Anticoagulant treatment for isolated distal deep vein thrombosis: a systematic review and meta-analysis

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SUPPLEMENTARY MATERIALS

Complete references list of studies included in the analysis

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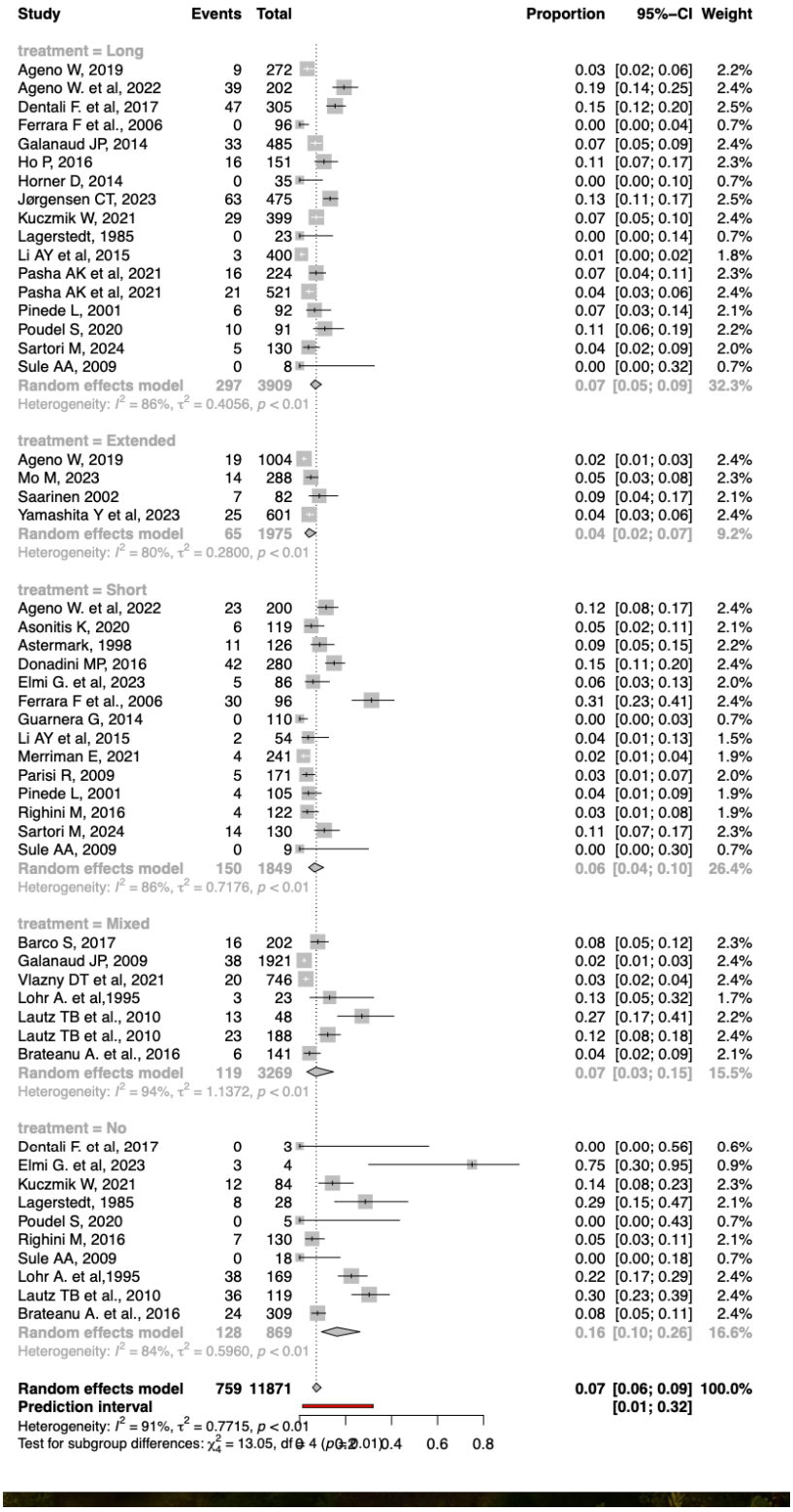
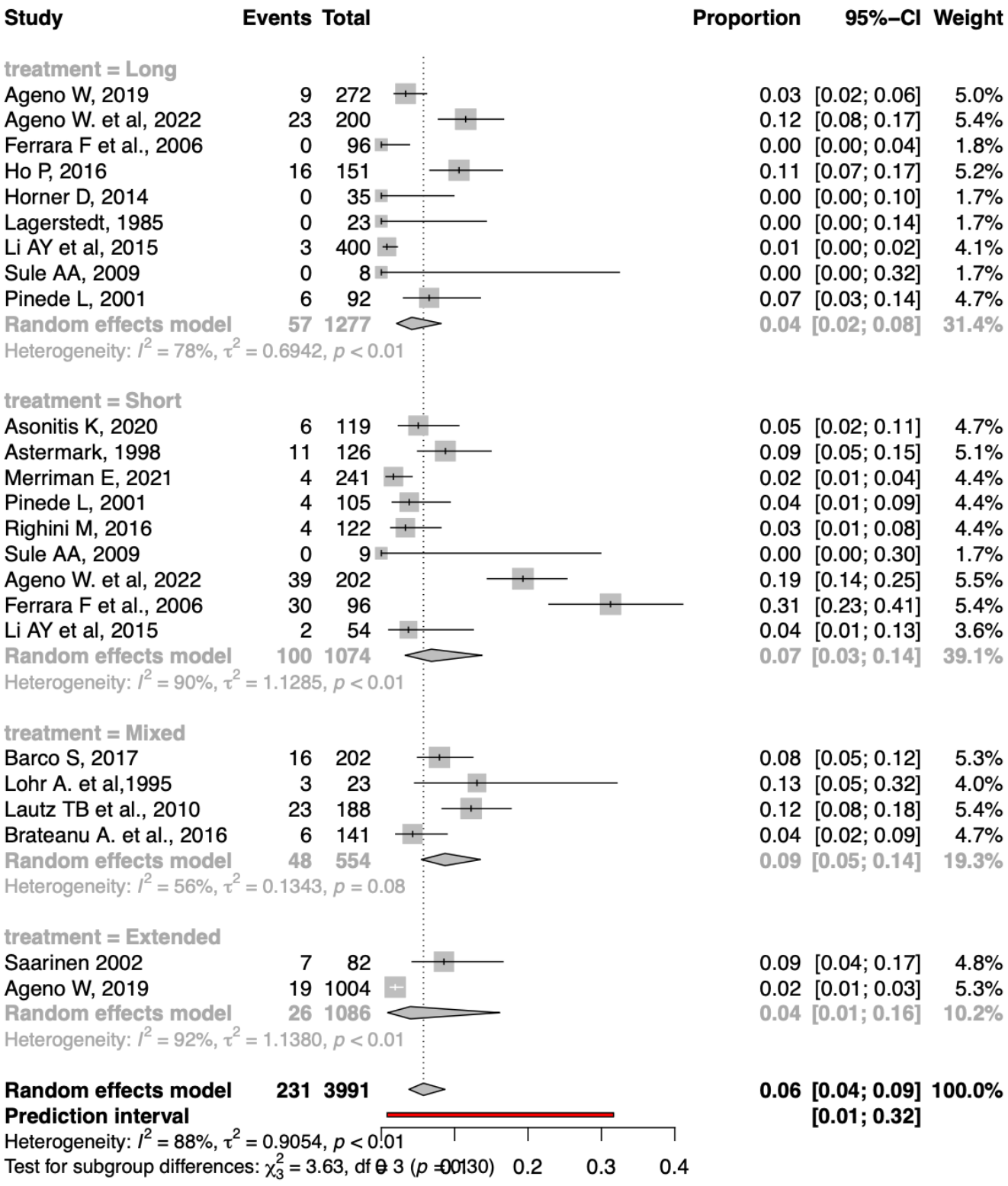
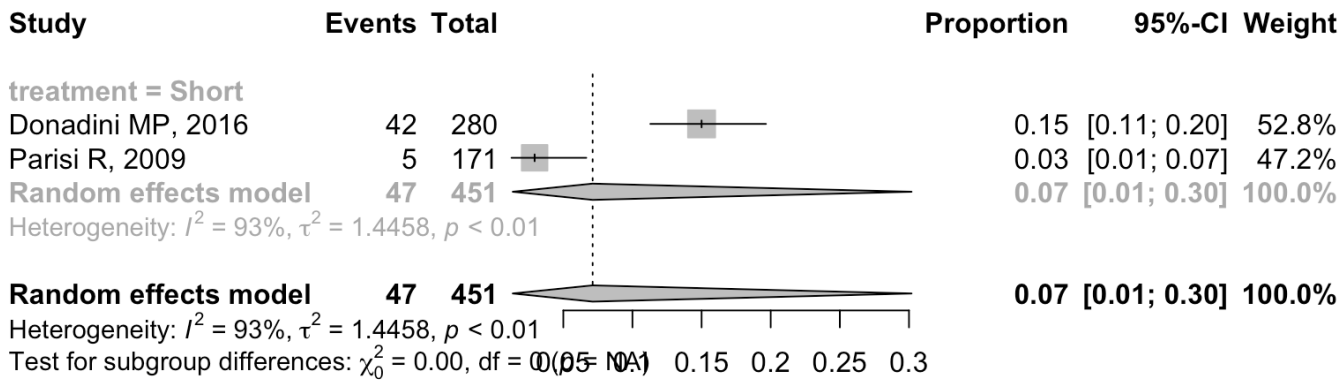
Supplementary Figure 1. Recurrent deep vein thrombosis sorted by the duration of anticoagulation



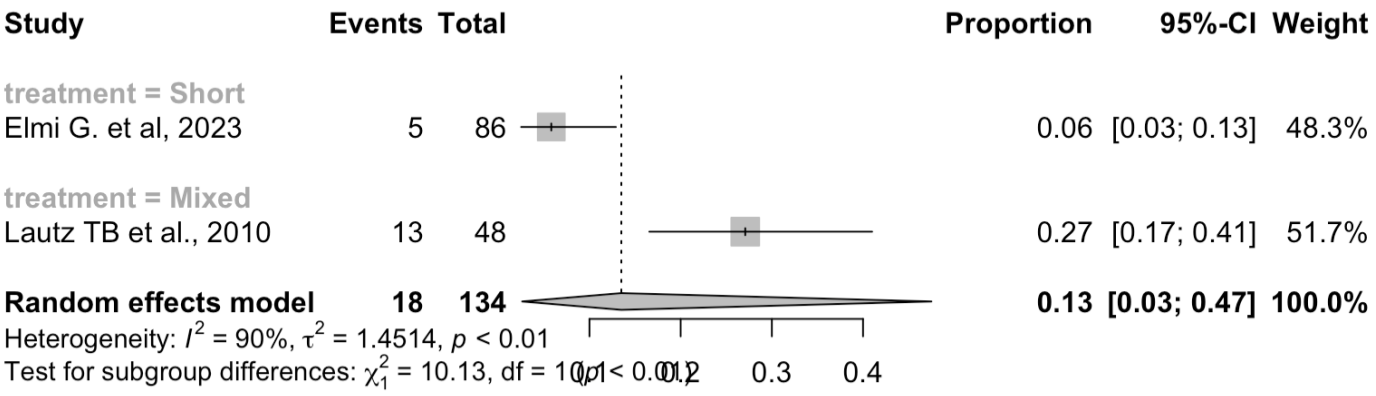
Supplementary Figure 2. Recurrent deep vein thrombosis in patients receiving therapeutic dose of anticoagulation, sorted by the duration of anticoagulation



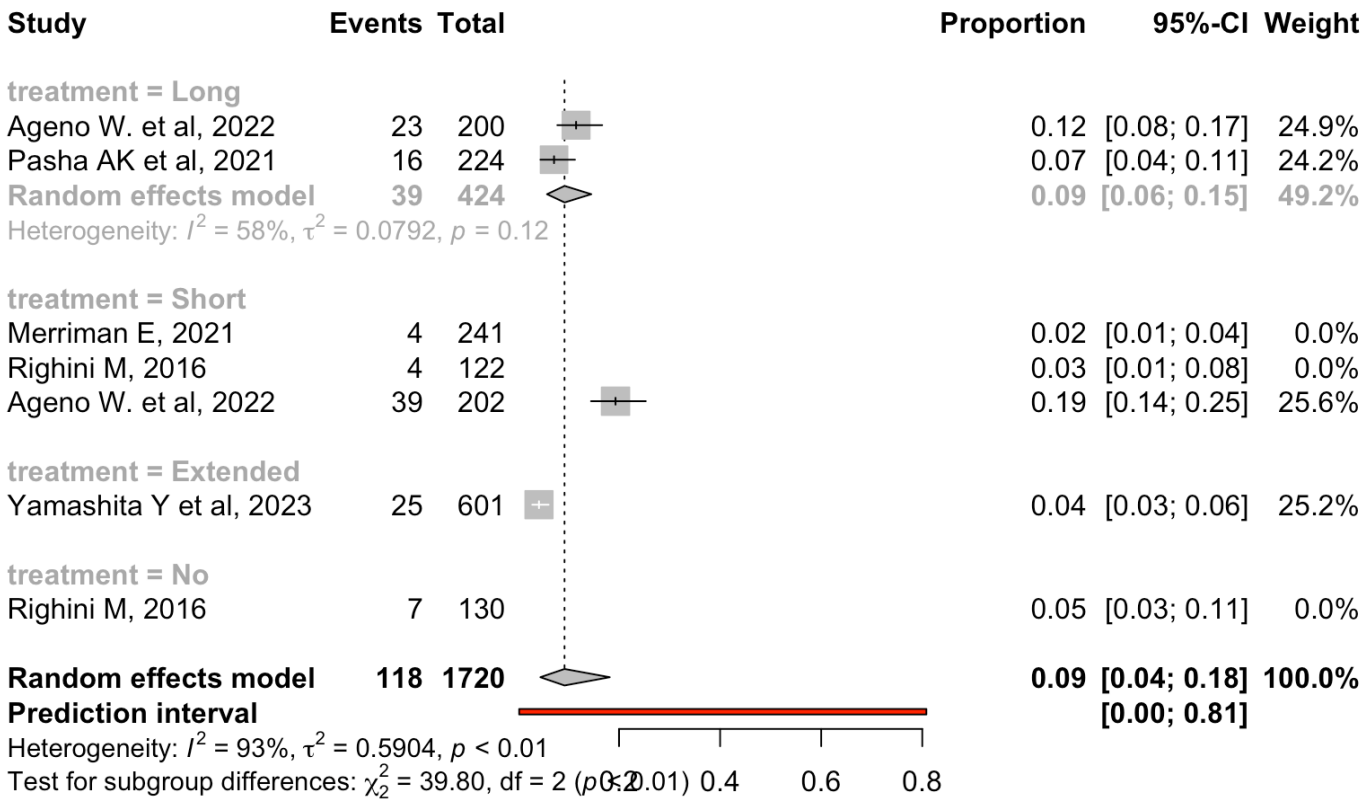
Supplementary Figure 3. Recurrent deep vein thrombosis in patients receiving intermediate dose of anticoagulation, sorted by the duration of anticoagulation



