Supplementary

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

Pubmed

1 ("COVID-19"[Mesh]) OR (COVID 19[Title/Abstract] OR 2019-nCoV Infection[Title/Abstract] OR 2019-nCoV Infection[Title/Abstract] OR 2019-nCoV 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 2019-nCoV 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])

3 ("Anticoagulants"[Mesh]) OR ((((((((((((Anticoagulant Drug[Title/Abstract]) OR (Drug, Anticoagulant[Title/Abstract])) OR (Anticoagulant Agents[Title/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 (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]))

4 ("Heparin"[Mesh]) OR (((((((((Unfractionated Heparin[Title/Abstract]) OR (Heparin, Unfractionated[Title/Abstract])) OR (Heparinic Acid[Title/Abstract])) OR (Liquaemin[Title/Abstract])) OR (Sodium Heparin[Title/Abstract])) OR (Heparin, Sodium[Title/Abstract])) OR (Heparin Sodium[Title/Abstract])) OR (alpha-Heparin[Title/Abstract])) OR (alpha Heparin[Title/Abstract]))

5 ("Warfarin"[Mesh]) OR ((((((((((4-Hydroxy-3-(3-oxo-1-phenylbutyl)-2H-1-benzopyran-2-one[Title/Abstract]) OR (Apo-Warfarin[Title/Abstract])) OR (Aldocumar[Title/Abstract])) OR (Coumadin[Title/Abstract])) OR (Marevan[Title/Abstract])) OR (Warfarin Potassium[Title/Abstract])) OR (Potassium, Warfarin[Title/Abstract])) OR (Warfarin Sodium[Title/Abstract])) OR (Sodium, Warfarin[Title/Abstract])) OR (Coumadine[Title/Abstract]))

6 ("Factor Xa Inhibitors"[Mesh]) OR ((((((((((((Factor 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]))

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

Cochrane Library

1 COVID-19 OR COVID 19 OR 2019-nCoV 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

1 (COVID-19 or COVID 19 or 2019-nCoV 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).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 Agent or Agent, 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.

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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

1 COVID-19 OR COVID 19 OR 2019-nCoV 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 'single-blind 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

