

SUPPLEMENTARY MATERIALS

TABLE

TABLE S1. Patient characteristics by thrombin generation results one year after index venous thromboembolism (VTE)

Characteristic*	All n (%) or median (IQ-range)	With thrombin generation result n (%) or median (IQ-range)	Without thrombin generation result n (%) or median (IQ-range)	P-value
Total number of patients	995	551	444	
Patient age (years)	75.0 (69.0; 81.0)	74.0 (69.0; 79.0)	76.0 (71.0; 83.0)	<0.001
Female sex	466 (47%)	232 (42%)	234 (53%)	0.001
Index VTE event				0.868
PE only	553 (56%)	309 (56%)	244 (55%)	
DVT only	307 (31%)	170 (31%)	137 (31%)	
PE and DVT	135 (14%)	72 (13%)	63 (14%)	
Index DVT type*				0.018
proximal DVT only	197 (20%)	99 (18%)	98 (22%)	
distal DVT only	109 (11%)	56 (10%)	53 (12%)	
proximal and distal DVT	134 (13%)	87 (16%)	47 (11%)	
Type of index VTE				<0.001
cancer-related VTE	179 (18%)	60 (11%)	119 (27%)	
provoked index VTE	215 (22%)	113 (21%)	102 (23%)	
unprovoked index VTE	599 (60%)	378 (69%)	221 (50%)	
Current oestrogen therapy during the last 3 months	32 (3%)	18 (3%)	14 (3%)	1.000
Immobilization during the last 3 months	219 (22%)	95 (17%)	124 (28%)	<0.001
Major surgery during the last 3 months	150 (15%)	80 (15%)	70 (16%)	0.593
Prior VTE	283 (28%)	168 (30%)	115 (26%)	0.137
PTS*	503 (51%)	291 (53%)	212 (48%)	0.173
History of major bleeding	101 (10%)	43 (8%)	58 (13%)	0.008
Chronic liver disease	14 (1%)	8 (1%)	6 (1%)	1.000
Chronic renal disease	185 (19%)	98 (18%)	87 (20%)	0.461
Chronic or acute heart failure	115 (12%)	65 (12%)	50 (11%)	0.842
Cerebrovascular disease (stroke, TIA)	92 (9%)	43 (8%)	49 (11%)	0.079
Diabetes mellitus	155 (16%)	87 (16%)	68 (15%)	0.930
BMI >30 kg m⁻²*	238 (24%)	136 (25%)	102 (23%)	0.653
High risk of fall	457 (46%)	234 (42%)	223 (50%)	0.010
Acute rheumatic disease during the last 3 months	32 (3%)	17 (3%)	15 (3%)	0.857
Inflammatory bowel disease	32 (3%)	17 (3%)	15 (3%)	0.857

Severe infection or sepsis during the last 3 months	83 (8%)	44 (8%)	39 (9%)	0.646
Anemia*	389 (39%)	181 (33%)	208 (47%)	<0.001
Platelet count <150 G L⁻¹*	140 (14%)	79 (14%)	61 (14%)	0.713
Concomitant antiplatelet therapy	322 (32%)	174 (32%)	148 (33%)	0.540
Concomitant antiplatelet/NSAID therapy	381 (38%)	204 (37%)	177 (40%)	0.358
Arterial hypertension	640 (64%)	356 (65%)	284 (64%)	0.947
Heart rate ≥110 beats min⁻¹*	88 (9%)	46 (8%)	42 (9%)	0.577
Systolic BP <100 mmHg*	35 (4%)	11 (2%)	24 (5%)	0.005
Respiratory rate ≥30 min⁻¹*	33 (3%)	15 (3%)	18 (4%)	0.380
Temperature <36°C*	70 (7%)	35 (6%)	35 (8%)	0.320
Arterial oxygen saturation <90%*	107 (11%)	51 (9%)	56 (13%)	0.075
D-dimer at the time of the index VTE*	2507.0 (1579.3; 3811.3)	2456.0 (1598.0; 3746.5)	2615.0 (1570.0; 3967.0)	0.399
Factor VIII >164%*	573 (58%)	334 (61%)	239 (54%)	0.715
Factor IX >134% (females) >138% (males)*	157 (16%)	87 (16%)	70 (16%)	0.371
Factor XI >139% (females) >138% (males)*	96 (10%)	53 (10%)	43 (10%)	0.510
Fibrinogen >4.2 g L⁻¹*	511 (51%)	298 (54%)	213 (48%)	0.726
Factor V Leiden mutation, present*	82 (8%)	53 (10%)	29 (7%)	0.290
Factor II G20210A mutation, present*	49 (5%)	31 (6%)	18 (4%)	0.553
Overall anticoagulation duration (days)	413 (178; 896)	668.0 (213.0; 979.0)	246.0 (95.5; 639.5)	<0.001
Anticoagulation duration until one year after the index VTE (days)	324 (171; 368)	353.0 (194.0; 365.0)	232.5 (95.5; 407.5)	0.003
Anticoagulation duration from one year after the index VTE (days)	276 (0; 688)	344.0 (0.0; 693.0)	119.0 (0.0; 678.0)	0.059

BP, blood pressure; BMI, body mass index; DVT, deep vein thrombosis; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; PE, pulmonary embolism; PTS, post-thrombotic syndrome; TIA, transient ischemic attack. *Values were missing for index DVT type (56%), presence of PTS (3%), BMI > 30 kg m⁻² (1%), anemia (7%), platelet count of <150 G L⁻¹ (7%), heart rate of ≥ 110 beats min⁻¹ (2%), systolic BP of < 100 mmHg (2%), respiratory rate of ≥ 30 min⁻¹ (21%), temperature of < 36°C (8%), arterial oxygen saturation of < 90% (23%), D-dimer at the time of the index VTE (15%), factor VIII of > 164% (13%), factor IX of > 134% (females) and > 138% (males) (13%), factor XI of > 139% (women) and > 138% (males) (13%), fibrinogen of > 4.2 g/L (13%), factor V Leiden mutation present (11%), factor II G20210A mutation present (11%), anticoagulation duration from 12 months after the index VTE (34%).

TABLE S2. Characteristics of patients with results of thrombin generation with/without thrombomodulin one year after index venous thromboembolism (VTE)

Characteristic*	All patients n (%) or median (IQ- range)	Not under anticoagulation one year after index VTE n (%) or median (IQ-range)	Under anticoagulation one year after index VTE n (%) or median (IQ-range)	P-value
Total number of patients	535	222	313	
Patient age (years)	74.0 (69.0; 79.0)	74.0 (68.0; 78.0)	74.0 (69.0; 80.0)	0.400
Female sex	226 (42%)	103 (46%)	133 (39%)	0.110
Index VTE event				<0.001
PE only	298 (56%)	106 (48%)	192 (61%)	
DVT only	166 (31%)	95 (43%)	71 (23%)	
PE and DVT	71 (13%)	21 (9%)	50 (16%)	
Index DVT type*	96 (18%)	44 (20%)	51 (17%)	<0.001
proximal DVT only	96 (18%)	44 (20%)	52 (17%)	
distal DVT only	56 (10%)	40 (18%)	16 (5%)	
proximal and distal DVT	85 (16%)	32 (14%)	53 (17%)	
Type of index VTE				<0.001
cancer-related VTE	59 (11%)	27 (12%)	32 (10%)	
provoked index VTE	109 (20%)	68 (31%)	41 (13%)	
unprovoked index VTE	367 (69%)	127 (57%)	240 (77%)	
Current oestrogen therapy during the last 3 months	17 (3%)	9 (4%)	8 (3%)	0.332
Immobilization during the last 3 months	94 (18%)	59 (27%)	35 (11%)	<0.001
Major surgery during the last 3 months	78 (15%)	52 (23%)	26 (8%)	<0.001
Prior VTE	160 (30%)	28 (13%)	132 (42%)	<0.001
PTS*	286 (53%)	120 (54%)	166 (53%)	0.721
History of major bleeding	43 (8%)	18 (8%)	25 (8%)	1.000
Chronic liver disease	8 (1%)	4 (2%)	4 (1%)	0.724
Chronic renal disease	94 (18%)	33 (15%)	61 (19%)	0.205
Chronic or acute heart failure	60 (11%)	16 (7%)	44 (14%)	0.017
Cerebrovascular disease (stroke, TIA)	41 (8%)	13 (6%)	28 (9%)	0.248
Diabetes mellitus	85 (16%)	36 (16%)	49 (16%)	0.905
BMI >30 kg m⁻²*	131 (24%)	52 (23%)	79 (25%)	0.683
High risk of fall	225 (42%)	90 (41%)	135 (43%)	0.594
Acute rheumatic disease during the last 3 months	17 (3%)	9 (4%)	8 (3%)	0.332
Inflammatory bowel disease	17 (3%)	7 (3%)	10 (3%)	1.000
Severe infection or sepsis during the last 3 months	42 (8%)	16 (7%)	26 (8%)	0.745
Anemia*	178 (33%)	83 (37%)	95 (30%)	0.035
Platelet count <150 G L⁻¹*	78 (15%)	29 (13%)	49 (16%)	0.615