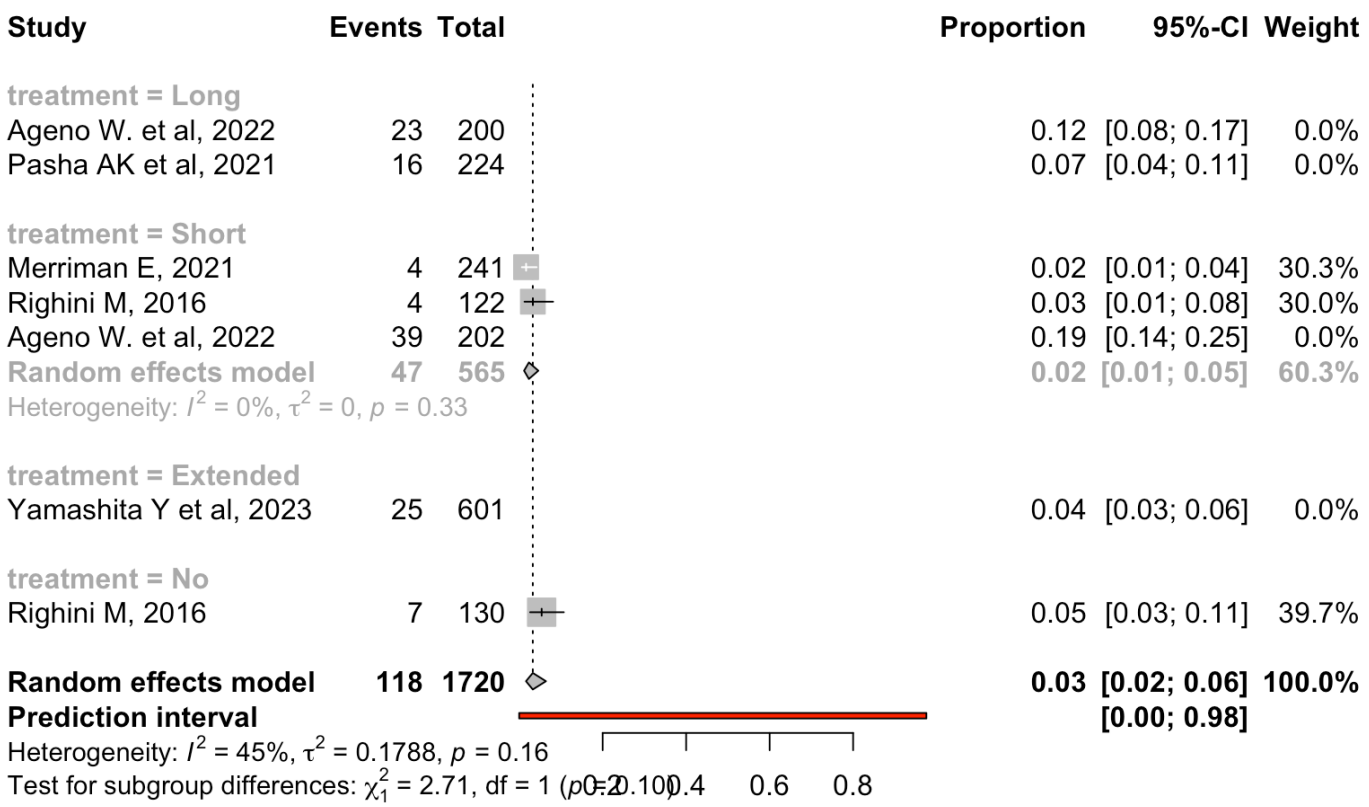
Supplementary Figure 4. Recurrent deep vein thrombosis in patients receiving prophylactic dose of anticoagulation, sorted by the duration of anticoagulation



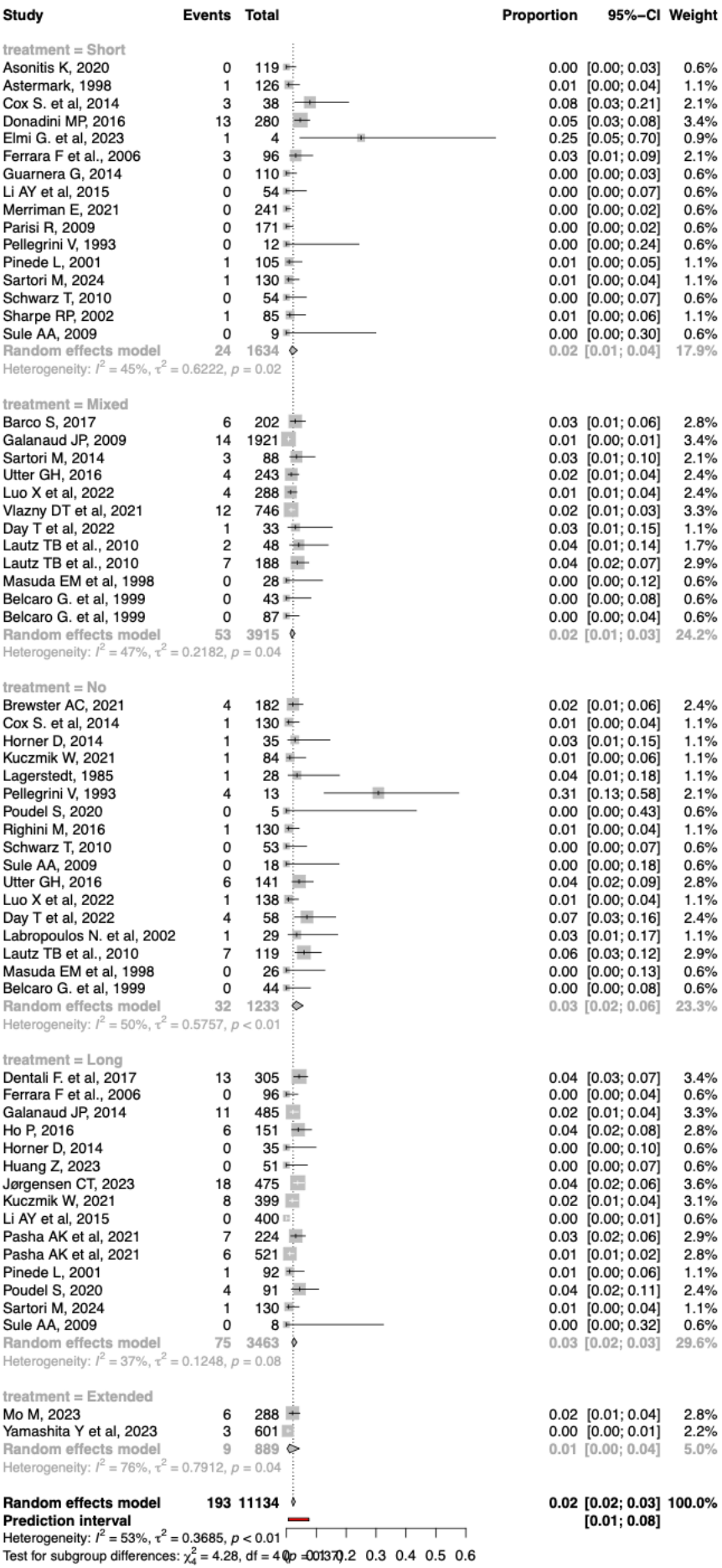
Supplementary Figure 5. Recurrent deep vein thrombosis in high-risk patients, sorted by the duration of anticoagulation



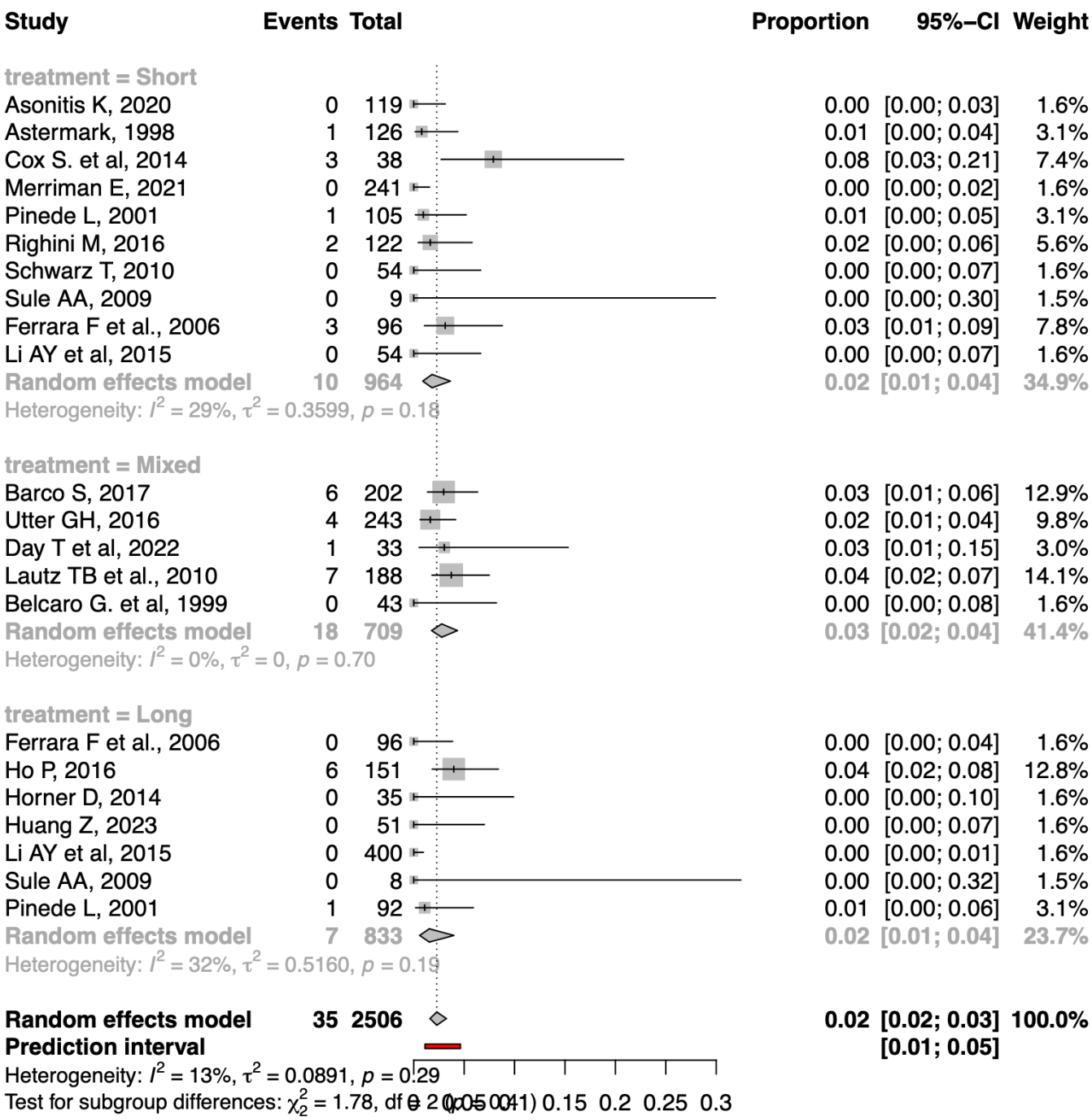
Supplementary Figure 6. Recurrent deep vein thrombosis in low-risk patients, sorted by the duration of anticoagulation



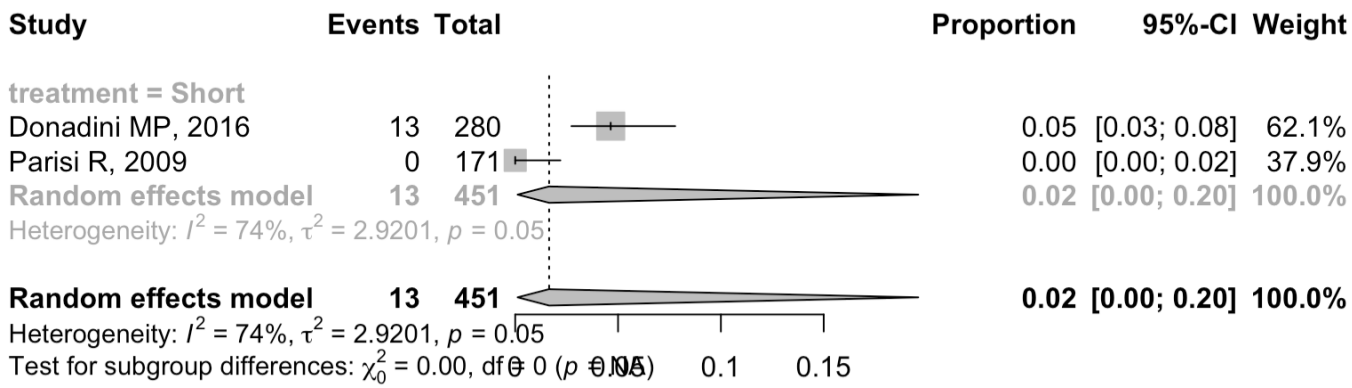
Supplementary Figure 7. Pulmonary embolism sorted by the duration of anticoagulation



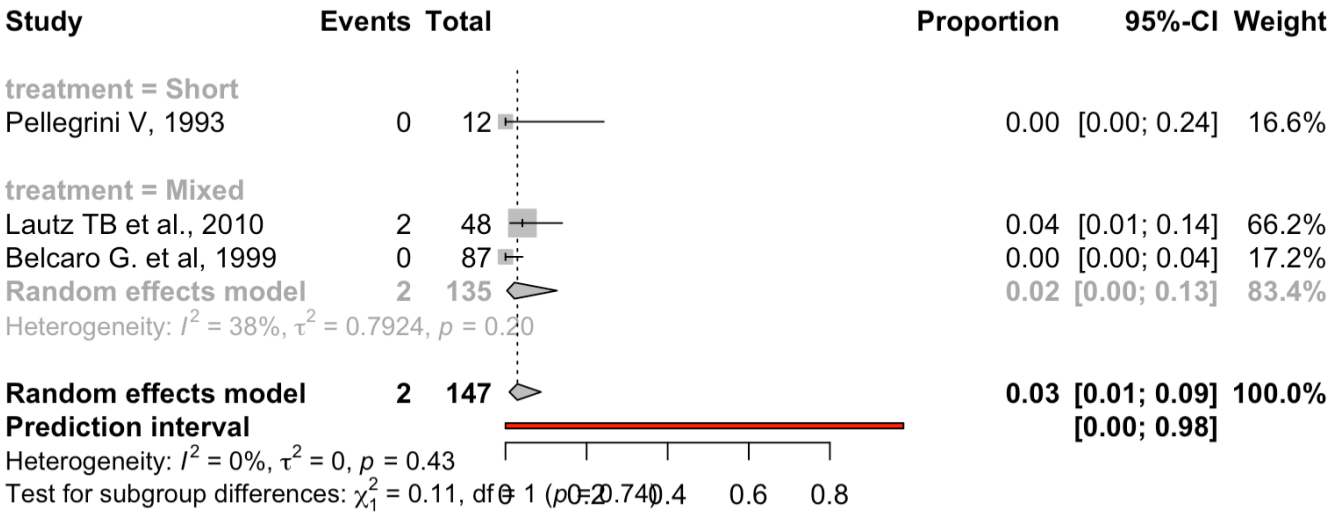
Supplementary Figure 8. Pulmonary embolism in patients receiving therapeutic dose of anticoagulation, sorted by the duration of anticoagulation



