

Appendix I

Search strategies

1.1 PubMed Search Query

“atrial fibrillation”[MeSH Terms] AND (“brain hemorrhage”[Title/Abstract] OR “intracerebral hemorrhage”[Title/Abstract] OR “cerebral hemorrhage”[Title/Abstract] OR “intracranial hemorrhage”[Title/Abstract]) AND (“Anticoagulants”[MeSH Terms] OR “warfarin”[Title/Abstract] OR “vitamin k antagonist”[Title/Abstract] OR “NOAC”[Title/Abstract] OR “novel oral anticoagulant”[Title/Abstract] OR “non vitamin K anticoagulant”[Title/Abstract] OR “DOAC”[Title/Abstract] OR “rivaroxaban”[Title/Abstract] OR “edoxaban”[Title/Abstract] OR “apixaban”[Title/Abstract] OR “dabigatran”[Title/Abstract])

1.2 EmBase Search Query

- #1. ‘atrial fibrillation’/exp
- #2. ‘brain hemorrhage’:ab,ti
- #3. ‘intracranial hemorrhage’:ab,ti
- #4. ‘intracerebral hemorrhage’:ab,ti
- #5. ‘cerebral hemorrhage’:ab,ti
- #6. #2 OR #3 OR #4 OR #5
- #7. ‘anticoagulant agent’/exp
- #8. ‘warfarin’:ab,ti
- #9. ‘vitamin k antagonist’:ab,ti
- #10. ‘noac’:ab,ti
- #11. ‘novel oral anticoagulant’:ab,ti
- #12. ‘non vitamin k anticoagulant’:ab,ti
- #13. ‘doac’:ab,ti
- #14. ‘rivaroxaban’:ab,ti
- #15. ‘dabigatran’:ab,ti
- #16. ‘apixaban’:ab,ti
- #17. ‘edoxaban’:ab,ti
- #18. #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
- #19. #1 AND #6 AND #18

1.3 Cochrane Search Query

- #1 MeSH descriptor: [Atrial Fibrillation] explode all trees
- #2 MeSH descriptor: [Intracranial Hemorrhages] explode all trees
- #3 (“intracerebral hemorrhage”):ti,ab,kw
- #4 (cerebral hemorrhage):ti,ab,kw
- #5 #2 or #3 or #4
- #6 MeSH descriptor: [Anticoagulants] explode all trees
- #7 (anticoagulation):ti,ab,kw OR (NOAC):ti,ab,kw OR (novel oral anticoagulant):ti,ab,kw OR (non vitamin k antagonist):ti,ab,kw AND (“Warfarin”):ti,ab,kw (Word variations have been searched)
- #8 (DOAC):ti,ab,kw OR (rivaroxaban):ti,ab,kw OR (edoxaban):ti,ab,kw OR (apixaban):ti,ab,kw AND (dabigatran):ti,ab,kw (Word variations have been searched)
- #9 #7 or #8
- #10 #1 and #5 and #9

