Thrombosis Research 176 (2019) 46–53

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

A changing landscape: Temporal trends in incidence and characteristics of patients hospitalized with venous thromboembolism 2006–2015

A.M. Münster[a], T.B. Rasmussen[b], A.M. Falstie-Jensen[b], L. Harboe[c], G. Stynes[d], L. Dybro[e], M.L. Hansen[f], A. Brandes[g,h], E.L. Grove[i,j], S.P. Johnsen[b,k,*]

[a] Unit for Thrombosis Research, Esbjerg, Hospital of South West Jutland, Denmark
[b] Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark
[c] Bristol-Myers Squibb, Copenhagen, Denmark
[d] Bristol-Myers Squibb, London, United Kingdom
[e] Pfizer, Copenhagen, Denmark
[f] Department of Cardiology, Gentofte Hospital, Copenhagen, Denmark
[g] Department of Cardiology, Odense University Hospital, Odense, Denmark
[h] Department of Clinical Research, the Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark
[i] Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark
[j] Department of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark
[k] Danish Center for Clinical Health Services Research, Department of Clinical Medicine, Aalborg University and Aalborg University Hospital, Denmark

ARTICLE INFO

Keywords:
Epidemiology
Venous thromboembolism
Pulmonary embolism
Peep vein thrombosis
Incidence

ABSTRACT

Background: Venous thromboembolism (VTE) has major clinical and public health impact. However, only sparse data on calendar time trends in incidence from unselected populations reflecting current clinical practice are available.

Objectives: To examine temporal trends in the incidence and characteristics of patients hospitalized with first-time VTE in Denmark between 2006 and 2015.

Patients/Methods: Using nationwide health care registries, we calculated yearly hospitalization rates for first-time VTE from 2006 to 2015. The rates were standardized to the age and sex distribution in 2006. Based on the hospitalization and prescription history of each patient, we assessed the risk profile and evaluated changes over time.

Results: We identified 67,426 patients with a first-time VTE hospitalization. The age- and sex-standardized incidence rate increased from 12.6 (95% CI: 12.3–12.9) per 10,000 person years at risk in 2006 to 15.1 (95% CI: 14.7–15.4) in 2015, corresponding to an increase of 19.8%. The increase was due to a 73.9% increase in the standardized incidence rate of pulmonary embolism (PE), whereas no increase was observed for deep vein thrombosis. The risk profile changed with an increasing proportion of elderly patients and patients with co-morbidity (proportion of patients with a Charlson's Comorbidity Index score of ≥ 1).

Conclusions: The hospitalization rate of first-time VTE, and particularly PE, has increased substantially within the last decade in Denmark. In addition, the risk profile of the VTE population has changed with more elderly and more patients with comorbidity being diagnosed. Further efforts are warranted to explore the changes in VTE epidemiology and the clinical implications.

1. Introduction

Venous thromboembolism (VTE) is a common condition which consists of two related conditions: deep vein thrombosis (DVT) and pulmonary embolism (PE). Venous thromboembolism is associated with increased mortality and serious adverse outcomes including

Abbreviations: VTE, Venous Thromboembolism; DVT, Deep venous thrombosis; PE, Pulmonary embolism; CI, Confidence interval; DNPR, The Danish National Patient Registry; ICD-10, International Classification of Diseases, 10th revision; CT, Computed tomography; ABC, Approximate bootstrap confidence intervals; SD, Standard deviation

* Corresponding author at: Danish Center for Clinical Health Services Research, Department of Clinical Medicine, Aalborg University, Sdr. Skovvej 15, 9000 Aalborg, Denmark.
E-mail address: soeren.johnsen@rn.dk (S.P. Johnsen).

https://doi.org/10.1016/j.thromres.2019.02.009
Received 9 November 2018; Received in revised form 31 January 2019; Accepted 9 February 2019
Available online 13 February 2019

postthrombotic syndrome and pulmonary hypertension [1–3]. Overall, VTE is among the three most common causes of cardiovascular death, only exceeded by acute coronary syndrome and stroke [4].

The incidence of VTE in the Western population has typically been reported to be one to two cases per 1000 persons per year [5]. However, the risk profile of the general population has changed during the last decades which may have implications for the incidence of VTE. The population is getting older with increasing comorbidity [6]. In addition, less traumatic surgical techniques have been developed and fast-track surgical approaches have been implemented, thus, reducing the extent of immobilization. Furthermore, there is increased focus on the use of standardized thromboprophylaxis [7]. Importantly, only sparse data from unselected real-life VTE populations reflecting current clinical practice is available. Hence, the aim of this study was to examine temporal trends in the incidence and characteristics of patients hospitalized with first-time VTE in Denmark between 2006 and 2015.

2. Methods

2.1. Design and setting

We conducted a population-based historical study based on national Danish registries covering the entire population (≈5.7 million). The Danish National Health Service provides universal tax-supported health care to all residents guaranteeing unrestricted access to general practitioners and hospitals and partial reimbursement for prescribed medications [8].

2.2. Data sources

The study was based on individual-level record linkage of high-quality medical registries with information on hospitalization history, drug use and vital status:

The Danish Civil Registration System has been updated on a daily basis since 1968 by using a civil registration number unique to each Danish citizen encoding sex and date of birth, which makes unambiguous linkages between the population-based registers possible [9]. The registry holds electronic records of all changes in vital status and migration for the entire Danish population, including changes in address, date of emigration, and date of death.

