

# A randomised controlled trial of extended anticoagulation treatment versus standard treatment for the prevention of recurrent venous thromboembolism (VTE) and post-thrombotic syndrome in patients being treated for a first episode of unprovoked VTE (the ExACT study)

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**Table 1- Baseline Characteristics**

<b>Characteristic</b>	<b>Discontinued AT N=134</b>	<b>Extended AT N=139</b>	<b>Total N=273</b>
<b>Age at time of randomisation</b>			
Mean (SD)	63.3 (12.7)	62.2 (13.0)	62.7 (12.8)
Median (IQR)	64.5 (55.6-74.0)	64.4 (53.3-72.4)	64.4 (54.4-72.7)
<b>Sex, n (%)</b>			
Female	44 (32.8)	45 (32.4)	89 (32.6)
Male	90 (67.2)	94 (67.6)	184 (67.4)
<b>Diagnosis (DVT/PE)<sup>1</sup>, n (%)</b>			
Unprovoked DVT	69 (51.5)	70 (50.4)	139 (50.9)
Unprovoked PE	65 (48.5)	69 (49.6)	134 (49.1)
<b>Ethnicity, n (%)</b>			
White	131 (97.8)	131 (94.2)	262 (96.0)
Mixed	1 (0.8)	0 (0.0)	1 (0.4)
Asian or Asian British	0 (0.0)	3 (2.2)	3 (1.1)
Black or Black British	2 (1.5)	5 (3.6)	7 (2.6)
Other ethnic groups	0 (0.0)	0 (0.0)	0 (0.0)
<b>Smoking status, n (%)</b>			
Non-smoker	63 (47.0)	60 (43.2)	123 (45.1)
Ex-smoker	48 (35.8)	60 (43.2)	108 (39.6)
Current smoker	19 (14.2)	18 (13.0)	37 (13.6)
Smokes occasionally	4 (3.0)	1 (0.7)	5 (1.8)
<b>Alcohol consumption, n (%)</b>			
No	44 (32.8)	51 (36.7)	95 (34.8)
Yes	90 (67.2)	88 (63.3)	178 (65.2)
<b>BMI classification, n (%)</b>			
Underweight (<18.5)	2 (1.5)	0 (0.0)	2 (0.7)
Normal range (18.5-24.99)	47 (35.1)	47 (33.8)	94 (34.4)
Overweight (25-29.99)	51 (38.1)	53 (38.1)	104 (38.1)
Obese (≥30)	33 (24.6)	37 (26.6)	70 (25.6)
Missing	1 (0.8)	2 (1.4)	3 (1.1)
<b>Family history of VTE, n (%)</b>			
No	102 (76.1)	102 (73.4)	204 (74.7)
Yes	32 (23.9)	37 (26.6)	69 (25.3)
<b>Previous medical history</b>			
<b>Stroke, n (%)</b>			
No	130 (97.0)	136 (97.8)	266 (97.4)
Yes	4 (3.0)	3 (2.2)	7 (2.6)
<b>Transient Ischaemic Attack (TIA), n (%)</b>			

