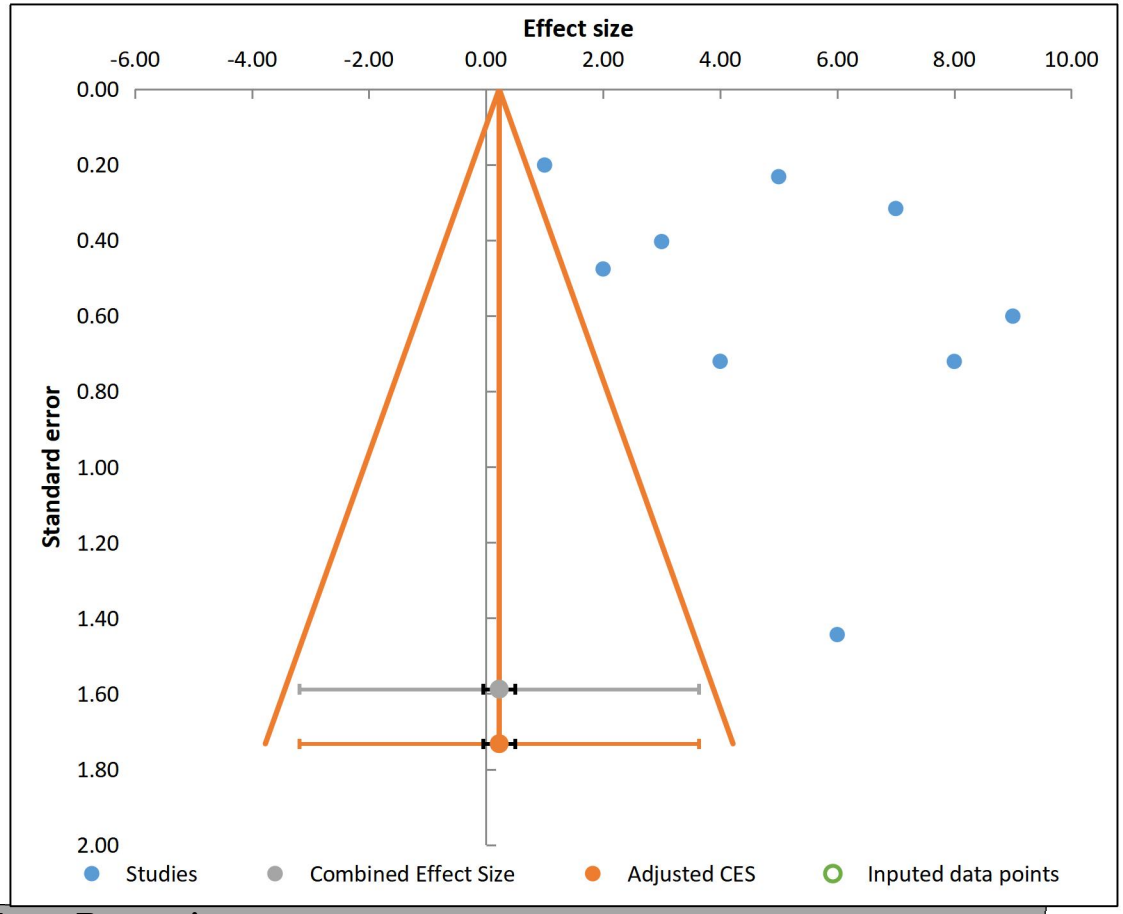
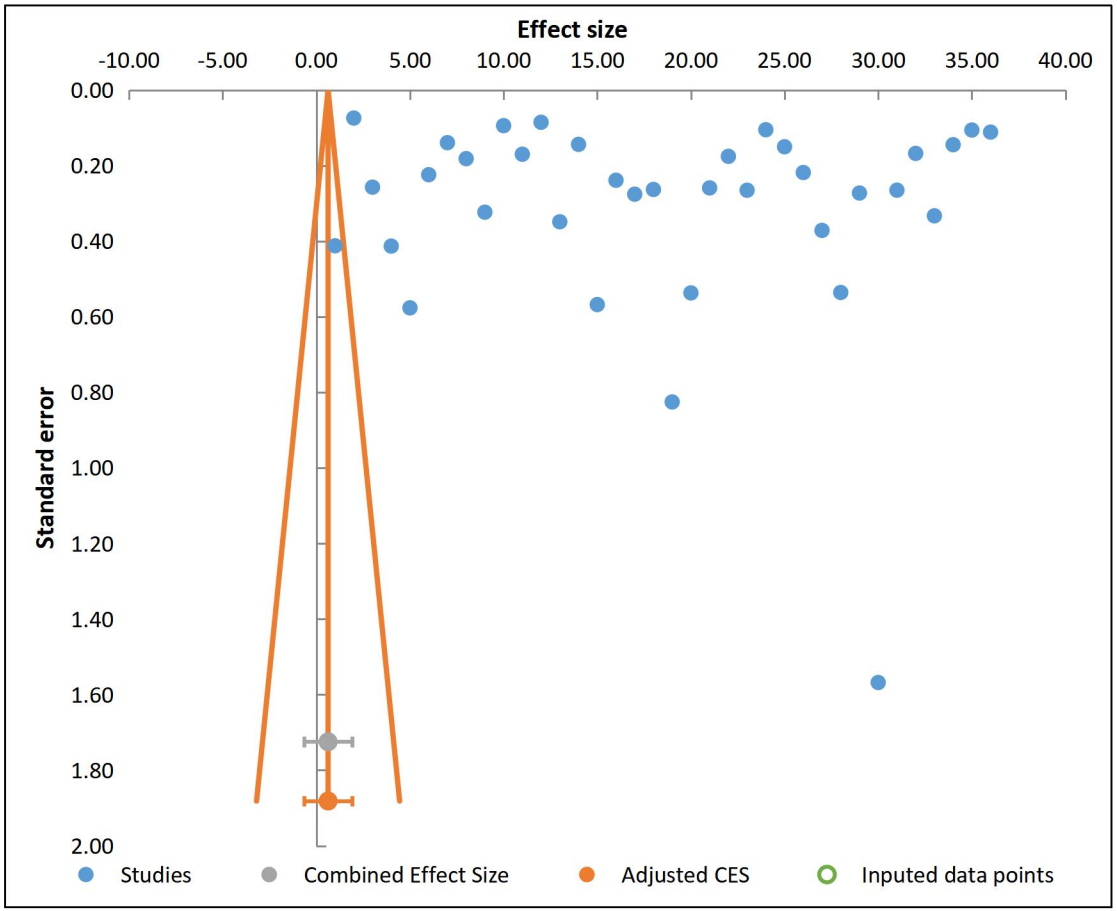
A



