Appendix 1 Search strategy for the network meta-analysis of anticoagulant therapy in COVID-19

Pubmed

- ("COVID-19" [Mesh]) OR (COVID 19 [Title/ 1 Abstract] OR 2019-nCoV Infection[Title/Abstract] OR 2019-nCoV Infection[Title/Abstract] OR 2019nCoV Infections[Title/Abstract] OR Infection, 2019-nCoV[Title/Abstract] OR SARS-CoV-2 Infection[Title/Abstract] OR Infection, SARS-CoV-2[Title/Abstract] OR SARS-CoV-2 Infection[Title/ Abstract] OR SARS-CoV-2 Infections[Title/Abstract] OR 2019 Novel Coronavirus Disease[Title/Abstract] OR 2019 Novel Coronavirus Infection[Title/ Abstract] OR COVID-19 Virus Infection[Title/ Abstract] OR COVID 19 Virus Infection[Title/ Abstract] OR COVID-19 Virus Infections[Title/ Abstract] OR Infection, COVID-19 Virus[Title/ Abstract] OR Virus Infection, COVID-19[Title/ Abstract] OR COVID19[Title/Abstract] OR Coronavirus Disease 2019[Title/Abstract] OR Disease 2019, Coronavirus[Title/Abstract] OR Coronavirus Disease-19[Title/Abstract] OR Coronavirus Disease 19[Title/Abstract] OR Severe Acute Respiratory Syndrome Coronavirus 2 Infection[Title/Abstract] OR COVID-19 Virus Disease[Title/Abstract] OR COVID 19 Virus Disease[Title/Abstract] OR COVID-19 Virus Diseases[Title/Abstract] OR Disease, COVID-19 Virus[Title/Abstract] OR Virus Disease, COVID-19[Title/Abstract] OR SARS Coronavirus 2 Infection[Title/Abstract] OR 2019nCoV Disease[Title/Abstract] OR 2019-nCoV Disease[Title/Abstract] OR 2019-nCoV Diseases[Title/ Abstract] OR Disease, 2019-nCoV[Title/Abstract] OR COVID-19 Pandemic[Title/Abstract] OR COVID 19 Pandemic[Title/Abstract] OR Pandemic, COVID-19[Title/Abstract] OR COVID-19 Pandemics[Title/ Abstract])
- 2 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh])

Abstract])) OR (Agents, Anticoagulant[Title/ Abstract])) OR (Anticoagulation Agents[Title/ Abstract])) OR (Agents, Anticoagulation[Title/ Abstract])) OR (Anticoagulant Drugs[Title/ Abstract])) OR (Drugs, Anticoagulant[Title/ Abstract])) OR (Drugs, Anticoagulant[Title/ Abstract])) OR (Anticoagulant Agent[Title/Abstract])) OR (Agent, Anticoagulant[Title/Abstract])) OR (Anticoagulant[Title/Abstract])) OR (Indirect Thrombin Inhibitors[Title/Abstract])) OR (Inhibitors, Indirect Thrombin[Title/Abstract])) OR (Thrombin Inhibitors, Indirect[Title/Abstract]))

- ("Factor Xa Inhibitors" [Mesh]) OR ((((((((((((((((((6 Xa Inhibitor[Title/Abstract]) OR (Inhibitor, Factor Xa[Title/Abstract])) OR (Xa Inhibitor, Factor[Title/Abstract])) OR (Direct Factor Xa Inhibitors[Title/Abstract])) OR (Direct-Acting Oral Anticoagulants[Title/Abstract])) OR (Anticoagulants, Direct-Acting Oral[Title/Abstract])) OR (Direct Acting Oral Anticoagulants[Title/Abstract])) OR (Oral Anticoagulants, Direct-Acting[Title/Abstract])) OR (Direct Factor Xa Inhibitor[Title/Abstract])) OR (Direct-Acting Oral Anticoagulant[Title/Abstract])) OR (Anticoagulant, Direct-Acting Oral[Title/Abstract])) OR (Direct Acting Oral Anticoagulant[Title/Abstract])) OR (Oral Anticoagulant, Direct-Acting[Title/ Abstract]))