The Danish National Patient Registry (DNPR) covers all Danish hospitals and contains information on all patients discharged from non-psychiatric hospitals since 1977 and on all emergency room and outpatient specialty clinic visits since 1995 [10]. Each hospital discharge or outpatient visit is recorded in the registry with one primary diagnosis (the main cause of admission) and one or more secondary diagnoses classified according to the International Classification of Diseases, 10th revision (ICD-10) since 1994.

The Danish National Database of Reimbursed Prescriptions: includes information on reimbursed medications redeemed at all Danish community and outpatient pharmacies since 1 January 2004 [8]. Each time a prescription is redeemed, the patient's civil registration number, the redemption date, and the Anatomical Therapeutic Chemical Classification System code, type, and quantity of the drug are recorded.

2.3. Study population

All patients ≥18 years with a first-time hospitalization for VTE at any Danish hospital from 1 January 2006 through 31 December 2015 were identified. Patients admitted to hospital with an overnight stay as well as patients seen in outpatient clinics were included. Both primary and secondary diagnoses were considered. Patients, who were exclusively registered with an emergency room contact, were excluded due to a low predictive value [11]. The date of diagnosis was defined as index date. Index VTEs were further classified according to their projected risk of recurrent VTE: low-risk (e.g. patients with surgery, trauma or fracture occurring within 3 months before diagnosis and no permanent risk factors) or intermediate- and high risk (remaining patients including patients with unprovoked VTE, cancer, congenital or acquired thrombophilia, heart failure, autoimmune disorders, myeloproliferative neoplasms, paroxysmal nocturnal hemoglobinuria, severe obesity, pulmonary hypertension, and nephrotic syndrome) [12].

Using a recently validated algorithm for identifying VTE diagnoses with the highest positive predictive value, we also applied an alternative definition of first-time (index) VTE, i.e. an in- or outpatient diagnosis of DVT or PE among patients redeeming a prescription for anticoagulant drugs within 30 days after index date (Positive Predictive Value = 90%) [12]. This alternative definition was used in a sensitivity analysis (please see the statistical section).

2.4. Patient characteristics

We obtained information on the following variables for each patient in order to determine the risk profile:

- Within 3 months before VTE diagnosis: history of surgery, trauma or fracture.
- Up to 10 years before VTE diagnosis: History of cancer, congenital or acquired thrombophilia, heart failure, autoimmune disorders, myeloproliferative neoplasms, paroxysmal nocturnal hemoglobinuria, severe obesity, pulmonary hypertension, nephrotic syndrome, myocardial infarction, stroke, diabetes mellitus, atrial fibrillation, and history of bleeding. In addition, we computed the Charlson comorbidity index score which was adapted for use with hospital discharge registry data [13,14]. We defined three levels of comorbidity: a score of 0 (“low”); a score of 1–2 (“moderate comorbidity”); and a score > 2 (“high comorbidity”). Furthermore, we obtained information on filled prescriptions for antidiabetic drugs, anti-psychotics, postmenopausal hormone therapy, statins, low-dose aspirin, clopidogrel, dipyridamole, ticagrelor, and prasugrel. We used a 3-month time window preceding the index date for all drugs to identify ongoing treatment defined as at least one filled prescription. The exception was antidiabetic drugs where we used the entire available prescription history to identify patients with a history of diabetes.

Finally, we obtained information on in-hospital diagnostic work-up including the use of ventilation/perfusion lung scans and computed tomography (CT) scans as well as pulmonary angiography. A complete list of the codes used in the study is provided in Appendix A.

2.5. Statistical analysis

We calculated yearly hospitalization rates for first-time VTE (overall and separately for DVT and PE) from 2006 to 2015. Analyses were repeated separately for men and women. The rates were standardized to the age and sex distribution of the Danish population in 2006, and confidence intervals (CI) were calculated using the approximate bootstrap confidence intervals (ABC) [15]. Hospitalization rates were computed separately for all first-time VTE admissions and for all first time VTE admissions followed by the filling of at least one prescription for an anticoagulant drug, including vitamin K antagonists, Non-Vitamin K Antagonist Oral Anticoagulants or low-molecular weight heparin. This analysis was considered a sensitivity analysis to assess the robustness of the primary analysis as the sensitivity of the VTE diagnosis was lower when also requiring a filled anticoagulant prescription, however, the positive predictive value was higher using the later approach [12].