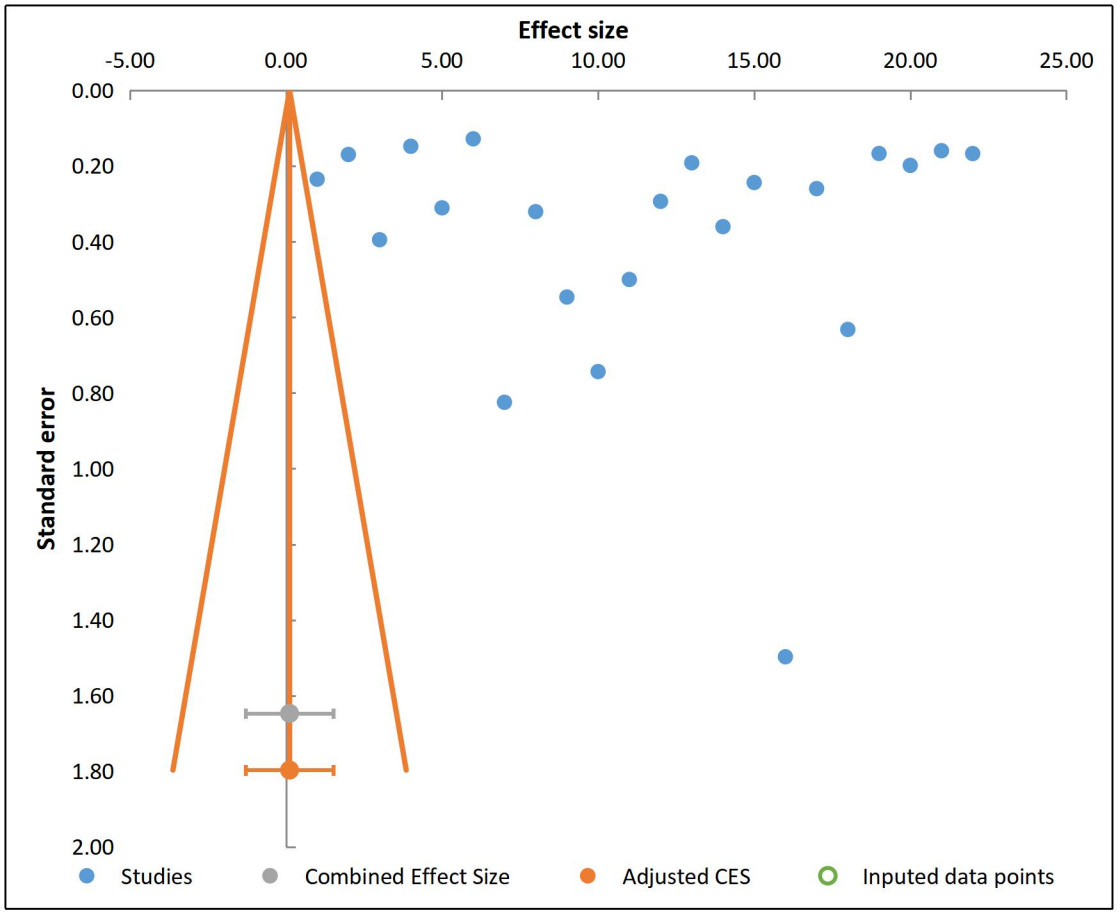
Egger Regression						
	Estimate	**SE**	**CI LL**	**CI UL**	**t test**	**p-value**
Intercept	-2.82	2.76	-9.20	3.55	-1.02	0.341
Slope	1.11	0.98	-1.16	3.38		

B



Egger Regression						
	Estimate	SE	CI LL	CI UL	t test	p-value
Intercept	-0.59	1.21	-3.05	1.87	-0.49	0.629
Slope	0.71	0.21	0.29	1.13		

C



Egger Regression						
	Estimate	**SE**	**CI LL**	**CI UL**	**t test**	**p-value**
Intercept	-0.35	1.45	-3.36	2.67	-0.24	0.814
Slope	0.19	0.33	-0.51	0.88		

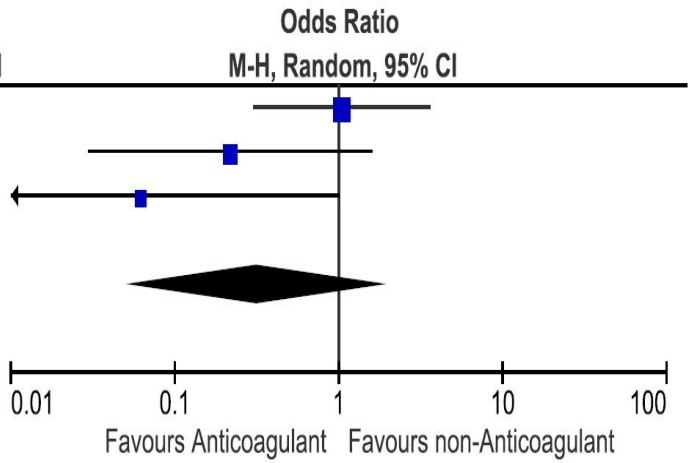
Supplementary Figure 1 Funnel plots for the publication bias. A: Thromboembolic events; B: Mortality; C: COVID-19 severity.

