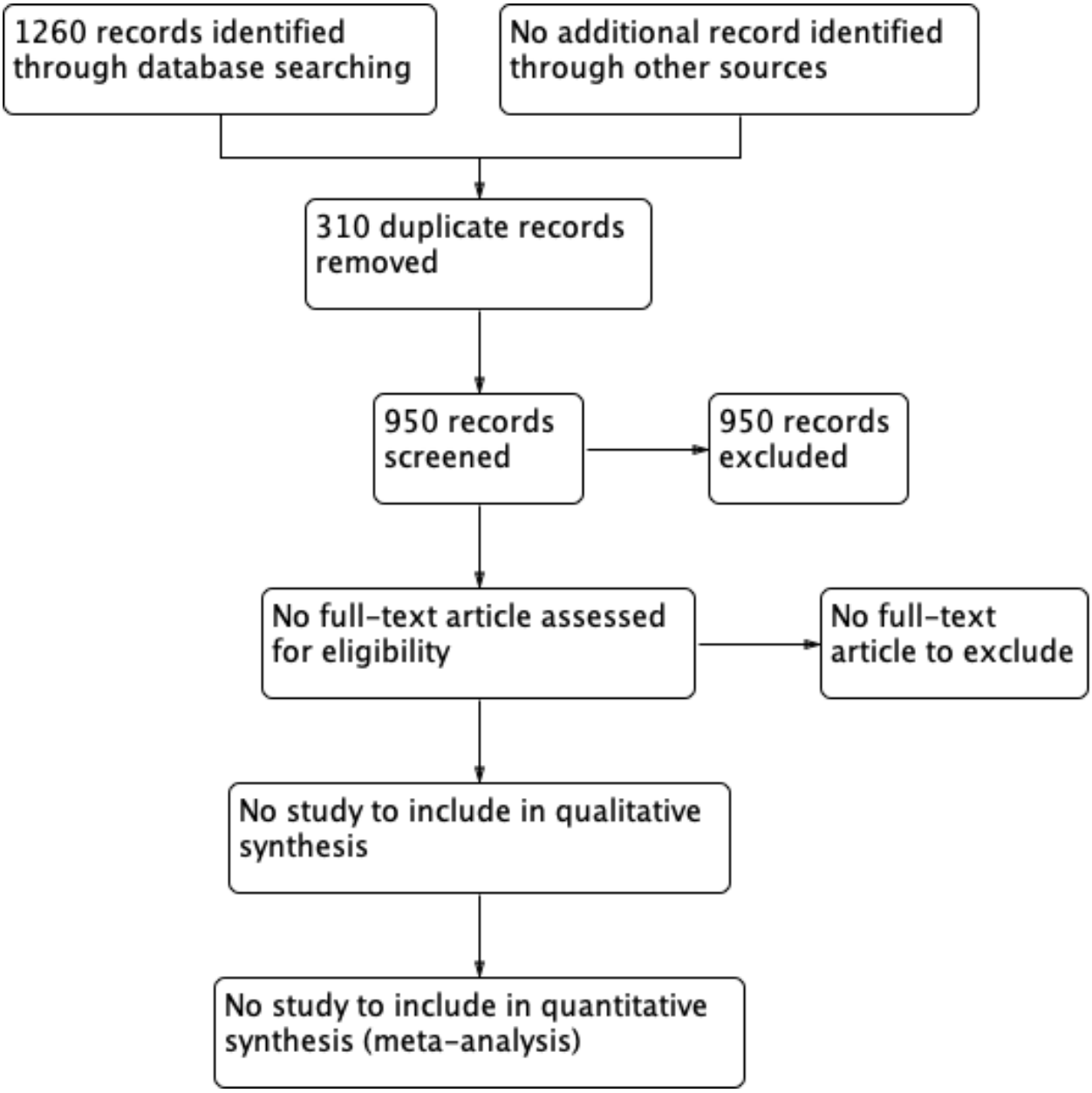
eFigure 1: Medical treatment



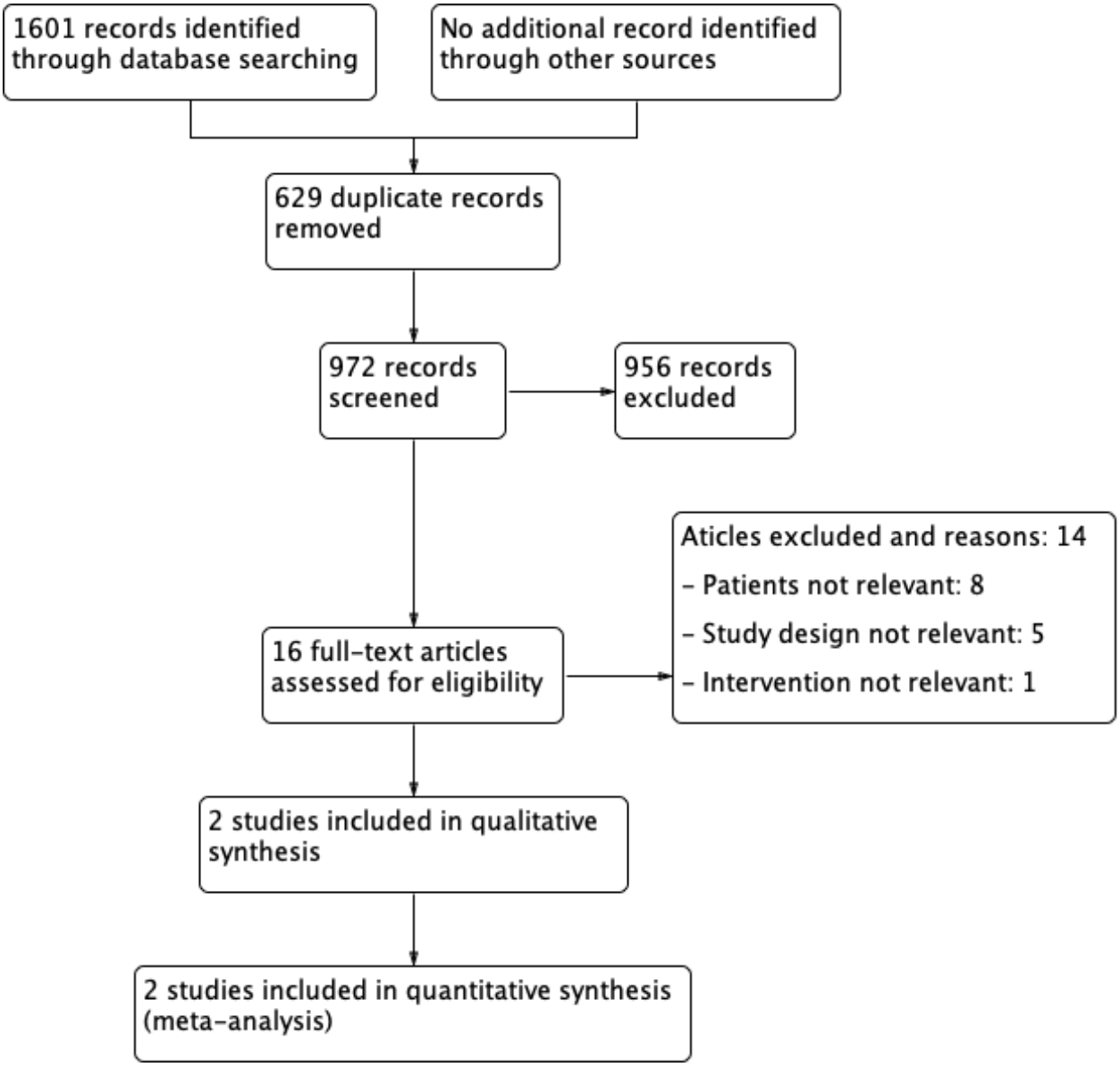
eFigure 2.1: Timing of medical treatment



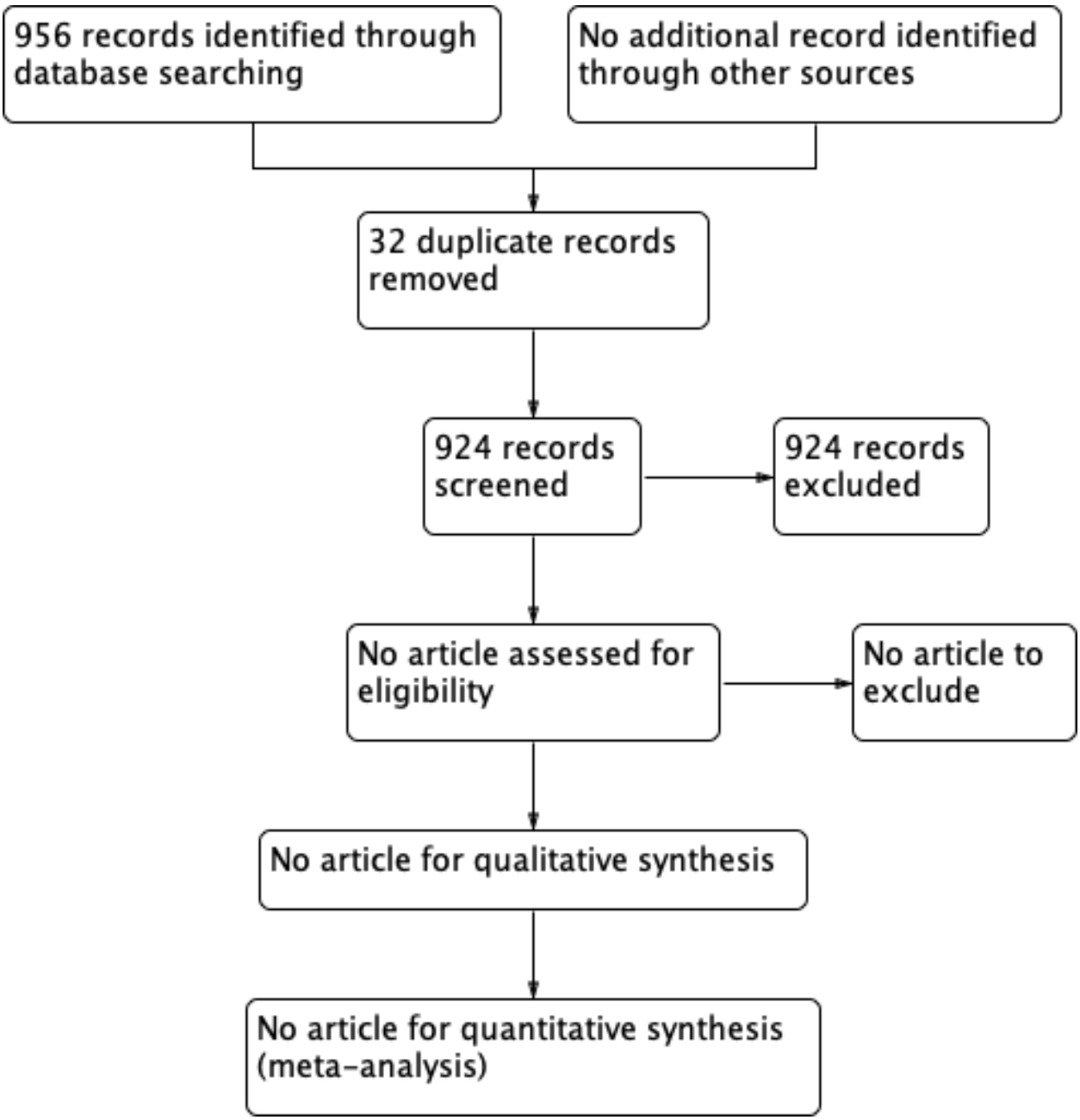
eFigure 2.2: Bridging of medical treatment