No	129 (96.3)	138 (99.3)	267 (97.8)
Yes	5 (3.7)	1 (0.7)	6 (2.2)
<b>Angina, n (%)</b>			
No	129 (96.3)	136 (97.8)	265 (97.1)
Yes	5 (3.7)	3 (2.2)	8 (2.9)
<b>Myocardial Infarction (MI), n (%)</b>			
No	133 (99.3)	134 (96.4)	267 (97.8)
Yes	1 (0.8)	5 (3.6)	6 (2.2)
<b>Ischaemic Heart Disease (IHD), n (%)</b>			
No	130 (97.0)	136 (97.8)	266 (97.4)
Yes	4 (3.0)	3 (2.2)	7 (2.6)
<b>Peripheral Vascular Disease (PVD), n (%)</b>			
No	134 (100.0)	134 (96.4)	268 (98.2)
Yes	0 (0.0)	5 (3.6)	5 (1.8)
<b>PTS score (categorical), n (%)</b>			
No PTS	70 (52.2)	66 (47.5)	136 (49.8)
Mild PTS	42 (31.3)	51 (36.7)	93 (34.1)
Moderate PTS	15 (11.2)	18 (13.0)	33 (12.1)
Severe PTS	5 (3.7)	2 (1.4)	7 (2.6)
Missing	2 (1.5)	2 (1.4)	4 (1.5)
<b>PTS score</b>			
Mean (SD)	5.2 (4.2)	5.1 (3.8)	5.2 (4.0)
Median (IQR)	4.0 (2.0-7.5)	5.0 (2.0-8.0)	4.0 (2.0-8.0)
Missing	2	2	4
<b>EQ-5D-3L</b>			
Mean (SD)	0.8 (0.2)	0.8 (0.3)	0.8 (0.3)
Median (IQR)	0.8 (0.7-1.0)	0.8 (0.7-1.0)	0.8 (0.7-1.0)
Missing	0	4	4
<b>VEINES-QOL score</b>			
Mean (SD)	48.2 (10.7)	49.6 (9.9)	48.9 (10.3)
Median (IQR)	51.1 (41.1-57.6)	53.0 (44.6-56.7)	52.1 (43.3-57.5)
Missing	0	2	2
<b>Health care utilisation due to PTS</b>			
<b>Patient receiving primary care treatment, n (%)</b>			
No	124 (92.5)	128 (92.1)	252 (92.3)
Yes	9 (6.7)	11 (7.9)	20 (7.3)
Missing	1 (0.8)	0 (0.0)	1 (0.4)
<b>Type of nurse patients were</b>			

<b>seen by, n (%)</b>			
Practice	2 (1.5)	1 (0.7)	3 (1.1)
District	0 (0.0)	0 (0.0)	0 (0.0)
HCA	0 (0.0)	0 (0.0)	0 (0.0)
None	59 (44.0)	70 (50.4)	129 (47.3)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Missing	73 (54.5)	68 (48.9)	141 (51.7)
<b>Patient receiving treatment for a leg ulcer, n (%)</b>			
No	66 (49.3)	71 (51.1)	137 (50.2)
Yes	1 (0.8)	2 (1.4)	3 (1.1)
Missing	67 (50.0)	66 (47.5)	133 (48.7)
<b>Patient receiving secondary care treatment, n (%)</b>			
No	131 (97.8)	135 (97.1)	266 (97.4)
Yes	1 (0.8)	4 (2.9)	5 (1.8)
Missing	2 (1.5)	0 (0.0)	2 (0.7)

<sup>1</sup>minimisation variable

**Table 2A - Primary and secondary outcomes**

Outcome	Discontinued AT N=134	Extended AT N=139	Adjusted hazard ratio (95% CI) <sup>†</sup>	P-value
<b>Primary outcome</b>				
Recurrent VTE				
No of participants with ≥ 1 event - n (%)	31 (23.1)	7 (5.0)	0.20 (0.09, 0.46)	<0.001
No. of events <sup>‡</sup>	32	7		
No./100 person-years <sup>‡</sup>	13.54	2.75		
<b>Secondary outcomes</b>				
Major bleeding events			2.99 (0.81, 11.05)	0.100
No of participants with ≥ 1 event - n (%)	3 (2.2)	9 (6.5)		
No. of events	3	9		
No./100 person-years <sup>‡</sup>	1.18	3.54		
Clinically relevant non-major bleeding events			1.51 (0.84, 2.71)	0.165
No of participants with ≥ 1 event and non-missing event dates <sup>*</sup> - n (%)	19 (14.2)	28 (20.1)		
No of participants with ≥ 1 event <sup>*</sup> - n (%)	21 (15.7)	32 (23.0)		
No. of events <sup>*</sup>	25	43		
No./100 person-years <sup>‡</sup>	8.13	12.50		