A

Study or Subgroup	Anticoagulant users Events	Total	non-anticoagulant users Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Buenen et al. 2021	3	53	21	387	43.2%	1.05 [0.30, 3.63]
Fauvel el al. 2020	1	47	101	1115	32.9%	0.22 [0.03, 1.60]
Spiegelenberg et al. 2021	0	92	77	964	23.9%	0.06 [0.00, 1.01]
Total (95% CI)		**192**		**2466**	**100.0%**	**0.32 [0.05, 1.98]**
Total events	4		199			

Heterogeneity: Tau² = 1.62; Chi² = 5.36, df = 2 (P = 0.07); I² = 63%

Test for overall effect: Z = 1.23 (P = 0.22)

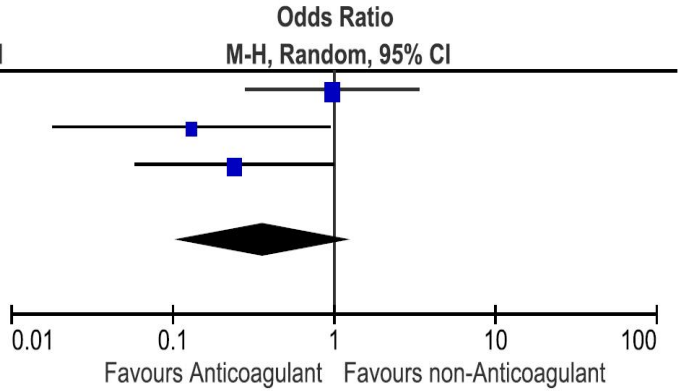


B

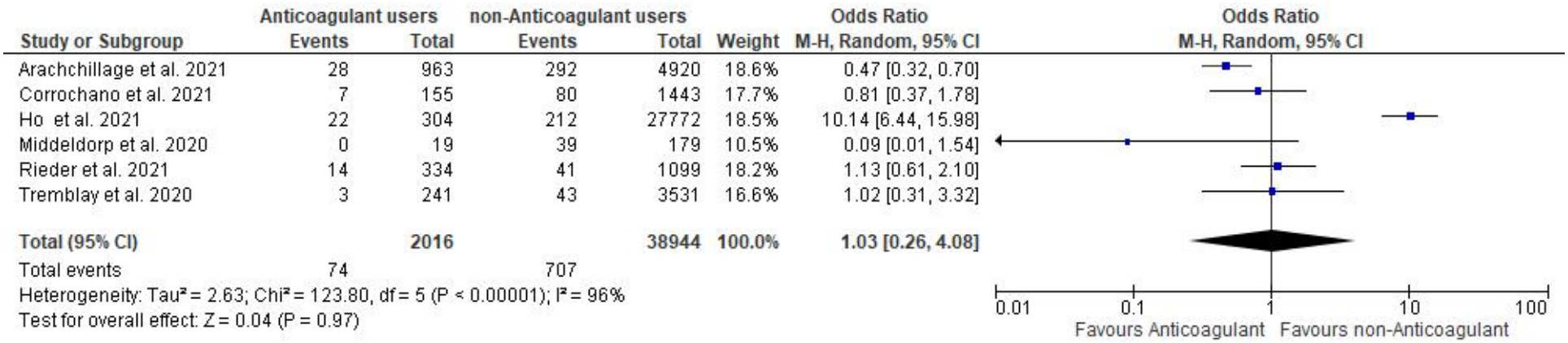
Study or Subgroup	Anticoagulant users Events	Total	non-anticoagulant users Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Buenen et al. 2021	3	57	21	387	39.8%	0.97 [0.28, 3.36]
Fauvel el al. 2020	1	78	101	1115	24.7%	0.13 [0.02, 0.95]
Spiegelenberg et al. 2021	2	98	77	964	35.5%	0.24 [0.06, 0.99]
Total (95% CI)		**233**		**2466**	**100.0%**	**0.36 [0.10, 1.25]**
Total events	6		199			

Heterogeneity: Tau² = 0.62; Chi² = 4.07, df = 2 (P = 0.13); I² = 51%

Test for overall effect: Z = 1.61 (P = 0.11)



C



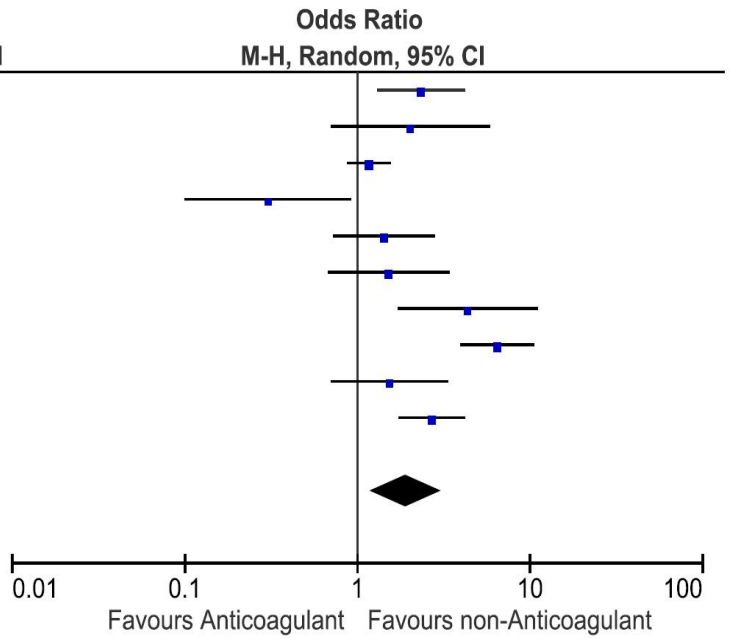
Supplementary Figure 2 Unadjusted Sub-group analysis for Thromboembolic events in prehospital use of Vitamin K Antagonists and Direct Oral Anticoagulants versus control cohort in COVID-19. A: Unadjusted Thromboembolic events in prehospital use of Vitamin K Antagonists versus control cohort; B: Unadjusted Thromboembolic events in prehospital use of Direct Oral Anticoagulants versus control cohort; C: Unadjusted Thromboembolic events in prehospital use of any Anticoagulants versus control cohort.