Concomitant antiplatelet therapy	167 (31%)	63 (28%)	104 (33%)	0.256
Concomitant antiplatelet/NSAID therapy	197 (37%)	74 (33%)	123 (39%)	0.173
Arterial hypertension	344 (64%)	140 (63%)	204 (65%)	0.647
Heart rate ≥ 110 beats min⁻¹*	44 (8%)	14 (6%)	30 (10%)	0.205
Systolic BP <100 mmHg*	11 (2%)	3 (1%)	8 (3%)	0.538
Respiratory rate ≥ 30 min⁻¹*	14 (3%)	4 (2%)	10 (3%)	0.411
Temperature <36°C*	34 (6%)	18 (8%)	16 (5%)	0.106
Arterial oxygen saturation <90%*	50 (9%)	15 (7%)	35 (11%)	0.278
D-dimer at the time of the index VTE*	2486.0 (1598.0; 3757.0)	2404.0 (1677.0; 3765.0)	2514.5 (1554.0; 3744.0)	0.980
Factor VIII >164%*	326 (61%)	126 (57%)	200 (64%)	0.123
Factor IX >134% (females) >138% (males)*	82 (15%)	42 (19%)	40 (13%)	0.050
Factor XI >139% (females) >138% (males)*	49 (9%)	21 (9%)	28 (9%)	0.879
Fibrinogen >4.2 g L⁻¹*	288 (54%)	113 (51%)	175 (56%)	0.355
Factor V Leiden mutation, present*	49 (9%)	19 (9%)	30 (10%)	<0.001
Factor II G20210A mutation, present*	30 (6%)	9 (4%)	21 (7%)	<0.001
Overall anticoagulation duration (days)	658.0 (210.0; 977.0)	191.5 (144.0; 283.0)	900.0 (710.0; 1225.5)	<0.001
Anticoagulation duration until one year after the index VTE (days)	353.0 (194.0; 365.0)	185.0 (119.5; 210.8)	364.0 (357.0; 371.0)	<0.001
Anticoagulation duration from one year after the index VTE (days)	344.0 (0.0; 691.0)	0.0 (0.0; 0.0)	535.0 (353.0; 871.0)	<0.001

BP, blood pressure; BMI, body mass index; DVT, deep vein thrombosis; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; PE, pulmonary embolism; PTS, post-thrombotic syndrome; TIA, transient ischemic attack. *Values were missing for index DVT type (56%), presence of PTS (2%), anemia (8%), platelet count of <150 G L⁻¹ (8%), heart rate of ≥ 110 beats min⁻¹ (3%), systolic BP of < 100 mmHg (2%), respiratory rate of ≥ 30 min⁻¹ (25%), temperature of $< 36^\circ\text{C}$ (7%), arterial oxygen saturation of $< 90\%$ (24%), D-dimer at the time of the index VTE (8%), factor VIII of $> 164\%$ (7%), factor IX of $> 134\%$ (females) and $> 138\%$ (males) (7%), factor XI of $> 139\%$ (women) and $> 138\%$ (males) (7%), fibrinogen of > 4.2 g/L (7%), factor V Leiden mutation present (5%), factor II G20210A mutation present (5%).

TABLE S3. Characteristics of patients with results of normalized assays with/without thrombomodulin one year after index venous thromboembolism (VTE)

Characteristic*	All patients n (%) or median (IQ- range)	Not under anticoagulation one year after index VTE n (%) or median (IQ-range)	Under anticoagulation one year after index VTE n (%) or median (IQ-range)	P-value
Total number of patients	320	122	198	
Patient age (years)	73.0 (68.0; 78.8)	73.0 (68.0; 79.0)	73.0 (68.0; 78.0)	0.972
Female sex	124 (39%)	55 (45%)	69 (35%)	0.077
Index VTE event				<0.001
PE only	182 (57%)	57 (47%)	125 (63%)	
DVT only	96 (30%)	55 (45%)	41 (21%)	
PE and DVT	42 (13%)	10 (8%)	32 (16%)	
Index DVT type*				0.001
proximal DVT only	52 (16%)	20 (16%)	32 (16%)	
distal DVT only	37 (12%)	27 (22%)	10 (5%)	
proximal and distal DVT	49 (15%)	18 (15%)	31 (16%)	
Type of index VTE				<0.001
cancer-related VTE	42 (13%)	17 (14%)	25 (13%)	
provoked index VTE	66 (21%)	42 (34%)	24 (12%)	
unprovoked index VTE	212 (66%)	63 (52%)	149 (75%)	
Current oestrogen therapy during the last 3 months	9 (3%)	5 (4%)	4 (2%)	0.310
Immobilization during the last 3 months	59 (18%)	37 (30%)	22 (11%)	<0.001
Major surgery during the last 3 months	49 (15%)	33 (27%)	16 (8%)	<0.001
Prior VTE	106 (33%)	19 (16%)	87 (44%)	<0.001
PTS*	163 (51%)	60 (49%)	103 (52%)	0.907
History of major bleeding	27 (8%)	12 (10%)	15 (8%)	0.537
Chronic liver disease	6 (2%)	2 (2%)	4 (2%)	1.000
Chronic renal disease	58 (18%)	22 (18%)	36 (18%)	1.000
Chronic or acute heart failure	28 (9%)	6 (5%)	22 (11%)	0.067
Cerebrovascular disease (stroke, TIA)	25 (8%)	8 (7%)	17 (9%)	0.669
Diabetes mellitus	46 (14%)	17 (14%)	29 (15%)	1.000
BMI >30 kg m⁻²*	77 (24%)	26 (21%)	51 (26%)	0.420
High risk of fall	124 (39%)	45 (37%)	79 (40%)	0.637
Acute rheumatic disease during the last 3 months	11 (3%)	5 (4%)	6 (3%)	0.754
Inflammatory bowel disease	9 (3%)	5 (4%)	4 (2%)	0.310
Severe infection or sepsis during the last 3 months	29 (9%)	10 (8%)	19 (10%)	0.841
Anemia*	109 (34%)	48 (39%)	61 (31%)	0.045
Platelet count <150 G L⁻¹*	52 (16%)	15 (12%)	37 (19%)	0.208
Concomitant antiplatelet therapy	99 (31%)	36 (30%)	63 (32%)	0.710

Concomitant antiplatelet/NSAID therapy	113 (35%)	38 (31%)	75 (38%)	0.231
Arterial hypertension	194 (61%)	76 (62%)	118 (60%)	0.640
Heart rate ≥ 110 beats min⁻¹*	26 (8%)	7 (6%)	19 (10%)	0.294
Systolic BP <100 mmHg*	5 (2%)	1 (1%)	4 (2%)	0.654
Respiratory rate ≥ 30 min⁻¹*	9 (3%)	3 (2%)	6 (3%)	1.000
Temperature <36°C*	21 (7%)	9 (7%)	12 (6%)	0.490
Arterial oxygen saturation <90%*	32 (10%)	9 (7%)	23 (12%)	0.433
D-dimer at the time of the index VTE*	2394.0 (1519.3; 3766.3)	2386.5 (1508.3; 3875.8)	2401.0 (1518.3; 3696.8)	0.938
Factor VIII >164%*	204 (64%)	73 (60%)	131 (66%)	0.428
Factor IX >134% (females) >138% (males)*	45 (14%)	19 (16%)	26 (13%)	0.505
Factor XI >139% (females) >138% (males)*	30 (9%)	13 (11%)	17 (9%)	0.551
Fibrinogen >4.2 g L⁻¹*	171 (53%)	59 (48%)	112 (57%)	0.269
Factor V Leiden mutation, present*	27 (8%)	7 (6%)	20 (10%)	0.215
Factor II G20210A mutation, present*	16 (5%)	3 (2%)	13 (7%)	0.120
Overall anticoagulation duration (days)	606.5 (211.0; 896.5)	191.0 (120.8; 253.0)	731.5 (665.5; 952.5)	<0.001
Anticoagulation duration until one year after the index VTE (days)	355.5 (199.3; 366.0)	183.5 (116.0; 210.0)	364.0 (357.0; 371.3)	<0.001
Anticoagulation duration from one year after the index VTE (days)	262.0 (0.0; 521.0)	0.0 (0.0; 0.0)	376.5 (337.8; 592.5)	<0.001

BP, blood pressure; BMI, body mass index; DVT, deep vein thrombosis; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; PE, pulmonary embolism; PTS, post-thrombotic syndrome; TIA, transient ischemic attack. *Values were missing for index DVT type (57%), presence of PTS (2%), anemia (8%), platelet count of <150 G L⁻¹ (8%), heart rate of ≥ 110 beats min⁻¹ (3%), systolic BP of < 100 mmHg (2%), respiratory rate of ≥ 30 min⁻¹ (26%), temperature of $< 36^\circ\text{C}$ (7%), arterial oxygen saturation of $< 90\%$ (22%), D-dimer at the time of the index VTE (9%), factor VIII of $> 164\%$ (9%), factor IX of $> 134\%$ (females) and $> 138\%$ (males) (9%), factor XI of $> 139\%$ (women) and $> 138\%$ (males) (9%), fibrinogen of > 4.2 g/L (9%), factor V Leiden mutation present (6%), factor II G20210A mutation present (6%).

TABLE S4. Incidence rate of venous thromboembolism (VTE) recurrence, major bleeding, or overall mortality per 100 person-years - from 12 months until 36 months after index VTE in anticoagulated patients.