<sup>†</sup> Adjusting for baseline diagnosis (DVT/PE).  
<sup>‡</sup> One participant in the discontinued AT group had two thrombotic events within the two year follow-up period.  
<sup>\*</sup> Number of events per 100 person-years was calculated only for the first events with a non-missing event time.  
<sup>\*</sup> 2 participants in the discontinued AT group and 7 in the extended AT group had two or more thrombotic events within the two year follow-up period, resulting in 15 repeated occurrences in total. Among the 53 time to first events, 6 events (2 in the discontinued AT group and 4 in the extended AT group) had their event time missing (all of which should have occurred before the end of two-year follow up by checking the corresponding visit number); so only 47 events contributed to the calculation of the adjusted hazard ratio.

**Table 2B. Sub-Group analysis of primary and secondary outcomes**

Characteristic	Discontinued AT N=134		Extended AT N=139		Hazard ratio (95% CI) <sup>†</sup>	P-value for interaction
	N of events (%)	N/100 person-years	N of events (%)	N/100 person- years		
<b>Recurrent VTE</b>						
Sex						0.099
Male	23 (25.6)	15.26	3 (3.2)	1.75	0.11 (0.03, 0.38)	
Female	8 (18.2)	10.23	4 (8.9)	4.83	0.48 (0.14, 1.59)	
Age						0.267
≤ 65 years	17 (23.3)	13.77	2 (2.8)	1.52	0.11 (0.03, 0.48)	
> 65 years	14 (23.0)	13.28	5 (7.5)	4.07	0.31 (0.11, 0.85)	
<b>Major bleeding events</b>						
Sex						0.961
Male	2 (2.2)	1.18	6 (6.4)	3.57	2.92 (0.59, 14.48)	
Female	1 (2.3)	1.18	3 (6.7)	3.49	3.13 (0.33, 30.12)	
Age						0.190
≤ 65 years	2 (2.7)	1.45	2 (2.8)	1.50	1.01 (0.14, 7.17)	
> 65 years	1 (1.6)	0.86	7 (10.5)	5.79	6.89 (0.85, 56.03)	

<sup>†</sup> Adjusting for baseline diagnosis (DVT/PE), the interaction between treatment and each of the two covariates (age and sex), separately, together with their main effects.

**Table 3A. Association of baseline D-dimer and risk of VTE recurrence**

D-dimer at baseline ( $\mu\text{g/ml}$ )	No recurrence (N=235)	Recurrent venous thromboembolism (N=38)	Total (N=273)
Baseline D-dimer < 0.5 (%)	216 (86.74)	33 (13.25)	249
Baseline D-dimer $\geq$ 0.5 (%)	9 (75)	3 (25)	12
Missing	10	2	12

**Table 3B The Therapeutic Time in Range (TTR) for the Intervention group (extended AT) by the recurrence of venous thromboembolism (18 participants with zero TTRs were excluded)**

TTR	No recurrence (N=116)	Recurrent venous thromboembolism (N=5)*	Total (N=121)
Mean (sd)	76.27 (15.27)	83.93 (13.86)	76.59 (15.24)
Median (IQR)	77.03 (67.81-86.53)	76.95 (75.22-97.63)	77.02 (68.21-86.66)

\*2 patients excluded, 1 patient received rivaroxaban and 1 patient did not attend for INR monitoring