A

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	non-Anticoagulant Events	non-Anticoagulant Total	Weight	Odds Ratio M-H, Random, 95% CI
Buenen et al. 2021	25	53	107	387	10.9%	2.34 [1.30, 4.19]
Covino et al. 2021	7	18	22	92	7.8%	2.02 [0.70, 5.86]
Fröhlich et al. 2021	72	223	1400	4824	12.5%	1.17 [0.87, 1.55]
Fumagalli et al. 2021	5	22	33	67	7.6%	0.30 [0.10, 0.92]
Gülcü et al. 2021	10	68	554	5124	10.3%	1.42 [0.72, 2.80]
Harrison et al. 2021	9	28	213	894	9.4%	1.51 [0.68, 3.40]
Hozayen et al. 2021	5	67	99	5437	8.6%	4.35 [1.71, 11.05]
Rivera-Caravaca et al. 2020	57	82	233	892	11.5%	6.45 [3.94, 10.56]
Russo et al. 2021	10	33	84	380	9.6%	1.53 [0.70, 3.35]
Spiegelenberg et al. 2021	39	92	207	964	11.8%	2.69 [1.73, 4.18]
Total (95% CI)		**686**		**19061**	**100.0%**	**1.91 [1.20, 3.06]**
Total events	239		2952			

Heterogeneity: Tau² = 0.44; Chi² = 52.50, df = 9 (P < 0.00001); I² = 83%

Test for overall effect: Z = 2.72 (P = 0.007)

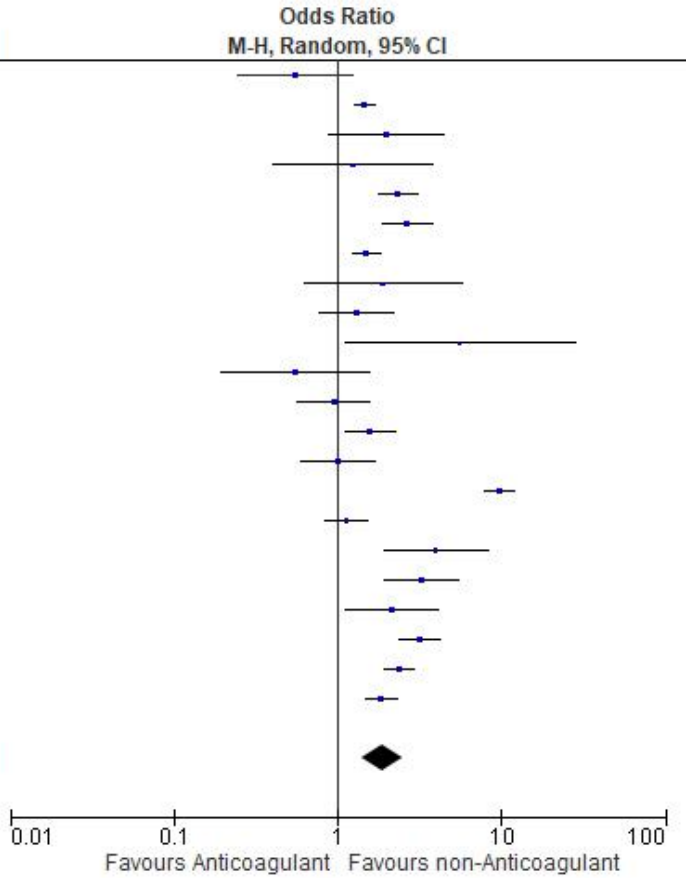


B

Study or Subgroup	Anticoagulant users Events	Total	non-Anticoagulant users Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Ageno et al. 2021	10	43	39	110	3.9%	0.55 [0.25, 1.24]
Arachchillage et al. 2021	346	963	1373	4920	5.5%	1.45 [1.25, 1.68]
Boari et al. 2020	11	29	54	229	3.9%	1.98 [0.88, 4.45]
Brouns et al. 2020	9	16	26	51	3.1%	1.24 [0.40, 3.83]
Chocron et al. 2021	84	382	268	2466	5.3%	2.31 [1.76, 3.04]
Corrochano et al. 2021	55	155	249	1443	5.1%	2.64 [1.85, 3.77]
Denas et al. 2021	189	651	866	4046	5.4%	1.50 [1.25, 1.81]
Hanif et al. 2020	14	33	7	25	3.1%	1.89 [0.62, 5.77]
Iaccarino et al. 2021	18	125	257	2252	4.7%	1.31 [0.78, 2.19]
Ménager et al. 2020	3	9	6	73	2.1%	5.58 [1.11, 28.16]
Natali et al. 2020	5	22	52	149	3.2%	0.55 [0.19, 1.57]
Olcott et al. 2021	38	81	110	228	4.8%	0.95 [0.57, 1.58]
Parker et al. 2021	66	164	260	868	5.2%	1.57 [1.12, 2.22]
Philipose et al. 2020	29	68	170	398	4.7%	1.00 [0.59, 1.68]
Reilev et al.2020	163	577	414	10545	5.4%	9.63 [7.84, 11.84]
Rieder et al. 2021	76	334	227	1099	5.3%	1.13 [0.84, 1.52]
Rodrı´guez-Molinero et al. 2020	15	34	64	384	4.1%	3.95 [1.91, 8.18]
Schiavone et al. 2021	29	65	154	779	4.7%	3.27 [1.94, 5.50]
Tehrani et al. 2020	20	49	50	206	4.4%	2.15 [1.12, 4.13]
Tremblay et al. 2020	81	241	486	3531	5.3%	3.17 [2.39, 4.21]
van Haaps et al. 2021	194	445	629	2561	5.4%	2.37 [1.93, 2.92]
Wargny et al. 2021	149	501	428	2293	5.4%	1.84 [1.48, 2.29]
Total (95% CI)		**4987**		**38656**	**100.0%**	**1.88 [1.40, 2.52]**
Total events	1604		6189			

