**SUPPLEMENTARY MATERIALS**

**TABLE**

**Table S1.** Patient characteristics by thrombin generation testing status one year after index venous thromboembolism (VTE)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristic\*** | **All n (%) or median (IQ-range)** | **Tested****n (%) or median (IQ-range)** | **Untested****n (%) or median (IQ-range)** | ***P*-value** |
| **Total number of patients** | 995 | 565 | 430 |   |
| **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%)  |  239 (42%)  |  227 (53%)  |  0.001  |
| **Index VTE event** |   |   |   |  0.788  |
|  **PE only** |  553 (56%)  |  317 (56%)  |  236 (55%)  |   |
|  **DVT only** |  307 (31%)  |  175 (31%)  |  132 (31%)  |   |
|  **PE and DVT** |  135 (14%)  |  73 (13%)  |  62 (14%)  |   |
| **Index DVT type\*** |   |   |   |  0.014  |
|  **proximal DVT only** |  197 (20%)  |  101 (18%)  |  96 (22%)  |   |
|  **distal DVT only** |  109 (11%)  |  58 (10%)  |  51 (12%)  |   |
|  **proximal and distal DVT** |  134 (13%)  |  89 (16%)  |  45 (10%)  |   |
| **Type of index VTE** |   |   |   | <0.001  |
|  **cancer-related VTE** |  179 (18%)  |  64 (11%)  |  115 (27%)  |   |
|  **provoked index VTE** |  215 (22%)  |  114 (20%)  |  101 (23%)  |   |
|  **unprovoked index VTE** |  599 (60%)  |  387 (68%)  |  212 (49%)  |   |
| **Current oestrogen therapy during the last 3 months** |  32 (3%)  |  19 (3%)  |  13 (3%)  |  0.857  |
| **Immobilization during the last 3 months** |  219 (22%)  |  96 (17%)  |  123 (29%)  | <0.001  |
| **Major surgery during the last 3 months** |  150 (15%)  |  81 (14%)  |  69 (16%)  |  0.474  |
| **Prior VTE** |  283 (28%)  |  172 (30%)  |  111 (26%)  |  0.136  |
| **PTS\*** |  503 (51%)  |  295 (52%)  |  208 (48%)  |  0.299  |
| **History of major bleeding** |  101 (10%)  |  44 (8%)  |  57 (13%)  |  0.006  |
| **Chronic liver disease** |  14 (1%)  |  8 (1%)  |  6 (1%)  |  1.000  |
| **Chronic renal disease** |  185 (19%)  |  101 (18%)  |  84 (20%)  |  0.511  |
| **Chronic or acute heart failure** |  115 (12%)  |  67 (12%)  |  48 (11%)  |  0.765  |
| **Cerebrovascular disease (stroke, TIA)** |  92 (9%)  |  44 (8%)  |  48 (11%)  |  0.077  |
| **Diabetes mellitus** |  155 (16%)  |  89 (16%)  |  66 (15%)  |  0.930  |
| **BMI >30 kg m-2\*** |  238 (24%)  |  141 (25%)  |  97 (23%)  |  0.499  |
| **High risk of fall** |  457 (46%)  |  238 (42%)  |  219 (51%)  |  0.004  |
| **Acute rheumatic disease during the last 3 months** |  32 (3%)  |  18 (3%)  |  14 (3%)  |  1.000  |
| **Inflammatory bowel disease** |  32 (3%)  |  19 (3%)  |  13 (3%)  |  0.857  |
| **Severe infection or sepsis during the last 3 months** |  83 (8%)  |  47 (8%)  |  36 (8%)  |  1.000  |
| **Anemia\*** |  389 (39%)  |  189 (33%)  |  200 (47%)  | <0.001  |
| **Platelet count <150 G L-1\*** |  140 (14%)  |  79 (14%)  |  61 (14%)  |  1.000  |
| **Concomitant antiplatelet therapy** |  322 (32%)  |  177 (31%)  |  145 (34%)  |  0.412  |
| **Concomitant antiplatelet/NSAID therapy** |  381 (38%)  |  207 (37%)  |  174 (40%)  |  0.211  |
| **Arterial hypertension** |  640 (64%)  |  365 (65%)  |  275 (64%)  |  0.947  |
| **Heart rate ≥110 beats min-1\*** |  88 (9%)  |  47 (8%)  |  41 (10%)  |  0.573  |
| **Systolic BP <100 mmHg\*** |  35 (4%)  |  12 (2%)  |  23 (5%)  |  0.009  |
| **Respiratory rate ≥30 min-1\*** |  33 (3%)  |  15 (3%)  |  18 (4%)  |  0.291  |
| **Temperature <36C°\*** |  70 (7%)  |  36 (6%)  |  34 (8%)  |  0.379  |
| **Arterial oxygen saturation <90%\*** |  107 (11%)  |  54 (10%)  |  53 (12%)  |  0.141  |
| **D-dimer at the time of the index VTE\*** |  2507.0 (1579.3; 3811.3) |  2482.0 (1599.0; 3757.0) |  2615.0 (1548.0; 3993.0) |  0.427  |
| **Factor VIII >164%\*** |  573 (58%)  |  345 (61%)  |  228 (53%)  |  0.884  |
| **Factor IX >134% (females) >138% (males\*** |  157 (16%)  |  90 (16%)  |  67 (16%)  |  0.417  |
| **Factor XI >139% (females) >138% (males)\*** |  96 (10%)  |  56 (10%)  |  40 (9%)  |  0.660  |
| **Fibrinogen >4.2 g L-1\*** |  511 (51%)  |  307 (54%)  |  204 (47%)  |  0.832  |
| **Factor V Leiden mutation, present\*** |  82 (8%)  |  54 (10%)  |  28 (7%)  |  0.343  |
| **Factor II G20210A mutation, present\*** |  49 (5%)  |  32 (6%)  |  17 (4%)  |  0.549  |
| **Overall anticoagulation duration (days)** | 413 (178; 896) |  645.0 (213.0; 976.0) |  242.0 (94.0; 636.5) | <0.001  |
| **Anticoagulation duration until one year after the index VTE (days)** | 324 (171; 368) |  354.0 (194.0; 365.0) |  225.0 (94.0; 435.0) |  0.003  |
| **Anticoagulation duration from one year after the index VTE (days)** | 276 (0; 688) |  338.0 (0.0; 685.5) |  110.0 (0.0; 697.5) |  0.117  |

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%).

**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 grey boxes indicate patients with VTE recurrence and the white 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 thromboembolim (VTE) using 13.6 pM tissue factor without activated protein C. The grey boxes indicate patients with VTE recurrence and the white 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 thromboembolim (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 grey boxes indicate patients with VTE recurrence and the white 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 grey boxes indicate patients who had a major bleeding event and the white 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 thromboembolim using 13.6 pM tissue factor without activated protein C (APC). The grey boxes indicate patients who had a major bleeding event and the white 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 thromboembolim 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 grey boxes indicate patients who had a major bleeding event and the white 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 thromboembolim using 1 pM tissue factor without thrombomodulin (TM). The grey boxes indicate patients who died and the white 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 thromboembolim 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 grey boxes indicate patients who died and the white 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 grey boxes indicate patients who died and the white 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 grey boxes indicate patients who died and the white 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