7 #3 OR #4 OR #5 OR #6

8 #1 AND #2 AND

https://dx.doi.org/10.21037/jtd-24-744

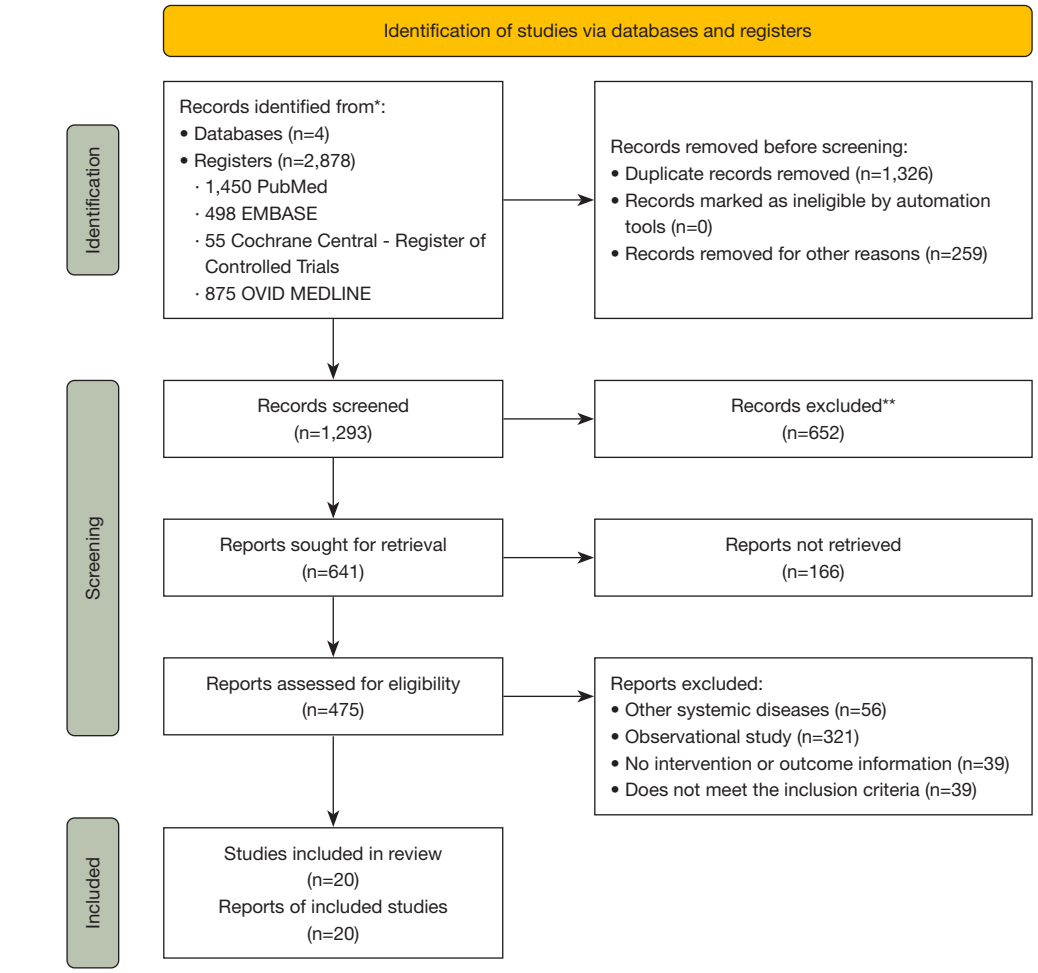

Figure S1 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.

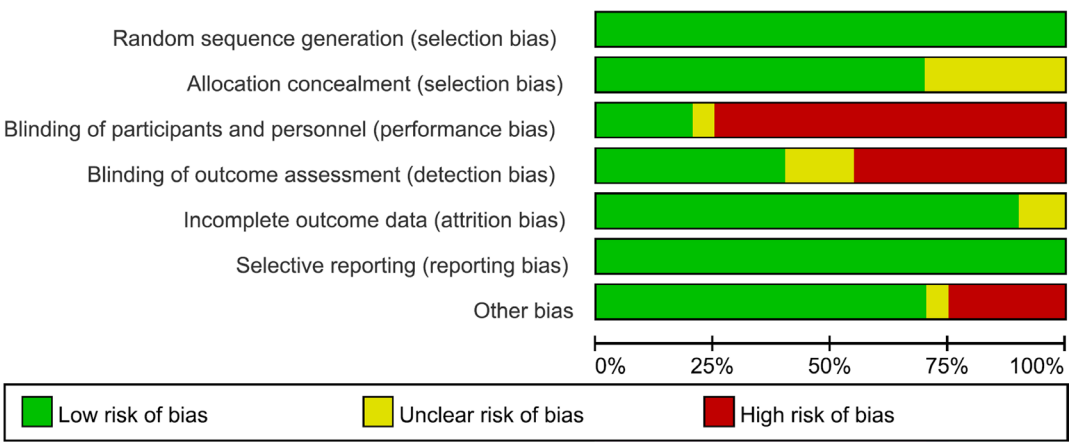

Figure S2 Risk of bias assessment.