Heterogeneity: Tau² = 0.40; Chi² = 330.68, df = 21 (P < 0.00001); I² = 94%

Test for overall effect: Z = 4.21 (P < 0.0001)

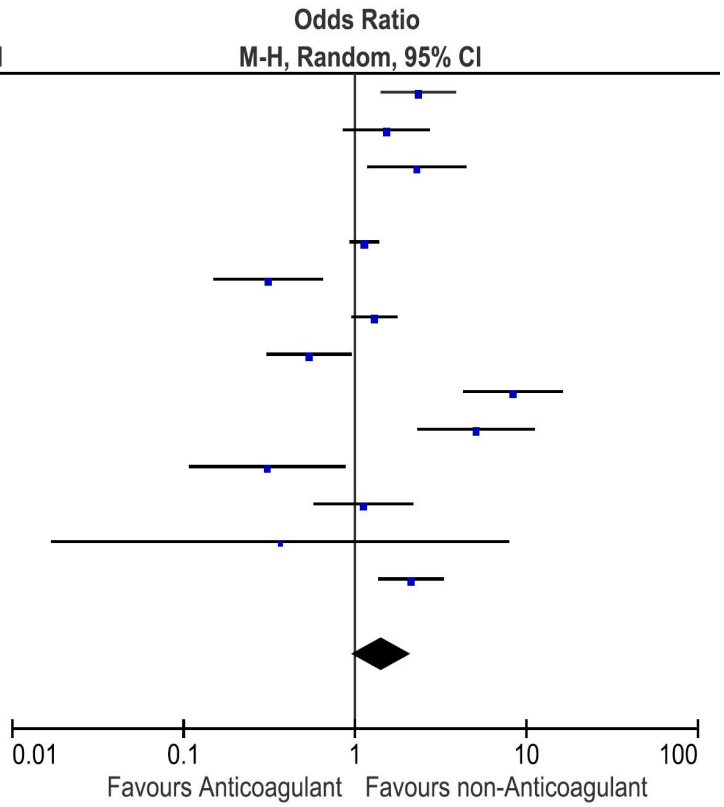


C

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	non-Anticoagulant Events	non-Anticoagulant Total	Weight	Odds Ratio M-H, Random, 95% CI
Aslan et al. 2021	23	79	244	1631	8.7%	2.33 [1.41, 3.87]
Buenen et al. 2021	21	57	107	387	8.3%	1.53 [0.85, 2.73]
Covino et al. 2021	31	74	22	92	7.9%	2.29 [1.18, 4.46]
Flam et al. 2020	140	0	46	0		Not estimable
Fröhlich et al. 2021	161	508	1400	4824	9.9%	1.13 [0.93, 1.38]
Fumagalli et al. 2021	16	69	33	67	7.5%	0.31 [0.15, 0.65]
Gülcü et al. 2021	52	383	554	5124	9.6%	1.30 [0.95, 1.76]
Harrison et al. 2021	15	104	213	894	8.4%	0.54 [0.31, 0.95]
Hozayen et al. 2021	11	82	99	5437	7.9%	8.35 [4.29, 16.25]
Rivera-Caravaca et al. 2020	18	28	233	892	7.3%	5.09 [2.32, 11.19]
Rossi et al. 2020	7	26	24	44	6.0%	0.31 [0.11, 0.88]
Russo et al. 2021	13	54	84	380	7.9%	1.12 [0.57, 2.18]
Ruzhentsova et al. 2021	0	26	2	50	1.4%	0.37 [0.02, 7.91]
Spiegelenberg et al. 2021	36	98	207	964	9.0%	2.12 [1.37, 3.29]
Total (95% CI)		**1588**		**20786**	**100.0%**	**1.42 [0.95, 2.12]**
Total events	544		3268			

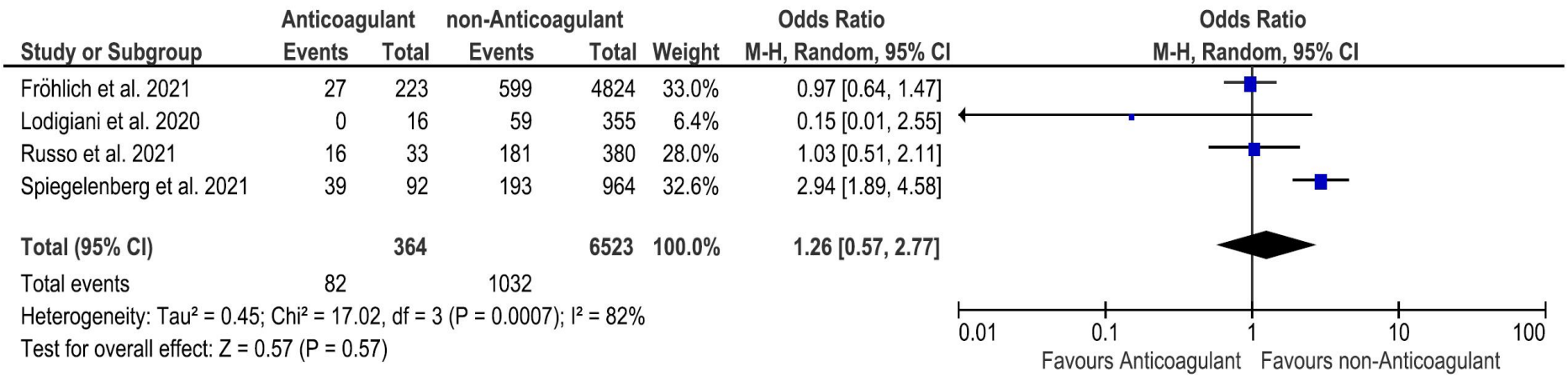
Heterogeneity: Tau² = 0.41; Chi² = 88.90, df = 12 (P < 0.00001); I² = 87%

Test for overall effect: Z = 1.73 (P = 0.08)



Supplementary Figure 3 Unadjusted Sub-group analysis for Mortality in prehospital use of Vitamin K Antagonists and Direct Oral Anticoagulants versus control cohort in COVID-19. A: Unadjusted Mortality in prehospital use of Vitamin K Antagonists versus control cohort; B: Unadjusted Mortality in prehospital use of any Anticoagulants versus control cohort; C: Unadjusted Mortality in prehospital use of Direct Oral Anticoagulants versus control cohort.