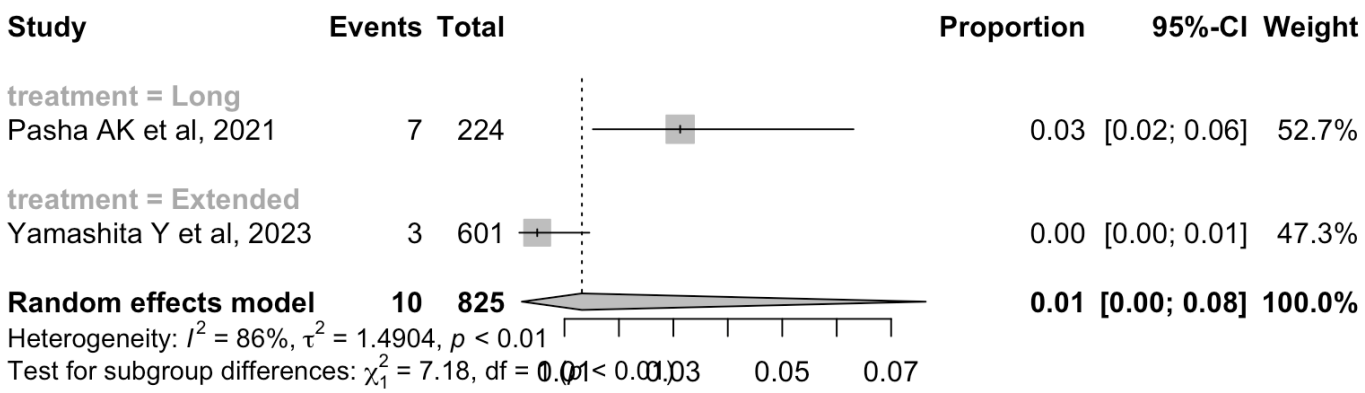
Supplementary Figure 9. Pulmonary embolism in patients receiving intermediate dose of anticoagulation, sorted by the duration of anticoagulation



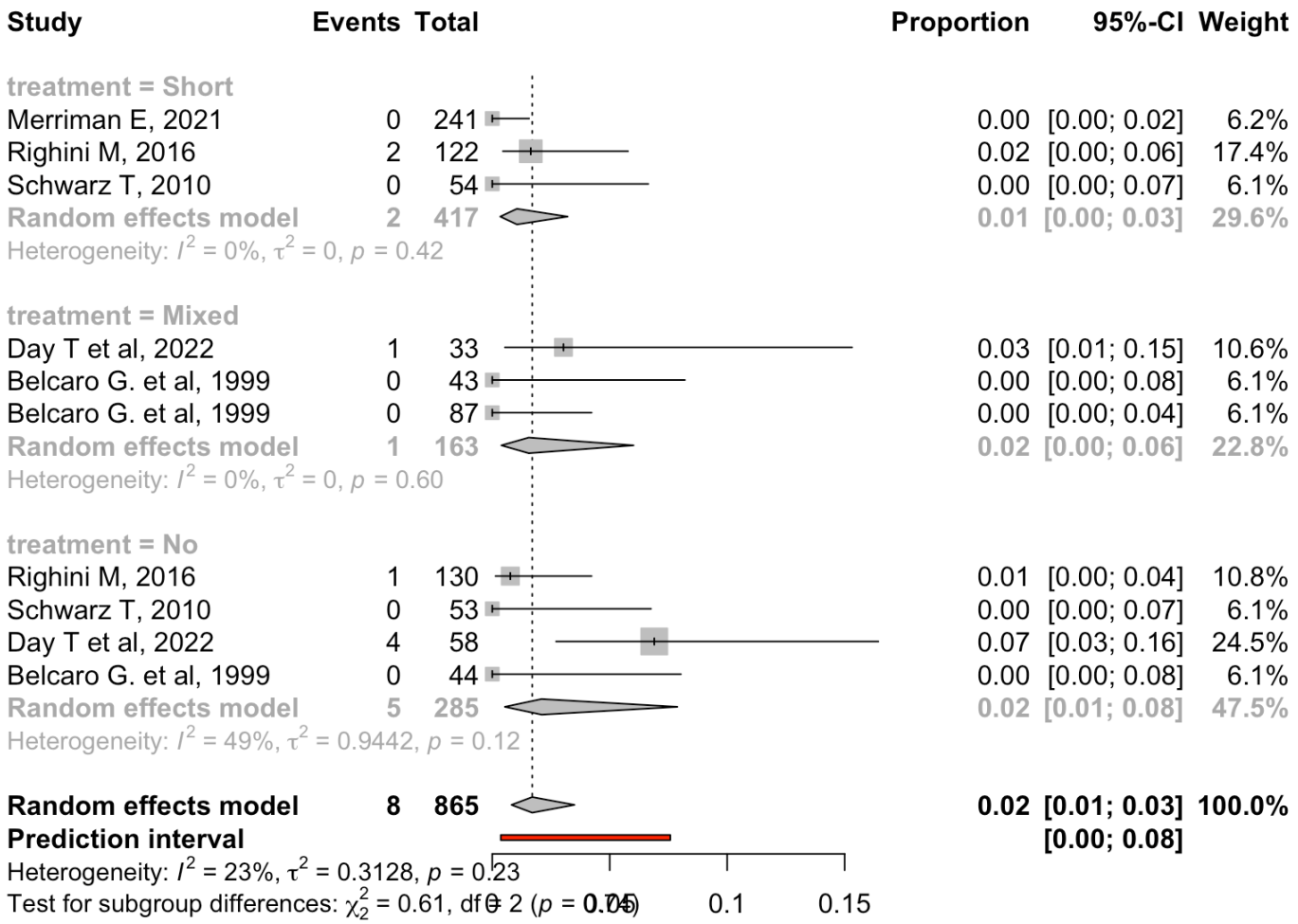
Supplementary Figure 10. Pulmonary embolism in patients receiving prophylactic dose of anticoagulation, sorted by the duration of anticoagulation



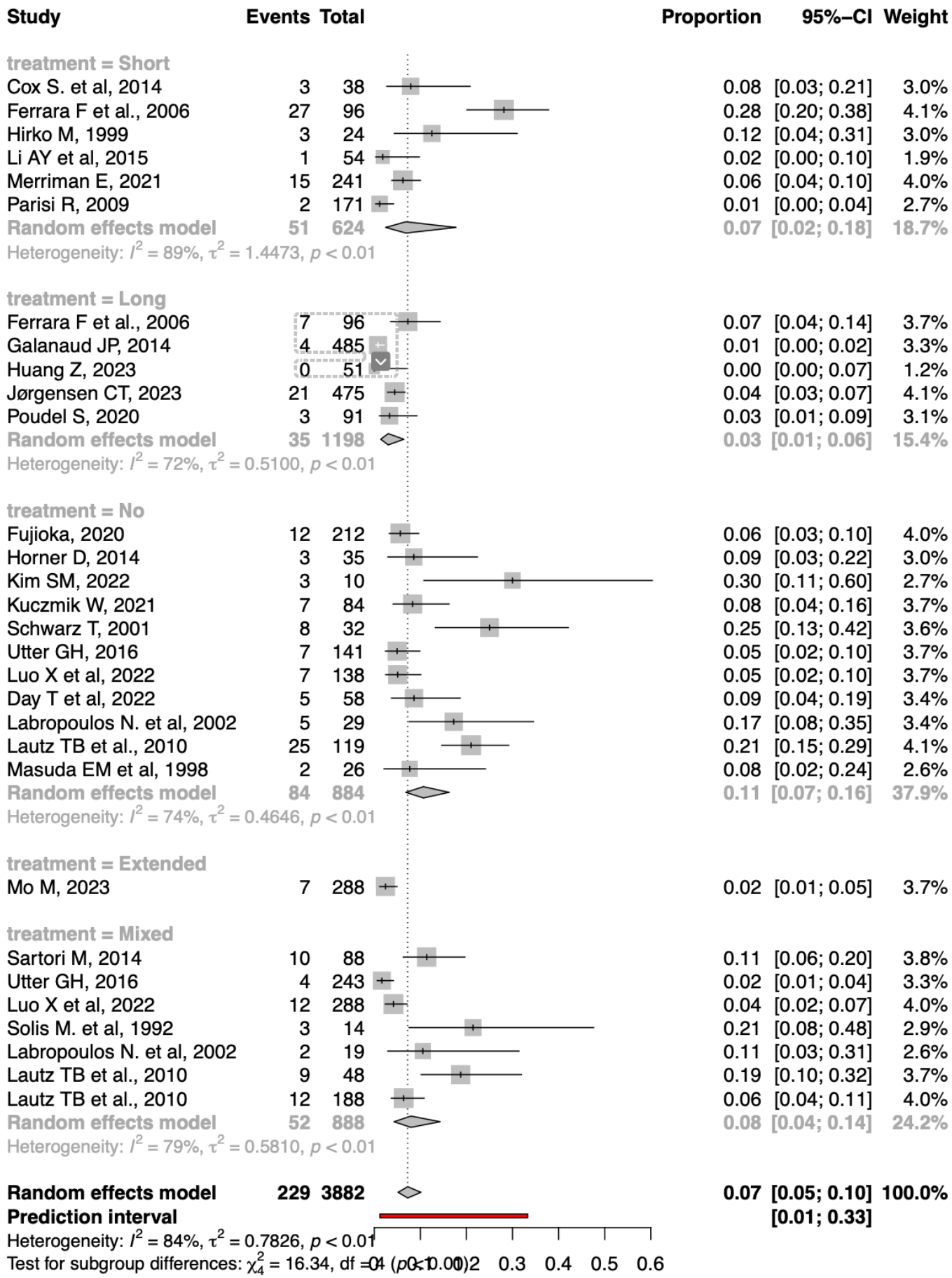
Supplementary Figure 11. Pulmonary embolism in high-risk patients, sorted by the duration of anticoagulation



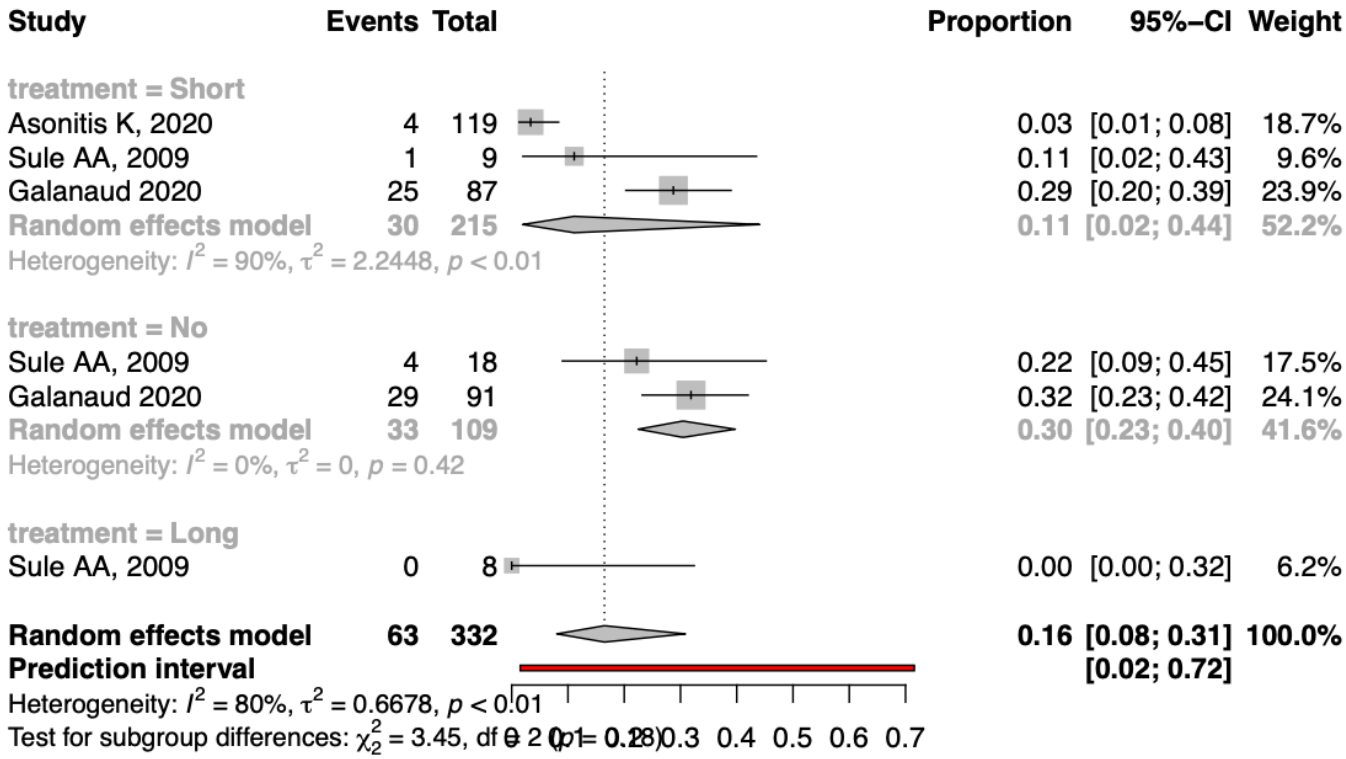
Supplementary Figure 12. Pulmonary embolism in low-risk patients, sorted by the duration of anticoagulation