		No of patients	No of events/ person-years	Incidence rate (95%-CI)
Peak ratio obtained in presence/absence of TM				
VTE recurrence				
	All	307	10 / 455.2	2.2 (1.2 to 4.1)
	≤ median	154	9 / 229.6	3.9 (2.0 to 7.5)
	> median	153	1 / 225.6	0.4 (0.1 to 3.1)
Major bleeding				
	All	307	13 / 455.7	2.9 (1.7 to 4.9)
	≤ median	154	5 / 233.9	2.1 (0.9 to 5.1)
	> median	153	8 / 221.8	3.6 (1.8 to 7.2)
Overall mortality				
	All	307	21 / 461.5	4.6 (3.0 to 7.0)
	≤ median	154	10 / 235.5	4.2 (2.3 to 7.9)
	> median	153	11 / 226.0	4.9 (2.7 to 8.8)
Normalized peak ratio in presence/absence of TM				
VTE recurrence				
	All	198	3 / 259.1	1.2 (0.4 to 3.6)
	≤ median	99	2 / 127.8	1.6 (0.4 to 6.3)
	> median	99	1 / 131.3	0.8 (0.1 to 5.4)
Major bleeding				
	All	198	9 / 256.9	3.5 (1.8 to 6.7)
	≤ median	99	2 / 129.7	1.5 (0.4 to 6.2)
	> median	99	7 / 127.3	5.5 (2.6 to 11.5)
Overall mortality				
	All	198	11 / 260.9	4.2 (2.3 to 7.6)
	≤ median	99	4 / 129.7	3.1 (1.2 to 8.2)
	> median	99	7 / 131.3	5.3 (2.5 to 11.2)
ETP ratio obtained in presence/absence of TM				
VTE recurrence				

	All	307	10 / 455.2	2.2 (1.2 to 4.1)
	≤ median	154	7 / 231.2	3.0 (1.4 to 6.4)
	> median	153	3 / 224.0	1.3 (0.4 to 4.2)
Major bleeding				
	All	307	13 / 455.7	2.9 (1.7 to 4.9)
	≤ median	154	5 / 235.1	2.1 (0.9 to 5.1)
	> median	153	8 / 220.6	3.6 (1.8 to 7.3)
Overall mortality				
	All	307	21 / 461.5	4.6 (3.0 to 7.0)
	≤ median	154	11 / 236.7	4.6 (2.6 to 8.4)
	> median	153	10 / 224.8	4.4 (2.4 to 8.3)

Normalized ETP ratio obtained in presence/absence of TM

VTE recurrence				
	All	198	3 / 259.1	1.2 (0.4 to 3.6)
	≤ median	99	1 / 126.6	0.8 (0.1 to 5.6)
	> median	99	2 / 132.5	1.5 (0.4 to 6.0)
Major bleeding				
	All	198	9 / 256.9	3.5 (1.8 to 6.7)
	≤ median	99	3 / 127.7	2.3 (0.8 to 7.3)
	> median	99	6 / 129.3	4.6 (2.1 to 10.3)
Overall mortality				
	All	198	11 / 260.9	4.2 (2.3 to 7.6)
	≤ median	99	5 / 128.0	3.9 (1.6 to 9.4)
	> median	99	6 / 132.9	4.5 (2.0 to 10.0)

All experiments have been conducted in presence of 1 pM tissue factor (TF)

TABLE S5. Discriminative power of thrombin generation parameters involving thrombomodulin (TM) for outcomes – from 1 year to 3 years following the index venous thromboembolism (VTE) in patients under anticoagulation.

Thrombin generation parameters measured one year after the index VTE	No. of events/no. of patients	C-statistics (95% confidence interval)
Peak ratio obtained in presence/absence of TM		
VTE recurrence	10/307	0.74 (0.60 to 0.88)
Major bleeding	13/307	0.60 (0.45 to 0.74)
Overall mortality	21/307	0.56 (0.42 to 0.70)
Normalized peak ratio obtained in presence/absence of TM		
VTE recurrence	3/198	0.69 (0.37 to 1.02)
Major bleeding	9/198	0.60 (0.46 to 0.74)
Overall mortality	11/198	0.46 (0.24 to 0.68)
ETP ratio obtained in presence/absence of TM		
VTE recurrence	10/307	0.65 (0.45 to 0.84)
Major bleeding	13/307	0.56 (0.41 to 0.71)
Overall mortality	21/307	0.55 (0.39 to 0.70)
Normalized ETP ratio obtained in presence/absence of TM		
VTE recurrence	3/198	0.56 (0.11 to 1.01)
Major bleeding	9/198	0.59 (0.43 to 0.75)
Overall mortality	11/198	0.49 (0.26 to 0.71)

All experiments have been conducted in presence of 1 pM tissue factor

TABLE S6. Association between thrombin generation parameters and venous thromboembolism (VTE) recurrence, major bleeding and overall mortality – from 1 year to 3 years following the index VTE in patients under anticoagulation.

	n/N (%)	Crude subhazard ratio (95% confidence interval)	Adjusted subhazard ratio (95% confidence interval)
<i>Peak ratio obtained in presence/absence of TM (TF 1 pM)</i>			
VTE recurrence	10/307 (3.3)	0.11 (0.03 to 0.45)	0.12 (0.03 to 0.51)
Major bleeding	13/307 (4.2)	1.15 (0.87 to 1.54)	1.15 (0.87 to 1.54)
Overall mortality	21/307 (6.8)	0.34 (0.05 to 2.10)	0.34 (0.05 to 2.10)
<i>Normalized peak ratio obtained in presence/absence of TM (TF 1 pM)</i>			
VTE recurrence	3/198 (1.5)	0.37 (0.08 to 1.78)	0.38 (0.07 to 2.06)
Major bleeding	9/198 (4.5)	1.07 (0.90 to 1.26)	-
Overall mortality	11/198 (5.6)	0.91 (0.43 to 1.90)	-
<i>ETP ratio obtained in presence/absence of TM (TF 1 pM)</i>			
VTE recurrence	10/307 (3.3)	0.14 (0.02 to 1.01)	0.13 (0.02 to 0.90)
Major bleeding	13/307 (4.2)	1.66 (0.73 to 3.82)	1.72 (0.74 to 4.00)
Overall mortality	21/307 (6.8)	0.29 (0.03 to 2.39)	0.25 (0.03 to 2.08)
<i>Normalized ETP ratio obtained in presence/absence of APC (TF 13.6 pM)</i>			
VTE recurrence	11/290 (3.8)	1.09 (0.91 to 1.31)	1.13 (0.95 to 1.34)
Major bleeding	15/290 (5.2)	1.05 (0.89 to 1.25)	1.08 (0.90 to 1.29)
Overall mortality	22/290 (7.6)	0.79 (0.54 to 1.16)	0.92 (0.70 to 1.21)

Abbreviations: APC, activated protein C; ETP, endogenous thrombin potential; TM, thrombomodulin. Adjustments: VTE recurrence was adjusted for age, cancer, provoked VTE, prior VTE, overt pulmonary embolism, renal disease and periods of anticoagulation (oral or parenteral anticoagulation) as a time-varying covariable.[1-10] Major bleeding was adjusted for age, cancer, provoked VTE, prior VTE, overt pulmonary embolism, renal disease, history of major bleeding, anemia, antiplatelet therapy and periods of anticoagulation as time-varying covariate.[11-26] Mortality was adjusted for age, gender, cancer, provoked VTE, prior VTE, overt pulmonary embolism, renal disease, history of major bleeding, heart failure, chronic lung disease, high pulse, low blood pressure, low oxygen, and periods of anticoagulation as a time-varying covariate.[7, 27]

FIGURES

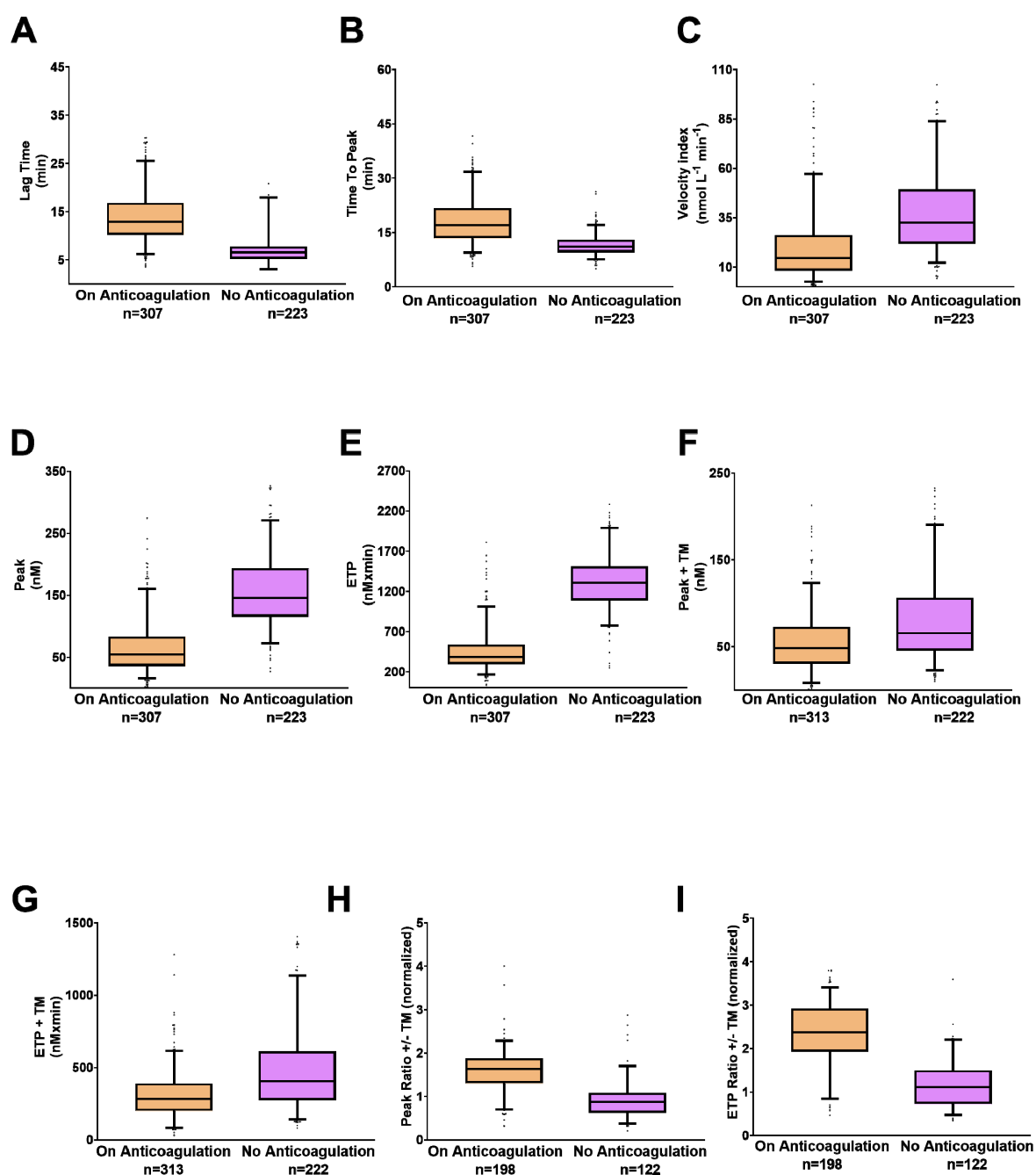


FIGURE S1. Thrombin generation parameters in patients under anticoagulation and not under anticoagulation 12 months after the index venous thromboembolism using 1pM tissue factor without thrombomodulin (TM) (A-E), with TM (F-G) and normalized ratio with and without TM for peak (H) and endogenous thrombin potential (ETP) (I). Box-plots of thrombin generation parameters are presented as median with interquartile range (5-95%).

