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Anticoagulant therapy after venous thromboembolism and 10-year mortality

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ABSTRACT

Background: Pulmonary embolism (PE) is associated with a higher long-term mortality than deep vein thrombosis (DVT). This association may be related to inadequate antithrombotic therapy.
Methods: Incident VTE patients during the period 1997–2012 were identified in Danish nationwide registries. Two landmark populations were defined, consisting of patients alive at 30 days (30 d), and at 180 days (180 d) after discharge. Patients were classified according to anticoagulant usage at the landmark (30 d: prescription purchase 0–30 d post-discharge; 180 d: prescription purchase in 0–30 d and 90–180 d). Mortality rates were compared using multivariate Cox regression.
Results: The 30 d mortality risk among PE patients was high compared to DVT patients (19.9% vs. 4.4%). In the 30 d-landmark population (n = 62695), 34.9% of DVT patients and 21.3% of PE patients had not redeemed a prescription for anticoagulants. There was no material difference in 10-year mortality between anticoagulated PE patients and anticoagulated DVT patients. There was a higher 10-year mortality rate among non-anticoagulated PE patients compared to anticoagulated DVT patients (MRR: 1.26, 95% CI: 1.20–1.33). Findings in the 180 d-landmark population also indicated materially similar 10-year mortality rates between anticoagulated PE patients and anticoagulated DVT patients.
Conclusions: The 10-year mortality rate of patients surviving the initial 30 d critical period following incident PE was not increased compared to patients with incident DVT, as long as patients initiated and persisted with anticoagulant therapy. Increased focus on antithrombotic therapy in PE patients and reasons for early therapy discontinuation may be warranted.

1. Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively known as venous thromboembolism (VTE), are often regarded and treated as a common disease [1,2]. For example, no distinction between DVT and PE was made in several (but not all) of the recent randomized clinical trials of non-vitamin K anticoagulant (AC) drugs for VTE [3–6]. This lack of distinction may not be universally appropriate when it comes to long-term prognosis. A recent Danish population-based cohort showed a large excess mortality among PE patients compared to DVT patients within the first 30 days of diagnosis (30 day mortality: 31% vs. 3.0%), but also an excess longer-term mortality with PE (30–364 day mortality: 20% vs. 13%) [7].

A contributing factor to longer-term differences in mortality between DVT and PE could be inadequate antithrombotic therapy. International guidelines for secondary prevention after VTE published during the last decade [8–12] have formed the basis for the Danish guidelines. The broad general recommendation is for antithrombotic therapy to cover at least 3 months after VTE diagnosis, depending on whether or not the diagnosis could be attributed to a provoking factor (e.g. surgery or trauma). More specifically, 3 months (provoked) or 6 months (unprovoked) of antithrombotic therapy is recommended for first-time DVT; versus 6 months (provoked) and 12 months (unprovoked) of therapy with PE.

The extent to which the guidelines for antithrombotic therapy after VTE are followed in practice is an open issue; even if physicians adhere to guidelines for VTE management, patients may choose to discontinue therapy [13]. It is also an open issue whether guideline adherence can be linked to an improvement in long-term prognosis. In the present study, we approached these issues from an observational perspective, posing the following two questions: a) to which extent do VTE patients commence AC therapy shortly after discharge, and does AC therapy modify

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the association between VTE type and long-term mortality; and b), to which extent do VTE patients persist with AC therapy for an extended period of time, and does extended AC therapy modify the association between VTE type and long-term mortality?

We explored these questions by using individual-level data from nationwide Danish administrative registries to carry out landmark analyses of 10-year mortality in the at-risk population at 30 d and 180 d after discharge with a VTE diagnosis.

2. Methods

We performed a registry-based nationwide cohort study of all incident VTE diagnoses registered in the Danish population in the period January 1, 1997, to December 31, 2012. Specifically, we utilized the civil registration number assigned to all residents in Denmark [14] to link individual-level administrative registry data on incident VTE diagnoses, comorbid conditions, medication usage, and vital status.

Retrospective studies do not require ethical approval in Denmark.

2.1. Study data

We identified in the Danish National Patient Register [15] all diagnoses of DVT and PE (International Classification of Diseases 10th revision [ICD10] codes provided in the Supplementary Material) in the period from January 1, 1997, to December 31, 2012. For patients with both a DVT and a PE diagnosis during the same hospitalization period, a PE diagnosis was registered. Medication usage was ascertained from the Danish National Prescription Registry [16], which records anatomical therapeutic chemical classification (ATC) code and purchase date of all prescription purchases. We defined 'anticoagulant medication' to include vitamin K antagonists (ATC: B01AA), low-molecular weight heparins (ATC: B01AB), and rivaroxaban (ATC: B01AF01). Other new oral anticoagulants were not approved for the VTE indication until late in the study period and were hence not included. Comorbid conditions were identified in the Danish National Patient Register, ICD-10 codes are defined in Table 1. We calculated a Charlson score at the time of VTE diagnosis, using a validated definition based on ICD-10 codes [17].