A

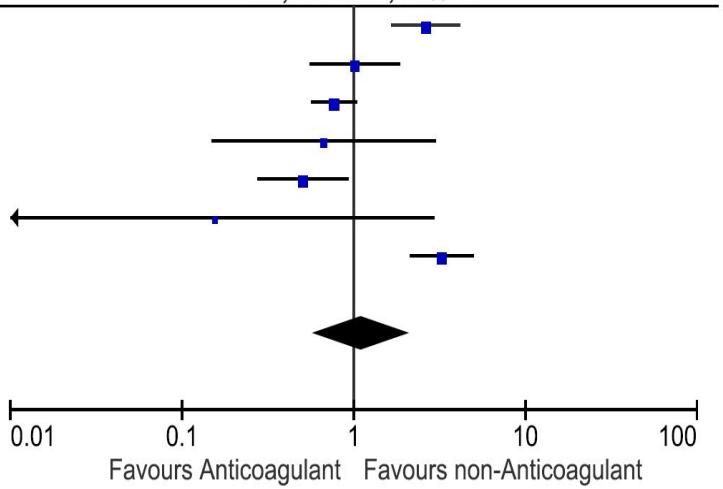


B

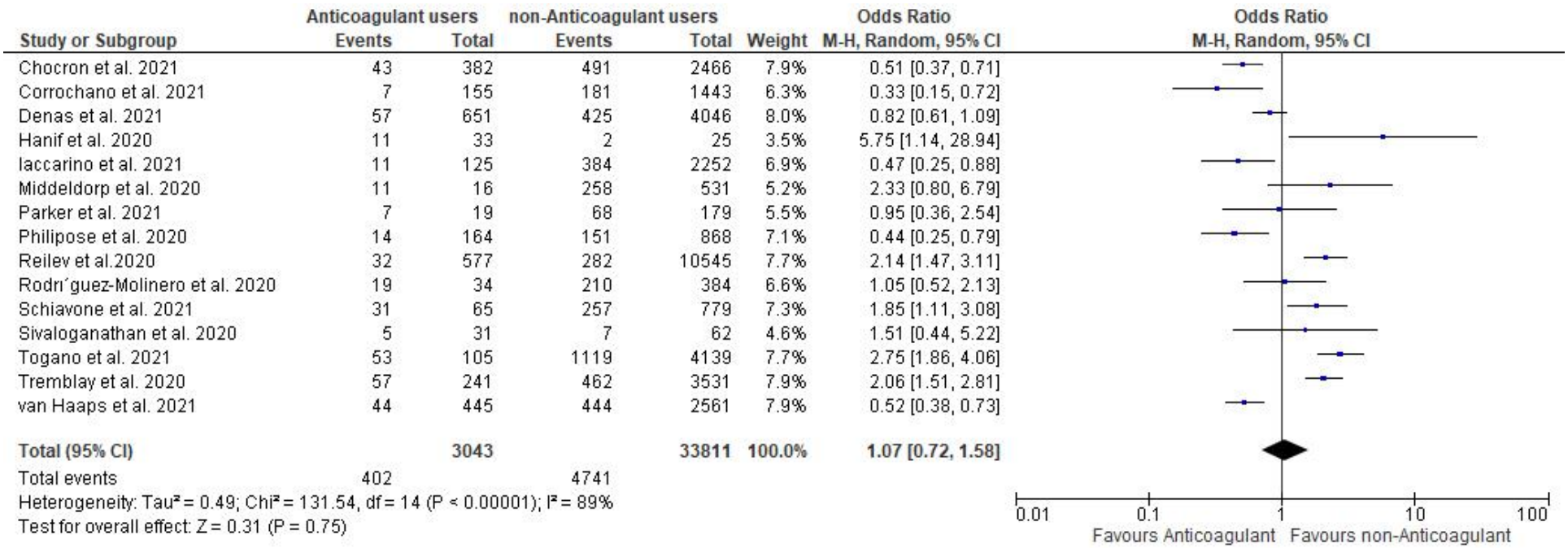
Study or Subgroup	Anticoagulant Events	Anticoagulant Total	non-Anticoagulant Events	non-Anticoagulant Total	Weight	Odds Ratio M-H, Random, 95% CI
Aslan et al. 2021	34	79	363	1631	17.5%	2.64 [1.67, 4.18]
Flam et al. 2020	40	103703	14	36875	16.4%	1.02 [0.55, 1.87]
Fröhlich et al. 2021	50	508	599	4824	18.4%	0.77 [0.57, 1.04]
Lodigiani et al. 2020	2	17	59	355	9.6%	0.67 [0.15, 3.00]
Russo et al. 2021	17	54	181	380	16.4%	0.51 [0.27, 0.93]
Ruzhentsova et al. 2021	0	26	5	50	4.0%	0.16 [0.01, 2.94]
Spiegelenberg et al. 2021	44	98	193	964	17.7%	3.26 [2.12, 4.99]
Total (95% CI)		**104485**		**45079**	**100.0%**	**1.12 [0.58, 2.15]**
Total events	187		1414			

Heterogeneity: Tau² = 0.58; Chi² = 51.19, df = 6 (P < 0.00001); I² = 88%

Test for overall effect: Z = 0.33 (P = 0.74)



C



Supplementary Figure 4 Unadjusted Sub-group analysis for disease severity in prehospital use of Vitamin K Antagonists and Direct Oral Anticoagulants versus control cohort in COVID-19. A: Unadjusted Severity in prehospital use of Vitamin K Antagonists versus control cohort; B: Unadjusted Severity in prehospital use of Direct Oral Anticoagulants versus control cohort; C: Unadjusted Severity in prehospital use of any Anticoagulants versus control cohort.