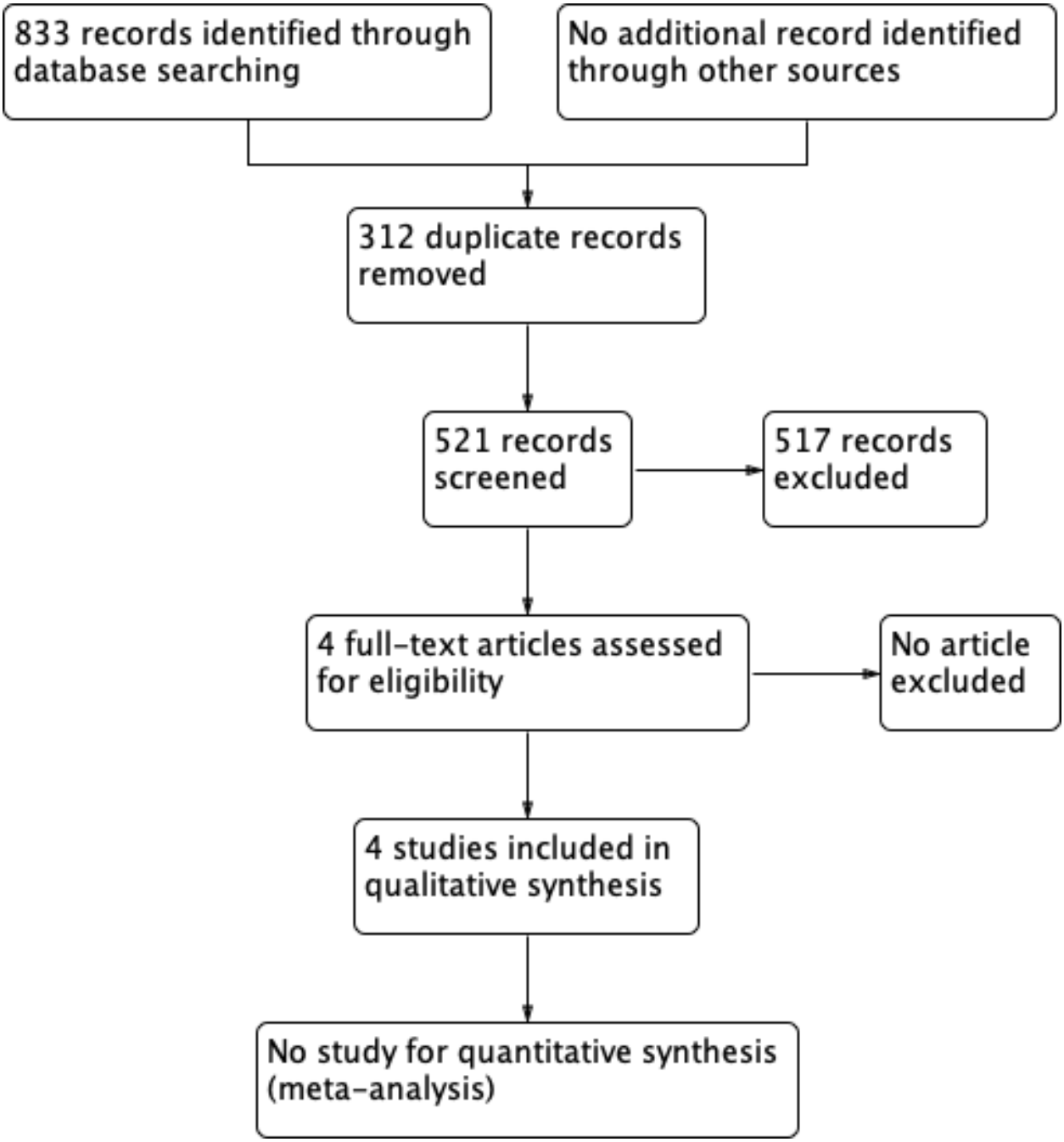
eFigure 3: Treatment by means of occlusion of the left atrial appendage



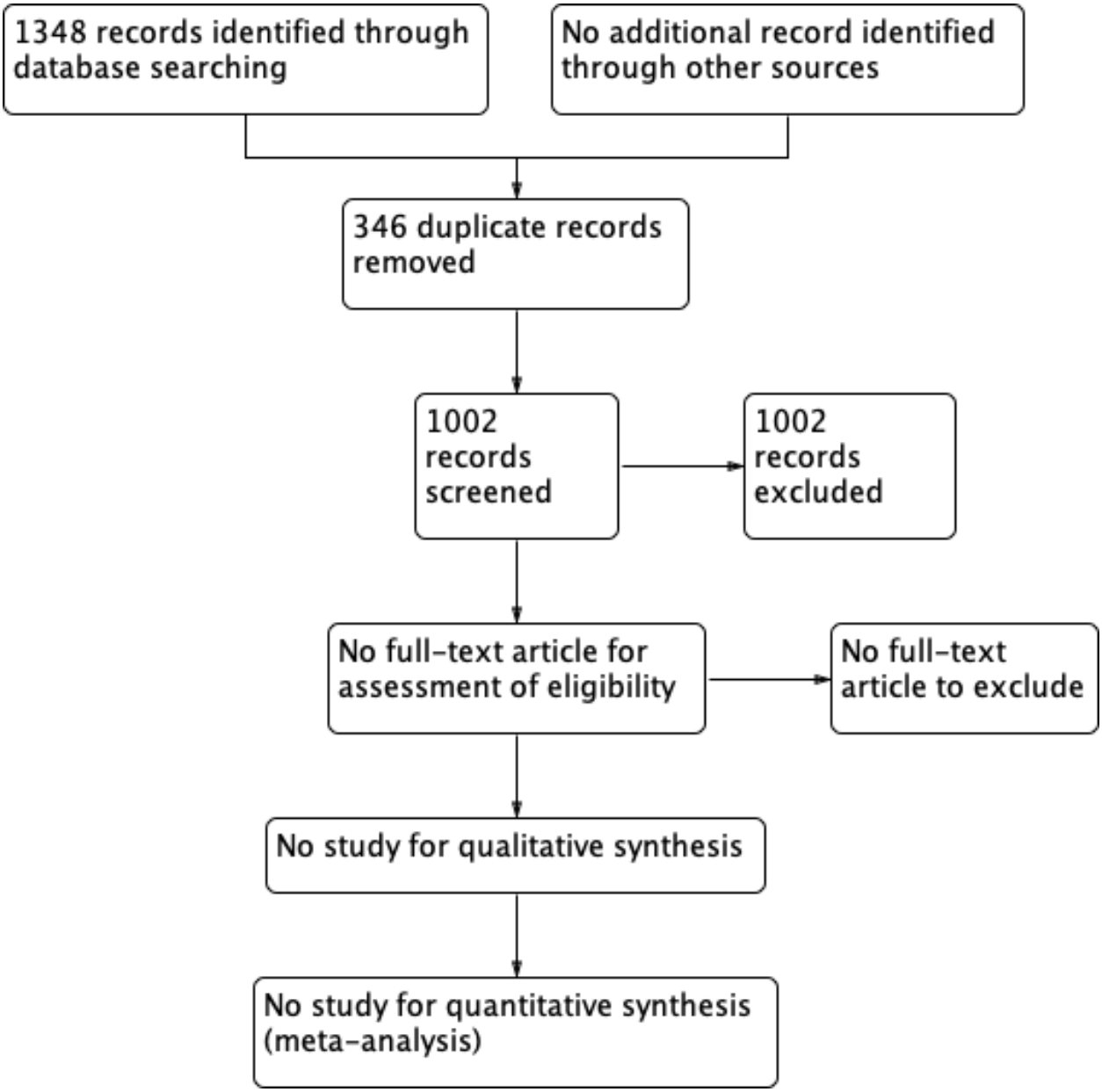
eFigure 4: (Re-)starting medical treatment in patients with previous intracerebral haemorrhage



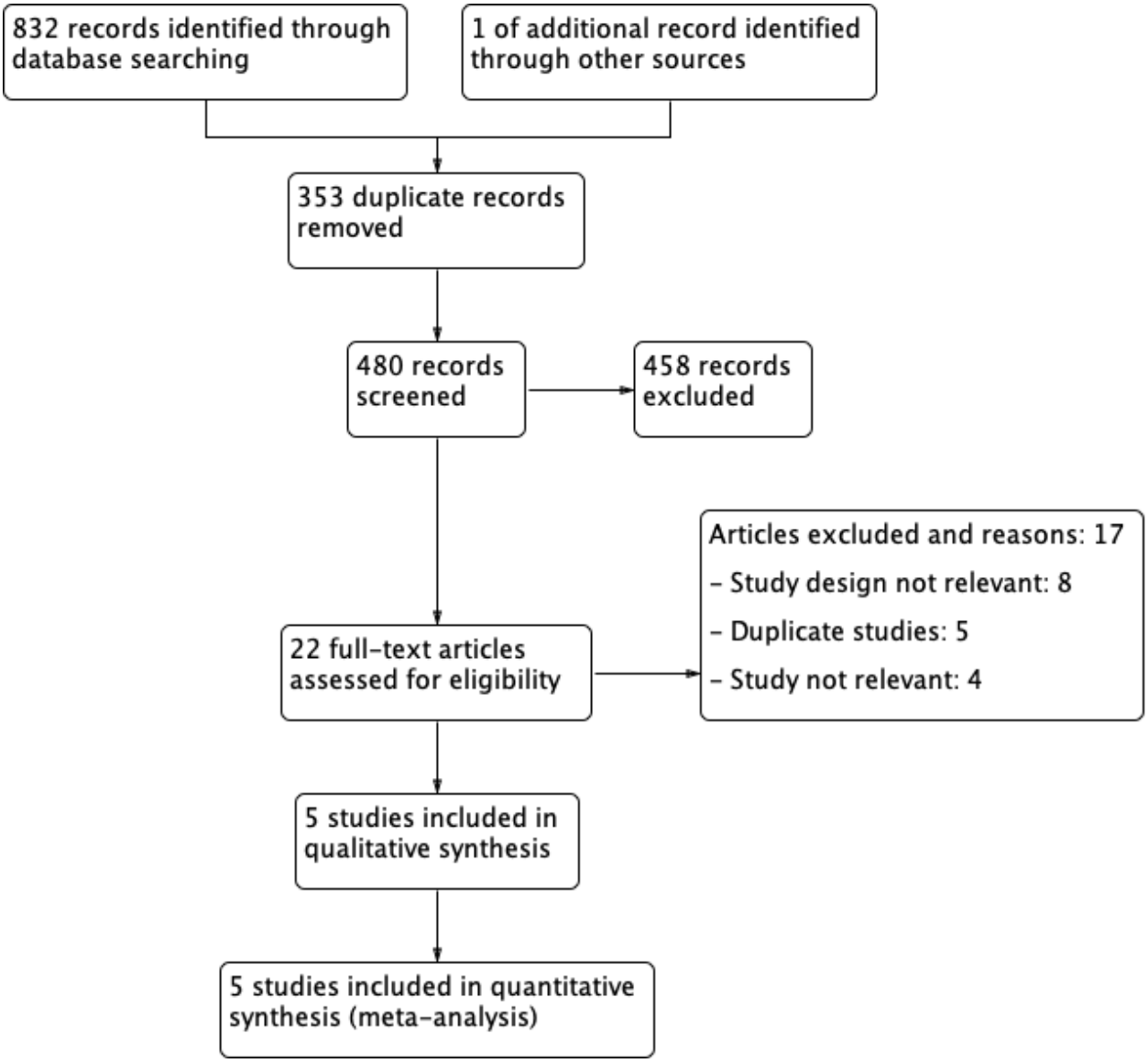
eFigure 5.2: Medical treatment in patients with cognitive deficits