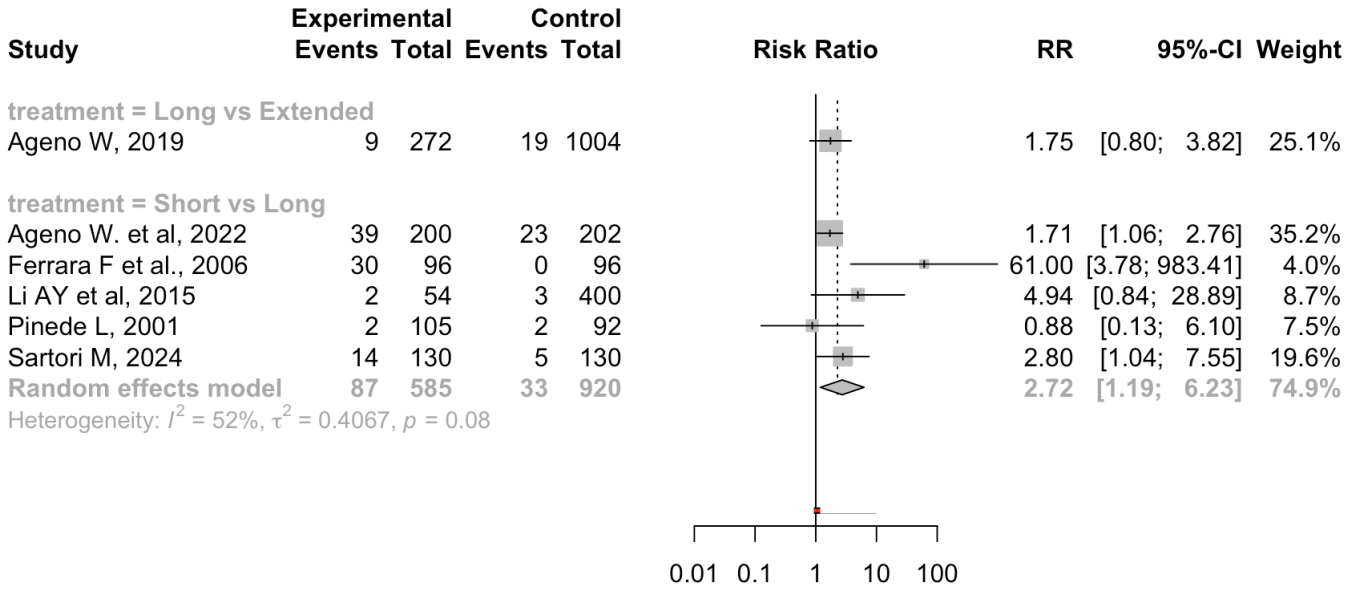
Supplementary Figure 13. Proximal progression of thrombosis sorted by the duration of anticoagulation



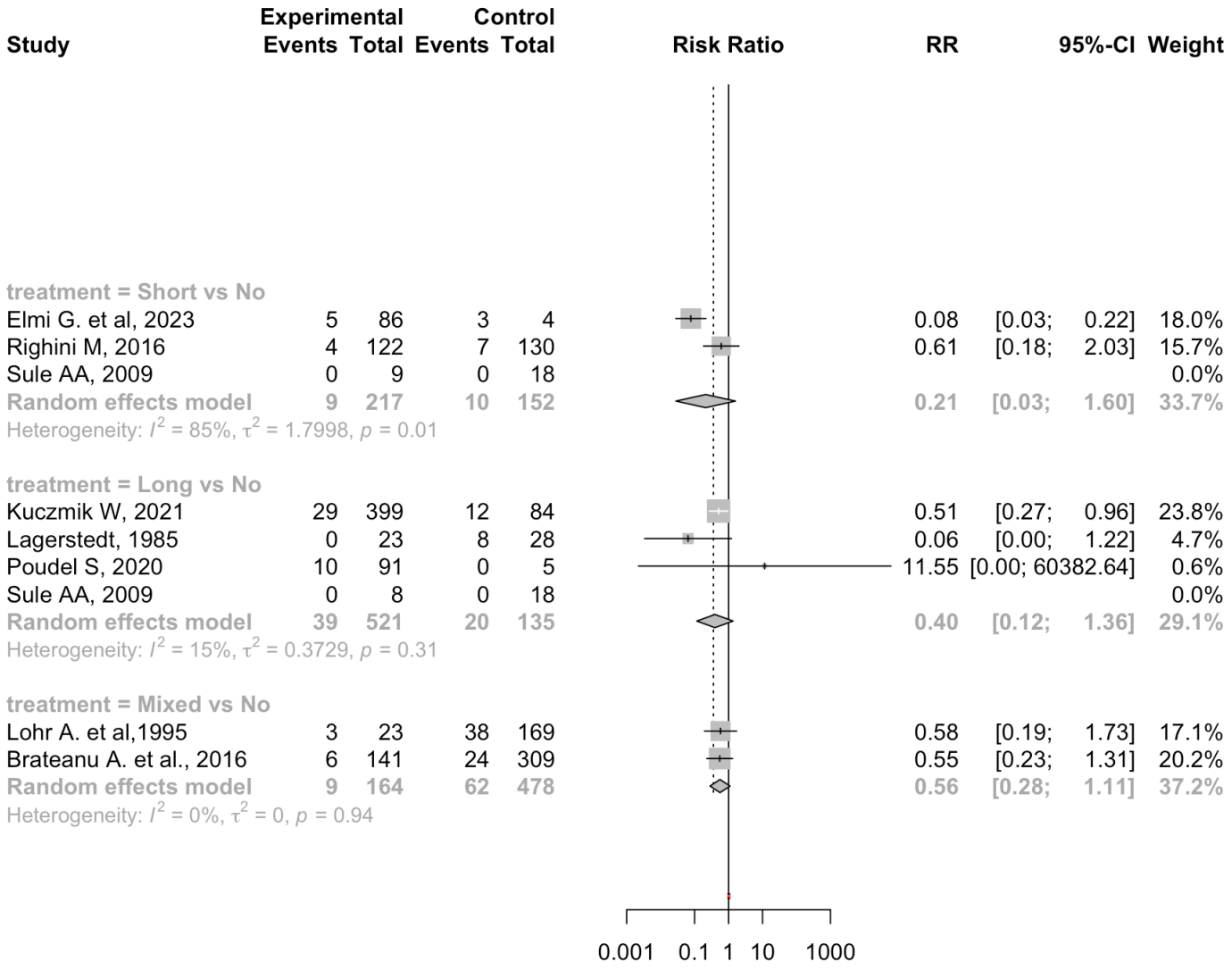
Supplementary Figure 14. Post-thrombotic syndrome sorted by the duration of anticoagulation



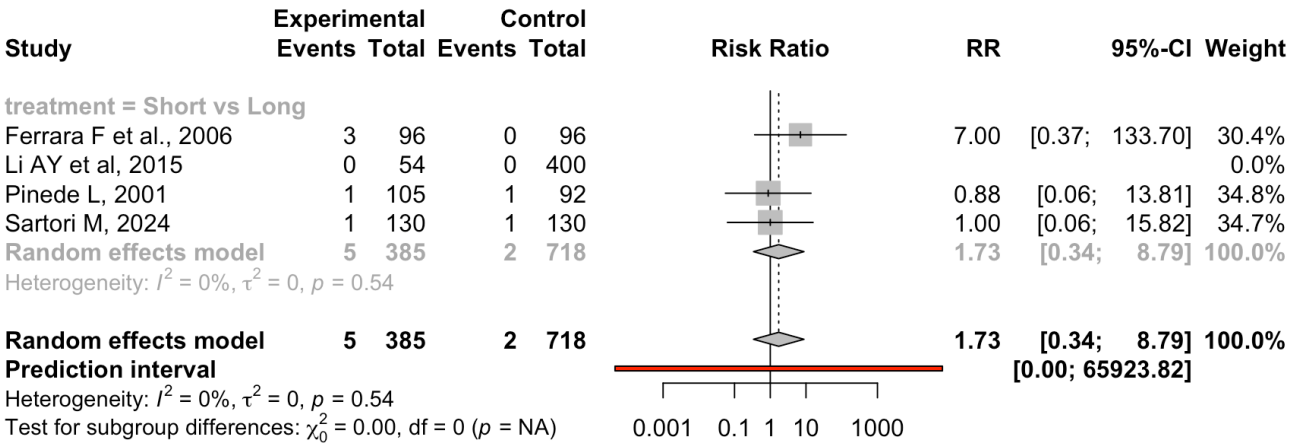
Supplementary Figure 15. Recurrent deep vein thrombosis in patients receiving different duration of anticoagulation



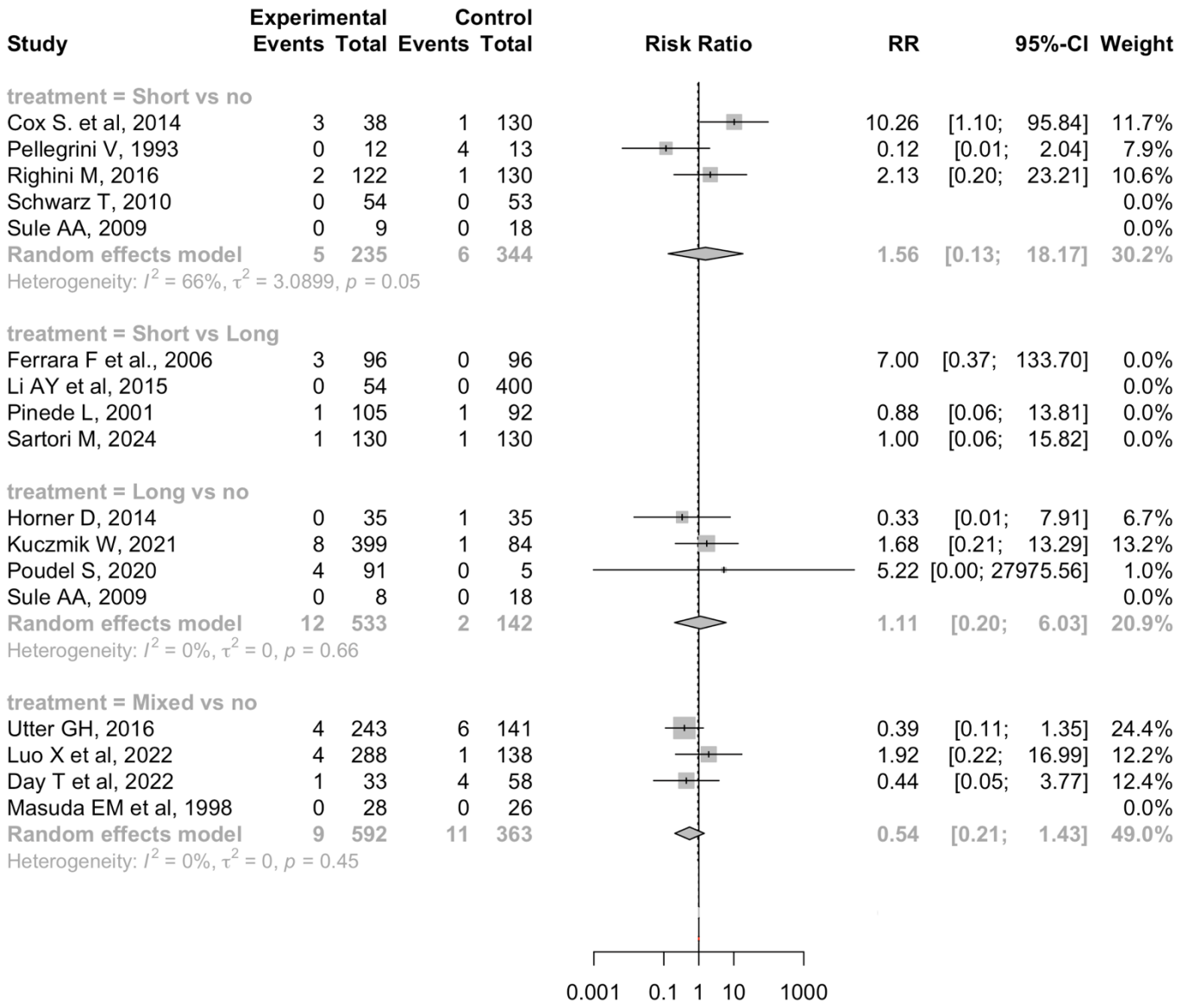
Supplementary Figure 16. Recurrent deep vein thrombosis in patients receiving or not anticoagulation, sorted by the duration of anticoagulation



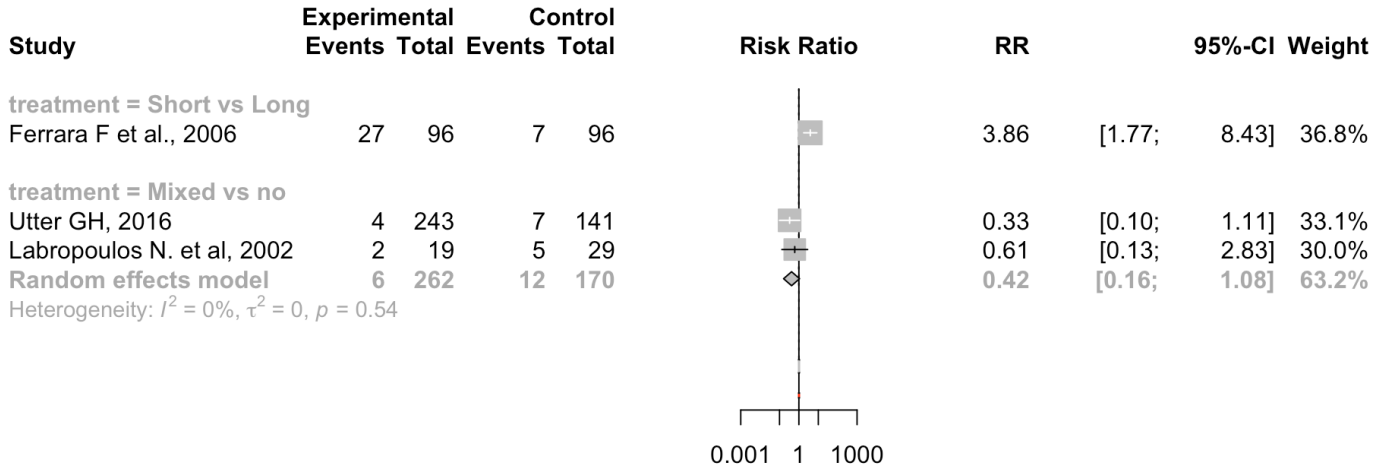
Supplementary Figure 17. Pulmonary embolism in patients receiving different duration of anticoagulation