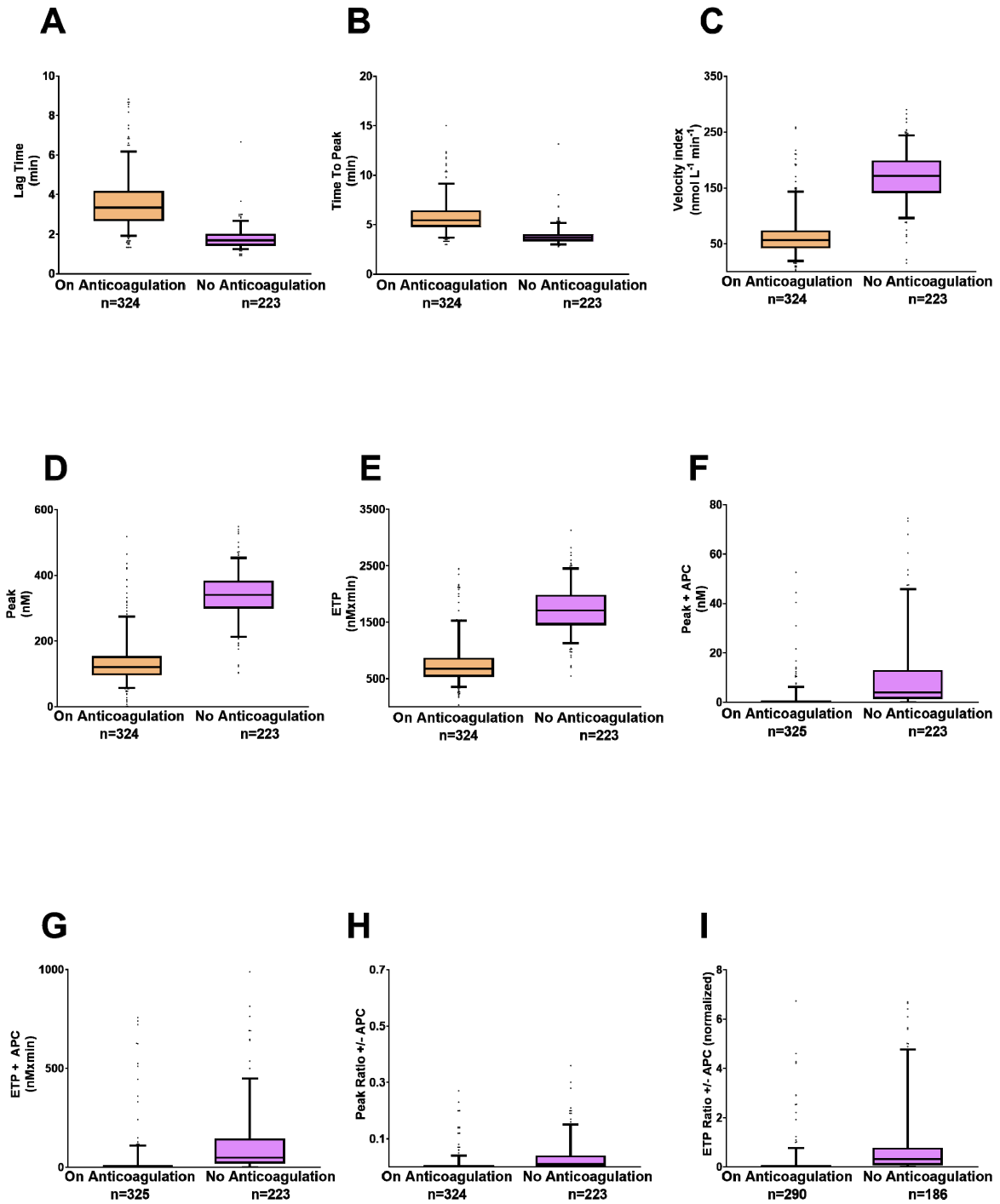


FIGURE S2. Thrombin generation in patients under anticoagulation and not under anticoagulation 12 months after the index venous thromboembolism using 13.6 pM tissue factor without activated protein C (APC) (A-E), with APC (F-G) and ratio with and without APC for peak (H) and normalized ratio with and without APC for endogenous thrombin potential (ETP) (I). Box-plots of thrombin generation parameters are presented as median with interquartile range (5-95%).

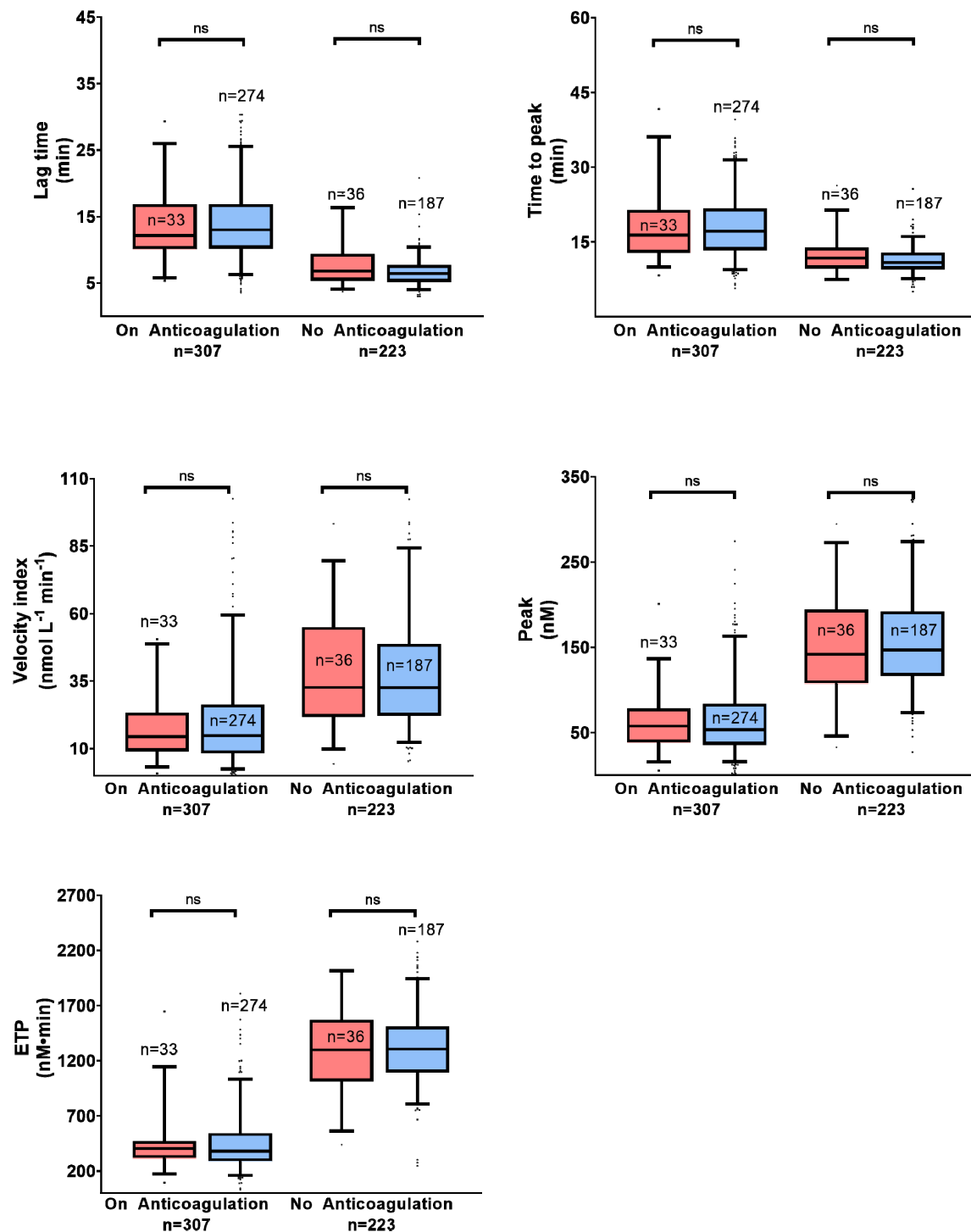


Figure S3. Thrombin generation parameters in patients under anticoagulation and not under anticoagulation after index venous thromboembolism (VTE) using 1 pM tissue factor without thrombomodulin. The red boxes indicate patients with VTE recurrence and the blue boxes, those without VTE recurrence up to 24 months following the index VTE. Box-plots of thrombin generation parameters are presented as median with interquartile range (5-95%). Groups were compared using Mann-Whitney U test. ETP, endogenous thrombin potential; ns, not significant