- 7 #3 OR #4 OR #5 OR #6
- 8 #1 AND #2 AND #7

Cochrane Library

- COVID-19 OR COVID 19 OR 2019-nCoV 1 Infection OR 2019-nCoV Infection OR 2019-nCoV Infections OR Infection, 2019-nCoV OR SARS-CoV-2 Infection OR Infection, SARS-CoV-2 OR SARS-CoV-2 Infection OR SARS-CoV-2 Infections OR 2019 Novel Coronavirus Disease OR 2019 Novel Coronavirus Infection OR COVID-19 Virus Infection OR COVID 19 Virus Infection OR COVID-19 Virus Infections OR Infection, COVID-19 Virus OR Virus Infection, COVID-19 OR COVID19OR Coronavirus Disease 2019 OR Disease 2019, Coronavirus OR CoronavirusDisease-19 OR Coronavirus Disease 19 OR Severe Acute Respiratory Syndrome Coronavirus 2 Infection OR COVID-19 Virus Disease OR COVID 19 Virus Disease OR COVID-19 Virus Diseases OR Disease, COVID-19 Virus OR Virus Disease, COVID-19 OR SARS Coronavirus 2 Infection OR 2019-nCoV Disease OR 2019-nCoV Disease OR 2019-nCoV Diseases OR Disease, 2019-nCoVOR COVID-19 Pandemic OR COVID 19 Pandemic OR Pandemic, COVID-19OR COVID-19 Pandemics
- 2 randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR drug therapy OR randomly OR trial OR groups) NOT (animals NOT humans)
- 3 Anticoagulant Drug or Drug, Anticoagulant or Anticoagulant Agents or Agents, Anticoagulant or Anticoagulation Agents or Agents, Anticoagulation or Anticoagulant Drugs or Drugs, Anticoagulant or Anticoagulant Agent or Agent, Anticoagulant or Anticoagulant or Indirect Thrombin Inhibitors or Inhibitors, Indirect Thrombin or Thrombin Inhibitors, Indirect
- 4 Unfractionated Heparin or Heparin, Unfractionated or Heparinic Acid or Liquaemin or Sodium Heparin or Heparin, Sodium or Heparin Sodium or alpha-Heparin or alpha Heparin
- 5 Apo-Warfarin or Aldocumar or Coumadin or Marevanor Warfarin Potassium or Potassium, Warfarin or Warfarin Sodiumor Sodium, Warfarin or Coumadine
- 6 Factor Xa Inhibitor or Inhibitor, Factor Xa or Xa Inhibitor, Factor or Direct Factor Xa Inhibits or Direct-Acting Oral Anticoagulants or Anticoagulants, Direct-

Acting Oral or Direct Acting Oral Anticoagulants or Oral Anticoagulants, Direct-Acting or Direct Factor Xa Inhibitor or Direct-Acting Oral Anticoagulant or Anticoagulant, Direct-Acting Oral or Direct Acting Oral Anticoagulant or Oral Anticoagulant, Direct-Acting

- 7 #3 OR #4 OR #5 OR #6
- 8 #1 AND #2 AND #7

Medline

- (COVID-19 or COVID 19 or 2019-nCoV Infection 1 or 2019-nCoV Infection OR 2019-nCoV Infections or Infection, 2019-nCoV or SARS-CoV-2 Infection OR Infection, SARS-CoV-2 or SARS CoV 2 Infection or SARS-CoV-2 Infections OR 2019 Novel Coronavirus Disease or 2019 Novel Coronavirus Infection or COVID-19 Virus Infection or COVID 19 Virus Infection or COVID-19 Virus Infections OR Infection. COVID-19 Virus or Virus Infection, COVID-19 or COVID19OR Coronavirus Disease 2019 or Disease 2019, Coronavirus or CoronavirusDisease-19 or Coronavirus Disease 19 or Severe Acute Respiratory Syndrome Coronavirus 2 Infection or COVID-19 Virus Disease or COVID 19 Virus Disease or COVID-19 Virus Diseases or Disease, COVID-19 Virus OR Virus Disease, COVID-19 or SARS Coronavirus 2 Infection or 2019-nCoV Disease OR 2019-nCoV Disease or 2019-nCoV Diseases or Disease, 2019-nCoVOR COVID-19 Pandemic or COVID 19 Pandemic or Pandemic, COVID-19OR COVID-19 Pandemics).ab, ti.
- 2 ((randomized controlled trial or controlled clinical trial).pt. or randomized. ab. or placebo. ab. or drug therapy. fs. or randomly. ab. or trial. ab. or groups. ab.) not (exp animals/ not humans.sh.)
- 3 (Anticoagulants or Anticoagulant Drug or Drug, Anticoagulant or Anticoagulant Agents or Agents, Anticoagulant or Anticoagulation Agents or Agents, Anticoagulation or Anticoagulant Drugs or Drugs, Anticoagulant or Anticoagulant Drugs or Drugs, Anticoagulant or Anticoagulant or Indirect Thrombin Inhibitors OR Inhibitors, Indirect Thrombin or Thrombin Inhibitors, Indirect). ab, ti. 72771
- 4 (Heparin or Unfractionated Heparin or Heparin, Unfractionated or Heparinic Acid or Liquaemin or Sodium Heparin or Heparin, Sodium or Heparin Sodium or alpha-Heparin or alpha Heparin). ab, ti.