Based on the hospitalization and prescription history of each patient, we assessed the risk profile and compared changes over time. The later analysis was conducted among patients with a VTE diagnosis and at least one filled prescription for an anticoagulant within 30 days after

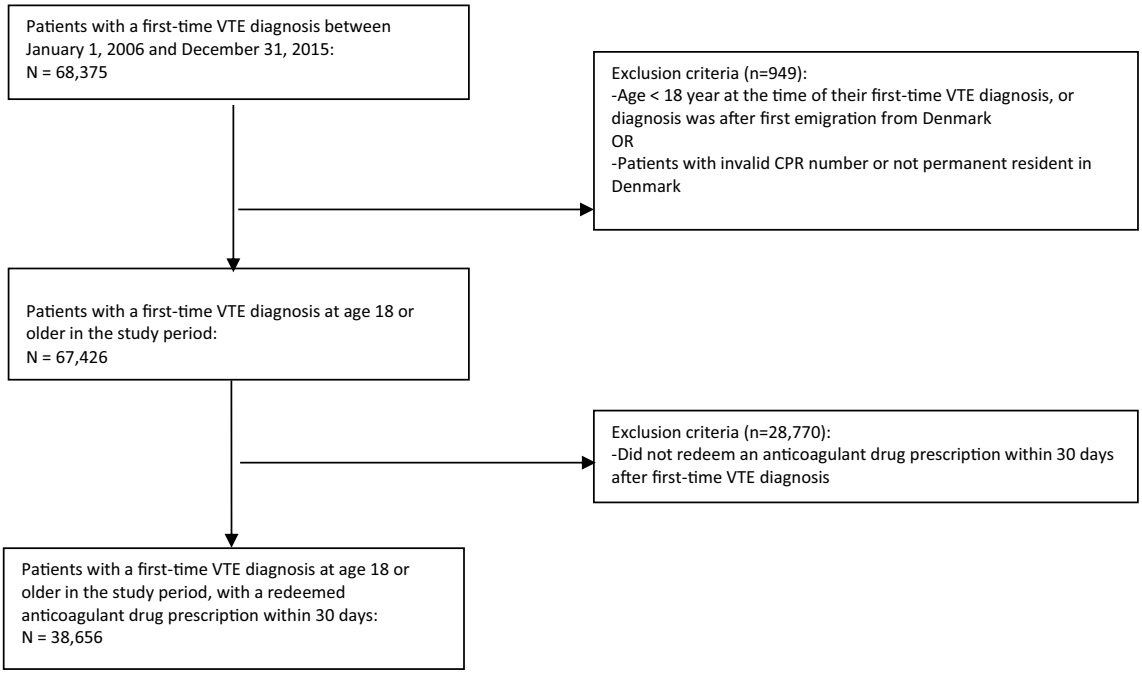

Fig. 1. Study population flowchart. VTE: venous thromboembolism.

the index event. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

The study was approved by the Danish Data Protection Agency (J.nr. KEA-2016-6). According to Danish law, ethical committee approval is not required for registry-based studies.

3. Results

We identified a total of 67,426 patients with a first-time hospitalization for VTE between 2006 and 2015. Of these, 38,656 (57.3%) filled an anticoagulant drug prescription within 30 days after the first-time VTE diagnosis (Fig. 1).

Table 1 and Fig. 2 present the age- and sex-standardized hospitalization rate of first time VTE according to calendar year.

Overall, the rate increased from 12.6 (95% CI: 12.3–12.9) per 10,000 person years at risk in 2006 to 15.1 (95% CI: 14.7–15.4) in 2015. This corresponded to an increase in the rate of VTE of 19.8%. Looking separately at DVT and PE, marked differences in the time trends were observed. Hence, first-time hospitalizations for DVT dropped 11.8% during the study period whereas the rate of PE increased by 73.9%. These time trends were confirmed when restricting to patients where the validity of the VTE diagnosis was supported by at least one filled prescription for an anticoagulant (Table 2). The patterns were also consistent when stratifying the analyses according to sex (data not shown).

The patient profile also appeared to change between 2006 and 2015, i.e., the mean age in the overall VTE population increased from 63.5 years (SD 17.2) in 2006 to 65.7 years (SD 16.5) in 2015. Table 3 presents patient characteristics according to calendar year of first-time VTE hospitalization among the VTE population who filled at least one prescription for an anticoagulant. The mean age of these confirmed VTE patients also increased from 63.6 years (SD 16.8) in 2006 to 65.2 (SD 16.7) years in 2015. This corresponded to an increase in the proportion of patients ≥60 years from 62.6% to 69.8%. An increasing comorbidity burden was also observed, i.e. the proportion of patients with a Charlson's Comorbidity Index score of ≥1 increased from 29.0% in 2006 to 46.0% in 2015. As a consequence of the increasing rate of PE, the proportion of VTE patients diagnosed with PE increased from 36.8% to 55.6% between 2006 and 2015. The diagnostic work-up also seemed to change during the study period with an increasing proportion of patients being examined with CT scanning or pulmonary angiography, i.e. from 13.9% to 42.8%. In contrast, a drop in the use of ventilation/perfusion lung scan from 22.5% to 15.5% was observed.

No substantial differences were observed for the remaining patient characteristics.

4. Discussion

Based on nationwide data from 2006 to 2015, this study has two main findings: First, the overall age– and sex-standardized hospitalization incidence rate increased significantly due to a marked increase in the rate of PE whereas a modest drop was observed for DVT. Secondly, during this period, the patient population with first-time VTE became significantly older and a higher proportion of the patients had comorbidities.