Supplementary Table 1 Detailed search strategy

Electronic database	Detailed search strategy
WHO Global research on coronavirus disease (COVID-19)	tw:((anticoagulants OR vitamin K antagonist OR VKA OR warfarin OR direct oral anticoagulants OR DOAC dabigatran OR rivaroxaban OR apixaban OR edoxaban OR warfarin OR heparin) AND (preadmission OR prehospital OR prior OR chronic OR premorbid))
LitCovid PubMed Database	(anticoagulants OR vitamin k antagonist OR VKA OR warfarin OR direct oral anticoagulants OR

	DOAC dabigatran OR rivaroxaban OR apixaban OR edoxaban OR warfarin OR heparin) AND (preadmission OR prehospital OR prior OR chronic OR premorbid)
Scopus	(COVID-19 OR SARS-CoV-2 OR corona virus) AND (anticoagulants OR vitamin k antagonist OR VKA OR warfarin OR direct oral anticoagulants OR DOAC dabigatran OR rivaroxaban OR apixaban OR edoxaban OR warfarin OR heparin) AND (preadmission OR prehospital OR prior OR chronic OR premorbid)

Supplementary Table 2 Assessment of methodological quality of the included studies using Newcastle Ottawa scale

Study	**SELECTION**				**Comparability of Cases and Controls on the Basis of the Design or Analysis**	**OUTCOME**			**Quality of evidence**	**risk of bias**
	Representativeness of the exposed cohort	**Selection of the non-exposed cohort**	**Ascertainment of the exposure**	**Outcome status at start of study**		**Assessment of the outcome**	**Length of follow-up**	**Adequacy of follow-up**		
Ageno et al. 2021[30]	*	*	*	*	*	*	*	*	High	Very Low risk of bias
Arachchillage et al. 2021[31]	*	*	*	-	-	*	*	*	Fair	Unclear risk of bias (not enough information to make a clear judgement)
Aslan et al. 2021[57]	*	*	*	-	*	*	*	*	Good	Low risk of bias but have some potential flaws

Bauer et al. 2020[72]	*	*	*	*	*	*	*	*	High	Very Low risk of bias
Boari et al. 2020[69]	*	*	*	*	*	*	*	*	High	Very Low risk of bias
Brouns et al 2020[55]	*	-	*	-	-	*	-	-	Poor	High risk of bias
Buenen et al. 2021[42]	*	*	*	-	*	*	*	*	Good	Low risk of bias but have some potential flaws
Chocron et al, 2021[43]	*	*	*	-	-	*	*	*	Fair	Unclear risk of bias (not enough information to make a clear judgement)
Corrochano M 2021[32]	*	*	*	*	*	*	*	*	High	Very Low risk of bias
Covino M 2021[44]	*	*	*	-	-	*	*	*	Fair	Unclear risk of bias (not enough information to make a clear judgement)
Denas G 2021[45]	*	*	*	*	*	*	*	*	High	Very Low risk of bias
Fauvel et	*	*	*	*	*	*	*	*	High	Very Low risk of

al 2020[56]										bias
Flam et al 2020[61]	*	*	*	*	*	*	*	*	High	Very Low risk of bias
Fröhlich et al. 2021[33]	*	*	*	-	*	*	*	*	Good	Low risk of bias but have some potential flaws
Fumagalli et al. 2021[46]	*	*	*	*	*	*	*	*	High	Very Low risk of bias
Gülcü et al. 2021[34]	*	*	*	-	*	*	*	*	Good	Low risk of bias but have some potential flaws
Hanif et al. 2020[35]	*	*	*	-	-	*	*	*	Fair	Unclear risk of bias (not enough information to make a clear judgement)
Harrison et al 2021[36]	*	*	*	*	*	*	*	*	High	Very Low risk of bias
Ho et al. 2021[47]	*	*	*	-	*	*	*	*	Good	Low risk of bias but have some potential flaws
Hozayen et al.	*	*	*	-	-	*	*	*	Fair	Unclear risk of bias (not enough

2021[37]										information to make a clear judgement)
Iaccarino et al. 2021[73]	*	*	*	*	*	*	*	*	High	Very Low risk of bias
Klok et al. 2020[62]	*	*	*	*	*	*	*	*	High	Very Low risk of bias
Li et al. 2020[38]	*	*	*	*	*	*	*	*	High	Very Low risk of bias
Lodigiani et al. 2020[74]	*	*	*	-	*	*	*	*	Good	Low risk of bias but have some potential flaws
Ménager et al. 2020[75]	*	*	*	*	*	*	*	*	High	Very Low risk of bias
Middeldorp et al. 2020[63]	*	*	*	-	-	*	*	*	Fair	Unclear risk of bias (not enough information to make a clear judgement)
Natali et al. 2020[64]	*	*	*	*	*	*	*	*	High	Very Low risk of bias
Olcott et	*	*	*	-	*	*	*	*	Good	Low risk of bias

al. 2021[48]										but have some potential flaws
Parker et al. 2021[49]	*	*	*	-	-	*	*	*	Fair	Unclear risk of bias (not enough information to make a clear judgement)
Philipose et al. 2020[67]	*	*	*	-	*	*	*	*	Good	Low risk of bias but have some potential flaws
Reilev et al.2020[65]	*	*	*	*	*	*	*	*	High	Very Low risk of bias
Rieder et al. 2020[39]	*	*	*	-	*	*	*	*	Good	Low risk of bias but have some potential flaws
Rivera-Caravaca et al. 2020[60]	*	*	*	-	-	*	*	*	Fair	Unclear risk of bias (not enough information to make a clear judgement)
Rivera-Caravaca et al. 2021[40]	*	*	*	*	*	*	*	*	High	Very Low risk of bias