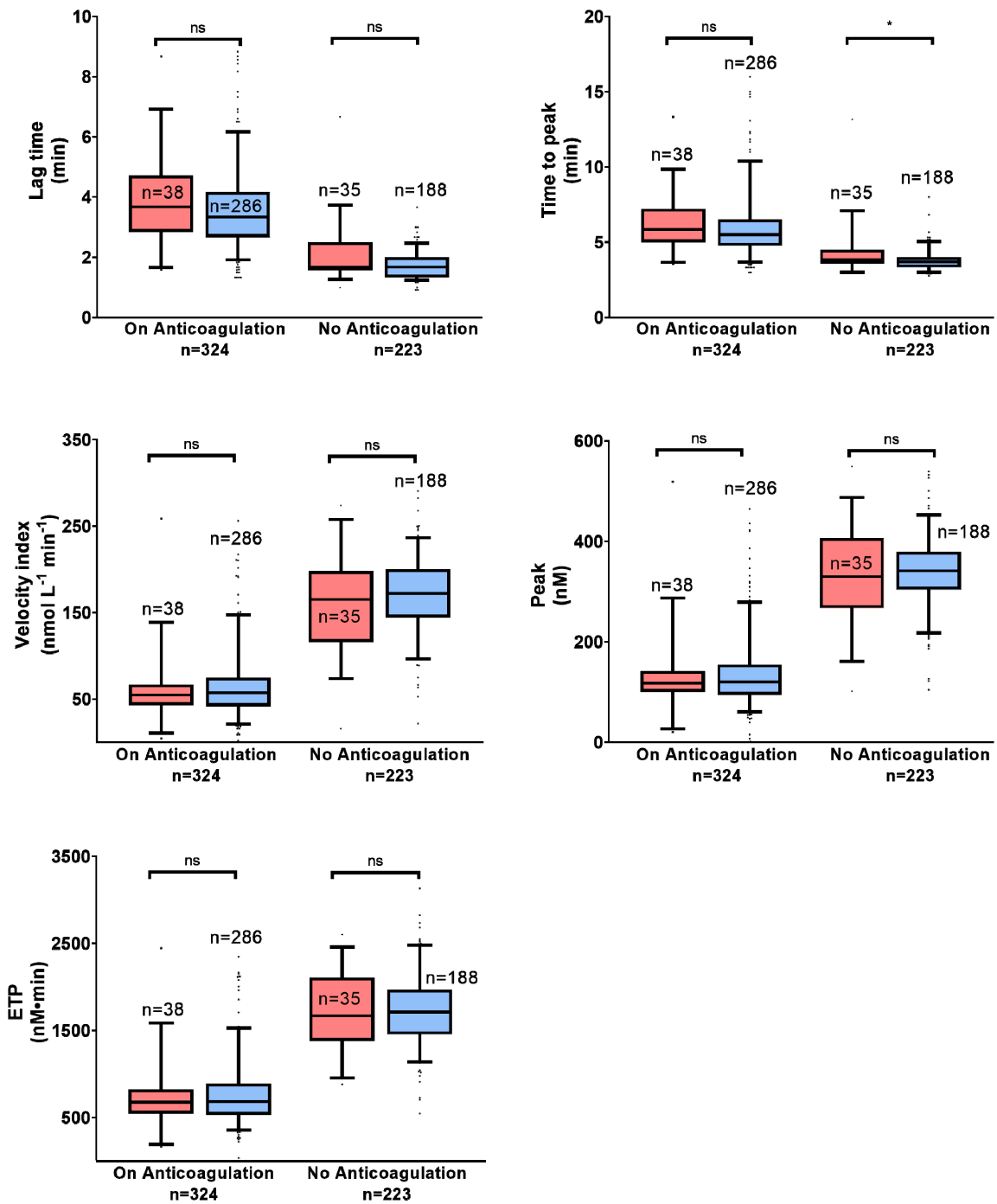


Figure S4. Thrombin generation parameters in patients under anticoagulation and not under anticoagulation after index venous thromboembolism (VTE) using 13.6 pM tissue factor without activated protein C. The red boxes indicate patients with VTE recurrence and the blue boxes, those without VTE recurrence up to 24 months following the index VTE. Box-plots of thrombin generation parameters are presented as median with interquartile range (5-95%). Groups were compared using the Mann-Whitney U test. ETP, endogenous thrombin potential; ns, not significant; *P<0.05

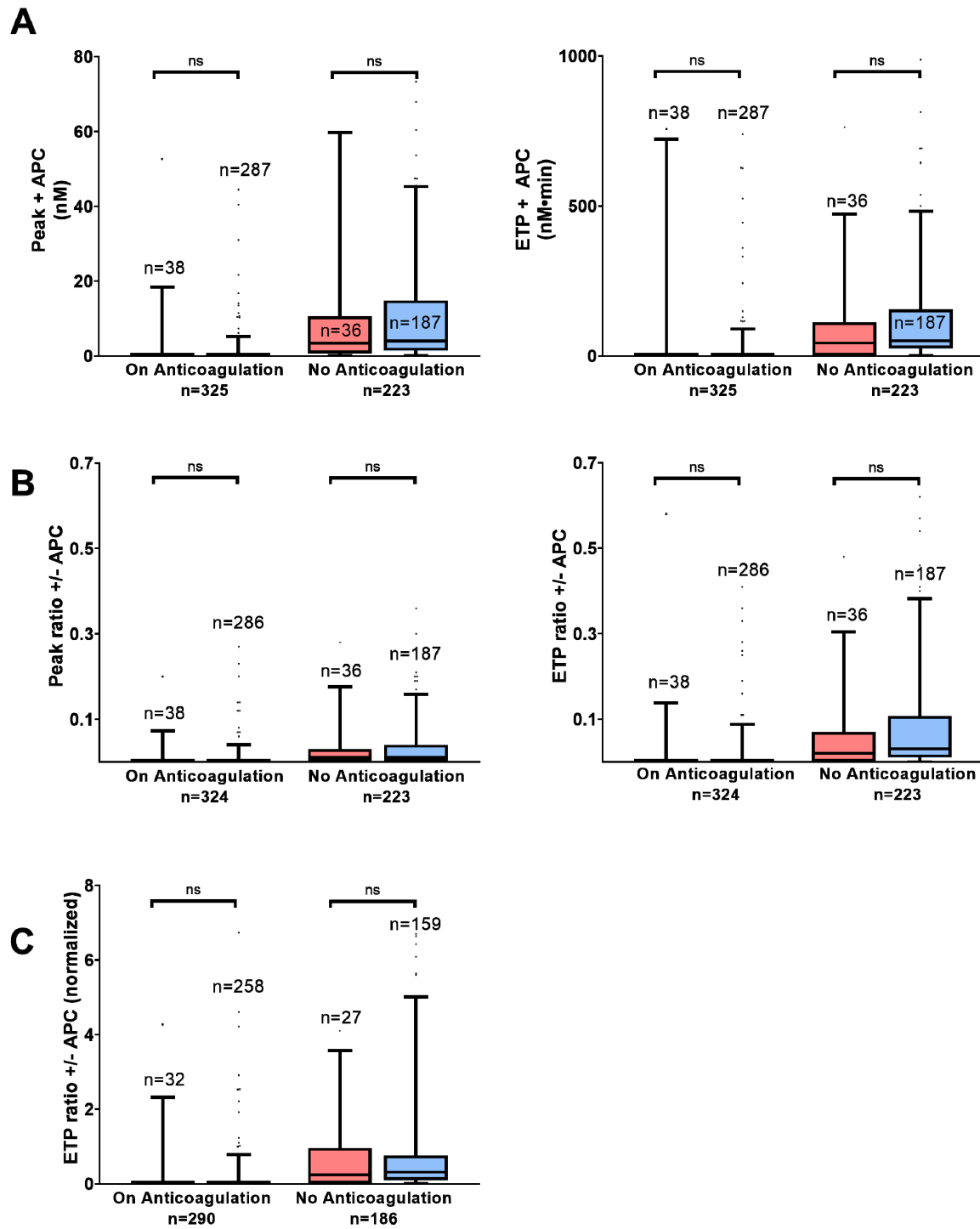


Figure S5. Peak and endogenous thrombin potential (ETP) in patients under anticoagulation and not under anticoagulation after index venous thromboembolism (VTE) using 13.6 pM tissue factor with activated protein C (APC) (A), peak and ETP ratio with and without APC (B), ETP with and without APC normalized with reference plasma (C). The red boxes indicate patients with VTE recurrence and the blue boxes, those without VTE recurrence up to 24 months following the index VTE. Box-plots of thrombin generation parameters presented as median with interquartile range (5-95%). Groups were compared using Mann-Whitney U test. ns, not significant