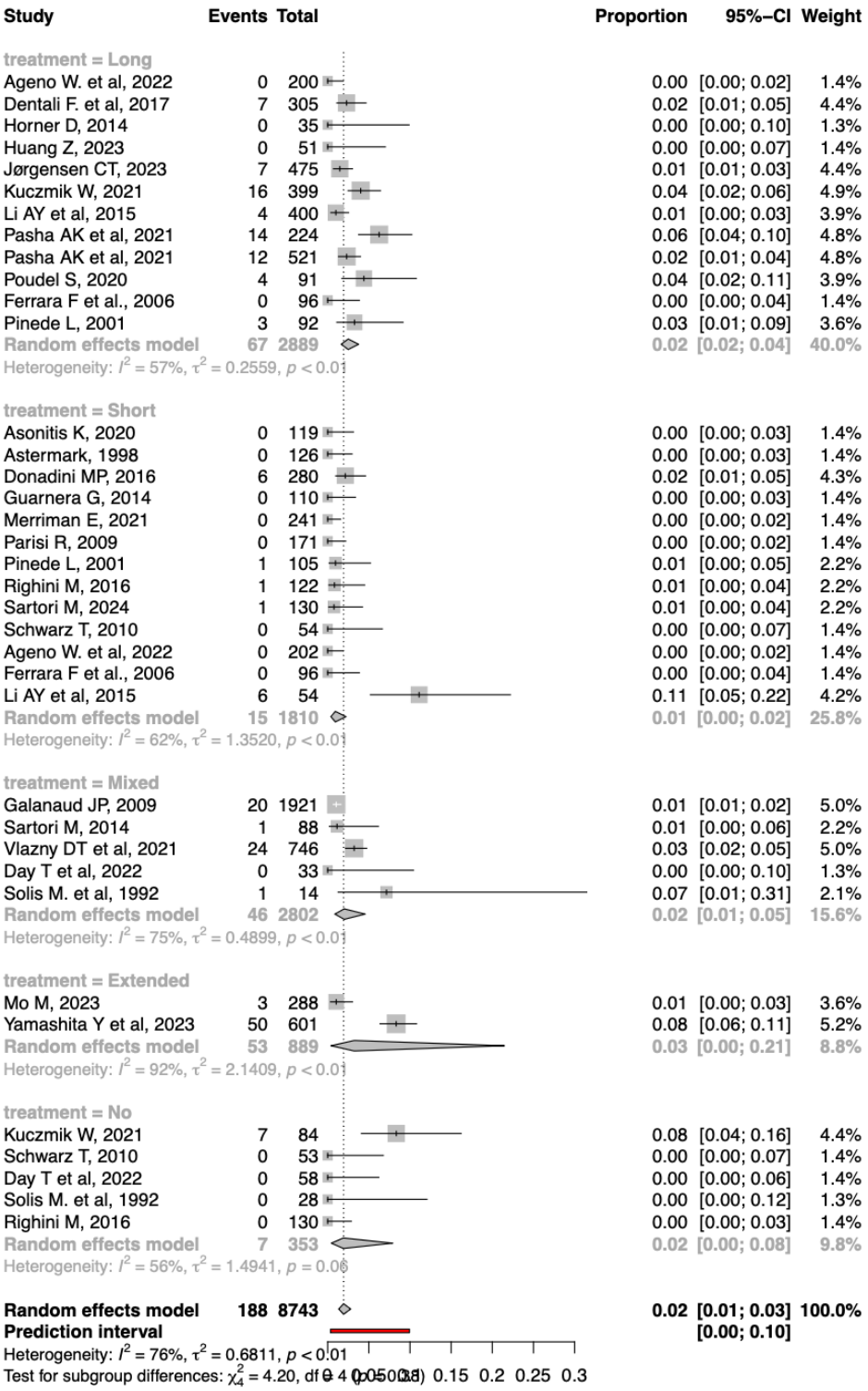
Supplementary Figure 18. Pulmonary embolism in patients receiving or not anticoagulation, sorted by the duration of anticoagulation



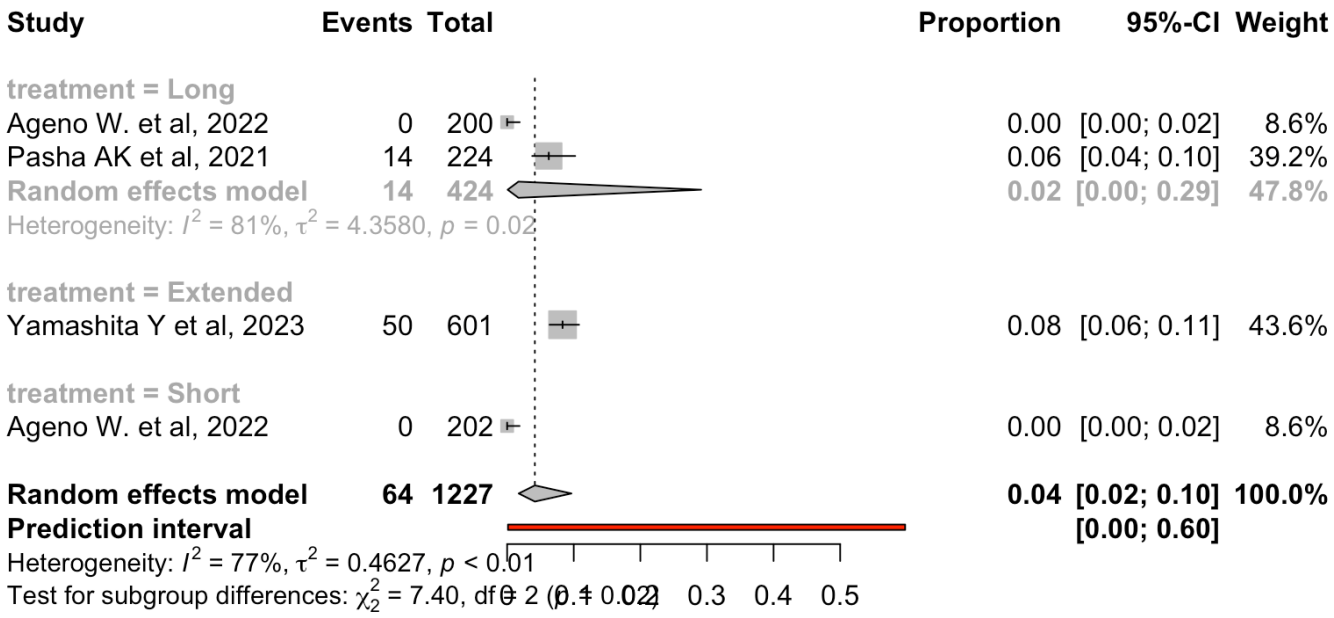
Supplementary Figure 19. Proximal progression of thrombosis in patients receiving different regimens of anticoagulation



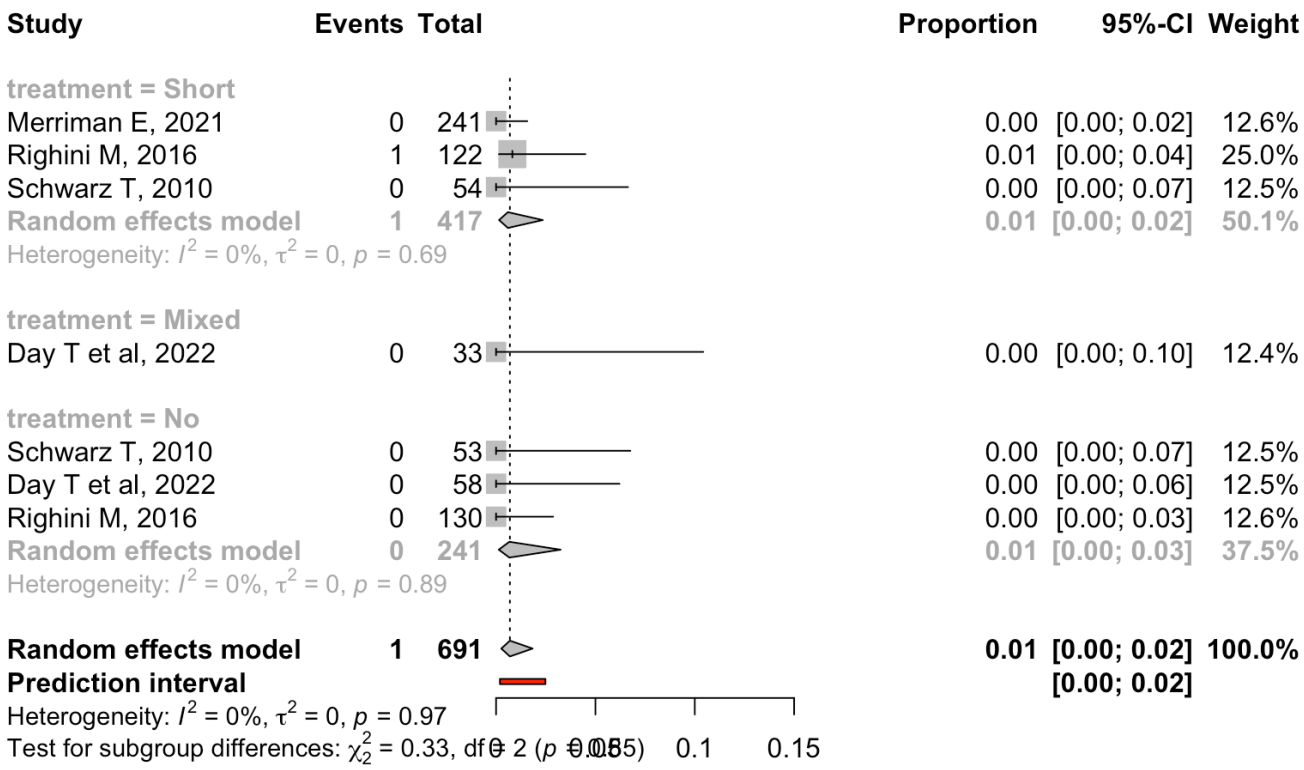
Supplementary Figure 20. Major bleeding sorted by the duration of anticoagulation



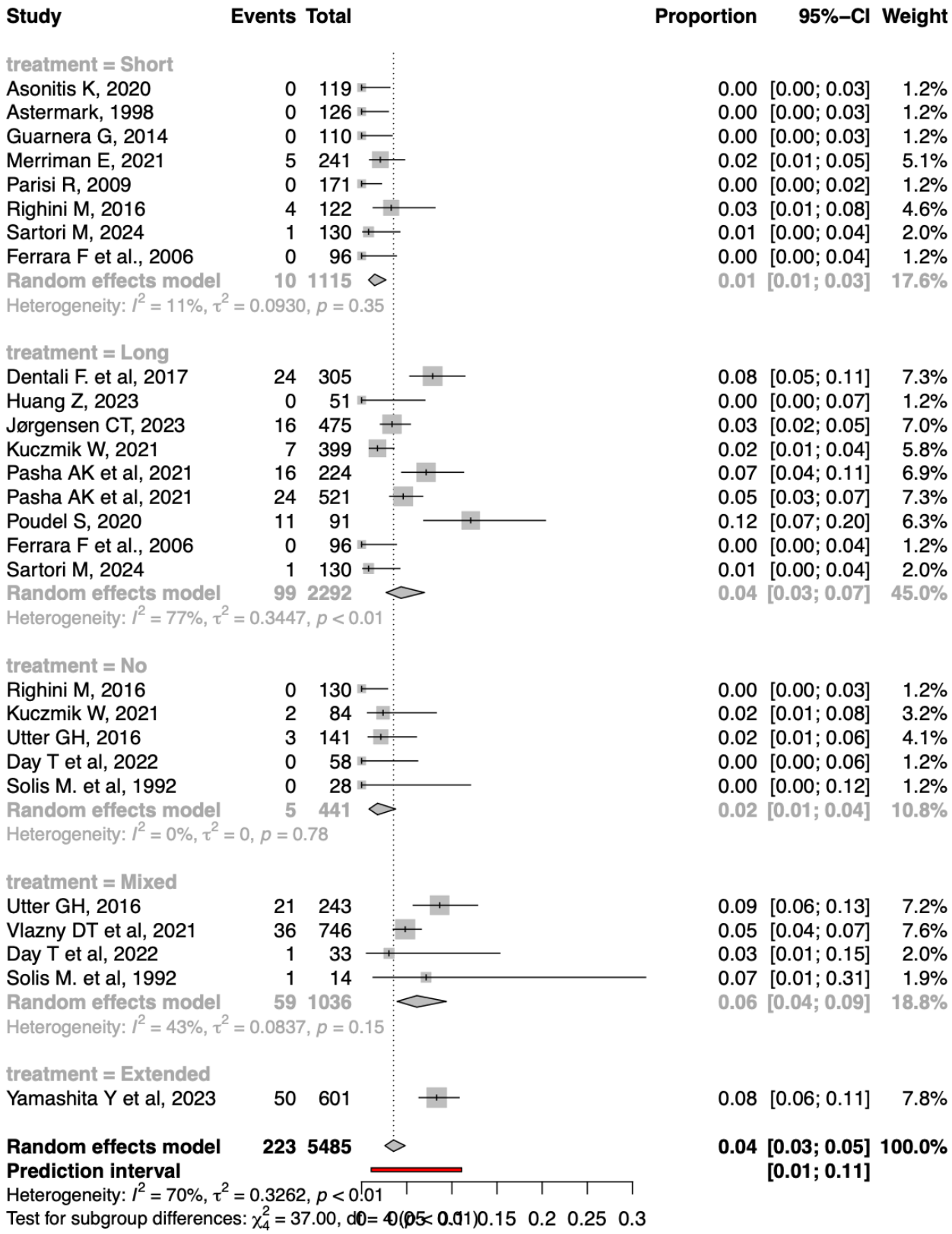
Supplementary Figure 21. Major bleeding in high-risk patients, sorted by the duration of anticoagulation



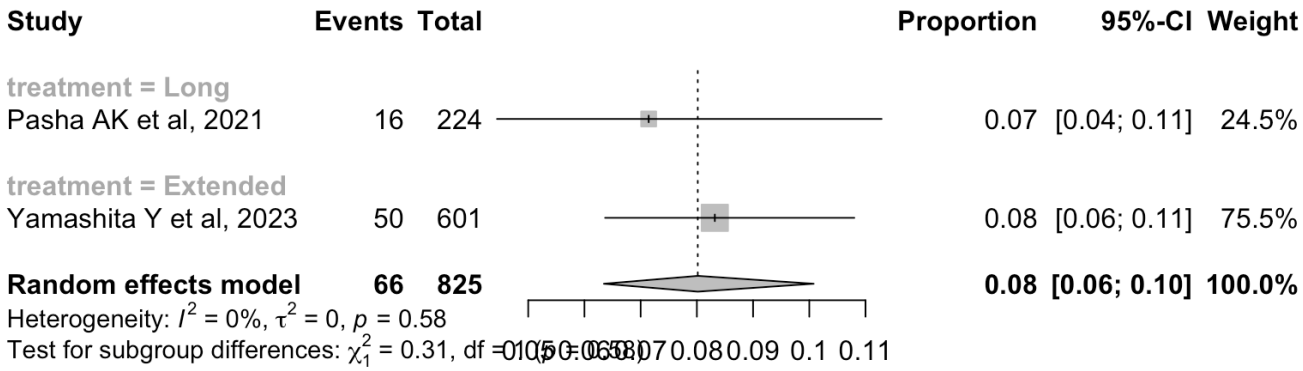
Supplementary Figure 22. Major bleeding in low-risk patients, sorted by the duration of anticoagulation