Our findings support and extend findings from previous studies reporting an increasing trend in the incidence of VTE [16–19]. Our study indicates that the increase is not only a historical phenomenon but rather an ongoing trend with a steady increase during the last decade owing to an increase in patients diagnosed with pulmonary embolism. Similar findings have previously been reported from the Tromsø cohort study (1996–2012) and, earlier, from the Worcester VTE-study (1985–2009) [18,19]. In line with the Tromsø study, we also noted a decrease in the incidence of DVT, as the hospitalized incidence rate of DVT in our study remained unchanged during the last decade. The similarities in the overall findings from our study and the studies from Tromsø and Worcester are striking when taking into account that there are clear differences in study design and populations between the three studies. Our data are based on nationwide Danish administrative registries covering the entire population, whereas the Tromsø and Worcester studies are based on prospective cohorts requiring active participation by study individuals. Our study population was similar in age compared with the Worchester study (mean age 65.0 vs 65.9 years) but was older than the Tromsø population (mean age 47 years). Furthermore, the validation of the VTE diagnosis was different as the diagnosis of VTE was validated through review of medical records in the two prospective studies, whereas we confirmed our primary findings using a validated registry-based algorithm i.e. restriction of the VTE population

Table 1
Hospitalization rate of first-time venous thromboembolism, including deep vein thrombosis and pulmonary embolism, in Denmark between 2006 and 2015. Crude and age- and sex standardized according to the Danish population in 2006. CI: confidence interval. PY: person years.

A:

	Overall			
Year	Number of cases	10,000 PY at risk	Incidence rate (95% CI) per 10,000 years of risk-time	Age- and sex-standardized incidence rate (95% CI) per 10,000 years of risk-time
2006	5755	457.63	12.58 (12.25;12.90)	12.58 (12.25;12.90)
2007	6021	458.72	13.13 (12.80;13.46)	13.03 (12.71;13.37)
2008	5755	459.70	12.52 (12.20;12.85)	12.35 (12.03;12.67)
2009	6173	460.10	13.42 (13.09;13.76)	13.14 (12.82;13.47)
2010	6338	460.37	13.77 (13.43;14.11)	13.39 (13.06;13.72)
2011	6302	460.40	13.69 (13.35;14.03)	13.18 (12.86;13.51)
2012	7047	460.16	15.31 (14.96;15.68)	14.58 (14.24;14.92)
2013	7421	459.55	16.15 (15.78;16.52)	15.24 (14.90;15.59)
2014	7465	458.30	16.29 (15.92;16.66)	15.10 (14.76;15.44)
2015	7547	456.34	16.54 (16.17;16.92)	15.07 (14.73;15.42)

B:

	Deep vein thrombosis				Pulmonary embolism			
Year	Number of Cases	10,000 PY at risk	Incidence rate (95% CI) per 10,000 years of risk-time	Age- and sex-standardized incidence rate (95% CI) per 10,000 years of risk-time	Number of Cases	10,000 PY at risk	Incidence rate (95% CI) per 10,000 years of risk-time	Age- and sex-standardized incidence rate (95% CI) per 10,000 years of risk-time
2006	3632	457.63	7.94 (7.68;8.20)	7.94 (7.68;8.20)	2123	457.63	4.64 (4.45;4.84)	4.64 (4.44;4.84)
2007	3739	458.72	8.15 (7.89;8.42)	8.10 (7.84;8.36)	2282	458.72	4.97 (4.77;5.18)	4.93 (4.73;5.14)
2008	3452	459.70	7.51 (7.26;7.76)	7.42 (7.17;7.67)	2303	459.70	5.01 (4.81;5.22)	4.93 (4.73;5.13)
2009	3636	460.10	7.90 (7.65;8.16)	7.76 (7.51;8.01)	2537	460.10	5.51 (5.30;5.73)	5.39 (5.18;5.60)
2010	3559	460.37	7.73 (7.48;7.99)	7.55 (7.30;7.80)	2779	460.37	6.04 (5.82;6.27)	5.84 (5.63;6.06)
2011	3360	460.40	7.30 (7.06;7.55)	7.06 (6.82;7.30)	2942	460.40	6.39 (6.16;6.63)	6.12 (5.90;6.35)
2012	3713	460.16	8.07 (7.81;8.33)	7.74 (7.49;7.99)	3334	460.16	7.25 (7.00;7.50)	6.84 (6.61;7.08)
2013	3802	459.55	8.27 (8.01;8.54)	7.89 (7.64;8.15)	3619	459.55	7.88 (7.62;8.14)	7.35 (7.11;7.59)
2014	3474	458.30	7.58 (7.33;7.84)	7.10 (6.87;7.35)	3991	458.30	8.71 (8.44;8.98)	7.99 (7.75;8.24)
2015	3452	456.34	7.56 (7.32;7.82)	7.00 (6.77;7.24)	4095	456.34	8.97 (8.70;9.25)	8.07 (7.82;8.32)