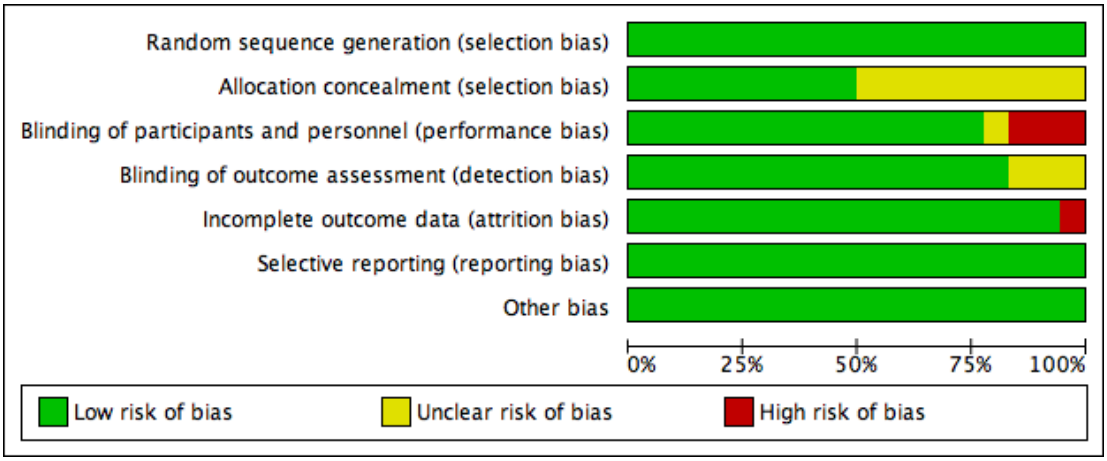
eFigure 5.3: Medical treatment in patients with signs of small vessel disease on MRI



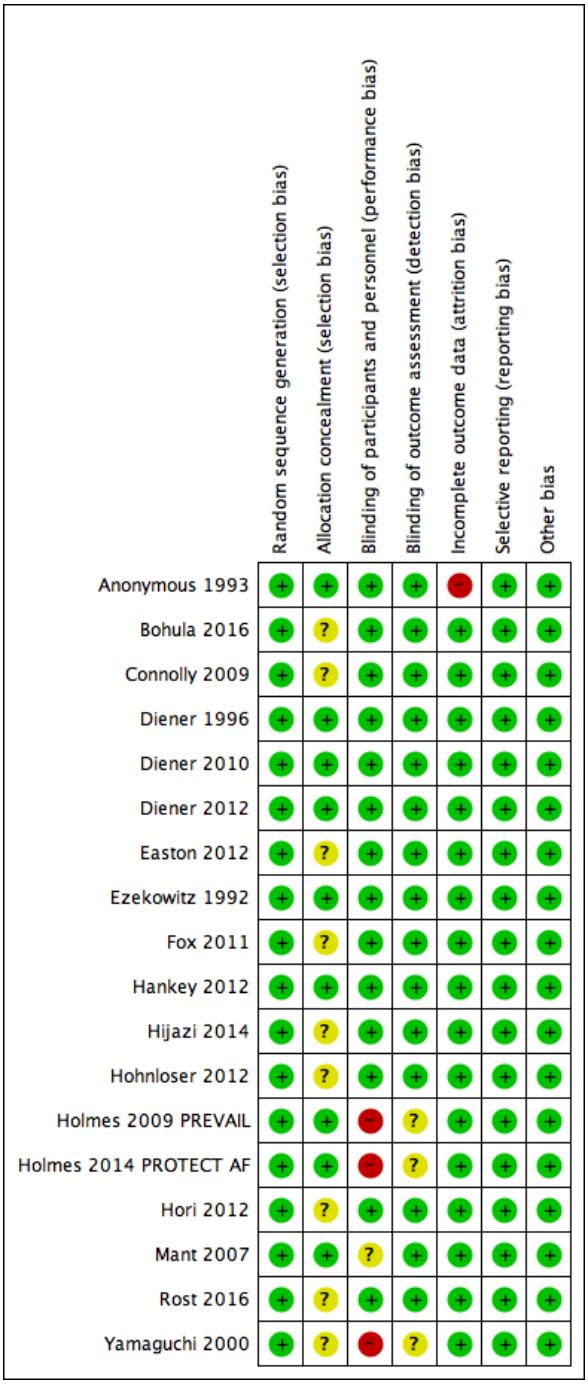
eFigure 5.4: Medical treatment in patients with renal failure



eFigure 6: Overall risk of bias of included studies



eFigure 7: Risk of bias of individual studies



1. Medical treatment in patients with ischemic stroke

eTable 2. Effect of Aspirin compared to Placebo in patients with previous ischemic stroke or TIA and AF

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	Placebo	Relative (95% CI)	Absolute (95% CI)		
Stroke and thromboembolism												
3	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [a]	119/542 (22.0%)	126/500 (25.2%)	**OR 0.83** (0.62 to 1.10)	**33 fewer per 1,000** (from 18 more to 79 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Ischemic stroke												
1	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [b]	64/404 (15.8%)	73/378 (19.3%)	**OR 0.79** (0.54 to 1.14)	**34 fewer per 1,000** (from 21 more to 79 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Intracerebral hemorrhage												
1	randomised trials	not serious	not serious	not serious	serious [c]	publication bias strongly suspected [b]	1/404 (0.2%)	0/378 (0.0%)	**OR 2.81** (0.11 to 69.29)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL
Major bleeding												
1	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [b]	6/404 (1.5%)	4/378 (1.1%)	**OR 1.41** (0.39 to 5.03)	**4 more per 1,000** (from 6 fewer to 40 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Non-fatal stroke, non-fatal MI and vascular death												
1	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [b]	124/404 (30.7%)	127/378 (33.6%)	**OR 0.88** (0.65 to 1.18)	**28 fewer per 1,000** (from 38 more to 88 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Death												
1	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [b]	102/404 (25.2%)	99/378 (26.2%)	**OR 0.95** (0.69 to 1.31)	**10 fewer per 1,000** (from 55 more to 65 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

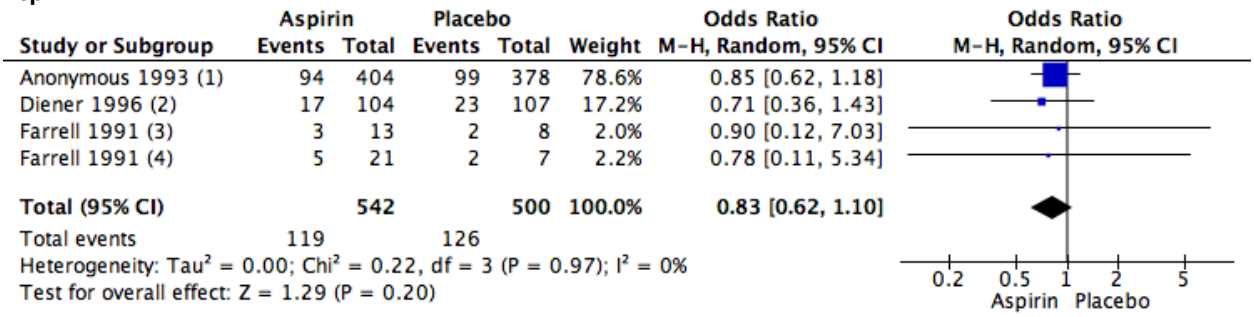
CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Three studies to report this outcome
b. Single study
c. Wide confidence intervals

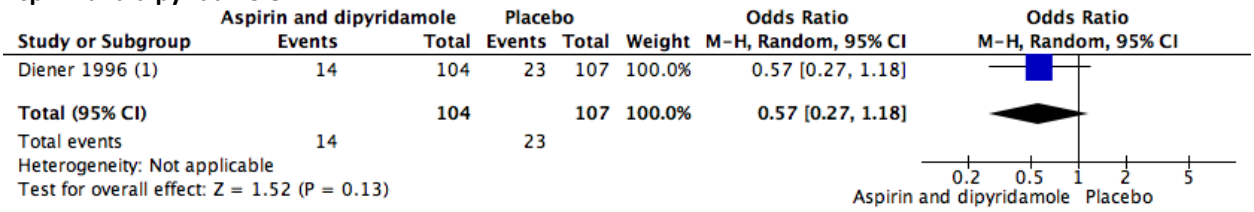
eFigure 8: Effect of antiplatelet drugs versus placebo on stroke or thromboembolism in patients with previous ischemic stroke or TIA and AF