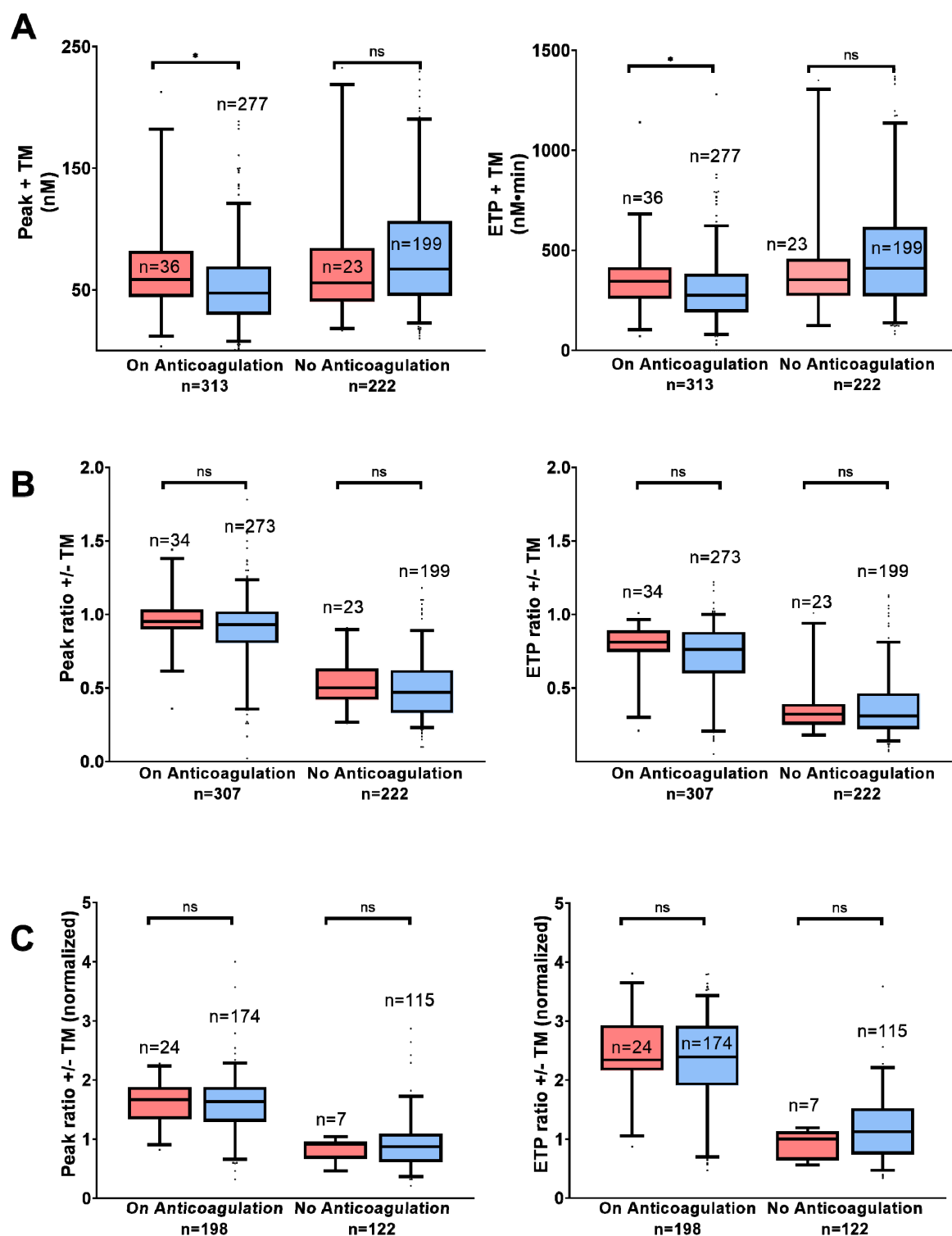


Figure S6. Peak and endogenous thrombin potential (ETP) in patients under anticoagulation and not under anticoagulation after index venous thromboembolism using 1 pM tissue factor with thrombomodulin (TM) (A); ratio (B) and normalized ratio (C) for peak and ETP with and without TM. The red boxes indicate patients who had a major bleeding event and the blue boxes, those without major bleeding up to 24 months following the index VTE. Box-plots of thrombin generation parameters are presented as median with interquartile range (5-95%) are indicated. Groups were compared using the Mann-Whitney U test. ns, not significant; *P<0.05

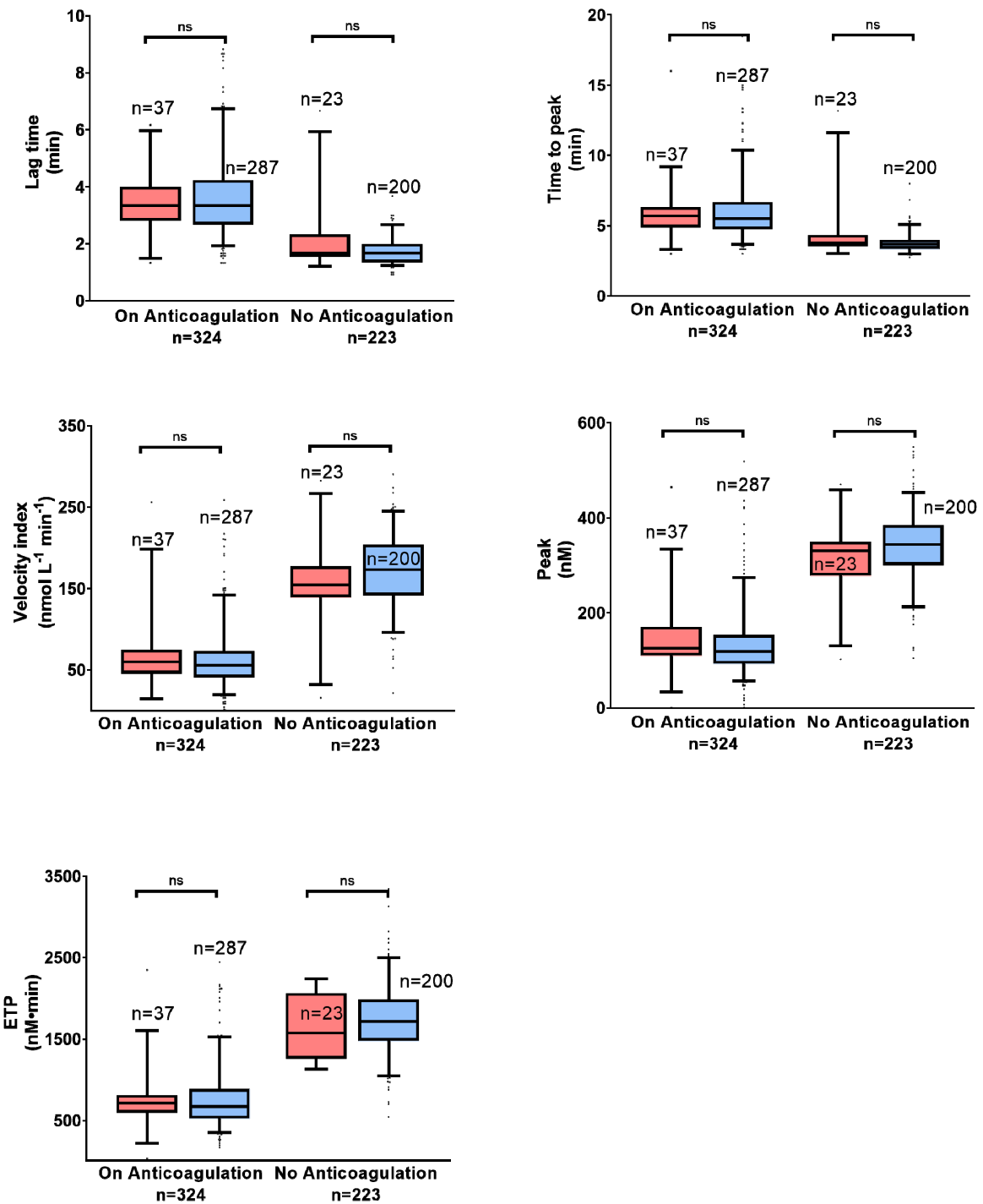


Figure S7. Thrombin generation parameters in patients under anticoagulation and not under anticoagulation after index venous thromboembolism using 13.6 pM tissue factor without activated protein C (APC). The red boxes indicate patients who had a major bleeding event and the blue boxes, those without major bleeding up to 24 months following the index VTE. Box-plots of thrombin generation parameters are presented as median with interquartile range (5-95%) are indicated. Groups were compared using the Mann-Whitney U test. ETP, endogenous thrombin potential, ns, not significant