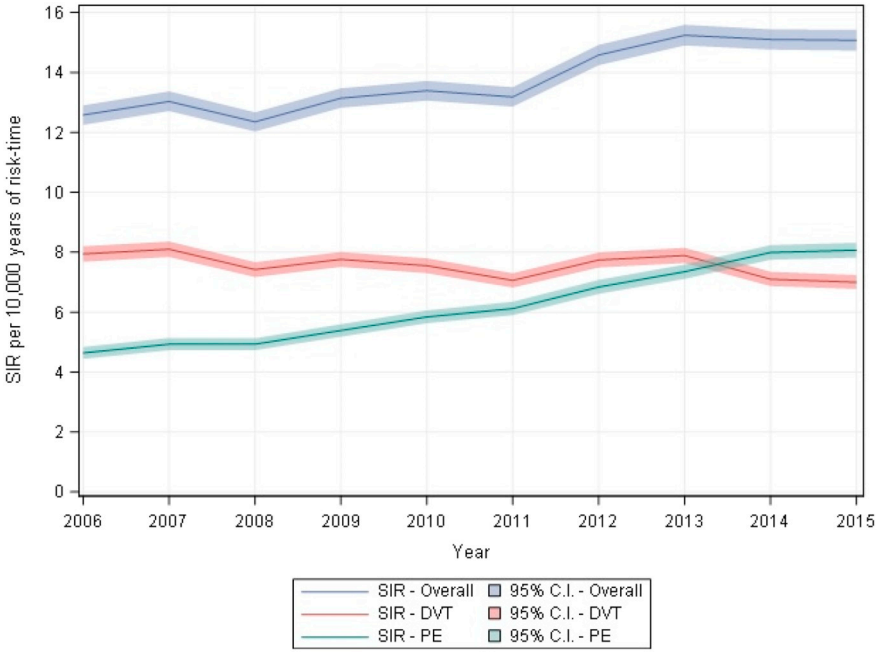

Fig. 2. Age- and sex standardized incidence rate (SIR) of first time hospitalization for venous thromboembolism in Denmark 2006–2015. Overall and specified as deep vein thrombosis (DVT) or pulmonary embolism (PE).

Table 2
Hospitalization rate of first-time venous thromboembolism, including deep vein thrombosis and pulmonary embolism, in Denmark between 2006 and 2015. Crude and age- and sex standardized according to the Danish population in 2006. Restricted to patients where the venous thromboembolism diagnosis was confirmed by a filled anticoagulant prescription within 30 days after prescription. CI: confidence interval. PY: person years.

A:

	Overall			
Year	Number of cases	10,000 PY at risk	Incidence rate (95% CI) per 10,000 years of risk-time	Age- and sex-standardized incidence rate (95% CI) per 10,000 years of risk-time
2006	3214	457.63	7.02 (6.78;7.27)	7.02 (6.78;7.27)
2007	3380	458.72	7.37 (7.12;7.62)	7.31 (7.07;7.56)
2008	3264	459.70	7.10 (6.86;7.35)	7.00 (6.76;7.24)
2009	3486	460.10	7.58 (7.33;7.83)	7.41 (7.17;7.66)
2010	3631	460.37	7.89 (7.63;8.15)	7.66 (7.41;7.91)
2011	3767	460.40	8.18 (7.92;8.45)	7.87 (7.62;8.12)
2012	3910	460.16	8.50 (8.23;8.77)	8.09 (7.83;8.34)
2013	4592	459.55	9.99 (9.71;10.29)	9.42 (9.15;9.70)
2014	4721	458.30	10.30 (10.01;10.60)	9.54 (9.27;9.81)
2015	4691	456.34	10.28 (9.99;10.58)	9.35 (9.09;9.63)

B:

	Deep vein thrombosis				Pulmonary embolism			
Year	Number of Cases	10,000 PY at risk	Incidence rate (95% CI) per 10,000 years of risk-time	Age- and sex-standardized incidence rate (95% CI) per 10,000 years of risk-time	Number of Cases	10,000 PY at risk	Incidence rate (95% CI) per 10,000 years of risk-time	Age- and sex-standardized incidence rate (95% CI) per 10,000 years of risk-time
2006	2031	457.63	4.44 (4.25;4.64)	4.44 (4.25;4.63)	1183	457.63	2.59 (2.44;2.74)	2.59 (2.44;2.74)
2007	2134	458.72	4.65 (4.46;4.85)	4.62 (4.43;4.82)	1246	458.72	2.72 (2.57;2.87)	2.69 (2.55;2.85)
2008	1938	459.70	4.22 (4.03;4.41)	4.16 (3.98;4.35)	1326	459.70	2.88 (2.73;3.04)	2.83 (2.68;2.99)
2009	1983	460.10	4.31 (4.12;4.50)	4.23 (4.04;4.42)	1503	460.10	3.27 (3.11;3.44)	3.19 (3.03;3.35)
2010	1974	460.37	4.29 (4.10;4.48)	4.18 (4.00;4.37)	1657	460.37	3.60 (3.43;3.78)	3.48 (3.32;3.65)
2011	1888	460.40	4.10 (3.92;4.29)	3.96 (3.78;4.14)	1879	460.40	4.08 (3.90;4.27)	3.91 (3.74;4.09)
2012	1930	460.16	4.19 (4.01;4.39)	4.02 (3.84;4.20)	1980	460.16	4.30 (4.12;4.50)	4.07 (3.89;4.25)
2013	2277	459.55	4.95 (4.76;5.16)	4.72 (4.53;4.91)	2315	459.55	5.04 (4.84;5.25)	4.70 (4.52;4.90)
2014	2114	458.30	4.61 (4.42;4.81)	4.31 (4.13;4.50)	2607	458.30	5.69 (5.47;5.91)	5.22 (5.03;5.43)
2015	2081	456.34	4.56 (4.37;4.76)	4.21 (4.03;4.39)	2610	456.34	5.72 (5.50;5.94)	5.15 (4.95;5.35)

to patients where the VTE diagnosis was supported by a least one filled prescription of anticoagulants [12]. The three studies in many ways have complementary methodological strengths and weaknesses. The fact that the findings from the studies were still quite similar strongly indicates that the observed development in VTE incidence most likely represents a real and widespread phenomenon.