Aspirin



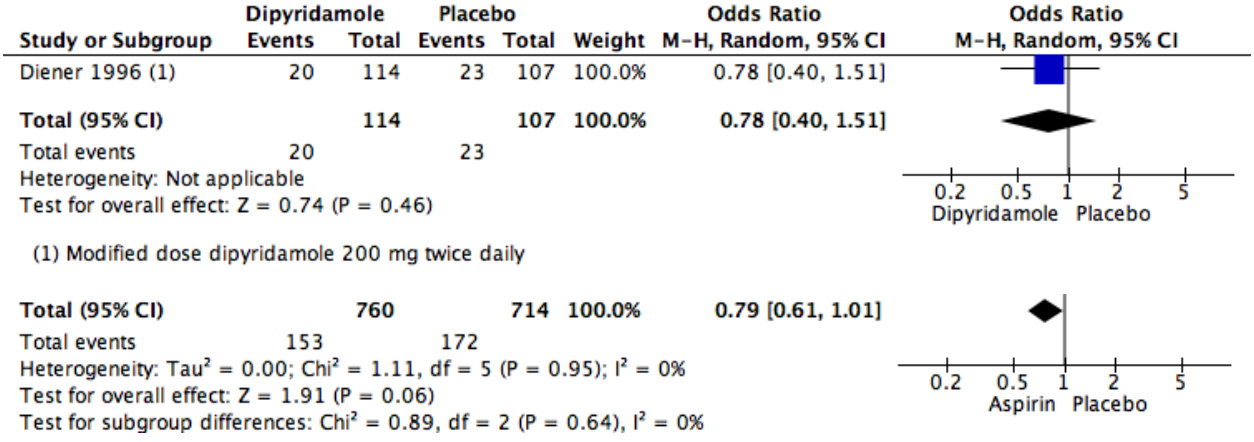
(1) Aspirin 300 mg; (2) Aspirin 25 mg twice daily; (3) Aspirin 1200 mg; (4) Aspirin 300 mg

Aspirin and dipyridamole



(1) Aspirin 25 mg twice daily and dipyridamole 200 mg twice daily

Dipyridamole

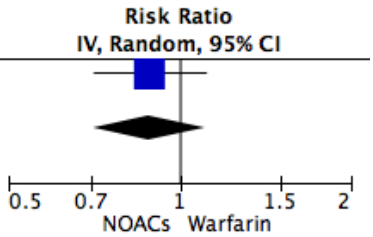


eFigure 9A. NOAC vs warfarin in patients with previous ischemic stroke or TIA and AF: Death

Apixaban (5 mg) twice daily

Study or Subgroup	NOACs Events	NOACs Total	Warfarin Events	Warfarin Total	Weight	Risk Ratio IV, Random, 95% CI
Easton 2012	129	1694	150	1742	100.0%	0.88 [0.71, 1.11]
Total (95% CI)		**1694**		**1742**	**100.0%**	**0.88 [0.71, 1.11]**
Total events	129		150			

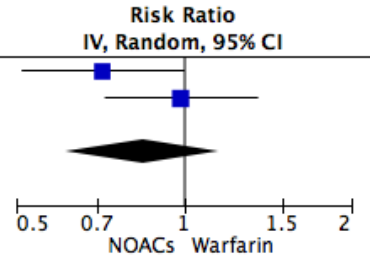
Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.29)



Dabigatran (110 mg, 150 mg) twice daily

Study or Subgroup	NOACs Events	NOACs Total	Warfarin Events	Warfarin Total	Weight	Risk Ratio IV, Random, 95% CI
Diener 2010 (110 mg)	77	1195	54	598	48.4%	0.71 [0.51, 1.00]
Diener 2010 (150 mg)	108	1233	53	597	51.6%	0.99 [0.72, 1.35]
Total (95% CI)		**2428**		**1195**	**100.0%**	**0.84 [0.61, 1.16]**
Total events	185		107			

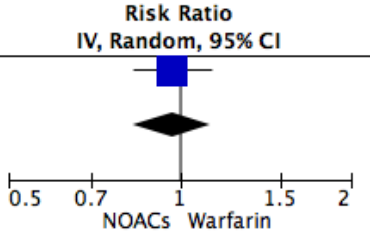
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 1.92$, df = 1 (P = 0.17); $I^2 = 48\%$
Test for overall effect: Z = 1.05 (P = 0.29)



Rivaroxaban (20 mg) daily

Study or Subgroup	NOACs Events	NOACs Total	Warfarin Events	Warfarin Total	Weight	Risk Ratio IV, Random, 95% CI
Hankey 2012	288	3754	294	3714	100.0%	0.97 [0.83, 1.13]
Total (95% CI)		**3754**		**3714**	**100.0%**	**0.97 [0.83, 1.13]**
Total events	288		294			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.69)



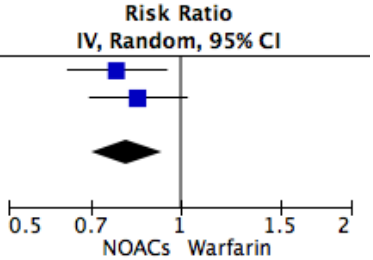
Edoxaban (60 mg, 30 mg) daily

Study or Subgroup	NOACs Events	NOACs Total	Warfarin Events	Warfarin Total	Weight	Risk Ratio IV, Random, 95% CI
Rost 2016 (30 mg)	215	2006	138	996	49.2%	0.77 [0.63, 0.94]
Rost 2016 (60 mg)	231	1976	138	995	50.8%	0.84 [0.69, 1.03]
Total (95% CI)		**3982**		**1991**	**100.0%**	**0.81 [0.70, 0.93]**
Total events	446		276			

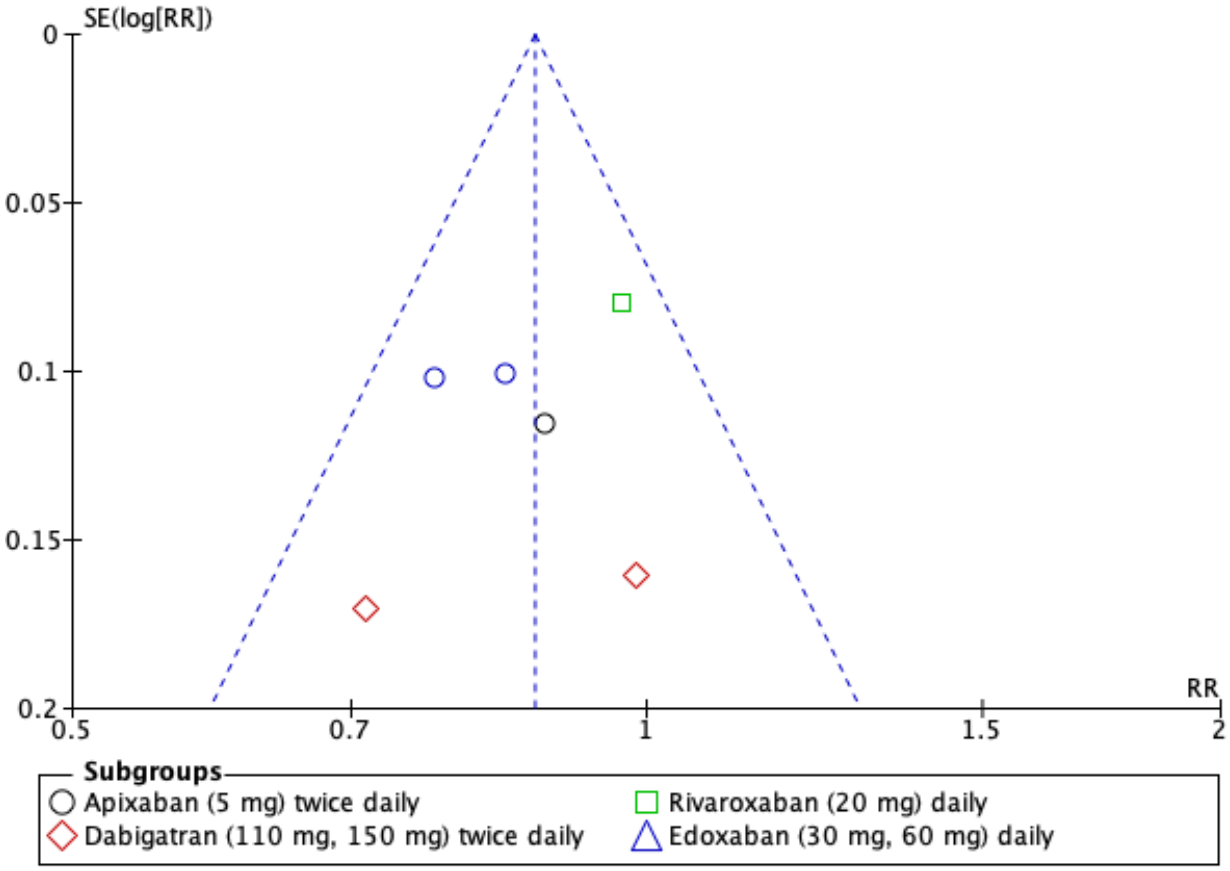
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.36$, df = 1 (P = 0.55); $I^2 = 0\%$
Test for overall effect: Z = 2.98 (P = 0.003)

Total (95% CI)		**11858**		**8642**	**100.0%**	**0.87 [0.80, 0.95]**
Total events	1048		827			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.25$, df = 5 (P = 0.39); $I^2 = 5\%$
Test for overall effect: Z = 2.97 (P = 0.003)
Test for subgroup differences: $Chi^2 = 2.95$, df = 3 (P = 0.40), $I^2 = 0\%$

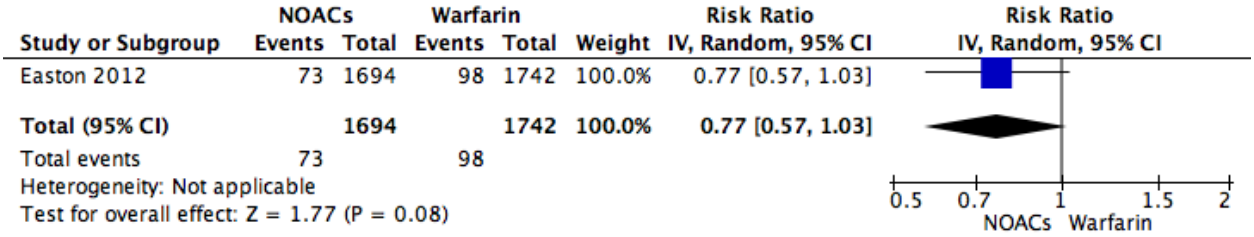


eFigure 9B. Funnel plot: NOAC vs warfarin in patients with previous ischemic stroke or TIA and AF: Death

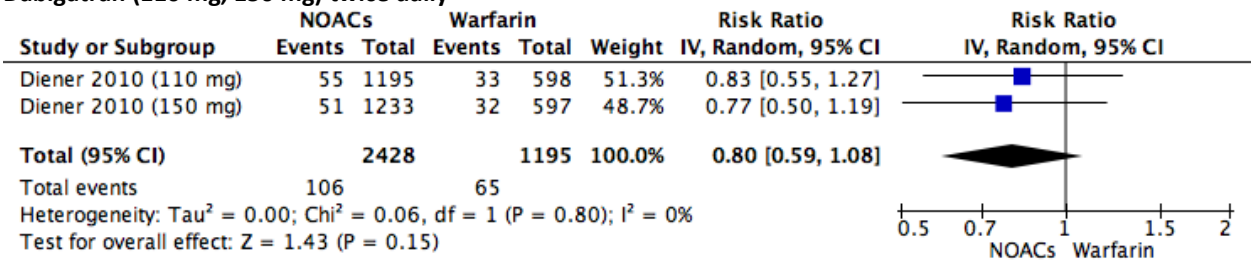


eFigure 10A. NOAC vs warfarin in patients with previous ischemic stroke or TIA and AF: Stroke or thromboembolism