Rodrı´guez-Molinero et al. 2020[68]	*	*	*	*	*	*	*	*	High	Very Low risk of bias
Rossi et al. 2020[59]	*	*	*	-	*	*	*	*	Good	Low risk of bias but have some potential flaws
Russo et al. 2021[50]	*	*	*	-	*	*	*	*	Good	Low risk of bias but have some potential flaws
Ruzhentsova et al. 2021[58]	*	*	*	-	-	*	*	*	Fair	Unclear risk of bias (not enough information to make a clear judgement)
Schiavone et al. 2021[76]	*	*	*	*	*	*	*	*	High	Very Low risk of bias
Sivalogana than et al. 2020[51]	*	*	*	-	*	*	*	*	Good	Low risk of bias but have some potential flaws
Spiegelen berg et al	*	*	*	-	-	*	*	*	Fair	Unclear risk of bias (not enough

2021[52]										information to make a clear judgement)
Tehrani et al. 2021[70]	*	*	*	*	*	*	*	*	High	Very Low risk of bias
Togano et al. 2021[41]	*	*	*	*	*	*	*	*	High	Very Low risk of bias
Tremblay et al. 2020[45]	*	*	*	*	*	*	*	*	High	Very Low risk of bias
van Haaps et al. 2021[53]	*	*	*	-	*	*	*	*	Good	Low risk of bias but have some potential flaws
Wargny et al. 2021[66]	*	*	*	-	-	*	*	*	Fair	Unclear risk of bias (not enough information to make a clear judgement)

Supplementary Table 3 Certainty of the evidence (GRADE) Profile at Outcome Level (Unadjusted)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Subgroup				
Mortality	98 per 1,000	**158 per 1,000** (130 to 191)	**OR 1.72** (1.37 to 2.17)	207292 (36 studies)	⊕⊕◯◯ LOW	Downgraded for retrospective nature of included studies, possible associated confounding, inconsistency in result, and publication bias and upgraded for large magnitude of effect
Mortality - Any anticoagulant	160 per 1,000	**264 per 1,000** (211 to 324)	**OR 1.88** (1.40 to 2.52)	43643 (22 studies)	⊕◯◯◯ Very LOW	Downgraded for retrospective nature of included studies, Undefined Anticoagulant use, possible associated confounding, inconsistency in result, and publication bias and upgraded for large magnitude of effect
Mortality - VKA	155 per 1,000	**259 per 1,000** (180 to 359)	**OR 1.91** (1.20 to 3.06)	19747 (10 studies)	⊕⊕◯◯ LOW	Downgraded for retrospective nature of included studies, possible associated confounding, inconsistency in result, and

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Subgroup				
						publication bias and upgraded for large magnitude of effect
Mortality - DOACs	157 per 1,000	**209 per 1,000** (151 to 283)	**OR 1.42** (0.95 to 2.12)	22374 (14 studies)	⊕⊕◯◯ LOW	Downgraded for retrospective nature of included studies, possible associated confounding, inconsistency in result, and publication bias and upgraded for large magnitude of effect
Severity	78 per 1,000	**84 per 1,000** (62 to 112)	**OR 1.08** (0.78 to 1.49)	186782 (22 studies)	⊕⊕◯◯ LOW	Downgraded for retrospective nature of included studies, possible associated confounding, inconsistency in result, and publication bias and upgraded for large magnitude of effect
Severity - Any anticoagulant	140 per 1,000	**149 per 1,000** (105 to 205)	**OR 1.07** (0.72 to 1.58)	36854 (15 studies)	⊕◯◯◯ Very LOW	Downgraded for retrospective nature of included studies, Undefined Anticoagulant use, possible associated confounding,

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Subgroup				
						inconsistency in result, and publication bias and upgraded for large magnitude of effect
Severity - VKA	158 per 1,000	**191 per 1,000** (97 to 342)	**OR 1.26** (0.57 to 2.77)	6887 (4 studies)	⊕⊕◯◯ LOW	Downgraded for retrospective nature of included studies, possible associated confounding, inconsistency in result, and publication bias and upgraded for large magnitude of effect
Severity - DOACs	31 per 1,000	**35 per 1,000** (18 to 65)	**OR 1.12** (0.58 to 2.15)	149564 (7 studies)	⊕⊕◯◯ LOW	Downgraded for retrospective nature of included studies, possible associated confounding, inconsistency in result, and publication bias and upgraded for large magnitude of effect
Thrombotic events	22 per 1,000	**15 per 1,000** (5 to 44)	**OR 0.67** (0.22 to 2.07)	43851 (9 studies)	⊕⊕◯◯ LOW	Downgraded for retrospective nature of included studies, possible associated confounding,

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Subgroup				
						inconsistency in result, and publication bias and upgraded for large magnitude of effect
Thrombotic events - Any anticoagulant	18 per 1,000	**19 per 1,000** (5 to 70)	**OR 1.03** (0.26 to 4.08)	40960 (6 studies)	⊕⊕◯◯ Low	Downgraded for retrospective nature of included studies, Undefined Anticoagulant use, possible associated confounding, inconsistency in result, and publication bias and upgraded for large magnitude of effect
Thrombotic events - VKA	81 per 1,000	**27 per 1,000** (4 to 148)	**OR 0.32** (0.05 to 1.98)	2658 (3 studies)	⊕⊕◯◯ Low	Downgraded for retrospective nature of included studies, possible associated confounding, inconsistency in result, and publication bias and upgraded for large magnitude of effect
Thrombotic events - DOAC	81 per 1,000	**31 per 1,000** (9 to 99)	**OR 0.36** (0.10 to 1.25)	2699 (3 studies)	⊕⊕◯◯ LOW	Downgraded for retrospective nature of included studies,

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Subgroup				
						possible associated confounding, inconsistency in result, and publication bias and upgraded for large magnitude of effect

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; O**R:** Odds ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.