# 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

| Characteristic | Discontinued AT N=134 | Extended AT N=139 | Total N=273 |
|---|---|---|---|
| **Age at time of randomisation** | | | |
| 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) |
| **Sex, n (%)** | | | |
| Female | 44 (32.8) | 45 (32.4) | 89 (32.6) |
| Male | 90 (67.2) | 94 (67.6) | 184 (67.4) |
| **Diagnosis (DVT/PE)[1], n (%)** | | | |
| Unprovoked DVT | 69 (51.5) | 70 (50.4) | 139 (50.9) |
| Unprovoked PE | 65 (48.5) | 69 (49.6) | 134 (49.1) |
| **Ethnicity, n (%)** | | | |
| 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) |
| **Smoking status, n (%)** | | | |
| 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) |
| **Alcohol consumption, n (%)** | | | |
| No | 44 (32.8) | 51 (36.7) | 95 (34.8) |
| Yes | 90 (67.2) | 88 (63.3) | 178 (65.2) |
| **BMI classification, n (%)** | | | |
| 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) |
| **Family history of VTE, n (%)** | | | |
| No | 102 (76.1) | 102 (73.4) | 204 (74.7) |
| Yes | 32 (23.9) | 37 (26.6) | 69 (25.3) |
| **Previous medical history** | | | |
| **Stroke, n (%)** | | | |
| No | 130 (97.0) | 136 (97.8) | 266 (97.4) |
| Yes | 4 (3.0) | 3 (2.2) | 7 (2.6) |
| **Transient Ischaemic Attack (TIA), n (%)** | | | |

| | | | |
|---|---|---|---|
| No | 129 (96.3) | 138 (99.3) | 267 (97.8) |
| Yes | 5 (3.7) | 1 (0.7) | 6 (2.2) |
| **Angina, n (%)** | | | |
| No | 129 (96.3) | 136 (97.8) | 265 (97.1) |
| Yes | 5 (3.7) | 3 (2.2) | 8 (2.9) |
| **Myocardial Infarction (MI), n (%)** | | | |
| No | 133 (99.3) | 134 (96.4) | 267 (97.8) |
| Yes | 1 (0.8) | 5 (3.6) | 6 (2.2) |
| **Ischaemic Heart Disease (IHD), n (%)** | | | |
| No | 130 (97.0) | 136 (97.8) | 266 (97.4) |
| Yes | 4 (3.0) | 3 (2.2) | 7 (2.6) |
| **Peripheral Vascular Disease (PVD), n (%)** | | | |
| No | 134 (100.0) | 134 (96.4) | 268 (98.2) |
| Yes | 0 (0.0) | 5 (3.6) | 5 (1.8) |
| **PTS score (categorical), n (%)** | | | |
| 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) |
| **PTS score** | | | |
| 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 |
| **EQ-5D-3L** | | | |
| 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 |
| **VEINES-QOL score** | | | |
| 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 |
| **Health care utilisation due to PTS** | | | |
| **Patient receiving primary care treatment, n (%)** | | | |
| 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) |
| **Type of nurse patients were** | | | |

| | | | |
|---|---|---|---|
| **seen by, n (%)** | | | |
| 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) |
| **Patient receiving treatment for a leg ulcer, n (%)** | | | |
| 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) |
| **Patient receiving secondary care treatment, n (%)** | | | |
| 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) |

[1]minimisation variable

## Table 2A - Primary and secondary outcomes

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

[†]Adjusting for baseline diagnosis (DVT/PE).

[±]One participant in the discontinued AT group had two thrombotic events within the two year follow-up period.

[‡]Number of events per 100 person-years was calculated only for the first events with a non-missing event time.

*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)[†] | P-value for interaction |
|---|---|---|---|---|---|---|
| | N of events (%) | N/100 person-years | N of events (%) | N/100 person-years | | |
| **Recurrent VTE** | | | | | | |
| 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) | |
| **Major bleeding events** | | | | | | |
| 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) | |

[†] 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 (µg/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 ≥ 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† (95% CI) | N | Adjusted mean† (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 | |

† 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† (95% CI) | N | Adjusted mean† (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 | |

† 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.