82941

- 5 (Apo-Warfarin or Aldocumar or Coumadin or Marevanor Warfarin Potassium or Potassium, Warfarin or Warfarin Sodiumor Sodium, Warfarin or Coumadine). ab, ti. 1109
- 6 (Factor Xa inhibitors or Factor Xa Inhibitor or Inhibitor, Factor Xa or Xa Inhibitor, Factor or Direct Factor Xa Inhibitors or Direct-Acting Oral Anticoagulants or Anticoagulants, Direct-Acting Oral or Direct Acting Oral Anticoagulants or Oral Anticoagulants, Direct-Acting or Direct Factor Xa Inhibitor or Direct-Acting Oral Anticoagulant or Anticoagulant, Direct-Acting Oral or Direct Acting Oral Anticoagulant or Oral Anticoagulant, Direct-Acting). ab, ti.
- 7 #3 OR #4 OR #5 OR #6
- 8 #1 AND #2 AND #7

Embase

COVID-19 OR COVID 19 OR 2019-nCoV 1 Infection OR 2019-nCoV Infection OR 2019-nCoV Infections OR Infection, 2019-nCoV OR SARS-CoV-2 Infection OR Infection, SARS-CoV-2 OR SARS-CoV-2 Infection OR SARS-CoV-2 Infections OR 2019 Novel Coronavirus Disease OR 2019 Novel Coronavirus Infection OR COVID-19 Virus Infection OR COVID 19 Virus Infection OR COVID-19 Virus Infections OR Infection, COVID-19 Virus OR Virus Infection, COVID-19 OR COVID19OR Coronavirus Disease 2019 OR Disease 2019, Coronavirus OR CoronavirusDisease-19 OR Coronavirus Disease 19 OR Severe Acute Respiratory Syndrome Coronavirus 2 Infection OR COVID-19 Virus Disease OR COVID 19 Virus Disease OR COVID-19 Virus Diseases OR Disease, COVID-19 Virus OR Virus Disease, COVID-19 OR SARS Coronavirus 2 Infection OR 2019-nCoV Disease OR 2019-nCoV Disease OR 2019-nCoV Diseases OR Disease, 2019-nCoVOR

COVID-19 Pandemic OR COVID 19 Pandemic OR Pandemic, COVID-19OR COVID-19 Pandemics

- 2 'crossover procedure': de OR 'double-blind procedure': de OR 'randomized controlled trial': de OR 'singleblind procedure': de OR (random* OR factorial* OR crossover* OR cross NEXT/1 over* OR placebo* OR doubl* NEAR/1 blind* OR singl* NEAR/1 blind* OR assign* OR allocat* OR volunteer*):de, ab, ti
- 3 Anticoagulants OR Anticoagulant Drug OR Drug, Anticoagulant OR Anticoagulant Agents OR Agents, Anticoagulant OR Anticoagulation Agents OR Agents, Anticoagulation OR Anticoagulant Drugs OR Drugs, Anticoagulant OR Anticoagulant Agent OR Agent, Anticoagulant OR Anticoagulant OR Indirect Thrombin Inhibitors OR Inhibitors, Indirect Thrombin OR Thrombin Inhibitors, Indirect
- 4 Heparin OR Unfractionated Heparin OR Heparin, Unfractionated OR Heparinic Acid OR Liquaemin OR Sodium Heparin OR Heparin, Sodium OR Heparin Sodium OR alpha-Heparin OR alpha Heparin
- 5 warfarin OR 4-Hydroxy-3-(3-oxo-1-phenylbutyl)-2H-1-benzopyran-2-one OR Apo-Warfarin OR Aldocumar OR Gen-Warfarin OR Warfant OR Coumadin OR Marevan OR Warfarin Potassium OR Potassium, Warfarin OR Warfarin Sodium OR Sodium, Warfarin OR Coumadine OR Tedicumar
- 6 Factor Xa inhibitors OR Factor Xa Inhibitor OR Inhibitor, Factor Xa OR Xa Inhibitor, Factor OR Direct Factor Xa Inhibitors OR Direct-Acting Oral Anticoagulants OR Anticoagulants, Direct-Acting Oral OR Direct Acting Oral Anticoagulants OR Oral Anticoagulants, Direct-Acting OR Direct Factor Xa Inhibitor OR Direct-Acting Oral Anticoagulant OR Anticoagulant, Direct-Acting Oral OR Direct Acting Oral Anticoagulant OR Oral Anticoagulant, Direct-Acting Oral Anticoagulant OR Oral Anticoagulant, Direct-Acting
- 7 #3 OR #4 OR #5 OR #6
- 8 #1 AND #2 AND