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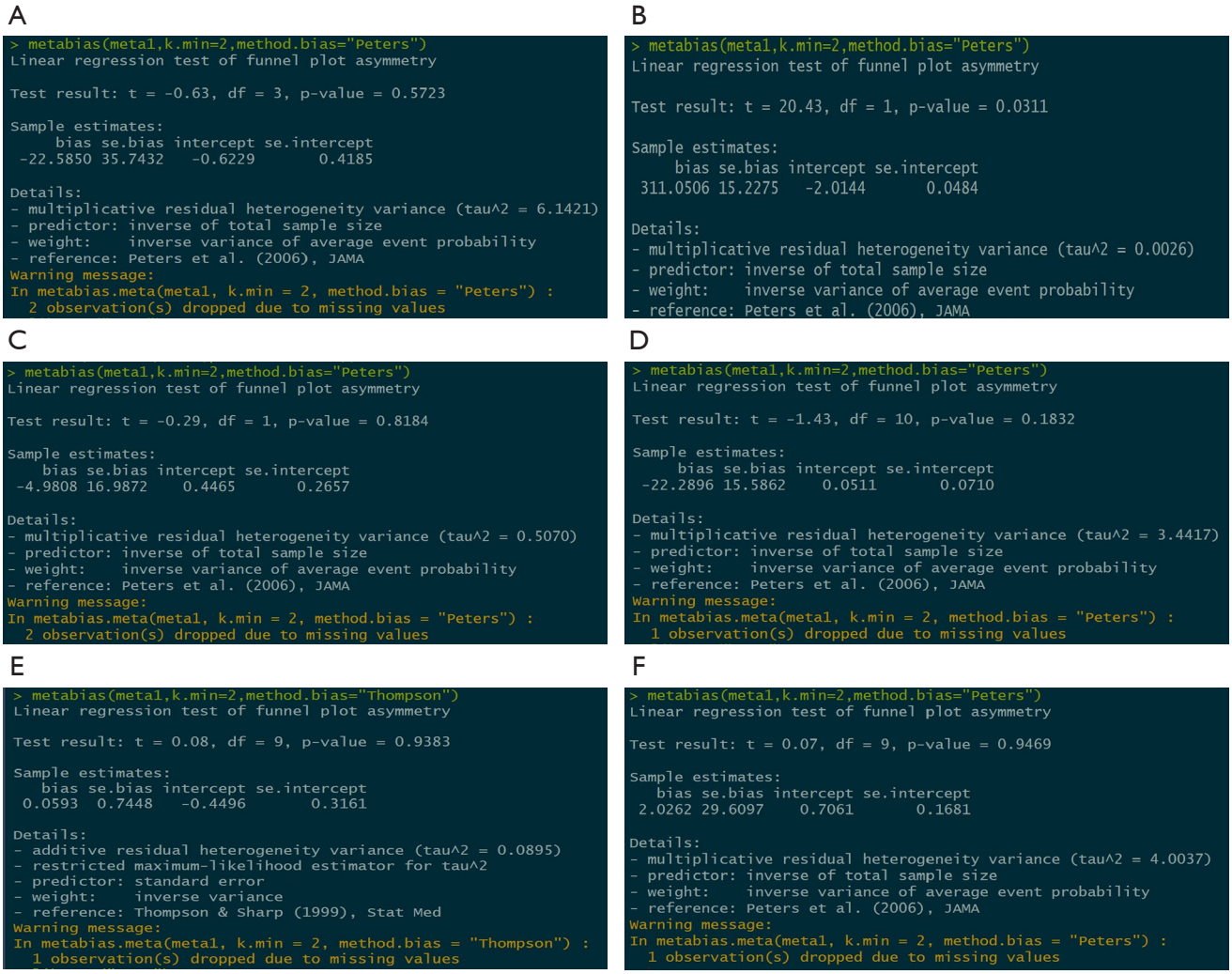

Figure S3 Publication bias test: (A-C) Peters test results of anticoagulants on all-cause mortality, thromboses and bleeding events, respectively; (D-F) Peters test results when analyzing the effect of anticoagulant dose on all-cause mortality and bleeding events, respectively. (E) The result of Thompson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

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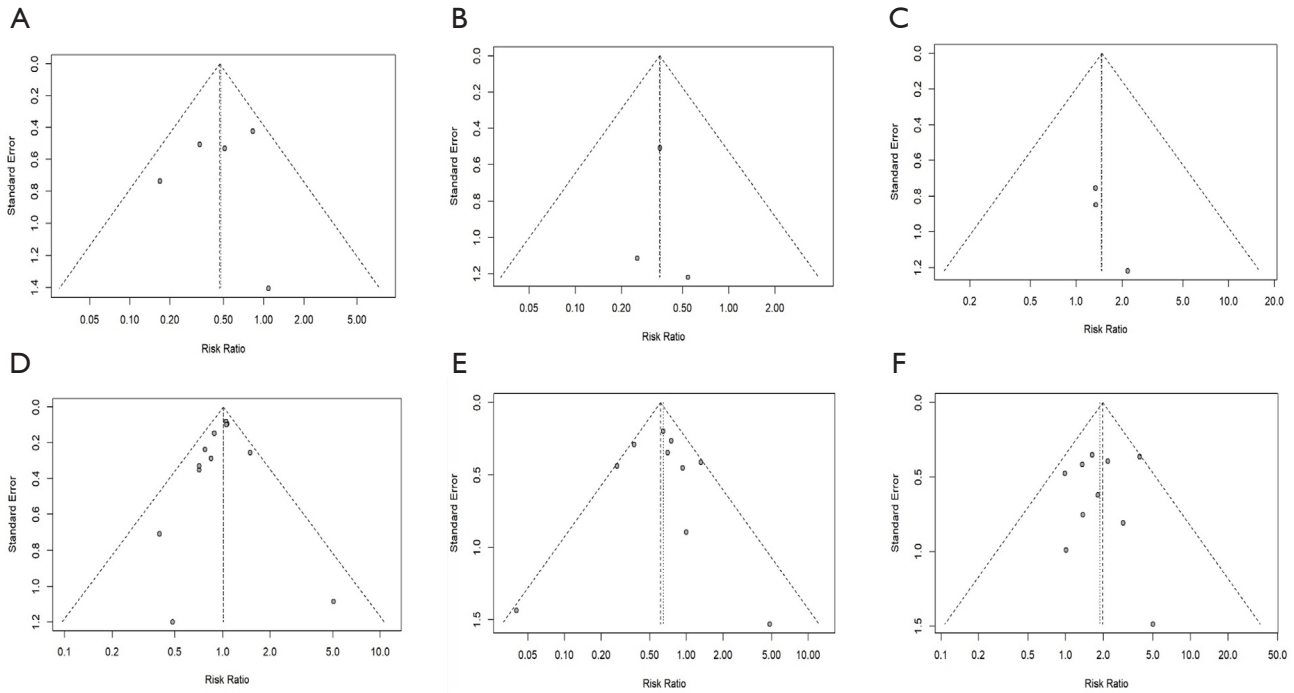