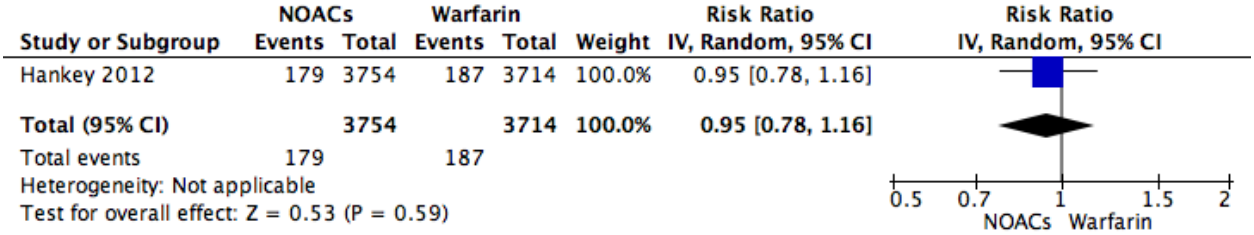
Apixaban (5 mg) twice daily



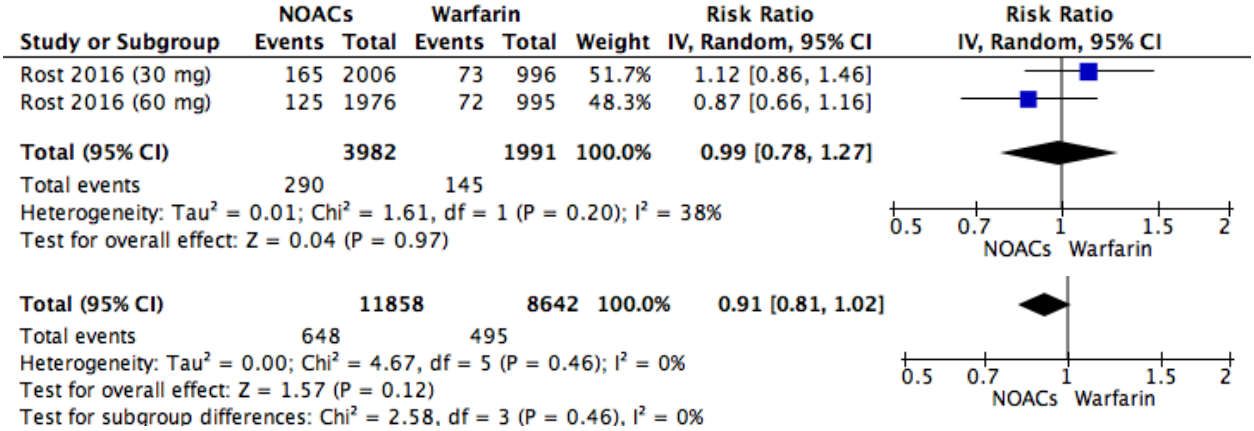
Dabigatran (110 mg, 150 mg) twice daily



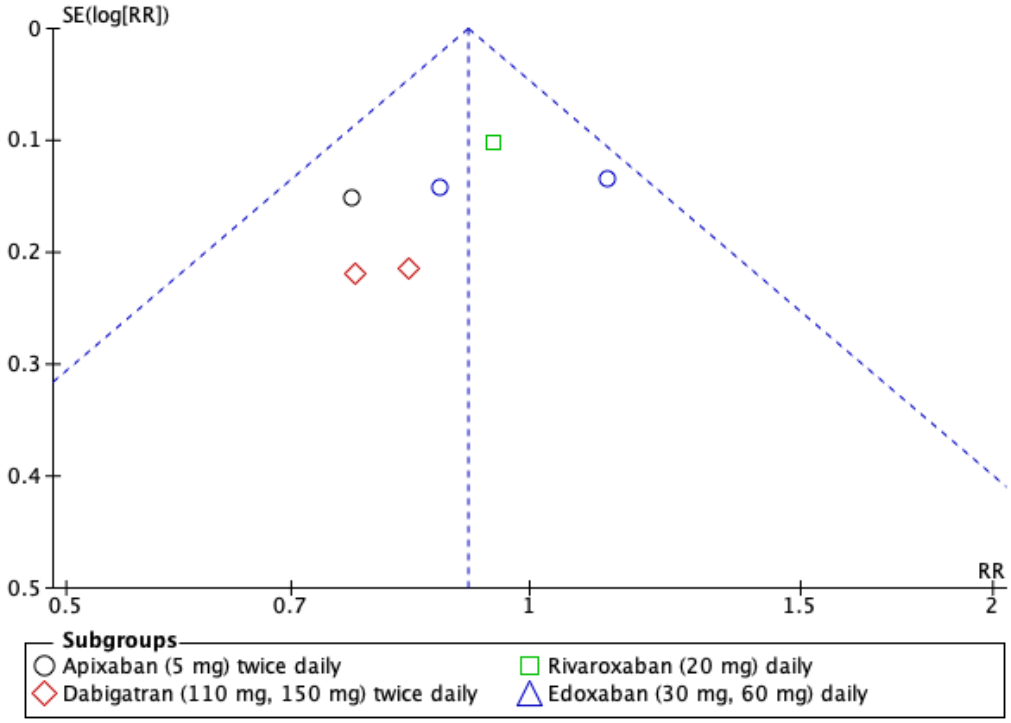
Rivaroxaban (20 mg) daily



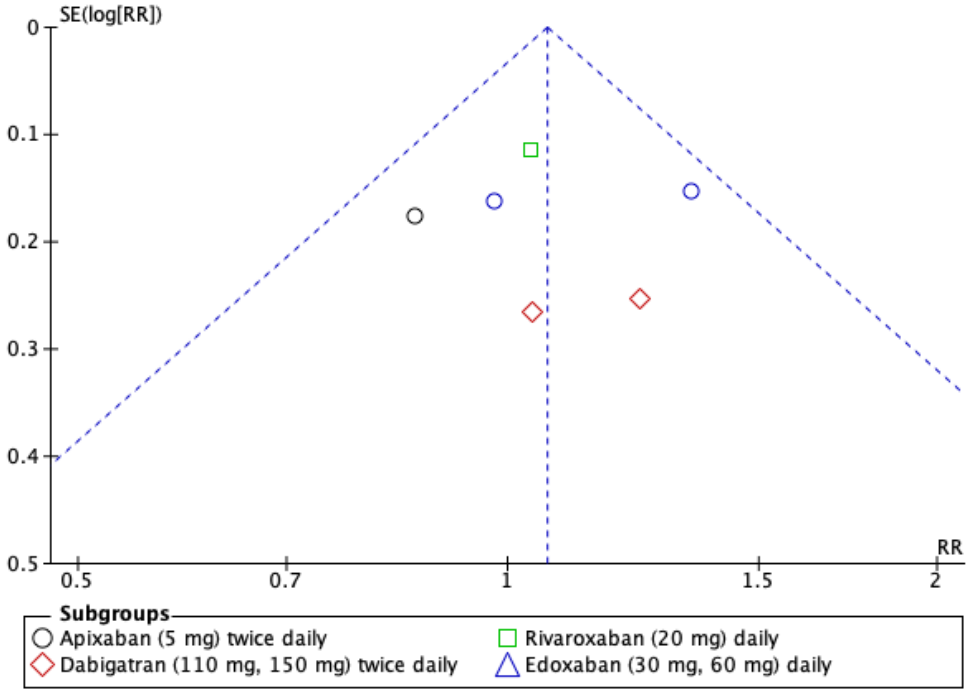
Edoxaban (60 mg, 30 mg) daily



eFigure 10B. Funnel plot: NOAC vs warfarin in patients with previous ischemic stroke or TIA and AF: Stroke or thromboembolism



eFigure 10C. Funnel plot: NOAC vs warfarin in patients with previous ischemic stroke or TIA and AF: Ischemic stroke



eTable 3: Effect of NOACs compared to warfarin on the various outcomes in patients with previous ischemic stroke or TIA with two dabigatran and edoxaban dosing regimens pooled separately and factor Xa inhibitors pooled separately

Outcome	Incidence (%)		n (N)	RR [95% CI]		
	NOAC	Warfarin			I^2, p	P value
Stroke or thromboembolism						
Overall	5.5% (648/11,858)	5.7% (495/8,642)	4 (20,500)	0.91 [0.81, 1.02]	0%, p=0.46	0.12
Ap,Riv,Ed (60mg), Da (150, 100 mg)	4.9% (483/9,852)	5.7% (495/8,642)	4 (18,494)	0.87 [0.75, 1.00]	0%, p=0.59	0.02
Ap,Riv,Ed (30mg),Da (150, 100 mg)	5.3% (523/9,882)	5.7% (495/8,642)	4 (18,524)	0.92 [0.79, 1.08]	31%, p=0.22	0.31
Ap,Riv,Ed (60mg),Da (150 mg)	4.9% (428/8,657)	5.7% (495/8,642)	4 (17,299)	0.86 [0.76, 0.98]	0%, p=0.59	0.02
Ap,Riv,Ed (60mg),Da (110 mg)	5.0% (432/8,619)	5.7% (495/8,642)	4 (17,261)	0.88 [0.77, 0.99]	0%, p=0.70	0.04
Ap,Riv,Ed (30mg),Da (150 mg)	5.4% (468/8,687)	5.7% (495/8,642)	4 (17,329)	0.92 [0.77, 1.10]	50%, p=0.11	0.36
Ap,Riv,Ed (30mg),Da (110 mg)	5.5% (472/8,649)	5.7% (495/8,642)	4 (17,291)	0.94 [0.80, 1.11]	39%, p=0.17	0.45
Xa inhibitors	5.7% (542/9,430)	5.8% (430/7,447)	3 (16,877)	0.93 [0.81, 1.07]	21%, p=0.28	0.32
Xa inhibitors Ap,Riv,Ed 60mg	5.1% (377/7424)	5.8% (430/7447)	3 (14,871)	0.88 [0.77, 1.01]	0%, p=0.50	0.06
Xa inhibitors Ap,Riv,Ed 30mg	5.6% (417/7,454)	5.8% (430/7,447)	3 (14,901)	0.95 [0.78, 1.17]	55%, p=0.11	0.65
Ischemic stroke						
Overall[a]	6.4% (254/3,982)	5.5% (109/1,991)	1 (5,973)	1.15 [0.84, 1.57]	51%, p=0.16	0.37
Ed 60 mg	5.3% (105/1,976)	5.5% (109/1,991)	1 (3,967)	0.97 [0.75, 1.26]	NA	0.82
Ed 30 mg	7.4% (149/2,006)	5.5% (109/1,991)	1 (3,997)	1.36 [1.07, 1.72]	NA	0.01
Xa inhibitors[a]	6.4% (254/3,982)	5.5% (109/1,991)	1 (5,973)	1.15 [0.84, 1.57]	51%, p=0.16	0.37
Xa inhibitors Ed 60 mg	5.3% (105/1,976)	5.5% (109/1,991)	1 (3,967)	0.97 [0.75, 1.26]	NA	0.82
Xa inhibitors Ed 30 mg	7.4% (149/2,006)	5.5% (109/1,991)	1 (3,997)	1.36 [1.07, 1.72]	NA	0.01
Intracerebral hemorrhage						
Overall	0.6% (69/11,858)	1.3% (110/8,642)	4 (20,500)	0.43 [0.29, 0.64]	34%, p=0.18	< 0.0001
Ap,Riv,Ed (60mg),Da (150, 100 mg)	0.6% (57/9,852)	1.3% (110/8,642)	4 (18,494)	0.44 [0.28, 0.69]	44%, p=0.13	0.0004
Ap,Riv,Ed (30mg),Da (150, 100 mg)	0.5% (53/9,882)	1.3% (110/8,642)	4 (18,524)	0.40 [0.25, 0.65]	45%, p=0.12	0.0002
Ap,Riv,Ed (60mg),Da (150 mg)	0.6% (55/8,657)	1.3% (110/8,642)	4 (17,299)	0.50 [0.35, 0.72]	20%, p=0.29	0.0002
Ap,Riv,Ed (60mg),Da (110 mg)	0.6% (52/8,619)	1.3% (110/8,642)	4 (17,261)	0.46 [0.27, 0.77]	53%, p=0.10	0.003