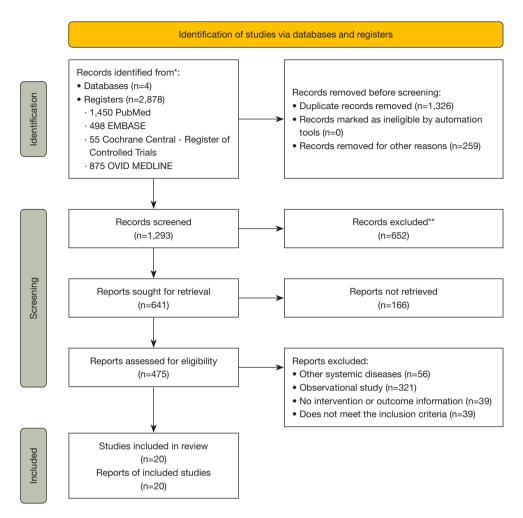


Figure S1 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.

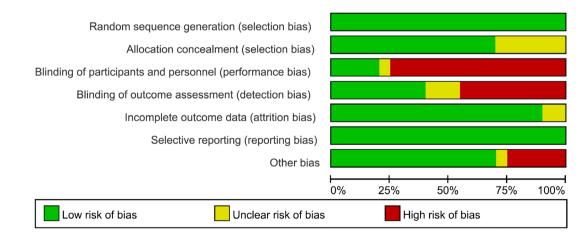


Figure S2 Risk of bias assessment.

A	В
> metabias(meta1,k.min=2,method.bias="Peters") Linear regression test of funnel plot asymmetry	<pre>> metabias(meta1,k.min=2,method.bias="Peters") Linear regression test of funnel plot asymmetry</pre>
Test result: t = -0.63, df = 3, p-value = 0.5723	Test result: $t = 20.43$, $df = 1$, p-value = 0.0311
Sample estimates: bias se.bias intercept se.intercept -22.5850 35.7432 -0.6229 0.4185	Sample estimates: bias se.bias intercept se.intercept 311.0506 15.2275 -2.0144 0.0484
Details: - multiplicative residual heterogeneity variance (tau^2 = 6.1421) - predictor: inverse of total sample size - weight: inverse variance of average event probability - reference: Peters et al. (2006), JAMA Warning message: In metabias.meta(meta1, k.min = 2, method.bias = "Peters") : 2 observation(s) dropped due to missing values	Details: - multiplicative residual heterogeneity variance (tau^2 = 0.0026) - predictor: inverse of total sample size - weight: inverse variance of average event probability - reference: Peters et al. (2006), JAMA
С	D
> metabias(metal,k.min=2,method.bias="Peters") Linear regression test of funnel plot asymmetry	<pre>> metabias(metal,k.min=2,method.bias="Peters") Linear regression test of funnel plot asymmetry</pre>
Test result: t = -0.29, df = 1, p-value = 0.8184	Test result: t = -1.43, df = 10, p-value = 0.1832
Sample estimates: bias se.bias intercept se.intercept -4.9808 16.9872 0.4465 0.2657	Sample estimates: bias se.bias intercept se.intercept -22.2896 15.5862 0.0511 0.0710
Details: - multiplicative residual heterogeneity variance (tau^2 = 0.5070) - predictor: inverse of total sample size - weight: inverse variance of average event probability - reference: Peters et al. (2006), JAMA Warning message: In metabias.meta(metal, k.min = 2, method.bias = "Peters") : 2 observation(s) dropped due to missing values	Details: - multiplicative residual heterogeneity variance (tau^2 = 3.4417) - predictor: inverse of total sample size - weight: inverse variance of average event probability - reference: Peters et al. (2006), JAMA Warning message: In metabias.meta(metal, k.min = 2, method.bias = "Peters") : 1 observation(s) dropped due to missing values
E	F
<pre>> metabias(meta1,k.min=2,method.bias="Thompson") Linear regression test of funnel plot asymmetry</pre>	> metabias(metal,k.min=2,method.bias="Peters") Linear regression test of funnel plot asymmetry
Test result: $t = 0.08$, $df = 9$, p-value = 0.9383	Test result: t = 0.07, df = 9, p-value = 0.9469
Sample estimates: bias se.bias intercept se.intercept 0.0593 0.7448 -0.4496 0.3161	Sample estimates: bias se.bias intercept se.intercept 2.0262 29.6097 0.7061 0.1681
<pre>Details: - additive residual heterogeneity variance (tau^2 = 0.0895) - restricted maximum-likelihood estimator for tau^2 - predictor: standard error - weight: inverse variance - reference: Thompson & Sharp (1999), Stat Med Warning message: In metabias.meta(meta1, k.min = 2, method.bias = "Thompson") : 1 observation(s) dropped due to missing values</pre>	Details: - multiplicative residual heterogeneity variance (tau^2 = 4.0037) - predictor: inverse of total sample size - weight: inverse variance of average event probability - reference: Peters et al. (2006), JAMA Warning message: In metabias.meta(metal, k.min = 2, method.bias = "Peters") : 1 observation(s) dropped due to missing values