Figure S4 Funnel plots: (A-C) the funnel plots to analyze the influence of anticoagulant therapy on all-cause mortality, thromboses and bleeding events, respectively; (D-F) the funnel plots to analyze the effects of anticoagulants dosage on all-cause mortality, risk of thrombotic events, and risk of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

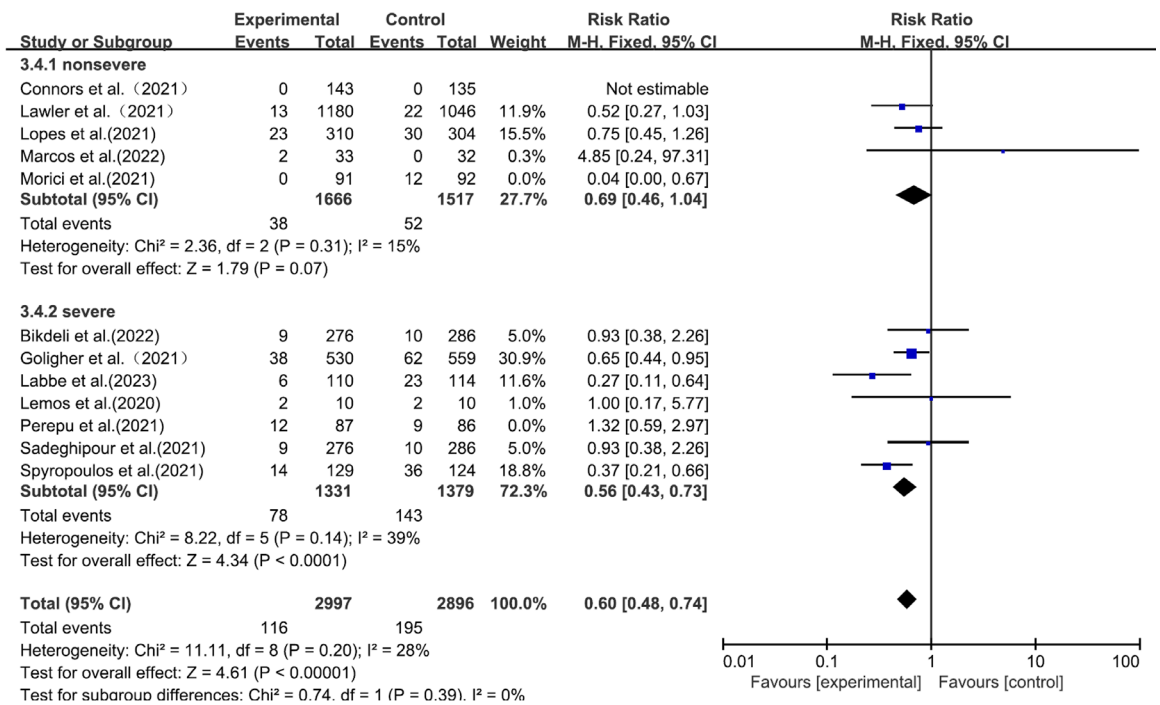

Figure S5 Heterogeneity analysis: Morici *et al.* (38) and Perepu *et al.* (43) may be the source of heterogeneity in the non-severe subgroup and the severe subgroup, respectively. CI, confidence interval.

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Table S1 The grade of evidence for all-cause mortality

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	All-caused mortality	Control	Relative risk (95% CI)	Absolute		
Whether anticoagulants 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 anticoagulants												
13	Randomised trials	Very serious[†]	No serious inconsistency	No serious indirectness	No serious imprecision	None[†]	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. CI, confidence interval.

Table S2 The grade of evidence for thromboembolism

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	All-caused mortality	Control	Relative risk (95% CI)	Absolute		
Whether anticoagulants 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 anticoagulants												
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. CI, confidence interval.

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Table S3 The grade of evidence for bleeding events

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	All-caused mortality	Control	Relative risk (95% CI)	Absolute		
Whether anticoagulants 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 anticoagulants												
12	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.

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