**Table 4A - Secondary outcomes (continuous)**

Outcome	Discontinued AT N=134		Extended AT N=139		P-value for time-treatment interaction
	N	Adjusted mean <sup>†</sup> (95% CI)	N	Adjusted mean <sup>†</sup> (95% CI)	
VEINES-QOL					0.766
6 months	118	50.13 (48.98, 51.29)	126	49.87 (48.74, 51.00)	
12 months	116	50.13 (48.97, 51.29)	124	50.34 (49.20, 51.48)	
18 months	112	50.74 (49.57, 51.91)	117	50.20 (49.04, 51.35)	
24 months	108	50.33 (49.14, 51.51)	120	50.30 (49.16, 51.45)	
EQ-5D-3L					0.908
6 months	118	0.80 (0.76, 0.83)	126	0.81 (0.78, 0.84)	
12 months	117	0.81 (0.77, 0.84)	124	0.81 (0.78, 0.85)	
18 months	113	0.82 (0.79, 0.86)	117	0.82 (0.79, 0.86)	
24 months	108	0.82 (0.79, 0.85)	120	0.81 (0.78, 0.85)	
Severity of PTS**					0.907
6 months	117	4.77 (4.24, 5.30)	126	4.73 (4.22, 5.25)	
12 months	116	4.68 (4.14, 5.21)	123	4.88 (4.36, 5.40)	
18 months	111	4.73 (4.19, 5.28)	115	4.96 (4.43, 5.49)	
24 months	110	5.00 (4.45, 5.54)	120	5.09 (4.57, 5.62)	
	N	%	N	%	
Category of PTS**					
6 months					
None (0-4)	66	49.25	71	51.08	
Mild (5-9)	42	31.34	36	25.90	
Moderate (10-14)	7	5.22	15	10.79	
Severe (≥15)	2	1.49	4	2.88	
12 months					
None (0-4)	67	50.00	71	51.08	
Mild (5-9)	38	28.36	38	27.34	
Moderate (10-14)	10	7.46	10	7.19	
Severe (≥15)	1	0.75	4	2.88	
18 months					
None (0-4)	63	47.01	63	45.32	
Mild (5-9)	39	29.10	37	26.62	
Moderate (10-14)	8	5.97	11	7.91	
Severe (≥15)	1	0.75	4	2.88	
24 months					
None (0-4)	66	49.25	65	46.76	
Mild (5-9)	29	21.64	37	26.62	
Moderate (10-14)	11	8.21	12	8.63	
Severe (≥15)	4	2.99	6	4.32	

<sup>†</sup> A linear mixed model was fitted adjusting for the corresponding baseline response, baseline diagnosis (DVT/PE), treatment, the time of assessments and the interaction between treatment and time. \*\*Worst score from both legs.

**Table 4b - Secondary outcomes (continuous) – PTS for participants diagnosed at baseline with unprovoked DVT**

Outcome	Discontinued AT N=69		Extended AT N=70		P-value for time-treatment interaction
	N	Adjusted mean <sup>†</sup> (95% CI)	N	Adjusted mean <sup>†</sup> (95% CI)	
Severity of PTS**					0.576
6 months	62	5.19 (4.44, 5.93)	65	5.16 (4.44, 5.89)	
12 months	63	4.76 (4.01, 5.50)	65	5.11 (4.39, 5.84)	
18 months	59	4.91 (4.15, 5.67)	62	5.64 (4.90, 6.38)	
24 months	59	5.41 (4.65, 6.17)	63	5.47 (4.74, 6.21)	
	N	%	N	%	
Category of PTS**					
6 months					
None (0-4)	30	43.48	37	52.86	
Mild (5-9)	27	39.13	18	25.71	
Moderate (10-14)	3	4.35	7	10.00	
Severe (≥15)	2	2.90	3	4.29	
12 months					
None (0-4)	33	47.83	40	57.14	
Mild (5-9)	23	33.33	18	25.71	
Moderate (10-14)	7	10.14	4	5.71	
Severe (≥15)	0	0.00	3	4.29	
18 months					
None (0-4)	33	47.83	31	44.29	
Mild (5-9)	19	27.54	21	30.00	
Moderate (10-14)	7	10.14	7	10.00	
Severe (≥15)	0	0.00	3	4.29	
24 months					
None (0-4)	31	44.93	32	45.71	
Mild (5-9)	18	26.09	21	30.00	
Moderate (10-14)	8	11.59	8	11.43	
Severe (≥15)	2	2.90	2	2.86	
<sup>†</sup> A linear mixed model was fitted adjusting for the corresponding baseline response, baseline diagnosis (DVT/PE), treatment, the time of assessments and the interaction between treatment and time. **Worst score from both legs.					