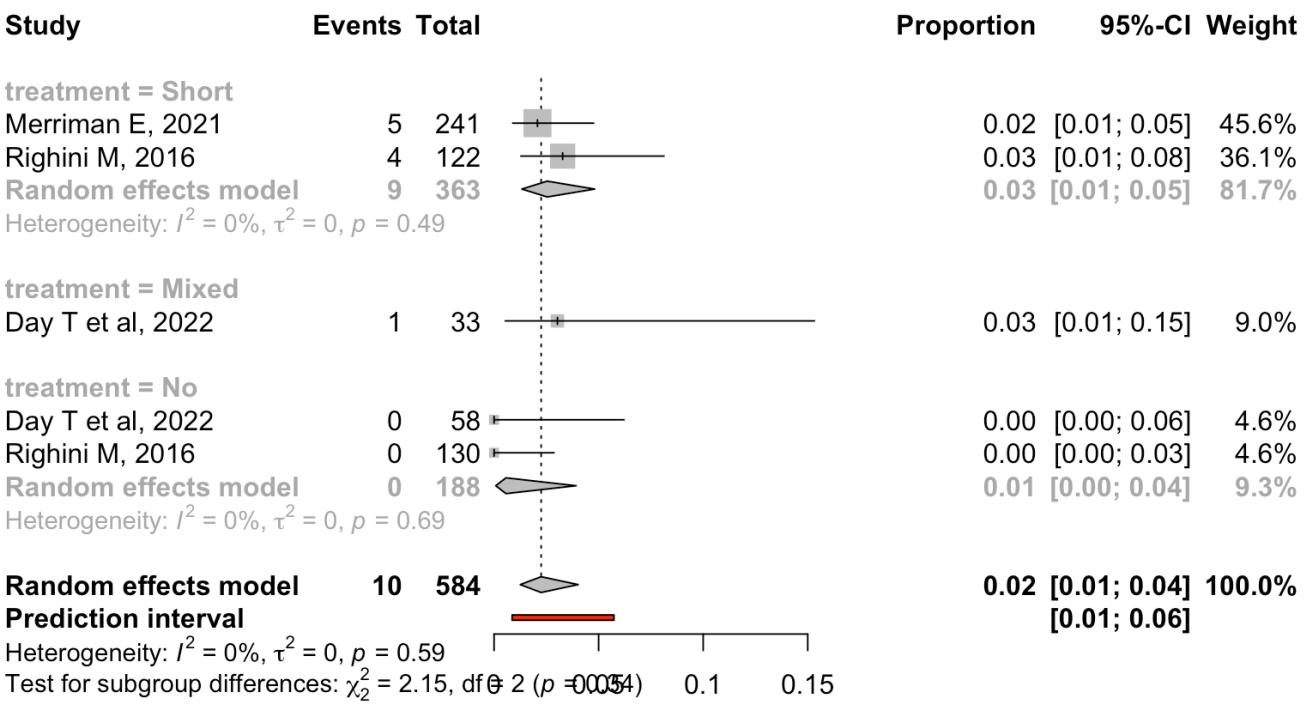
Supplementary Figure 23. Clinically relevant non-major bleeding events sorted by the duration of anticoagulation



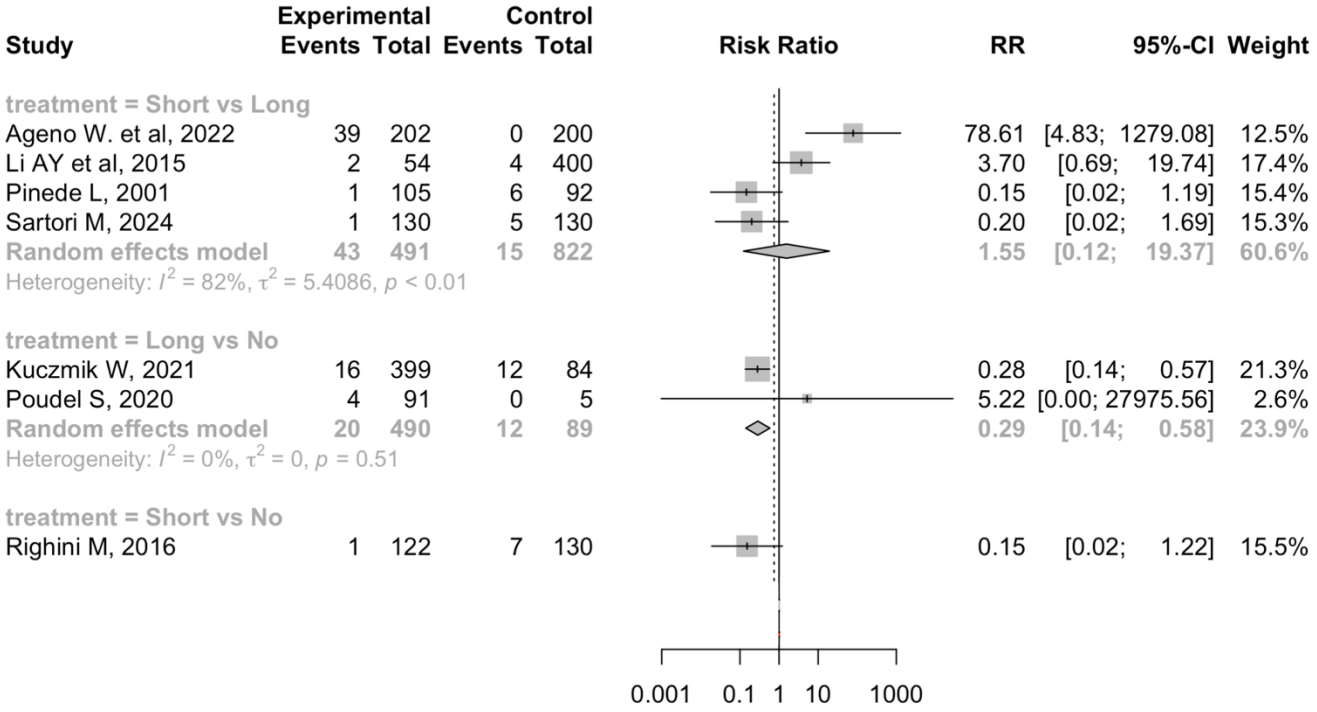
Supplementary Figure 24. Clinically relevant non-major bleeding in high-risk patients, sorted by the duration of anticoagulation



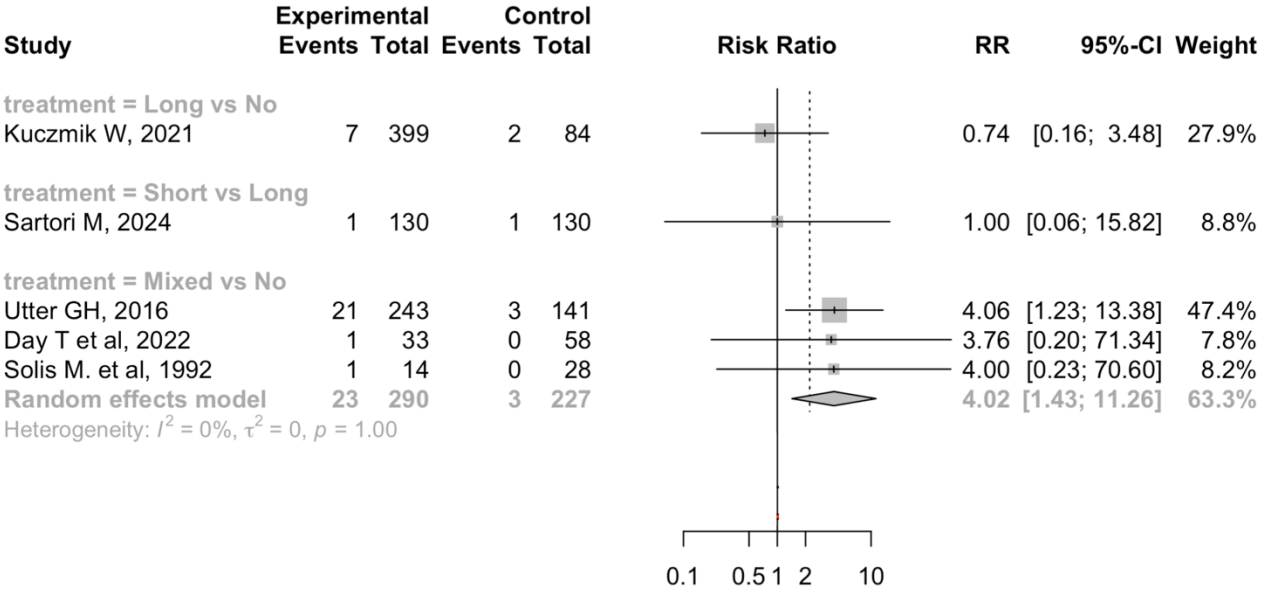
Supplementary Figure 25. Clinically relevant non-major bleeding in low-risk patients, sorted by the duration of anticoagulation



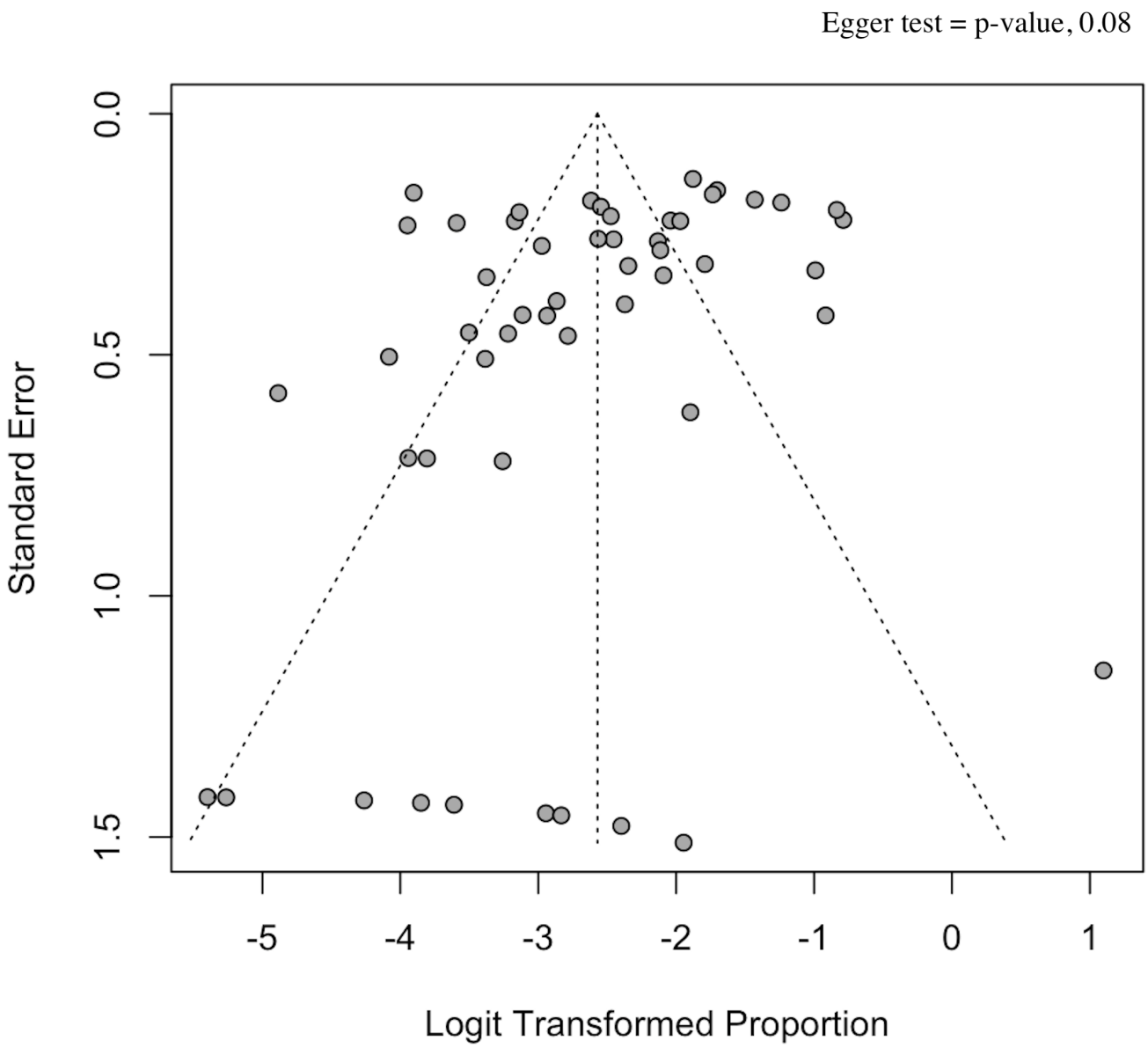
Supplementary Figure 26. Major bleeding in patients receiving different regimens of anticoagulation



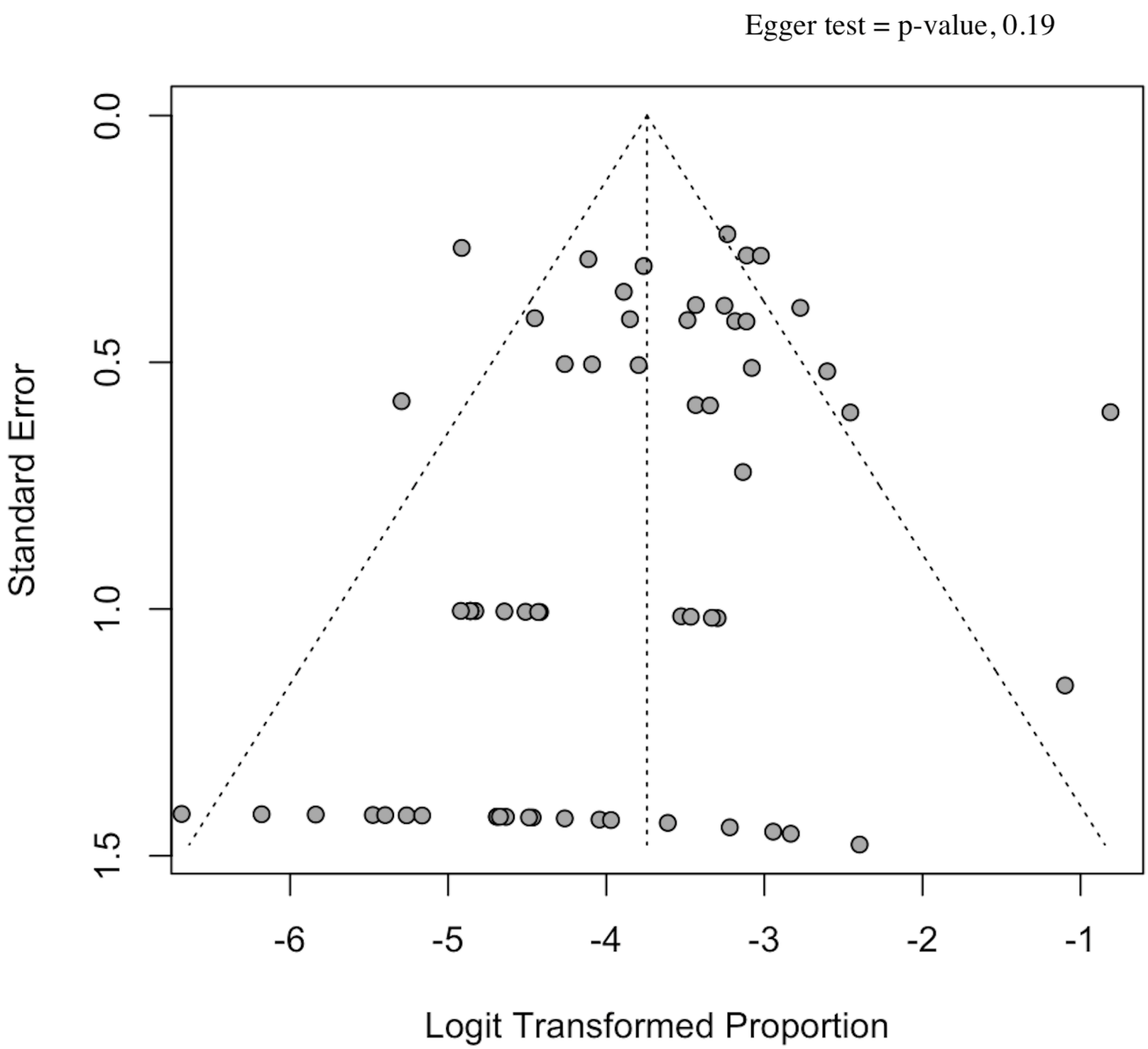
Supplementary Figure 27. Clinically relevant non-major bleeding in patients receiving different regimens of anticoagulation