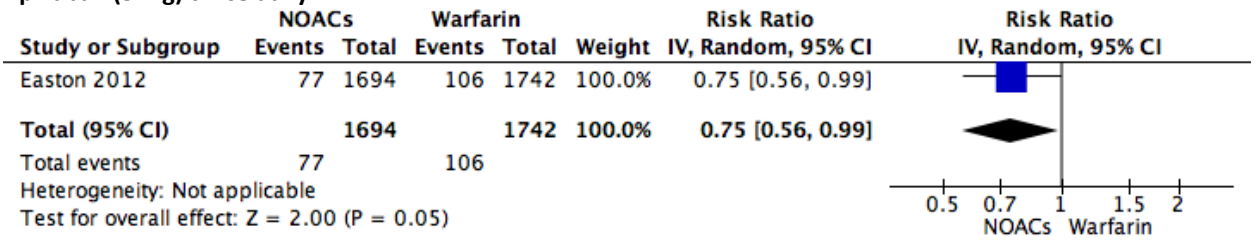
Outcome	Incidence (%)		n (N)	RR [95% CI]		
	NOAC	Warfarin			I^2, p	P value
Ap,Riv,Ed (30mg),Da (150 mg)	0.6% (51/8,687)	1.3% (110/8,642)	4 (17,329)	0.46 [0.30, 0.69]	29%, p=0.24	0.0002
Ap,Riv,Ed (30mg),Da (110 mg)	0.6% (48/8,649)	1.3% (110/8,642)	4 (17,291)	0.42 [0.24, 0.72]	56%, p=0.08	0.002
Xa inhibitors	0.7% (62/9,430)	1.2% (92/7,447)	3 (16,877)	0.52 [0.37, 0.72]	0%, p=0.42	<0.0001
Xa inhibitors Ap,Riv,Ed 60mg	0.7% (50/7,424)	1.2% (92/7,447)	3 (14,871)	0.55 [0.39, 0.78]	0%, p=0.38	0.0007
Xa inhibitors Ap,Riv,Ed 30mg	0.6% (46/7,454)	1.2% (92/7,447)	3 (14,901)	0.50 [0.33, 0.76]	29%, p=0.24	0.001
Major bleeding complications						
Overall	5.5% (649/11,858)	6.4% (551/8.642)	4 (20,500)	0.79 [0.64, 0.96]	67%, p=0.01	0.02
Ap,Riv,Ed (60mg),Da (150, 100 mg)	5.7% (560/9,852)	6.4% (551/8,642)	4 (18,494)	0.86 [0.75, 0.98]	25%, p=0.26	0.03
Ap,Riv,Ed (30mg),Da (150, 100 mg)	5.2% (511/9,882)	6.4% (551/8,642)	4 (18,524)	0.77 [0.60, 1.00]	77%, p=0.002	0.05
Ap,Riv,Ed (60mg),Da (150 mg)	5.7% (495/8,657)	6.4% (551/8,642)	4 (17,299)	0.90 [0.78, 1.02]	18%, p=0.34	0.10
Ap,Riv,Ed (60mg),Da (110 mg)	5.3% (458/8,619)	6.4% (551/8,642)	4 (17,261)	0.82 [0.71, 0.95]	27%, p=0.25	0.009
Ap,Riv,Ed (30mg),Da (150 mg)	5.1% (446/8,687)	6.4% (551/8,642)	4 (17,329)	0.79 [0.59, 1.07]	83%, p=0.0005	0.14
Ap,Riv,Ed (30mg),Da (110 mg)	4.7% (409/8,649)	6.4% (551/8,642)	4 (17,291)	0.72 [0.55, 0.95]	78%, p=0.003	0.02
Xa inhibitors	5.1% (482/9,430)	6.1% (456/7,447)	3 (16,877)	0.76 [0.59, 0.98]	74%, p=0.009	0.03
Xa inhibitors Ap,Riv,Ed 60mg	5.3% (393/7,424)	6.1% (456/7,447)	3 (14,871)	0.86 [0.75, 0.99]	9%, p=0.33	0.04
Xa inhibitors Ap,Riv,Ed 30mg	4.6% (344/7,454)	6.1% (456/7,447)	3 (14,901)	0.73 [0.51, 1.05]	85%, p=0.001	0.09
Death						
Overall	8.8% (1,048/11,858)	9.6% (827/8,642)	4 (20,500)	0.87 [0.80, 0.95]	5%, p=0.55	0.0003
Ap,Riv,Ed (60mg),Da (150, 100 mg)	8.5% (833/9,852)	9.6% (827/8,642)	4 (18,494)	0.89 [0.81, 0.98]	0%, p=0.45	0.02
Ap,Riv,Ed (30mg),Da (150, 100 mg)	8.3% (817/9,882)	9.6% (827/8,642)	4 (18,524)	0.87 [0.77, 0.97]	30%, p=0.22	0.02
Ap,Riv,Ed (60mg),Da (150 mg)	8.7% (756/8,657)	9.6% (827/8,642)	4 (17,299)	0.91 [0.83, 1.00]	0%, p=0.61	0.06
Ap,Riv,Ed (60mg),Da (110 mg)	8.4% (725/8,619)	9.6% (827/8,642)	4 (17,261)	0.88 [0.79, 0.97]	19%, p=0.19	0.02
Ap,Riv,Ed (30mg),Da (150 mg)	8.5% (740/8,687)	9.6% (827/8,642)	4 (17,329)	0.89 [0.79, 1.00]	32%, p=0.22	0.05
Ap,Riv,Ed (30mg),Da (110 mg)	8.2% (709/8,649)	9.6% (827/8,642)	4 (17,291)	0.85 [0.74, 0.97]	44%, p=0.15	0.01
Xa inhibitors	9.2% (863/9,430)	9.7% (720/7,447)	3 (16,877)	0.88 [0.79, 0.97]	8%, p=0.35	0.009
Xa inhibitors Ap,Riv,Ed 60mg	8.7% (648/7,424)	9.7% (720/7,447)	3 (14,871)	0.90 [0.82, 1.00]	0%, p=0.47	0.05

Outcome	Incidence (%)		n (N)	RR [95% CI]		
	NOAC	Warfarin			I^2, p	P value
Xa inhibitors Ap,Riv,Ed 30mg	8.5% (632/7,454)	9.7% (720/7,447)	3 (14,901)	0.87 [0.76, 1.01]	47%, p=0.15	0.06

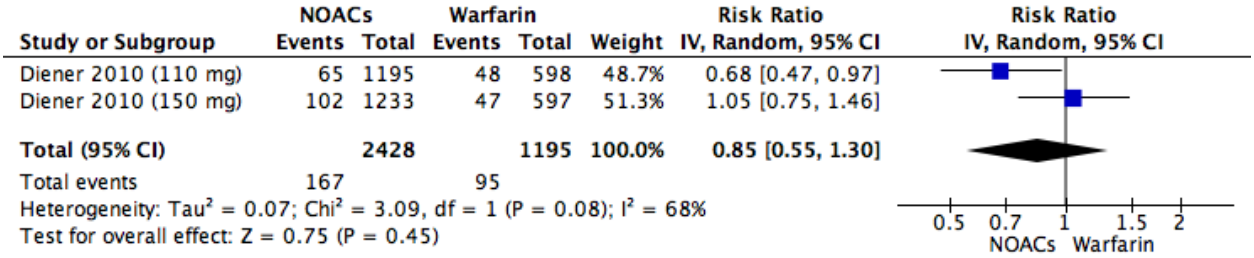
a: Data not reported on Apixaban, Rivaroxaban and Dabigatran; Ap,Riv,Ed,Da (150 mg): Apixaban, Rivaroxaban or Edoxaban, Dabigatran 150 mg; Ap,Riv,Ed,Da (110 mg): Apixaban, Rivaroxaban or Edoxaban, Dabigatran 110 mg; CI: Confidence interval; I^2, p: Heterogeneity; n: Number of studies; N: Number of patients; NA: Not applicable; p: Statistical significance value; RR: Risk Ratio; Xa inhibitors: Apixaban, Rivaroxaban or Edoxaban

eFigure 11A. NOAC vs warfarin in patients with previous ischemic stroke or TIA and AF: Major bleeding complications