Figure S3 Publication bias test: (A-C) Peters test results of anticoagulants on all-cause mortality, thromboses and bleeding events, respectively; (D-F) Peters test results when analyzing the effect of anticoagulant dose on all-cause mortality and bleeding events, respectively. (E) The result of Thompson test when analyzing the dose of anticoagulants on thromboses.

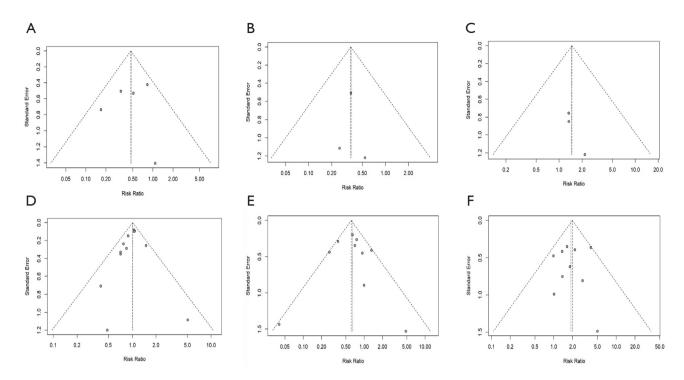


Figure S4 Funnel plots: (A-C) the funnel plots to analyze the influence of anticoagulant therapy on all-cause mortality, thromboses and bleeding events, respectively; (D-F) the funnel plots to analyze the effects of anticoagulants dosage on all-cause mortality, risk of thrombotic events, and risk of bleeding events, respectively.