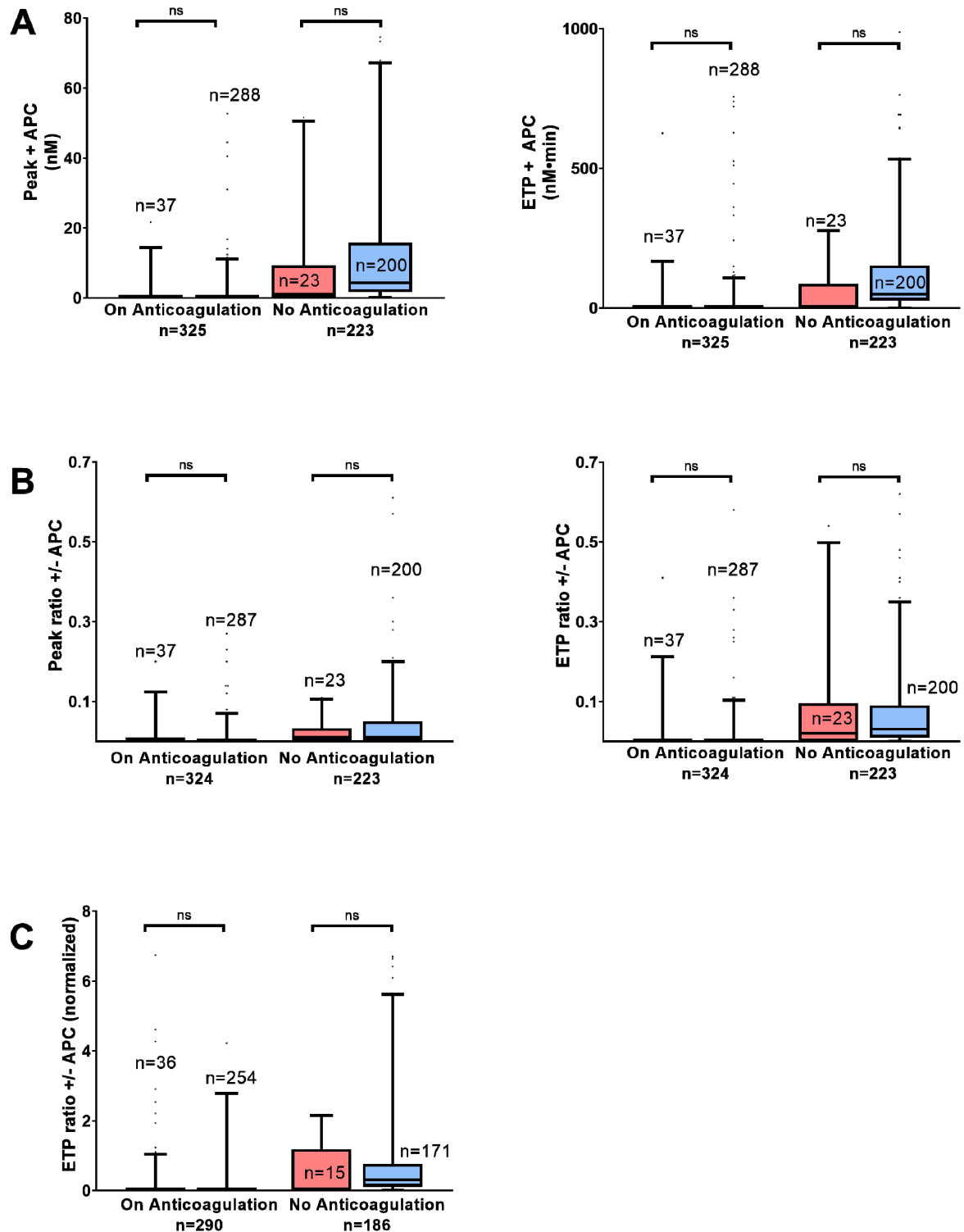


Figure S8. Thrombin generation parameters in patients under anticoagulation and not under anticoagulation after index venous thromboembolism using 13.6 pM tissue factor with activated protein C (APC) (A), calculated ratio for peak and endogenous thrombin potential (ETP) (B) and normalized ratio (C) for ETP with and without APC. The red boxes indicate patients who had a major bleeding event and the blue boxes, those without major bleeding up to 24 months following the index VTE. Box-plots of thrombin generation parameters are presented as median with interquartile range (5-95%) are indicated. Groups were compared using the Mann-Whitney U test. ns, not significant

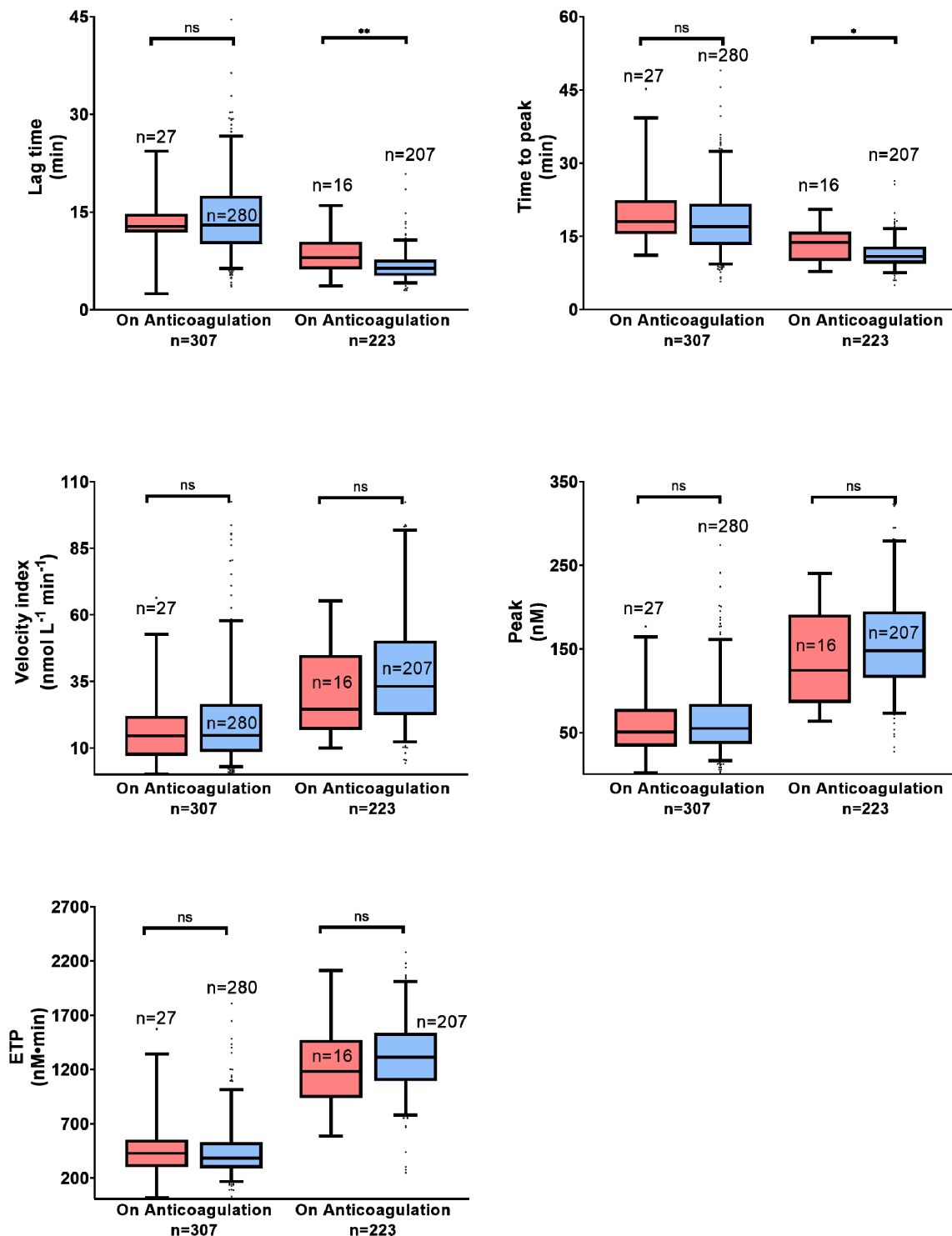


Figure S9. Thrombin generation parameters in patients under anticoagulation and not under anticoagulation after index venous thromboembolism using 1 pM tissue factor without thrombomodulin (TM). The red boxes indicate patients who died and the blue boxes, those who did not up to 24 months following the index VTE. Box-plots of thrombin generation parameters are presented as median with interquartile range (5-95%) are indicated. Groups were compared using the Mann-Whitney U test. ETP, endogenous thrombin potential; ns, not significant; **P<0.01, *P<0.05

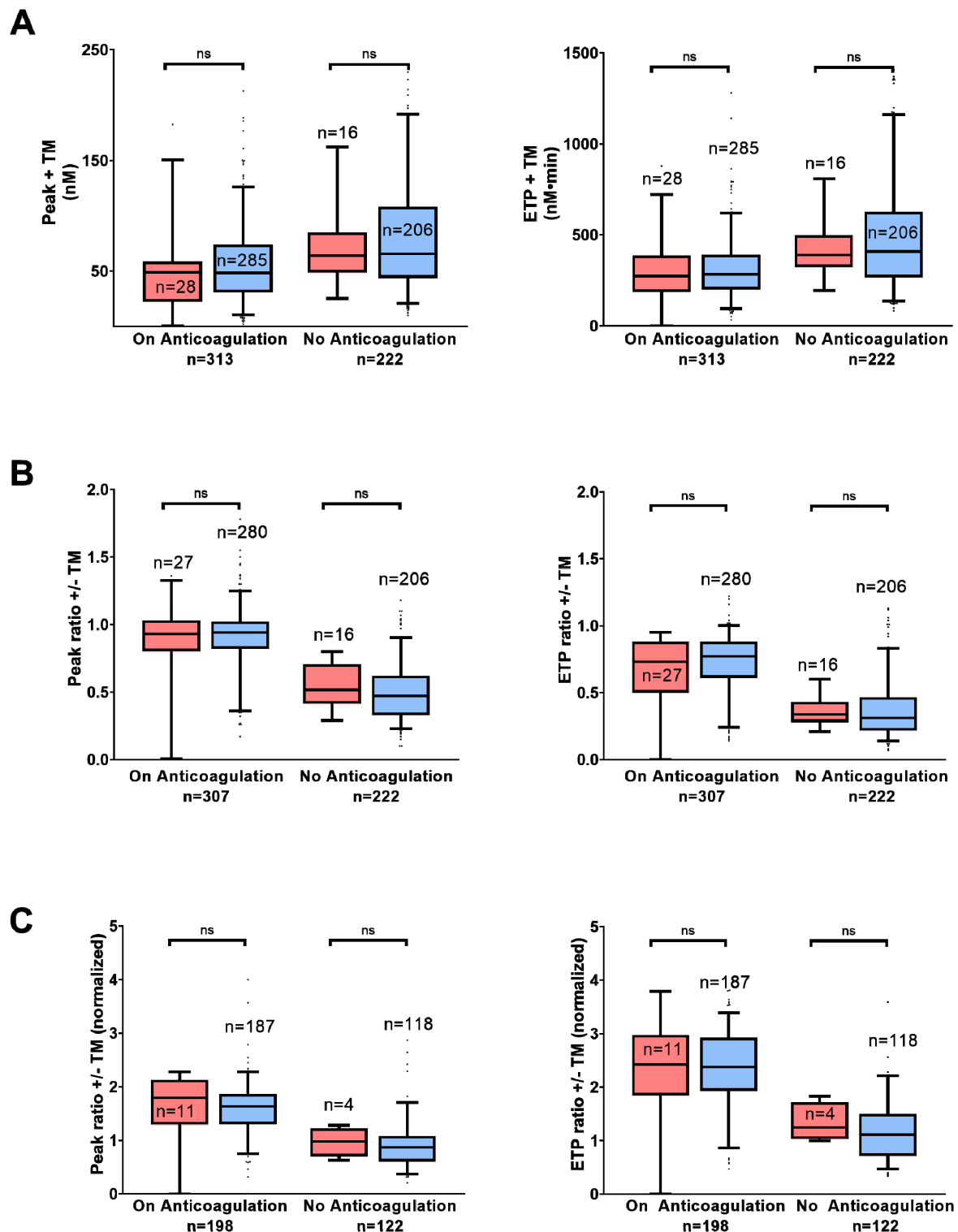


Figure S10. Peak and ETP in patients under anticoagulation and not under anticoagulation after index venous thromboembolism using 1 pM tissue factor with thrombomodulin (TM) (A), calculated ratio (B) and normalized ratio (C) for peak and endogenous thrombin potential (ETP) with and without TM. The red boxes indicate patients who died and the blue boxes, those who did not up to 24 months following the index VTE. Box-plots of thrombin generation parameters are presented as median with interquartile range (5-95%) are indicated. Groups were compared using the Mann-Whitney U test. ns, not significant