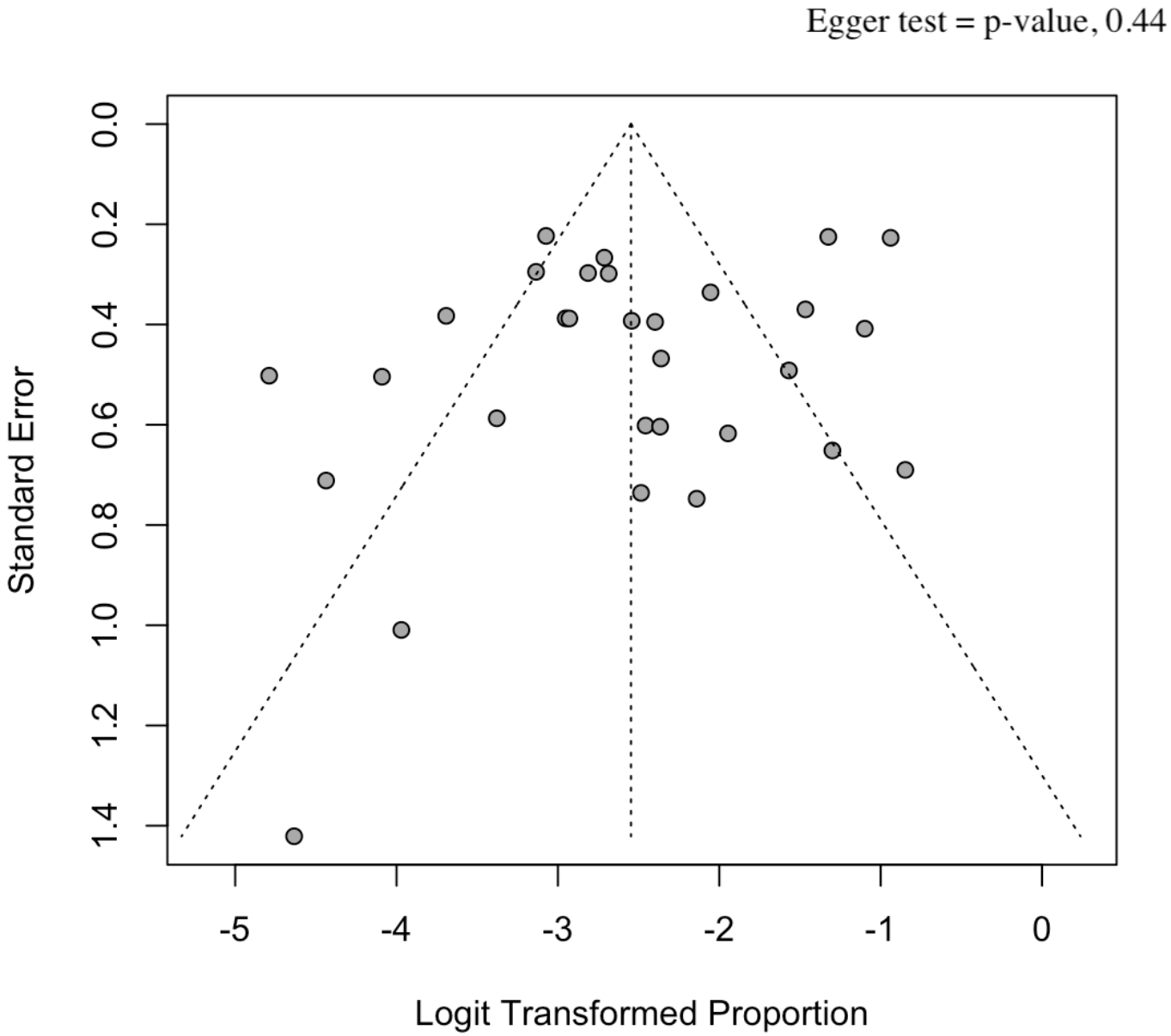
Supplementary Figure 28. Funnel plot for recurrent deep vein thrombosis



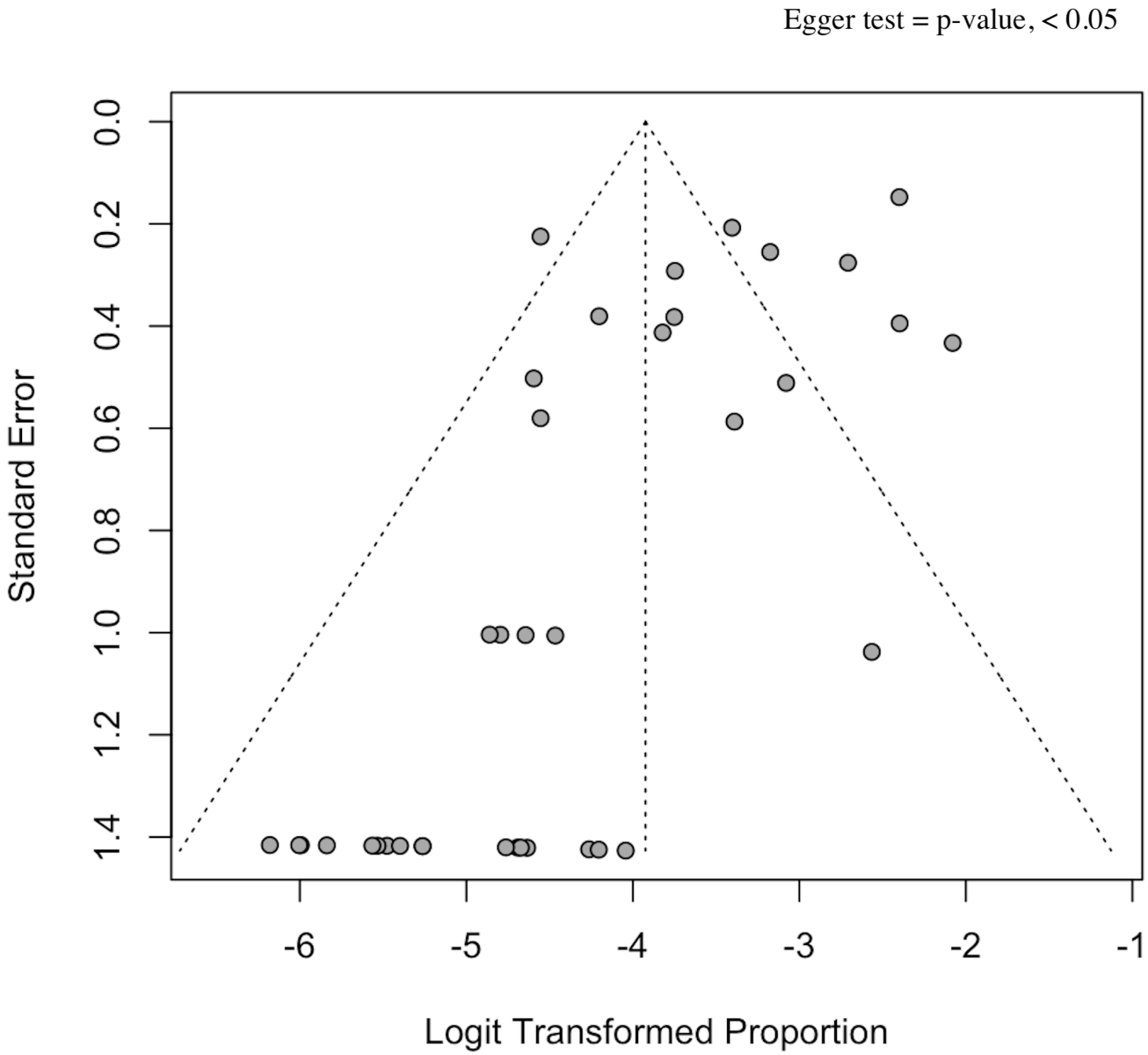
Supplementary Figure 29. Funnel plot for pulmonary embolism



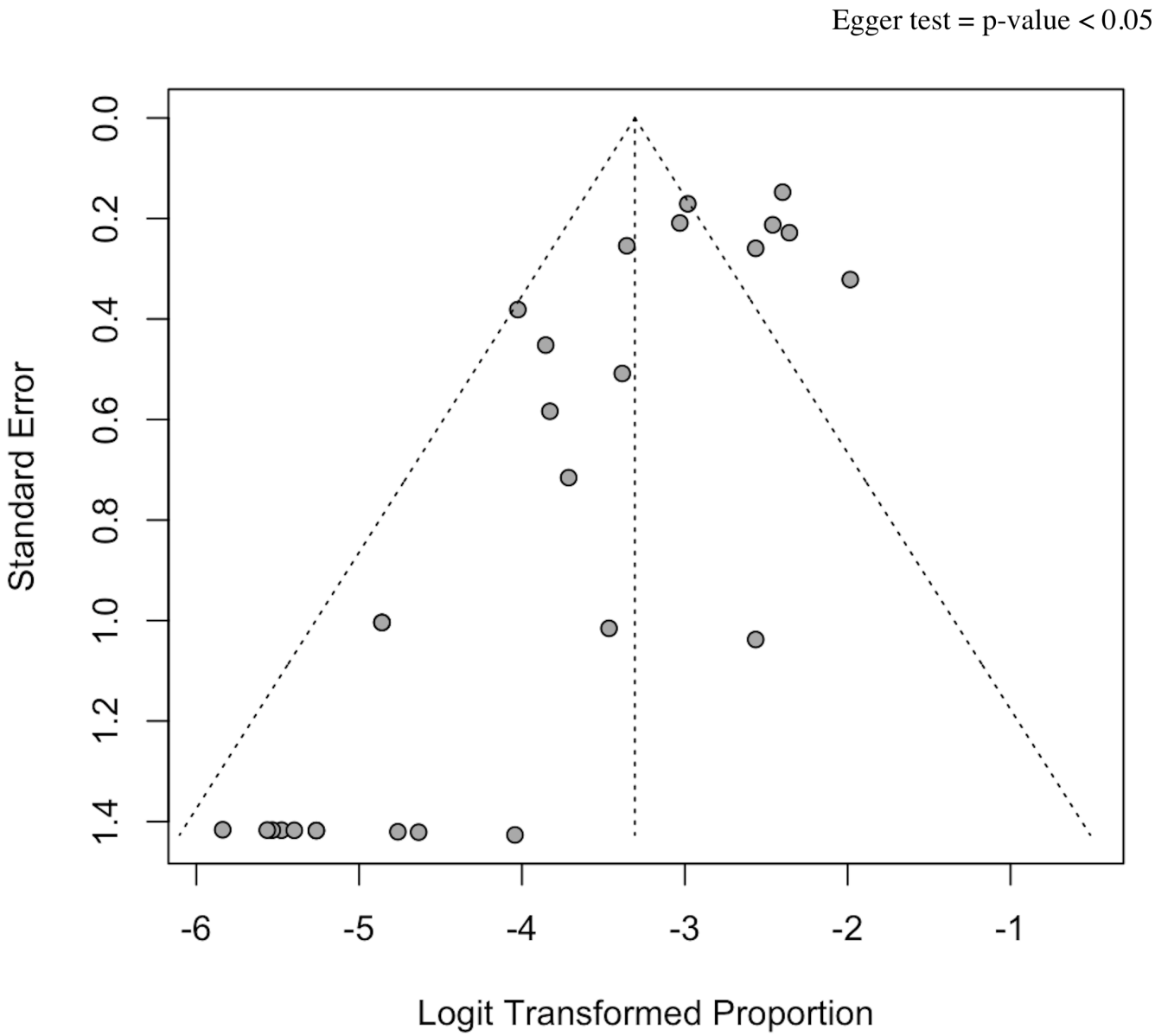
Supplementary Figure 30. Funnel plot for proximal progression of thrombosis



Supplementary Figure 31. Funnel plot for major bleeding



Supplementary Figure 32. Funnel plot for recurrent clinically relevant non-major bleeding