A potential explanation for at least part of the increase in the incidence of first-time hospitalizations with PE could be an increased diagnostic awareness of PE and switching from a first-line diagnostic procedure using ventilation/perfusion lung scan, which is not as sensitive and available around the clock, to computed tomography scanning [20]. We did indeed observe a three-fold increase in the use of CT-based diagnosing among hospitalized Danish PE patients between 2006 and 2015, while the use of ventilation/perfusion lung scan decreased slightly in the same period corresponding to an overall increased use of PE diagnostics. The more widespread use of CT may result in more cases of asymptomatic PE being diagnosed. In 2012, a nationwide standardized diagnostic approach was introduced in Denmark in order to optimize the immediate (within 28 days) diagnostic work-up of patients with suspected cancer. The diagnostic work-up for these patients often include a spiral CT scan of the chest. This intervention could potentially have added to the detection of more asymptomatic PEs. However, our data could not support this as only 2.34% of the PE-diagnoses in 2015 were a consequence of this diagnostic approach. It is not possible to determine whether the increased incidence of PE in recent studies, including ours, is mainly due to increased use of imaging modalities that are very sensitive for diagnosing (asymptomatic) PE or to improved clinical awareness. However, the dramatic increase in the hospitalization rate of first time PE should remain a cause of clinical concern since the 30-day mortality rate following PE remains high and still approximately twice as high in patients with PE as in patients with DVT [1,5,21].

VTE is predominantly a disease related to older age and the incidence increases exponentially with increasing age with PE being the primary clinical presentation among the elderly [16,17]. The increasing average age of the Danish population may therefore contribute to an increasing incidence of VTE in general and PE in particular. However, age per se did not explain the increase in the hospitalization rates in our study since it was also observed after standardizing for changes in the age distribution over time. Still, increasing age is associated with increasing levels of comorbidity, and the comorbidity burden did indeed increase among the VTE patients in our study. It is known that risk factors for VTE may act in a synergistic way and the increasing level of comorbidity may therefore partly explain the increased incidence of this multifactorial disease [22,23].

4.1. Study strengths and limitations

The strengths of our study include the access to nationwide registries covering the entire population, which reduces the risk of selection bias and provided up-to-date information. In addition, information on a broad range of risk factors as well as diagnostic procedures enabled us to describe the VTE population in detail, although data on some risk factors were missing, e.g. use of oral contraceptives. The most important limitation is the fact that the study only included VTE events leading to hospitalization. Danish clinical guidelines recommend hospital referral of all patients with VTE and we included all patients with either a hospital admission or a contact to an

Table 3
Patient characteristics according to year of admission among patients with a first-time diagnosis of venous thromboembolism 2006–2015.

A:

Year of venous thromboembolism diagnosis 2006–2010

	2006		2007		2008		2009		2010	
	N	%	N	%	N	%	N	%	N	%
Number of patients	3214	8.31	3380	8.74	3264	8.44	3486	9.02	3631	9.39
Men	1582	49.22	1583	46.83	1596	48.90	1694	48.59	1805	49.71
Pulmonary embolism	1183	36.81	1246	36.86	1326	40.63	1503	43.12	1657	45.63
Age groups	354	11.01	379	11.21	341	10.45	351	10.07	343	9.45
18–40										
40–60	848	26.38	870	25.74	808	24.75	876	25.13	874	24.07
60–80	1459	45.40	1521	45.00	1504	46.08	1602	45.96	1669	45.97
80 +	553	17.21	610	18.05	611	18.72	657	18.85	745	20.52
Low-risk patients[a]	259	8.06	277	8.20	254	7.78	285	8.18	301	8.29
-Pregnancy[b]	15	5.79	13	4.69	12	4.72	19	6.67	11	3.65
-Surgery[b]	224	86.49	235	84.84	200	78.74	240	84.21	266	88.37
-Trauma/fracture[b]	82	31.66	83	29.96	97	38.19	93	32.63	98	32.56
High-risk patients[c]	2955	91.9	3103	91.8	3010	92.2	3201	91.8	3330	91.7
-Unprovoked venous thromboembolism[d]	2382	80.61	2434	78.44	2285	75.91	2314	72.29	2357	70.78
-Cancer[d]	353	11.95	413	13.31	448	14.88	534	16.68	599	17.99
-Congenital or acquired thrombophilia[d]	3	0.10	14	0.45	10	0.33	18	0.56	18	0.54
-Heart failure[d]	105	3.55	100	3.22	96	3.19	149	4.65	159	4.77
-Autoimmune disorders[d]	97	3.28	127	4.09	148	4.92	164	5.12	186	5.59
-Severe obesity[d]	63	2.13	67	2.16	98	3.26	127	3.97	124	3.72
-Pulmonary hypertension[d]	12	0.41	13	0.42	16	0.53	22	0.69	14	0.42
-Nephrotic syndrome[d]	3	0.10	2	0.06	4	0.13	2	0.06	5	0.15
Other comorbidity										
Diabetes mellitus[e]	182	5.66	215	6.36	217	6.65	234	6.71	262	7.22
Ischemic stroke[e]	49	1.52	78	2.31	96	2.94	133	3.82	112	3.08
Acute myocardial infarction[e]	51	1.59	61	1.80	66	2.02	58	1.66	85	2.34
Atrial fibrillation[e]	89	2.77	106	3.14	128	3.92	167	4.79	187	5.15
Bleeding history[e]	112	3.48	155	4.59	146	4.47	223	6.40	223	6.14
Modified Charlson Comorbidity Index[f]										
0 point	2282	71.00	2254	66.69	2073	63.51	2081	59.70	2106	58.00
1–2 points	668	20.78	805	23.82	844	25.86	967	27.74	1011	27.84
3 + points	264	8.21	321	9.50	347	10.63	438	12.56	514	14.16
Hospitalized within 30 days before VTE	549	17.08	649	19.20	597	18.29	725	20.80	738	20.32
Current medication use[g]:										
Antidiabetic drugs	184	5.72	206	6.09	187	5.73	205	5.88	219	6.03
Antipsychotics	174	5.41	189	5.59	177	5.42	173	4.96	179	4.93
Postmenopausal hormone therapy	170	5.29	165	4.88	165	5.06	173	4.96	159	4.38
Statins	385	11.98	482	14.26	504	15.44	546	15.66	601	16.55
Antiplatelets drugs	527	16.40	588	17.40	563	17.25	644	18.47	671	18.48
Computed tomography	446	13.88	596	17.63	757	23.19	925	26.53	1158	31.89
Lung scintigraphy	723	22.50	638	18.88	567	17.37	572	16.41	546	15.04
Diagnostic work-up on suspicion of cancer	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