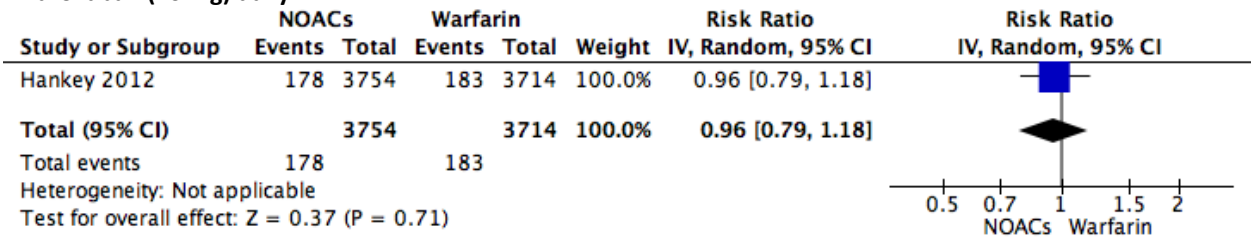
Apixaban (5 mg) twice daily



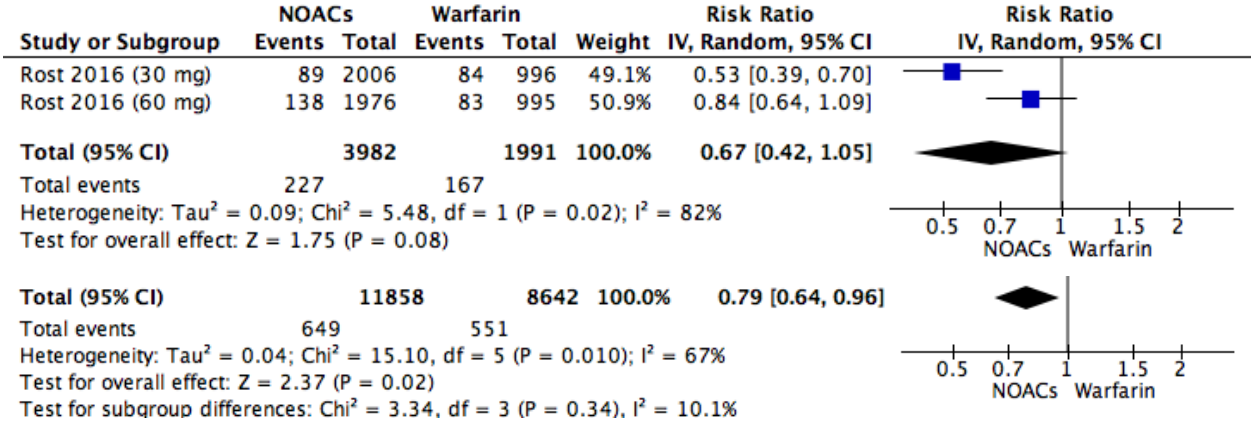
Dabigatran (110 mg, 150 mg) twice daily



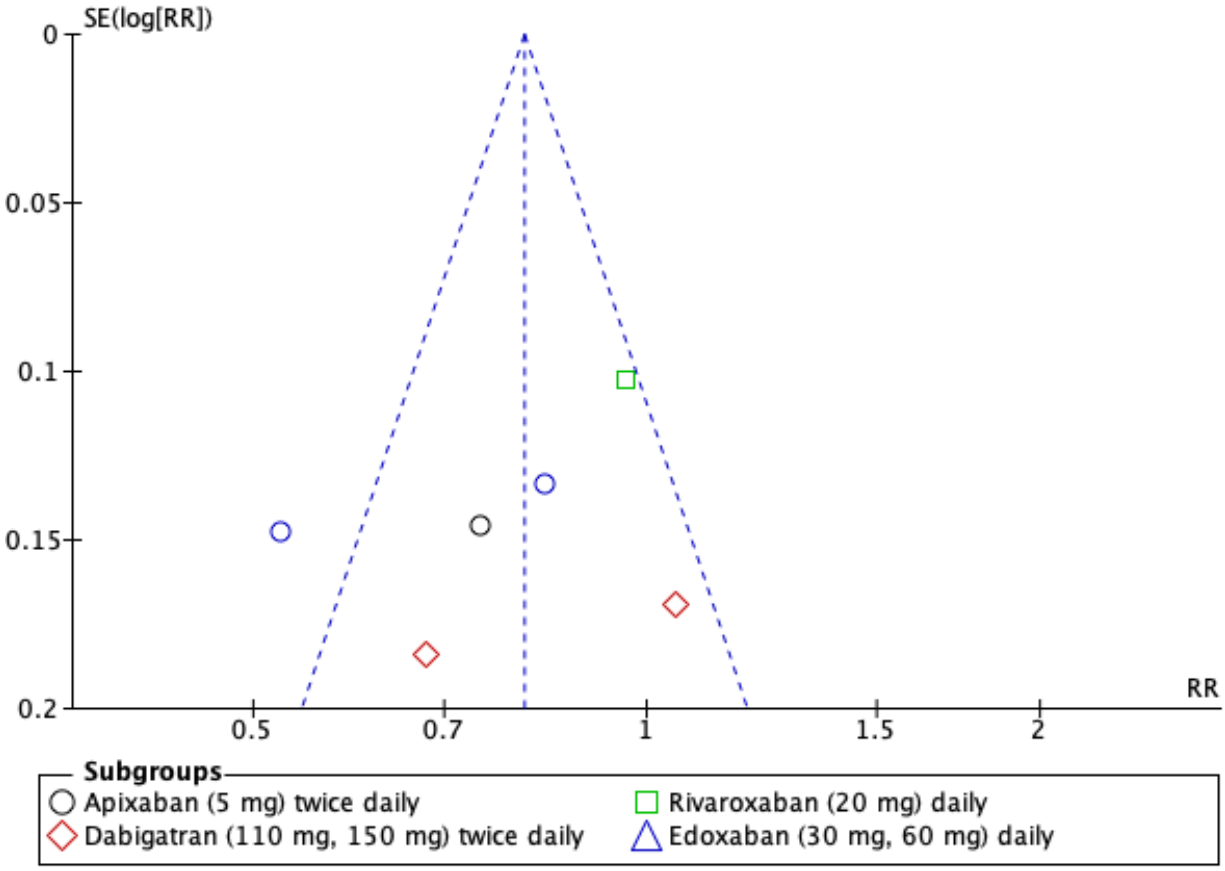
Rivaroxaban (20 mg) daily



Edoxaban (60 mg, 30 mg) daily



eFigure 11B. Funnel plot: NOAC vs warfarin in patients with previous ischemic stroke or TIA and AF: Major bleeding complications



eTable 4. Effect of NOACs (Apixaban, Dabigatran, Rivaroxaban or Edoxaban) compared to Warfarin on death in patients with previous stroke or TIA with two dabigatran and edoxaban dosing regimens pooled separately and factor Xa inhibitors pooled separately

Outcome	Incidence (%)		n (N)	RR [95% CI]	I^2, p	P value
	NOAC	Warfarin				
Death						
Overall	**8.8% (1,048/11,858)**	**9.6% (827/8,642)**	**4(20,500)**	**0.87 [0.80, 0.95]**	**5%, p=0.55**	**0.0003**
Ap,Riv,Ed (60mg),Da (150, 100 mg)	**8.5% (833/9,852)**	**9.6% (827/8,642)**	**4(18,494)**	**0.89 [0.81, 0.98]**	**0%, p=0.45**	**0.02**
Ap,Riv,Ed (30mg),Da (150, 100 mg)	**8.3% (817/9,882)**	**9.6% (827/8,642)**	**4(18,524)**	**0.87 [0.77, 0.97]**	**30%, p=0.22**	**0.02**
Ap,Riv,Ed (60mg),Da (150 mg)	8.7% (756/8,657)	9.6% (827/8,642)	4(17,299)	0.91 [0.83, 1.00]	0%, p=0.61	0.06
Ap,Riv,Ed (60mg),Da (110 mg)	**8.4% (725/8,619)**	**9.6% (827/8,642)**	**4(17,261)**	**0.88 [0.79, 0.97]**	**19%, p=0.19**	**0.02**
Ap,Riv,Ed (30mg),Da (150 mg)	**8.5% (740/8,687)**	**9.6% (827/8,642)**	**4(17,329)**	**0.89 [0.79, 1.00]**	**32%, p=0.22**	**0.05**
Ap,Riv,Ed (30mg),Da (110 mg)	**8.2% (709/8,649)**	**9.6% (827/8,642)**	**4(17,291)**	**0.85 [0.74, 0.97]**	**44%, p=0.15**	**0.01**
Xa inhibitors	**9.2% (863/9,430)**	**9.7% (720/7,447)**	**3(16,877)**	**0.88 [0.79, 0.97]**	**8%, p=0.35**	**0.009**
Xa inhibitors Ap,Riv,Ed 60mg	**8.7% (648/7,424)**	**9.7% (720/7,447)**	**3(14,871)**	**0.90 [0.82, 1.00]**	**0%, p=0.47**	**0.05**
Xa inhibitors Ap,Riv,Ed 30mg	8.5% (632/7,454)	9.7% (720/7,447)	3(14,901)	0.87 [0.76, 1.01]	47%, p=0.15	0.06

Ap,Riv,Ed,Da (150 mg): Apixaban, Rivaroxaban or Edoxaban, Dabigatran 150 mg; Ap,Riv,Ed,Da (110 mg): Apixaban, Rivaroxaban or Edoxaban, Dabigatran 110 mg; CI: Confidence interval; I^2, p: Heterogeneity; n: Number of studies; N: Number of patients; NA: Not applicable; p: Statistical significance value; RR: Risk Ratio; Xa inhibitors: Apixaban, Rivaroxaban or Edoxaban

eTable 5. Effect of NOACs (Apixaban, Dabigatran, Rivaroxaban or Edoxaban) compared to Warfarin on intracerebral hemorrhage and major bleeding complications in patients with previous stroke or TIA with two dabigatran and edoxaban dosing regimens pooled separately and factor Xa inhibitors pooled separately

