Regular Article

Long-term death and recurrence in patients with acute venous thromboembolism: The MASTER registry

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Abstract

Background: The long-term clinical outcome of VTE has been essentially assessed in cohorts of selected patients. The aim of this multicenter registry was to prospectively assess the long-term clinical outcome in a cohort of unselected patients with objectively confirmed acute VTE.

Materials and Methods: Death and VTE recurrence at 24 months were the main study outcomes. Univariate and multivariate survival analyses were performed according to the Kaplan-Meyer and Cox proportional hazard model, respectively.

Results: 2119 patients with acute VTE were included in the registry: 1541 (72.7%) with deep vein thrombosis, 206 (9.7%) with pulmonary embolism and 372 (17.6%) with both. Information about death was available in 2021 patients (95.4%) and about recurrence in 1988 patients (93.8%). 167 patients (4.55% patient-year) died during follow-up. After adjusting for age, cancer (Hazard ratio [HR]: 7.2; 95%CI 4.8-10.8), long-term heparin treatment (HR: 2.5; 95%CI 1.8-3.5), in-hospital management of VTE (HR: 2.0; 95%CI 1.3-3.0), and ileo-caval thrombosis (HR: 1.7; 95%CI 1.2-2.4) were found to be independent predictors of death. 124 (3.63% patient-year) patients had a VTE recurrence during follow-up. In-hospital management of VTE (HR: 1.8; 95%CI 1.2-2.9), male gender (HR: 1.7; 95%CI 1.2-2.4) were independent risk factors for recurrent VTE. Cancer (HR: 1.6; 95%CI 1.0-2.8) showed a trend for increased risk of VTE recurrence (p=0.056). The reported rate of major bleeding was 2.5%.

Conclusions: In a large cohort of unselected VTE patients, cancer, ileo-caval thrombosis, long-term heparin treatment and in-hospital management were associated with increased mortality during long-term follow-up. In-hospital management, male gender were associated with an increased risk of VTE recurrence.

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Patients

We included consecutive patients, aged 18 years or older, with an acute symptomatic, objectively confirmed VTE (deep vein thrombosis, pulmonary embolism or both), who survived after the acute phase of disease and had a life-expectancy of at least 3 months. The study was performed in 25 Italian centers. The study design and the inclusion and exclusion criteria were previously reported in details [7]. The registry did not issue diagnosis algorithms or guidelines for patient management. The follow up period started at the time of first VTE.

Data Collection

Clinical information were captured through an electronic data network, at the time of the index event and at follow-up visits scheduled for up to 24 months. Demographic characteristics, clinical presentation, risk factors for VTE, diagnostic workup and treatment of the index event were previously reported in details [7] and summarized in Table 1.

The major epidemiological features of the overall study MASTER cohort did not differ from those of patients included in the analyses of death and recurrence (Table 2).

Long-term Death and its Major Determinants

Information about death at 24 month-follow up were available in 2021 patients (95.4%): 1002 males and 1019 females. 167 (4.53%p-y) patients died (Fig. 1). Mortality was 1.43%p-y in patients with unprovoked VTE, 20.32%p-y in patients with cancer and 1.73%p-y patients with VTE associated with temporary risk factors (Log-Rank test = 362.7, p < 0.001).

Co-variates included in the analysis and relative HRs are shown in Table 3. Independent predictors of death were cancer (HR: 7.2; 95%CI 4.8-10.8), long-term heparin treatment (HR: 2.5; 95%CI 1.8-3.5), inhospital management of VTE (HR: 2.0; 95%CI 1.3-3.0), and ilio-caval thrombosis (HR: 1.7; 95%CI 1.2-2.4). Elastic stockings were associated with reduced mortality (HR: 0.6; 95%CI 0.5-0.8).

No significant difference in mortality rate between PE and DVT patients was observed.

Reurrence of Venous Thromboembolic Events and its Major Determinants

Information about recurrence of VTE were available in 1988 patients (93.8%): 963 males and 1025 females. 124 (3.63%p-y) patients presented at least one VTE recurrence (Fig. 2). 101 patients (81.5%) recurred with DVT and 23 patients (18.5%) with PE. The rate of recurrence 4.50%p-y in patients with unprovoked VTE, 4.80%p-y in patients with cancer and 2.06%p-y in patients with VTE associated with temporary risk factors (Log-Rank test = 14.60, p < 0.001).

The recurrence rates were 3.84%p-y in patient with DVT alone and 3.09%p-y (Log-Rank test = 1.05, n.s.) in those with PE (with or without DVT). Patients with PE as the index event presented VTE recurrence as PE in 2.7% and as DVT in 2.7% of cases. Patients with DVT as the index event presented VTE recurrence as PE in 0.6% and as DVT in 6.0% of cases. The type of the index event was a strong predictor of the type of recurrence (OR 10.7; 95% CI 3.5-34.4).