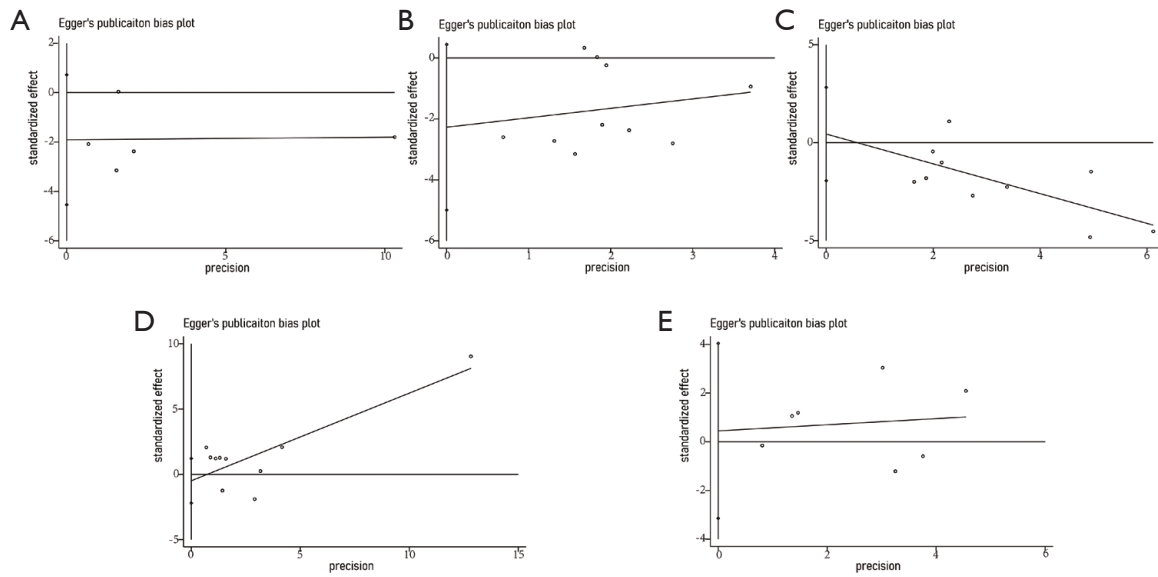


Figure S1 Egger's tests of the reported outcomes. (A) Ischemic stroke ($P=0.104$); (B) Ischemic stroke or systemic embolism ($P=0.09$); (C) All-cause death ($P=0.680$); (D) Intracranial hemorrhage recurrence ($P=0.520$); (E) Major hemorrhagic event ($P=0.762$).

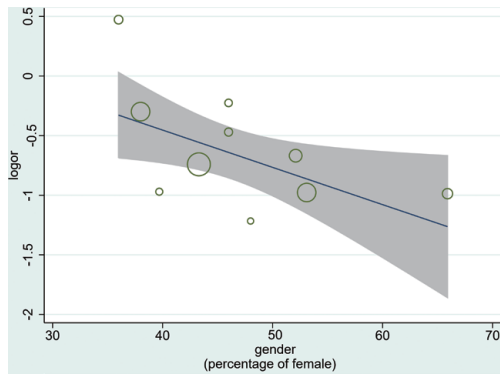


Figure S2 Meta-regression analyses of gender on all-cause death. Regression line and its prediction intervals (95% CIs) were presented in the figure. Coefficient =0.969, SE =0.012, $t=-2.54$, 95% CI: 0.942 to 0.997, $P=0.035$, adjusted $R^2=0.93$.

Table S1 Quality assessment of studies included in the meta-analysis

	Selection bias			Blinding of participants and personnel		Attrition bias	Reporting bias
	Random sequence generation	Allocation concealment	Consecutiveness	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Abrantes 2022	-	-	-	-	-	+	+
Chao 2016	-	-	+	-	-	-	+
Nielsen 2015	-	-	+	-	-	+	+
Nielsen 2017	-	-	+	-	-	+	+
Park 2016	-	-	+	-	-	+	+
Perreault 2019	-	-	-	-	-	+	+
Poli 2018	-	-	+	-	-	+	+
Sadighi 2020	-	-	+	-	-	+	+
Salman 2021	+	+	+	-	+	+	+
Schreuder 2021	+	+	+	-	+	+	+
Wu 2021	-	-	-	-	-	+	+

+, low risk of bias; -, high risk of bias.

Table S2 Results from single variable meta-regression analyses on all outcomes

Meta-regression (P value)	By age	By gender (female%)	By type of ICH	By CHA ₂ DS ₂ -VASc score	By type of OACs
IS	0.968	0.953	0.949	0.372	0.53
IS or SE	0.455	0.812	0.923	0.918	0.738
All-cause death	0.658	0.035*	0.856	0.539	0.397
ICH recurrence	0.183	0.488	0.57	0.799	0.553
Major bleeding	0.522	0.698	0.834	0.063	0.147

*, P<0.05. IS, ischemic stroke; SE, systemic embolism; ICH, intracranial hemorrhage; OACs, oral anticoagulants.

Table S3 Ongoing clinical trials evaluating effect of oral anticoagulants in atrial fibrillation patients with a history of intracranial hemorrhage

Study title	NCT identification number	Study population	Intervention	Comparator	Primary outcomes	Estimated enrollment number	Estimated completion date
STATICH	NCT03186729	Adults with intracerebral hemorrhage and an indication for antithrombotic drugs	Anticoagulant or antiplatelet drugs	No antithrombotic treatment	Fatal or non-fatal symptomatic intracerebral hemorrhage	500	Jun-23
A3ICH	NCT03243175	Adults with AF and recent spontaneous intracerebral hemorrhage	Apixaban/LAAC	No intervention	Composite of all fatal or non-fatal major cardiovascular/cerebrovascular ischemic or haemorrhagic intracranial/extracranial events	300	Dec-23
ASPIRE	NCT03907046	Adults with AF and recent spontaneous intracerebral hemorrhage	Apixaban	Aspirin	Stroke or death	700	Apr-24
ENRICH-AF	NCT03950076	Adults with AF and recent spontaneous intracranial hemorrhage	Edoxaban	Non-anticoagulant medical therapy	Stroke, Major hemorrhage	1200	Jul-23
PRESTIGE-AF	NCT03996772	Adults with AF and recent spontaneous intracerebral hemorrhage	Apixaban/Dabigatran/ Edoxaban/ Rivaroxaban	Antiplatelet or no antithrombotic drugs	Ischemic stroke, intracerebral hemorrhage	654	May-22

AF, atrial fibrillation; LAAC, left atrial appendage closure.