Outcome	Incidence (%)		n (N)	RR [95% CI]	I^2, p	P value
	NOAC	Warfarin				
Intracerebral hemorrhage[a]						
Overall	0.7% (26/3,754)	0.8% (31/3,714)	1(7,468)	0.83 [0.49, 1.39]	NA	0.48
Riv	0.7% (26/3,754)	0.8% (31/3,714)	1(7,468)	0.83 [0.49, 1.39]	NA	0.48
Xa inhibitors	0.7% (26/3,754)	0.8% (31/3,714)	1(7,468)	0.83 [0.49, 1.39]	NA	0.48
Major bleeding complications						
Overall	**5.5% (649/11,858)**	**6.4% (551/8.642)**	**4(20,500)**	**0.79 [0.64, 0.96]**	**67%, p=0.01**	**0.02**
Ap,Riv,Ed (60mg),Da (150, 100 mg)	**5.7% (560/9,852)**	**6.4% (551/8,642)**	**4(18,494)**	**0.86 [0.75, 0.98]**	**25%, p=0.26**	**0.03**
Ap,Riv,Ed (30mg),Da (150, 100 mg)	**5.2% (511/9,882)**	**6.4% (551/8,642)**	**4(18,524)**	**0.77 [0.60, 1.00]**	**77%, p=0.002**	**0.05**
Ap,Riv,Ed (60mg),Da (150 mg)	5.7% (495/8,657)	6.4% (551/8,642)	4(17,299)	0.90 [0.78, 1.02]	18%	0.10
Ap,Riv,Ed (60mg),Da (110 mg)	**5.3% (458/8,619)**	**6.4% (551/8,642)**	**4(17,261)**	**0.82 [0.71, 0.95]**	**27%, p=0.25**	**0.009**
Ap,Riv,Ed (30mg),Da (150 mg)	5.1% (446/8,687)	6.4% (551/8,642)	4(17,329)	0.79 [0.59, 1.07]	83%, p=0.0005	0.14
Ap,Riv,Ed (30mg),Da (110 mg)	**4.7% (409/8,649)**	**6.4% (551/8,642)**	**4(17,291)**	**0.72 [0.55, 0.95]**	**78%, p=0.003**	**0.02**
Xa inhibitors	5.1% (482/9,430)	6.1% (456/7,447)	3(16,877)	0.76 [0.59, 0.98]	74%, p=0.009	0.03
Xa inhibitors Ap,Riv,Ed 60mg	**5.3% (393/7,424)**	**6.1% (456/7,447)**	**3(14,871)**	**0.86 [0.75, 0.99]**	**9%, p=0.33**	**0.04**
Xa inhibitors Ap,Riv,Ed 30mg	4.6% (344/7,454)	6.1% (456/7,447)	3(14,901)	0.73 [0.51, 1.05]	85%, p=0.001	0.09

a: Data not reported on Apixaban, Edoxaban and Dabigatran; e: Data not reported on Rivaroxaban and Edoxaban; Ap,Riv,Ed,Da (150 mg): Apixaban, Rivaroxaban or Edoxaban, Dabigatran 150 mg; Ap,Riv,Ed,Da (110 mg): Apixaban, Rivaroxaban or Edoxaban, Dabigatran 110 mg; CI: Confidence interval; I^2, p: Heterogeneity; n: Number of studies; N: Number of patients; NA: Not applicable; NR: Not reported; p: Statistical significance value; RR: Risk Ratio; Xa inhibitors: Apixaban, Rivaroxaban or Edoxaban.

5.3: Medical treatment in patients with renal failure

eTable 6: Effect of NOAC compared to warfarin in patients with AF and renal failure (indirect evidence for patients with a previous stroke or TIA)

Outcome	Incidence (%)		n (N)	RR [95% CI]		
	NOAC	Warfarin			I^2, p	P value
Stroke or thromboembolism						
Mild RF	**2.6% (255/9,968)**	**3.3% (235/7,162)**	**3 (17,130)**	**0.73 [0.56, 0.97]**	**48%, p=0.12**	**0.03**
Moderate RF	4.5% (373/8,258)	4.7% (264/5,622)	5 (13,880)	0.87 [0.74, 1.04]	13%, p=0.33	0.13
Major bleeding complications						
Mild RF	**5.3% (503/9,472)**	**6.1% (408/6,668)**	**2 (16,140)**	**0.82 [0.72, 0.93]**	**0%, p=0.51**	**0.002**
Moderate RF	**6.7% (540/8,101)**	**8.4% (459/5,473)**	**4 (13,574)**	**0.73 [0.54, 0.99]**	**83%, p<0.0001**	**0.04**
Death						
Mild RF	**6.5% (617/9,472)**	**7.4% (495/6.668)**	**2 (16,140)**	**0.85 [0.73, 0.99]**	**42%, p=0.18**	**0.04**
Moderate RF	14.6% (774/5,302)	16.6% (664/3,997)	3 (9,299)	0.93 [0.80, 1.07]	50%, p=0.11	0.32

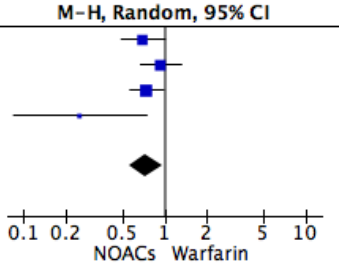
CI: Confidence interval; I^2, p: Heterogeneity; n: Number of studies; N: Number of patients; p: Statistical significance value; RR: Risk Ratio

eFigure 15. Effect of NOAC compared to warfarin in patients with AF and mild/moderate renal failure on stroke and or thromboembolism (indirect evidence for patients with a previous stroke or TIA)

Creatinine clearance 50-80 ml/min

Study or Subgroup	NOACs Events	Total	Warfarin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Hijazi 2014 RELY HD	70	2852	51	1449	28.5%	0.70 [0.49, 0.99]
Hijazi 2014 RELY LD	94	2803	52	1449	30.3%	0.93 [0.67, 1.30]
Hohnloser 2012, ARISTOTLE	87	3817	116	3770	35.5%	0.74 [0.56, 0.97]
Hori 2012 J-ROCKET AF (1)	4	496	16	494	5.6%	0.25 [0.08, 0.74]
Total (95% CI)		**9968**		**7162**	**100.0%**	**0.73 [0.56, 0.97]**
Total events	255		235			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 5.79$, df = 3 (P = 0.12); $I^2 = 48\%$
Test for overall effect: Z = 2.22 (P = 0.03)

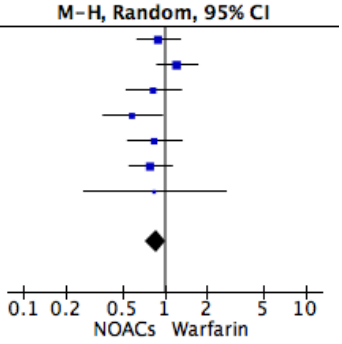


(1) Creatinine clearance > 50 ml/min

Creatinine clearance < 50 ml/min

Study or Subgroup	NOACs Events	Total	Warfarin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bohula ENGAGE AFTIMI HD	82	1379	45	681	19.5%	0.90 [0.63, 1.28]
Bohula ENGAGE AFTIMI LD	110	1334	46	681	21.4%	1.22 [0.88, 1.70]
Fox 2011 ROCKET-AF	34	1474	41	1476	12.9%	0.83 [0.53, 1.30]
Hijazi 2014 RELY HD	36	1232	28	563	11.3%	0.59 [0.36, 0.95]
Hijazi 2014 RELY LD	52	1196	29	563	13.2%	0.84 [0.54, 1.31]
Hohnloser 2012, ARISTOTLE	54	1502	69	1515	19.7%	0.79 [0.56, 1.12]
Hori 2012 J-ROCKET AF	5	141	6	143	2.1%	0.85 [0.26, 2.71]
Total (95% CI)		**8258**		**5622**	**100.0%**	**0.87 [0.74, 1.04]**
Total events	373		264			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.92$, df = 6 (P = 0.33); $I^2 = 13\%$
Test for overall effect: Z = 1.53 (P = 0.13)

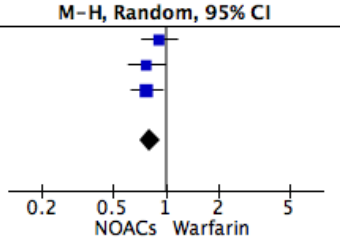


eFigure 16. Effect of NOAC compared to warfarin in patients with AF and mild/moderate renal failure on major bleeding complications (indirect evidence for patients with a previous stroke or TIA)

Creatinine clearance 50-80 ml/min

Study or Subgroup	NOACs Events	NOACs Total	Warfarin Events	Warfarin Total	Weight	Risk Ratio M-H, Random, 95% CI
Hijazi 2014 RELY HD	188	2852	104	1449	31.1%	0.92 [0.73, 1.16]
Hijazi 2014 RELY LD	158	2803	105	1449	29.2%	0.78 [0.61, 0.99]
Hohnloser 2012, ARISTOTLE	157	3817	199	3770	39.7%	0.78 [0.64, 0.96]
Total (95% CI)		**9472**		**6668**	**100.0%**	**0.82 [0.72, 0.93]**
Total events	503		408			

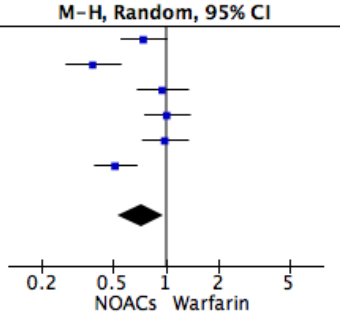
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.35$, df = 2 (P = 0.51); $I^2 = 0\%$
Test for overall effect: Z = 3.03 (P = 0.002)



Creatinine clearance < 50 ml/min

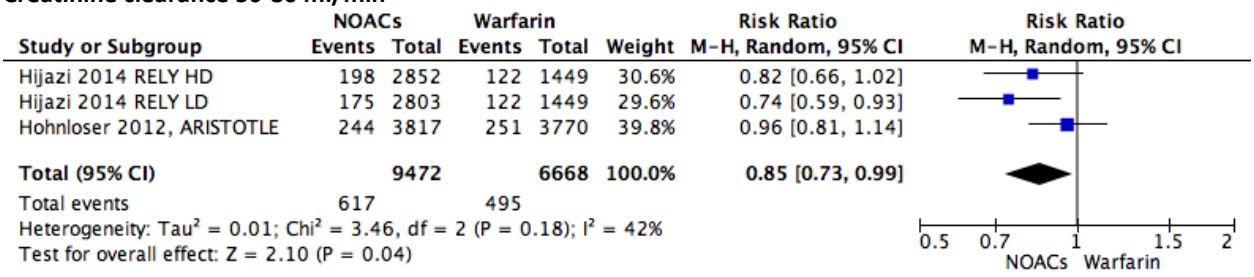
Study or Subgroup	NOACs Events	NOACs Total	Warfarin Events	Warfarin Total	Weight	Risk Ratio M-H, Random, 95% CI
Bohula ENGAGE AFTIMI HD	100	1372	66	678	16.9%	0.75 [0.56, 1.01]
Bohula ENGAGE AFTIMI LD	50	1325	66	678	15.8%	0.39 [0.27, 0.55]
Fox 2011 ROCKET-AF	66	1474	69	1476	16.3%	0.96 [0.69, 1.33]
Hijazi 2014 RELY HD	129	1232	58	563	16.9%	1.02 [0.76, 1.36]
Hijazi 2014 RELY LD	122	1196	58	563	16.9%	0.99 [0.74, 1.33]
Hohnloser 2012, ARISTOTLE	73	1502	142	1515	17.3%	0.52 [0.39, 0.68]
Total (95% CI)		**8101**		**5473**	**100.0%**	**0.73 [0.54, 0.99]**
Total events	540		459			

Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 29.78$, df = 5 (P < 0.0001); $I^2 = 83\%$
Test for overall effect: Z = 2.05 (P = 0.04)



eFigure 17. Effect of NOAC compared to warfarin in patients with AF and mild/moderate renal failure on all-cause mortality (indirect evidence for patients with a previous stroke or TIA)

Creatinine clearance 50-80 ml/min



Creatinine clearance < 50 ml/min