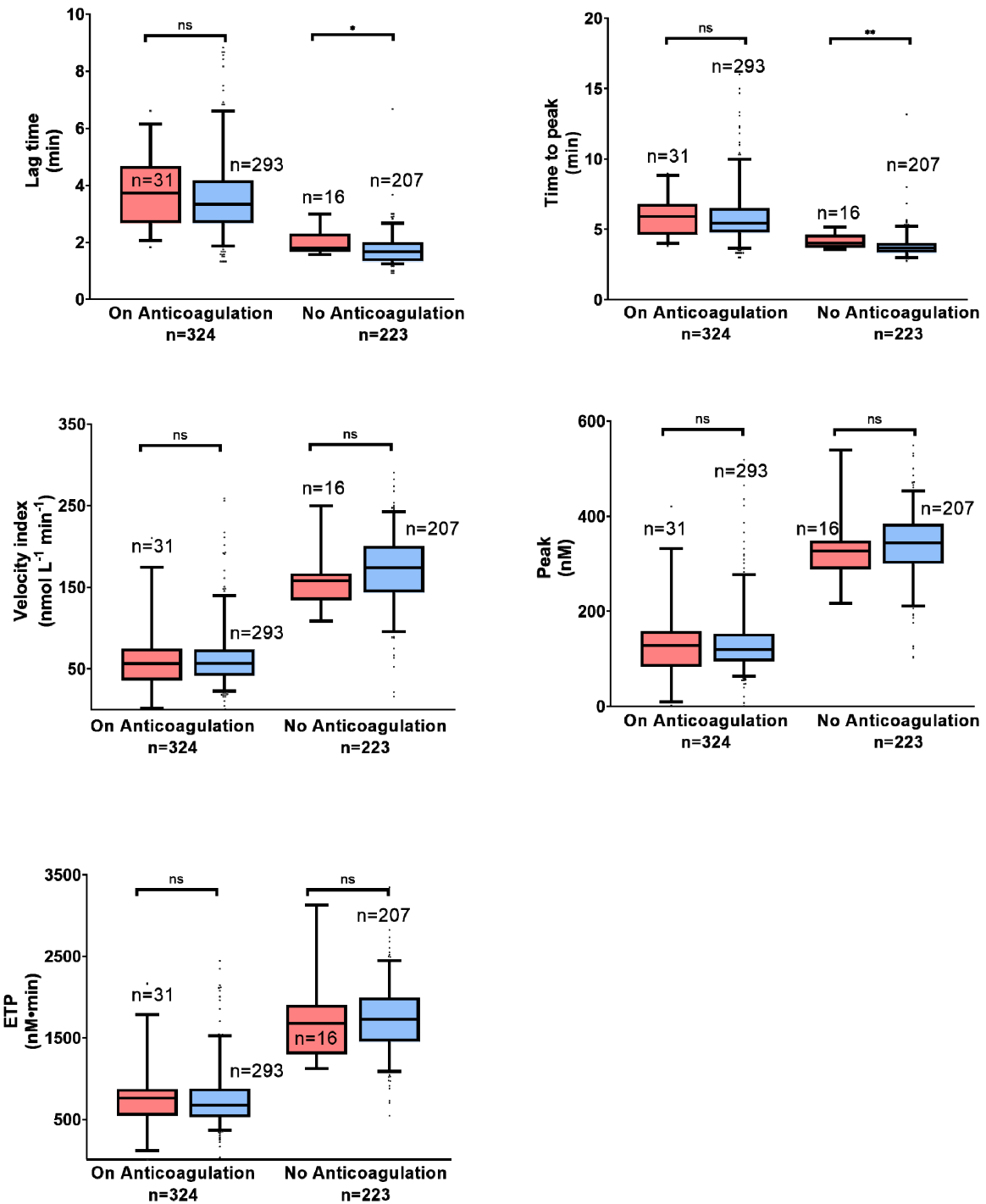


Figure S11. Thrombin generation parameters in patients under anticoagulation and not under anticoagulation after index venous thromboembolism using 13.6 pM tissue factor without activated protein C. The red boxes indicate patients who died and the blue boxes, those who did not up to 24 months following the index VTE. Box-plots of thrombin generation parameters are presented as median with interquartile range (5-95%) are indicated. Groups were compared using the Mann-Whitney U test. ETP, endogenous thrombin potential; ns, not significant; **P<0.01; *P<0.05

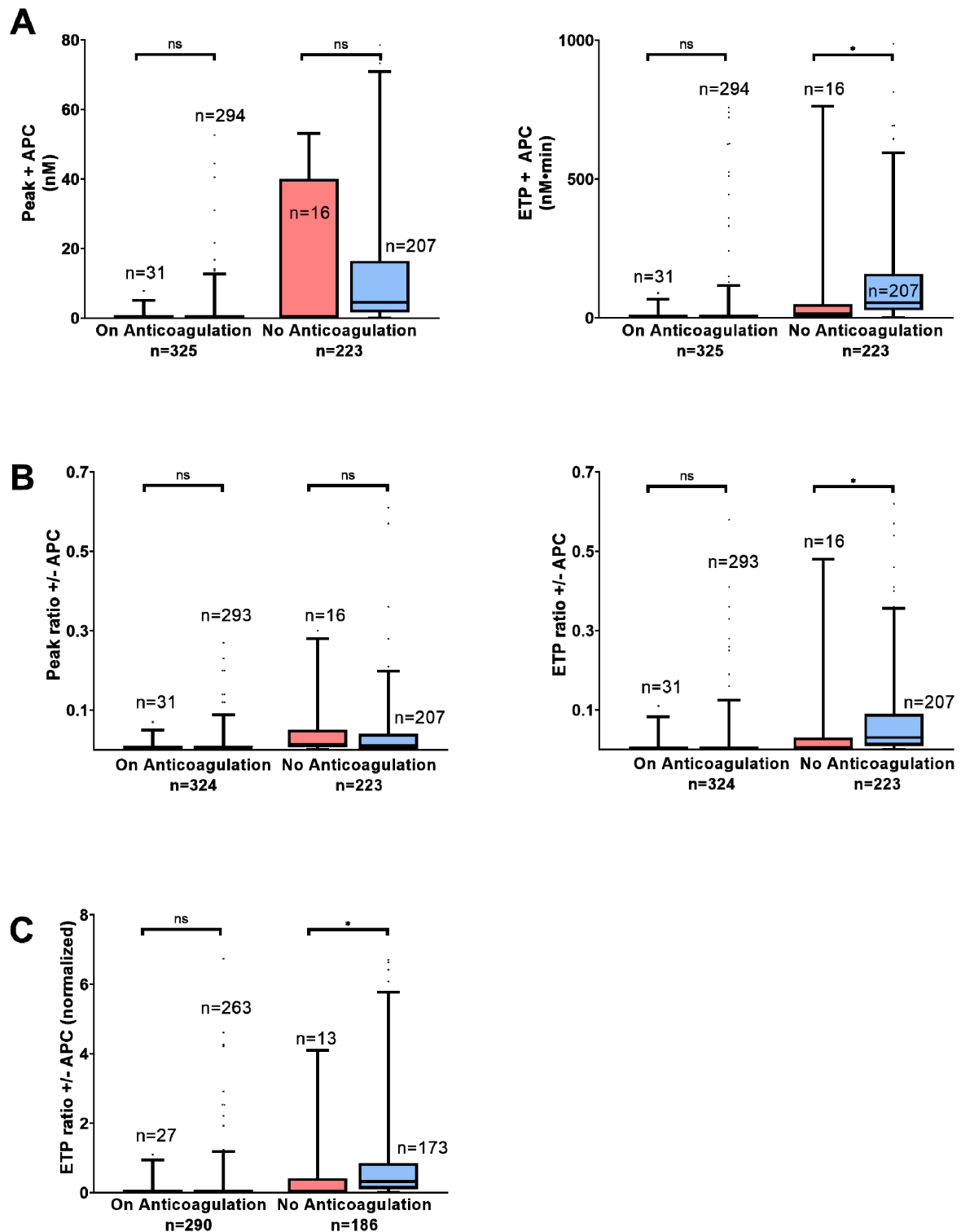


Figure S12. Peak and endogenous thrombin potential (ETP) in patients under anticoagulation and not under anticoagulation after index venous thromboembolism using 13.6 pM tissue factor with activated protein C (APC) (A), calculated ratio for endogenous thrombin potential (ETP) and peak (B) and normalized ratio (C) for peak and ETP with and without APC. The red boxes indicate patients who died and the blue boxes, those who did not up to 24 months following the index VTE. Box-plots of thrombin generation parameters are presented as median with interquartile range (5-95%) are indicated. Groups were compared using the Mann-Whitney U test. ns, not significant; *P<0.05

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