Supplementary Table 1. Characteristics of included studies

First author, year	Study design	Symptomatic IDDVT	Patients' class of risk	Main risk factors	Treatment duration cohorts		Dosage AC	Follow-up
Ageno W, 2019	PC	No	NA	Mixed	Long, 272	Extended, 1004	Therapeutic	12 months
Ageno W, 2022	RCT	Yes	High	Mixed	Long, 200	Short, 202	Therapeutic	24 months
Asonitis K, 2020	RC	No	NA	Not reported	Short, 119	-	Therapeutic	3 months
Astermark, 1998	PC	No	NA	Mixed	Short, 126	-	Therapeutic	24 months
Barco S, 2017	RC	Yes	NA	Mixed	Mixed, 202	-	Therapeutic	7.6 years
Belcaro G, 1997	RCT	Not reported	Low	Mixed	Mixed, 130	None, 44	Therapeutic, 43 Prophylactic, 87	6 months
Brateanu A, 2016	RC	Yes	NA	Mixed	Mixed, 141	None, 309	Therapeutic	3 months
Brewster AC, 2021	RC	No	NA	Mixed	No, 182	-		1 month
Cox S, 2014	RC	No	NA	Unprovoked	Short, 38	None, 130	Therapeutic	1 month
Day T, 2022	RC	No	Low	Surgery/trauma/immobilization	Mixed, 33	None, 58	Therapeutic	Not reported
Dentali F, 2017	PC	Yes	NA	Cancer	Long, 305	None, 3	Mixed	13.9 months
Donadini MP, 2016	PC	Yes	NA	Mixed	Short, 280	-	Intermediate	42.3 month
Elmi G, 2023	PC	Mixed	NA	Surgery/trauma/immobilization	Short, 86	-	Prophylactic	1 month
Ferrara F, 2006	RCT	Yes	NA	Surgery/trauma/immobilization	Long, 96	Short, 96	Therapeutic	4 months
Fujioka, 2020	RC	Mixed	NA	Mixed	No, 212	-		3 months
Galanaud JP, 2009	PC	Yes	NA	Mixed	Mixed, 1921	-	Not reported	3 months
Galanaud JP, 2014	PC	Yes	NA	Mixed	Long, 485	-	Mixed	3 years
Galanaud J, 2020	RCT	Yes	NA	Mixed	Short, 87	None, 91	Therapeutic	1 year
Guarnera G, 2014	PC	NA	NA	Mixed	Short, 110	-	Not reported	Not reported
Hirko M, 1999	RC	No	NA	Surgery/trauma/immobilization	Short, 24	None, 4	Therapeutic	1 year
Ho P, 2016	RC	Mixed	NA	Mixed	Long, 151	None, 4	Therapeutic	24 months
Horner D, 2014	RCT	Yes	NA	Mixed	Long, 35	None, 35	Therapeutic	3 months
Huang Z, 2023	PC	No	NA	Surgery/trauma/immobilization	Long, 51	-	Therapeutic	3 months

Jørgensen CT, 2023	PC	Yes	NA	Mixed	Long, 475	-	Not reported	4.7 years
Kim SM, 2022	RC	Not reported	NA	Mixed	Mixed, 96	None, 10	Not reported	15.5 months
Kuczmik W, 2021	PC	Mixed	NA	Mixed	Long, 399	None, 84	Not reported	8 months
Labropoulos N, 2002	PC	Yes	NA	Mixed	Mixed, 19	None, 29	Therapeutic	1 month
Lagerstedt, 1985	RCT	Yes	NA	Not reported	Long, 23	None, 28	Therapeutic	3 months
Lautz TB, 2010	PC	Mixed	NA	Mixed	Mixed, 236	None, 119	Prophylactic, 48 Therapeutic, 188	7.5 months
Li AY, 2015	RC	Mixed	NA	Not reported	Long, 400	Short, 54	Therapeutic	3 months
Lohr A,1995	PC	Mixed	NA	Mixed	Mixed, 23	None, 169	Therapeutic	1 month
Luo X, 2022	RC	Mixed	NA	Mixed	Mixed, 288	None, 138	Mixed	11.6 months
Masuda EM, 1998	RC	Mixed	NA	Mixed	Mixed, 28	None, 26	Not reported	3 years
Merriman E, 2021	PC	Yes	Low	Mixed	Short, 241	-	Therapeutic	3 months
Mo M, 2023	PC	Mixed	NA	Mixed	Extended, 288	-	Mixed	21.3 months
Parisi R, 2009	PC	Yes	NA	Mixed	Short, 171	-	Intermediate	3 months
Pasha AK, 2021	RC	Not reported	High	Cancer	Long, 224	-	Mixed	9 months
			NA	Mixed	Long, 521	-	Mixed	8 months
Pellegrini V, 1993	RCT	No	NA	Surgery/trauma/immobilization	Short, 12	None, 13	Prophylactic	13 months
Pinede L, 2001	RCT	Yes	NA	Mixed	Short, 105	Long, 92	Therapeutic	12 months
Poudel S, 2020	PC	Mixed	NA	Cancer	Long, 91	None, 5	Not	2 years
Righini M, 2016	RCT	Yes	Low	Mixed	Short, 122	None, 130	Therapeutic	3 months
Sales C, 2010	RC	Yes	NA	Surgery/trauma/immobilization	Mixed, 76	None, 65	Therapeutic	Not reported
Sartori M, 2014	PC	Yes	NA	Mixed	Mixed, 88	-	Mixed	24 months
Sartori M, 2024	RCT	Yes	NA	Not reported	Short, 130	Long, 130	Mixed	6 months
Schwarz T, 2001	RCT	Yes	NA	Mixed	Short, 52	None, 32	Therapeutic	3 months
Schwarz T, 2010	RCT	Yes	Low	Mixed	Short, 54	None, 53	Therapeutic	3 months
Sharpe RP, 2002	PC	NA	NA	Surgery/trauma/immobilization	Short, 85	-	Not reported	1 month
Solis M, 1992	PC	No	NA	Surgery/trauma/immobilization	Mixed, 14	None, 28	Therapeutic	Not reported
Sule AA, 200[36]	RC	Yes	NA	Mixed	Short, 9	None, 18	Therapeutic	7 months

					Long, 8			
Saarinen 2002	RC	Mixed	NA	Mixed	Extended, 82	-	Therapeutic	8.4 years
Utter GH, 2016	RC	Mixed	NA	Mixed	Mixed, 243	None, 141	Therapeutic	6 months
Vlazny DT, 2021	RC	No	NA	Mixed	Mixed, 746	-	Mixed	8.4 months
Yamashita Y, 2023	RCT	No	High	Cancer	Extended, 601	-	Mixed	1 year

Abbreviations: AC, anticoagulation; IDDVT, isolated distal deep vein thrombosis; NA, not available; RCT, randomized controlled trial, PC, observational prospective cohort; RC, observational retrospective cohort. Legend: short (<6 weeks), long (6-12 weeks), extended (>12 weeks), and mixed (mixed duration).

Supplementary Table 2. Pooled prevalence of the outcomes sorting studies by the type of anticoagulant therapy

Outcomes	Incidence (95% confidence intervals)	Number of studies	Heterogeneity
Recurrent deep vein thrombosis			
DOACs	8% (3% to 17%)	3	94%
VKAs	6% (3% to 17%)	6	86%
LMWHs	6% (3% to 10%)	10	82%
Pulmonary embolism			
DOACs	1% (0% to 4%)	2	76%
VKAs	2% (1% to 5%)	7	21%
LMWHs	2% (1% to 4%)	11	47%
Proximal progression			
DOACs	2% (1% to 5%)	1	Not applicable
VKAs	12% (5% to 28%)	2	81%
LMWHs	3% (0% to 28%)	3	88%
Post-thrombotic syndrome			
VKAs	6% (0% to 50%)	1	Not applicable
LMWHs	11% (2% to 44%)	3	90%
Major bleeding			
DOACs	2% (0% to 12%)	3	89%
VKAs	0% (0% to 2%)	2	0%
LMWHs	2% (1% to 3%)	10	11%
Clinically relevant non-major bleeding			
DOACs	8% (1% to 11%)	1	Not applicable
VKAs	1% (0% to 2%)	3	0%
LMWHs	1% (0% to 3%)	5	32%

Abbreviations: DOACs, direct oral anticoagulants; LMWHs, low molecular weight heparins; VKAs, vitamin K antagonists.

Supplementary Table 3. Pooled prevalence of the outcomes in randomized trials and prospective cohort studies

Outcomes	Incidence (95% confidence intervals)	Number of studies	Heterogeneity
Recurrent deep vein thrombosis	8% (6% to 11%)	38	92%
Pulmonary embolism	2% (2% to 3%)	42	60%
Proximal progression	7% (5% to 11%)	21	87%
Post-thrombotic syndrome	30% (24% to 38%)	2	0%
Major bleeding	2% (1% to 3%)	29	77%
Clinically relevant non-major bleeding	3% (2% to 5%)	21	75%

Supplementary Table 4. Risk ratios of the outcomes (sorted by type of treatment allocations) in randomized trials and prospective cohort studies

Outcomes, num	Incidence (95% confidence intervals)	Number of studies	Heterogeneity
Recurrent deep vein thrombosis			
Short vs Long therapy	2.52 (0.97 to 6.54)	5	59%
Long vs Extended therapy	1.75 (0.80 to 3.82)	1	Not applicable
Short vs No therapy	0.21 (0.03 to 1.60)	3	85%
Long vs No therapy	0.40 (0.12 to 1.36)	4	15%
Pulmonary embolism			
Short vs Long therapy	1.73 (0.34 to 8.79)	3	0%
Short vs No therapy	0.56 (0.03 to 9.61)	2	57%
Long vs No therapy	1.11 (0.20 to 6.03)	3	0%
Proximal progression			
Short vs Long therapy	3.86 (1.77 to 8.43)	1	Not applicable
Major bleeding			
Short vs Long therapy	1.18 (0.03 to 43.29)	3	86%
Short vs No therapy	0.15 (0.02 to 1.22)	1	Not applicable
Long vs No therapy	0.29 (0.14 to 0.58)	2	0%
Clinically relevant non-major bleeding			
Short vs Long therapy	1.0 (0.06 to 15.82)	1	Not applicable
Long vs No therapy	0.74 (0.16 to 3.48)	1	Not applicable

Supplementary Table 5. Pooled prevalence of the outcomes in high quality studies published since 2009

Outcomes	Incidence (95% confidence intervals)	Number of studies	Heterogeneity
Recurrent deep vein thrombosis	6% (4% to 10%)	11	93%
Pulmonary embolism	2% (1% to 3%)	10	71%
Proximal progression	8% (2% to 27%)	3	86%
Post-thrombotic syndrome	17% (6% to 39%)	2	91%
Major bleeding	2% (1% to 4%)	9	88%
Clinically relevant non-major bleeding	5% (3% to 7%)	7	73%

Supplementary Table 6. Patients' risk definitions

First author, year	Patients' Risk Definition
Ageno W., 2022	High-risk patients: age > 50 years; history of VTE; unprovoked IDDVT; secondary IDDVT that resulted in persistently reduced mobilisation; chronic underlying comorbidities (e.g., inflammatory bowel disease); known thrombophilia; IDDVT that involves the popliteal trifurcation; multiple and/or bilateral IDDVT. Cancer patients were excluded. All other patients were considered at low risk.
Merriman E., 2021	High-risk patients were excluded, defined as: patients with bilateral IDDVT, duration of symptoms for more than two weeks, DVT involving trifurcation or more proximal leg veins on imaging, prior DVT, active malignancy (present at time of diagnosis, or on treatment, or treatment completed within three months), ongoing risk factors for propagation, such as ongoing immobility (>50% of the day in bed or ≥72 h), plaster cast or non-weight bearing.
Righini M., 2016	The study excluded high-risk patients, defined as: patients with previous documented VTE, inpatients, and patients with cancer.

Abbreviations: DVT, deep vein thrombosis; IDDVT, isolated distal deep vein thrombosis; VTE, venous thromboembolism.

Supplementary Table 7. Anticoagulant dose definitions

First author, year	Anticoagulant Dose Definition
Ageno W., 2019	Therapeutic dose: the rivaroxaban cohort included patients who received rivaroxaban alone and those who had received heparin/fondaparinux for a maximum of 48 hours before initiating rivaroxaban treatment (15 mg BID for 21 days followed by 20 mg OD).
Ageno W., 2022	Therapeutic dose: rivaroxaban 15 mg BID for 3 weeks followed by rivaroxaban 20 mg OD for 3 weeks.
Astonitis K., 2020	Therapeutic dose: enoxaparin 1.5 mg/kg/day for a 40-day period in the absence of contra-indications.
Astermark J., 1998	Therapeutic dose: UFH regimen was an initial, intravenous bolus injection of 5000 IU followed by 250 IU/kg subcutaneously BID; dalteparin regimen was 200 IU/kg/day, followed by AVKs with a target INR between 2.0 and 3.0.
Day T., 2022	Prophylactic dose: UFH 5000 IU BID, or enoxaparin 40 mg OD, or renally adjusted dose equivalent.
Dentali F., 2017	Full therapeutic or intermediate dose of parenteral antithrombotic therapy was used in the vast majority of patients. VKAs with a target INR between 2.0 and 3.0.
Donadini MP., 2016	Patients were treated with LMWH for 4–6 weeks, given at a full therapeutic dose for 1 week followed by 50% of that dose for 3–5 weeks.
Elmi G., 2023	Prophylactic dose: enoxaparin 4000 IU OD; LMWH administration could be increased up to an intermediate dose (usually enoxaparin 6000 IU OD or 4000 IU BID).
Ferrara F., 2006	Therapeutic dose: nadroparin at 200 IU/kg/day, given in 2 doses.
Horner D., 2014	Therapeutic dose: initial therapeutic dose of dalteparin with phased transition to VKA for a total of 3 months. The target INR was 2.5 (range, 2.0-3.0).
Huang Z.,2023	Prophylactic dose: 0.4 ml enoxaparin OD, followed by rivaroxaban 10 mg OD. Therapeutic dose: 0.6 ml enoxaparin OD, followed by rivaroxaban 15 mg OD.
Lagerstedt CI., 1985	Therapeutic dose: 5-day course of UFH intravenously, 500-600 IU/kg/day in 6 divided doses, followed by warfarin with an INR of 2.5-4.2.
Merriman E., 2021	Therapeutic dose: full dose enoxaparin (1 mg/kg BID or 1.5 mg/kg OD) or rivaroxaban (15 mg BID) for two weeks.
Mo M., 2023	Full dose rivaroxaban 30 mg daily vs low dose rivaroxaban 15 mg daily at least for 3 months.
Pellegrini VD., 1993	Warfarin prophylaxis was administered to patients as a two-step regimen, beginning 7-14 days before surgery, to achieve an INR of 1.3-1.7 at the time of

	surgery. After surgery, INR of 1.7-2.5 for the duration of the hospitalization, which averaged 11 days.
Pinede L., 2001	Therapeutic dose: VKAs to an INR of 2.0 to 3.0.
Righini M., 2016	Therapeutic dose: nadroparin 171 IU/kg/day.
Sartori M., 2024	Patients were randomized to LMWH 1 mg/kg BID for 2 weeks followed by 1 mg/kg OD for 4 weeks or to enoxaparin 1 mg/kg BID and concurrent warfarin with a target INR of 2.5 for 3 months.
Schwarz T., 2010	Therapeutic dose: nadroparin 180 IU/kg OD.
Sule AA., 2009	Therapeutic dose: enoxaparin 1 mg/kg BID for 2 weeks or warfarin for 3 months with initial overlap of enoxaparin 1 mg/kg BID for 3 to 5 days until the INR was between 2.0 and 3.0.
Yamashita Y., 2023	Therapeutic dose: edoxaban 60 mg OD, or 30 mg OD in patients with a creatinine clearance of 30 to 50 mL per minute or a body weight of 60 kg or less or in those receiving concomitant treatment with potent P-glycoprotein inhibitors.

Abbreviations: APTT, activated partial thromboplastin time; BID, twice daily; DOACs, direct oral anticoagulants; INR, international normalized ratio; IU, international unit; LMWHs, low molecular weight heparins; OD, once daily; UFH, unfractionated heparin; VKAs, vitamin K antagonists.