Table 1
Codes used for defining medical conditions and medications

	Type	Codes
Medical condition		
Deep vein thrombosis	ICD-10	I801-I803, I808,I809,I822, I828,I829, O223, O229, O871, O879
	ICD-8	45100, 45108, 45109, 45190, 45192, 45199, 67101–67103, 67108, 67109
Pulmonary embolism	ICD-10	I26, O882
	ICD-8	450, 67309, 67319, 67399
Surgery	SKS[a]	D,B,K,L,J,M,H,P,Y,A,F,G,N
Trauma/fracture	ICD-10	S, T0 T10–T14
Myocardial infarction	ICD-10	I21–I23
Stroke	ICD-10	I63, I64
Cancer	ICD-10	C
Bleeding	ICD-10	I60–62, D62, J942, H113, H356, H431, N02, N95, R04, R31, R58, K250, K260, K270, K280, K290, S063C, S064, S065, S066
	ICD-8	430, 431, 53091, 53098, 531, 532, 533, 534
Charlson	ICD-8/10	Definitions in Thygesen et al. (2011). The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Med. Res. Methodol.; 11:83.
Medication		
Anticoagulant therapy	ATC	B01AA, B01AF01, B01AB
Hormonal treatment	ATC	G03C, G03F, G03AB
Platelet inhibitors	ATC	B01AC04, B01AC06

[a] Danish coding system for surgery and procedures (the Hospital Classification System).

Finally, information on gender and date of birth was obtained from the Danish Civil Registration System [14].

In order to restrict to incident VTE cases, patients with a prior PE or DVT diagnosis in the full Danish National Patient Register were excluded; alongside patients who had immigrated within 1 year of diagnosis; and patients with an ambulatory or emergency ward diagnosis of VTE. In order to restrict the study to new anticoagulant users, we excluded patients who had purchased anticoagulant medication within one year prior to the VTE diagnosis. We finally excluded patients with a history of bleeding, since medical management may be fundamentally different in this subgroup.

2.2. Landmark study populations

Landmarking is a focused way to study the time-dependent effect of a time-dependent exposure which may be particularly relevant for the clinical management of patients [18]. To apply landmarking to study the association between immediate/extended anticoagulant usage and 10-year mortality, we considered the at-risk populations (i.e. patients alive, living in Denmark, and not censored due to end of registry coverage) at landmark time points of 30 days (30 d) and 180 days (180 d) after hospital discharge following the VTE diagnosis that led to inclusion in the study. We used recent anticoagulant purchase in the two landmark populations as a proxy measure to determine whether patients were in anticoagulant therapy.

Accordingly, the 30 d-landmark population was the at-risk population at 30 d after discharge. Patients were classified according to whether they had purchased anticoagulant medication within 30 d after discharge ("initial anticoagulant usage"). The preliminary period of 30 d was employed to allow sufficient time for patients to redeem a prescription after discharge.

The 180 d-landmark population was the at-risk population at 180 d after discharge, with the additional requirement that patients had purchased anticoagulant medication within 30 d after discharge (i.e. had initiated anticoagulant therapy). Patients in the 180 d-landmark population were then classified according to whether they had purchased anticoagulants in a 90 d period up to the 180 d landmark ("extended anticoagulant usage"), reasoning that the typical patient persisting with therapy would purchase anticoagulants at least once during any 3-month period.

2.3. Statistical analysis

The 30 d- and 180 d-landmark populations were followed in the Danish National Patient Register from up to 10 years after the landmark time point; or time of death, emigration, or end of study (December 31, 2012), whichever came first. We provided descriptive summaries of population characteristics at the time of VTE diagnosis, stratified according to VTE type (DVT/PE) and anticoagulant usage status at the landmark (yes/no).

The Kaplan–Meier method was used to estimate crude mortality risk as a function of time. Cox proportional hazards regression was used to estimate mortality rate ratios (MRRs) for each combination of the VTE type (DVT/PE) and anticoagulant usage at the landmark (yes/no). Anticoagulated DVT patients comprised the reference group. To account for confounding by VTE type/indication for anticoagulant therapy, regression models were adjusted for the following baseline characteristics (at time of VTE diagnosis): sex (binary); age (restricted cubic spline); calendar time (categorical: 1997–2000; 2001–2004; 2005–2008; 2009–2012); Charlson score (categorical: 0; 1–2; >3). Since transient risk factors provoking the VTE may act as effect modifiers, we repeated the analysis after removing patients with recent cancer (within 1 year before baseline), or surgery/trauma (within 3 months before baseline).

Using a landmark time point of precisely 180 days to explore the role of "extended anticoagulant usage" was arguably arbitrary. To assess the sensitivity of MRRs to the timing of the landmark, we constructed *t*-day