	Experim		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Fixed, 95% C	I M-H. Fixed. 95% Cl
3.4.1 nonsevere							
Connors et al. (2021)	0	143	0	135		Not estimable	
Lawler et al. (2021)	13	1180	22	1046	11.9%	0.52 [0.27, 1.03]	
Lopes et al.(2021)	23	310	30	304	15.5%	0.75 [0.45, 1.26]	
Marcos et al.(2022)	2	33	0	32	0.3%	4.85 [0.24, 97.31]	
Morici et al.(2021)	0	91	12	92	0.0%	0.04 [0.00, 0.67]	
Subtotal (95% CI)		1666		1517	27.7%	0.69 [0.46, 1.04]	\bullet
Total events	38		52				
Heterogeneity: Chi ² = 2.36	, df = 2 (P =	= 0.31); I	² = 15%				
Test for overall effect: Z =	1.79 (P = 0	.07)					
3.4.2 severe							
Bikdeli et al.(2022)	9	276	10	286	5.0%	0.93 [0.38, 2.26]	
Goligher et al. (2021)	38	530	62	559	30.9%	0.65 [0.44, 0.95]	
Labbe et al.(2023)	6	110	23	114	11.6%	0.27 [0.11, 0.64]	
Lemos et al.(2020)	2	10	2	10	1.0%	1.00 [0.17, 5.77]	
Perepu et al.(2021)	12	87	9	86	0.0%	1.32 [0.59, 2.97]	
Sadeghipour et al.(2021)	9	276	10	286	5.0%	0.93 [0.38, 2.26]	
Spyropoulos et al.(2021)	14	129	36	124	18.8%	0.37 [0.21, 0.66]	
Subtotal (95% CI)		1331		1379	72.3%	0.56 [0.43, 0.73]	◆
Total events	78		143				
Heterogeneity: Chi ² = 8.22	df = 5 (P =	= 0.14):	$^{2} = 39\%$				
Test for overall effect: Z =							
Total (95% CI)		2997		2896	100.0%	0.60 [0.48, 0.74]	◆
Total events	116		195				
Heterogeneity: Chi ² = 11.1		= 0.20)					⊢ ⊢ ⊢ ⊢ ⊢ ⊢ ⊢ ⊢ ⊢ ⊢
Test for overall effect: $Z = 4$, ,	· · ·	. 2070				0.01 0.1 1 10 100
Test for subaroup difference	•	,	= 1 (P = () 39) l²	= 0%		Favours [experimental] Favours [control]
rest is: subaroub different		5.7 UI			0.0		

Figure S5 Heterogeneity analysis: Morici *et al.* (38) and Perepu *et al.* (43) may be the source of heterogeneity in the non-severe subgroup and the severe subgroup, respectively. CI, confidence interval.

Table S1 The grade of evidence for all-cause mortality

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	All-caused mortality	Control	Relative risk (95% Cl)	Absolute	Quality	Importance
Whether anticoa	agulants are used											
7	Randomised trials	Serious [†]	No serious inconsistency	No serious indirectness	No serious imprecision	Strong association	22/1,176 (1.9%)	45/1,189 (3.8%)	0.47 (0.29 to 0.76)	20 fewer per 1,000 (from 9 fewer to 27 fewer)	High	
						3%		16 fewer per 1,000 (from 7 fewer to 21 fewer)				
Types of anticoa	agulants											
13		No serious imprecision		640/3,221 (19.9%)	642/3,121 (20.6%)	1.01 (0.92 to 1.1)	2 more per 1,000 (from 16 fewer to 21 more)	Low				
								20.9%		2 more per 1,000 (from 17 fewer to 21 more)		

[†], no explanation was provided. Cl, confidence interval.

Table S2 The grade of evidence for thromboembolism

Quality assessm	nent						No. of patients		Effect		Quality	la se de se se
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	All-caused mortality	Control	Relative risk (95% CI)	Absolute	Quality	Importance
Whether anticoa	agulants are used											
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias [†] strong association	7/498 (1.4%)	20/511 (3.9%)	0.35 (0.15 to 0.83)	25 fewer per 1,000 (from 7 fewer to 33 fewer)	High	
								1.8%		12 fewer per 1,000 (from 3 fewer to 15 fewer)		
Types of anticoa	agulants											
12	Randomise trials	Serious [†]	Serious [†]	No serious indirectness	No serious imprecision	None [†]	128/3,175 (4%)	216/3,974 (7%)	0.59 (0.48 to 0.73)	29 fewer per 1,000 (from 19 fewer to 37 fewer)	Low	
								10.2%		42 more per 1,000 (from 28 fewer to 53 fewer)		

[†], no explanation was provided. Cl, confidence interval.

Table S3 The grade of evidence for bleeding events

Quality assessm	nent						No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	All-caused mortality	Control	Relative risk (95% CI)	Absolute	- Quality	Importance
Whether anticoa	agulants are used											
5	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	9/736 (1.2%)	6/758 (0.8%)	1.47 (0.54 to 4.00)	4 fewer per 1,000 (from 4 fewer to 24 more)	High	
								0.9%		4 fewer per 1,000 (from 4 fewer to 27 more)		
Types of anticoa	agulants											
	Randomise trials	Serious [†]	No serious inconsistency	No serious indirectness	No serious imprecision	None [†]	127/3,174 (4%)	63/3,078 (2%)	1.98 (1.47 to 2.66)	20 fewer per 1,000 (from 10 more to 34 more)	Moderate	
								1.9%		19 more per 1,000 (from 9 more to 32 more)		

[†], no explanation was provided. CI, confidence interval.