Co-variates included in the Cox model analysis and relative HR are shown in Table 4. In-hospital management of VTE (HR: 1.8; 95%CI 1.2-
2.9), male gender (HR: 1.7; 95%CI 1.2-2.4) were independent risk factors for recurrent VTE. Cancer (HR: 1.6; 95%CI 1.0-2.8) showed a trend for increased risk of VTE recurrence (p=0.056). The presence of temporary risk factors was associated with a significant reduction in the recurrent rate of VTE event (HR: 0.4; 95%CI 0.3-0.6).

No significant difference in the recurrent rate of VTE was observed between patients with lower-limb DVT or patients with upper limb DVT.

The death rate of patients with recurrent VTE was 16.5% in comparison with 4.2% of patients without recurrent VTE (Log-rank test = 8.97, p<0.001).

Major Bleeding

Information about bleeding, post-thrombotic syndrome, incident cancer, and arterial thrombosis was available in 1883 patients with at least one complete follow-up visit. The incidence of major bleeding was 2.5% (48/1883); 5.5% (20/363) in patients with cancer either known at the time of the study inclusion or diagnosed during the study period and 1.8% (28/1520) in patients without cancer, corresponding to an OR of 3.1 (95%CI 1.7-5.6). No fatal bleeding was reported.

Bleeding occurred in 1.7% and 2.7% (OR: 0.6; 95%CI 0.2-1.6) of patients while they were receiving heparin or vitamin K antagonists, respectively. In-hospital management of VTE (OR: 3.6; 95%CI 1.2-10.8), and cancer (OR: 3.2; 95%CI 1.6-6.5) were independent risk factors for bleeding complications.

Post-thrombotic Syndrome

The cumulative incidence of post-thrombotic syndrome was 9.7% (182/1883). The incidence was higher in patients with known cancer (92/363, 25.3%) than in patients without known cancer (90/1520, 5.9%) corresponding to an OR of 5.4 (95%CI 3.9-7.4).

The independent risk factors for post-thrombotic syndrome were: in-hospital management (OR: 2.5; 95%CI 1.6-4.1), and cancer (OR: 5.7; 95%CI 3.8-8.5) while the presence of temporary risk factors (OR: 0.7; 95%CI 0.5-1.0), and prescription of elastic stocking (OR: 0.8; 95%CI 0.5-1.1), were found as borderline significant protective factors for post-thrombotic syndrome.

Newly Diagnosed Cancer

The cumulative incidence of newly diagnosed cancer during 24-months follow up was 1.3% (25/1883). The type of cancer was: gastrointestinal cancer in 7 patients, genitourinary cancer in 5 patients, hematologic cancer in 4 patients, lung cancer in 3 patients, central nervous system cancer in 3 patients, breast cancer in 1 patient and other cancer types in 2 patients.
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Conflict of Interest Statement


Table 4
Multivariate analysis of predictors of VTE recurrence.

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Hazard Ratio</th>
<th>95%CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1.2</td>
<td>1.2–2.4</td>
<td>0.007</td>
</tr>
<tr>
<td>Age</td>
<td>1.0</td>
<td>0.9–1.1</td>
<td>0.919</td>
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<tr>
<td>In-hospital management of VTE</td>
<td>1.8</td>
<td>1.2–2.9</td>
<td>0.009</td>
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<td>Thrombolyis</td>
<td>0.4</td>
<td>0.1–1.7</td>
<td>0.223</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>0.8</td>
<td>0.5–1.3</td>
<td>0.424</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.6</td>
<td>1.0–2.8</td>
<td>0.056</td>
</tr>
<tr>
<td>Temporary risk factors</td>
<td>0.4</td>
<td>0.3–0.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>0.5</td>
<td>0.2–1.1</td>
<td>0.108</td>
</tr>
<tr>
<td>Prescription of elastic stockings</td>
<td>1.3</td>
<td>0.8–2.0</td>
<td>0.289</td>
</tr>
<tr>
<td>Long-term treatment with heparin</td>
<td>0.9</td>
<td>0.6–1.6</td>
<td>0.804</td>
</tr>
<tr>
<td>No anticoagulation</td>
<td>1.1</td>
<td>0.1–8.8</td>
<td>0.005</td>
</tr>
<tr>
<td>CavaI filter</td>
<td>1.1</td>
<td>0.8–3.8</td>
<td>0.139</td>
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<tr>
<td>Pulmonary embolism</td>
<td>1.2</td>
<td>0.8–1.7</td>
<td>0.261</td>
</tr>
<tr>
<td>Ileo-caval DVT</td>
<td>1.7</td>
<td>0.7–4.3</td>
<td>0.265</td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>1.7</td>
<td>0.7–4.0</td>
<td>0.199</td>
</tr>
<tr>
<td>Upper limb DVT</td>
<td>1.1</td>
<td>0.3–4.0</td>
<td>0.910</td>
</tr>
</tbody>
</table>

* confidence intervals.
Appendix I. Participating Investigators and Study Sites

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References