B:

Year of venous thromboembolism diagnosis 2011–2015

	2011		2012		2013		2014		2015		All patients	
	N	%	N	%	N	%	N	%	N	%	N	%
Number of patients	3767	9.74	3910	10.11	4592	11.88	4721	12.21	4691	12.14	38,656	100.00
Men (%)	1858	49.32	1965	50.26	2404	52.35	2430	51.47	2409	51.35	19,326	49.99
Pulmonary embolism	1879	49.88	1980	50.64	2315	50.41	2607	55.22	2610	55.64	18,306	47.36
Age groups	354	9.40	340	8.70	389	8.47	356	7.54	352	7.50	3559	9.21
18–40												
40–60	879	23.33	894	22.86	1078	23.48	1082	22.92	1065	22.70	9274	23.99
60–80	1768	46.93	1842	47.11	2152	46.86	2272	48.13	2296	48.94	18,085	46.78
80 +	766	20.33	834	21.33	973	21.19	1011	21.41	978	20.85	7738	20.02
Low-risk patients[a]	267	7.09	278	7.11	347	7.56	293	6.21	315	6.71	2876	7.44
-Pregnancy[b]	*11*	*4.12*	*16*	*5.76*	*11*	*3.17*	*11*	*3.75*	*10*	*3.17*	*129*	*4.49*
-Surgery[b]	*234*	*87.64*	*227*	*81.65*	*297*	*85.59*	*245*	*83.62*	*268*	*85.08*	*2436*	*84.70*
-Trauma/fracture[b]	*87*	*32.58*	*100*	*35.97*	*112*	*32.28*	*110*	*37.54*	*101*	*32.06*	*963*	*33.48*
High-risk patients[c]	3500	92.9	3632	92.9	4245	92.4	4428	93.8	4376	93.3	35,780	92.6
-Unprovoked venous thromboembolism[d]	*2499*	*71.40*	*2600*	*71.59*	*3026*	*71.28*	*3211*	*72.52*	*3230*	*73.81*	*26,338*	*73.61*
-Cancer[d]	*590*	*16.86*	*611*	*16.82*	*636*	*14.98*	*633*	*14.30*	*611*	*13.96*	*5428*	*15.17*
-Congenital or acquired thrombophilia[d]	*21*	*0.60*	*17*	*0.47*	*24*	*0.57*	*28*	*0.63*	*24*	*0.55*	*177*	*0.49*
-Heart failure[d]	*160*	*4.57*	*174*	*4.79*	*230*	*5.42*	*214*	*4.83*	*156*	*3.56*	*1543*	*4.31*

(*continued on next page*)

Table 3 (*continued*)

B:

Year of venous thromboembolism diagnosis 2011–2015

	2011		2012		2013		2014		2015		All patients	
	N	%	N	%	N	%	N	%	N	%	N	%
-Autoimmune disorders[d]	*186*	*5.31*	*202*	*5.56*	*252*	*5.94*	*254*	*5.74*	*255*	*5.83*	*1871*	*5.23*
-Severe obesity[d]	*160*	*4.57*	*169*	*4.65*	*248*	*5.84*	*266*	*6.01*	*278*	*6.35*	*1600*	*4.47*
-Pulmonary hypertension[d]	*15*	*0.43*	*19*	*0.52*	*25*	*0.59*	*18*	*0.41*	*32*	*0.73*	*186*	*0.52*
-Nephrotic syndrome[d]	*5*	*0.14*	*5*	*0.14*	*1*	*0.02*	*2*	*0.05*	*7*	*0.16*	*36*	*0.10*
Other comorbidity:												
Diabetes mellitus[e]	287	7.62	293	7.49	410	8.93	386	8.18	378	8.06	2864	7.41
Ischemic stroke[e]	156	4.14	169	4.32	207	4.51	216	4.58	215	4.58	1431	3.70
Acute myocardial infarction[e]	98	2.60	124	3.17	142	3.09	150	3.18	162	3.45	997	2.58
Atrial fibrillation[e]	220	5.84	232	5.93	294	6.40	305	6.46	240	5.12	1968	5.09
Bleeding history[e]	252	6.69	295	7.54	399	8.69	393	8.32	434	9.25	2632	6.81
Modified Charlson Comorbidity Index[f]												
0 point	2117	56.20	2142	54.78	2451	53.38	2509	53.15	2534	54.02	22,549	58.33
1–2 points	1089	28.91	1170	29.92	1377	29.99	1455	30.82	1362	29.03	10,748	27.80
3+ points	561	14.89	598	15.29	764	16.64	757	16.03	795	16.95	5359	13.86
Hospitalized within 30 days before VTE	763	20.25	761	19.46	880	19.16	830	17.58	834	17.78	7326	18.95
Current medication use[g]:												
Antidiabetic drugs	241	6.40	234	5.98	324	7.06	292	6.19	274	5.84	2366	6.12
Antipsychotics	201	5.34	189	4.83	262	5.71	234	4.96	231	4.92	2009	5.20
Postmenopausal hormone therapy	174	4.62	188	4.81	205	4.46	235	4.98	233	4.97	1867	4.83
Statins	705	18.72	674	17.24	926	20.17	865	18.32	871	18.57	6559	16.97
Antiplatelets drugs	726	19.27	765	19.57	801	17.44	753	15.95	720	15.35	6758	17.48
Computed tomography	1364	36.21	1509	38.59	1751	38.13	1937	41.03	2007	42.78	12,450	32.21
Lung scintigraphy	542	14.39	572	14.63	662	14.42	797	16.88	725	15.46	6344	16.41
Diagnostic work-up on suspicion of cancer	0	0.00	20	0.51	111	2.42	108	2.29	110	2.34	349	0.90

[a] Low-risk was defined as pregnancy, surgery or trauma/fracture within 3 months before index diagnosis.
[b] Percentage of all patients with low-risk VTE.
[c] High-risk was defined as unprovoked VTE or cancer, congenital or acquired thrombophilia, heart failure, autoimmune disorders, myeloproliferative neoplasms, paroxysmal nocturnal hemoglobinuria, severe obesity, pulmonary hypertension, or nephrotic syndrome within 10 years before index diagnosis.
[d] Percentage of all patients with high-risk VTE.
[e] Any inpatient or outpatient diagnosis within 10 years before.
[f] Based on Charlson comorbidity index scores of 0 (none), 1–2 (moderate) and ≥ 3 (severe).
[g] Prescription redemption within 90 days before the index date.

out-patient hospital clinic, however, we cannot exclude the possibility that some patients had been treated exclusively by their general practitioner although the number is expected to be very low. Furthermore, it is well-known that PE is frequently overlooked as the cause of death and since the autopsy rate in Denmark is low (i.e. well below 10%), it is evident that some cases of PE have been missed. This is however not a limitation that is unique to our study but a challenge for all studies on VTE epidemiology. Misclassification of the VTE diagnosis may occur in administrative registries and the quite low proportion of patients, who filled an anticoagulant prescription within 30 days after hospital admission in our study, may just illustrate this although other explanations are also likely to play an important role including continued hospital-based treatment (only out-of hospital anticoagulant treatment is captured), continued use of anticoagulant available from previously filled prescriptions for other indications, e.g. atrial fibrillation, and real undertreatment. We were not able to determine the individual impact of these factors. However, our findings were also confirmed when using a validated alternative algorithm for identifying VTE cases so it is highly unlikely that the results could be explained by misclassification.

In conclusion, the age- and sex standardized hospitalization rate of first-time VTE, and in particular PE, has increased substantially within the last decade in Denmark. This may reflect both a real increase in the incidence of VTE and increased diagnostic awareness.

In addition, the risk profile of the VTE population has changed with more elderly and patients with comorbidity being diagnosed. Further efforts are warranted to characterize the changes in VTE epidemiology and the potential clinical implications.

Funding sources

The study was supported by Bristol-Myers Squibb/Pfizer.

References

[1] K.K. Søgaard, M. Schmidt, L. Pedersen, E. Horváth-Puhó, H.T. Sørensen, 30-year mortality after venous thromboembolism, Circulation 130 (2014) 829–836.
[2] S.R. Kahn, I. Shrier, J.A. Julian, T. Ducruet, L. Arsenault, M.-J. Miron, A. Roussin, S. Desmarais, F. Joyal, J. Kasis, S. Solymoss, L. Desjardins, D.L. Lamping, M. Johri, J.S. Ginsberg, Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis, Ann. Intern. Med. 149 (2008) 698–707.
[3] Y.M. Ende-Verhaar, S. Cannegieter, A.V. Noordegraaf, M. Delcroix, P. Pruszczyk, A.T.A. Mairuhu, M.V. Huisman, F.A. Klok, Incidence of chronic thromboembolic pulmonary hypertension and acute pulmonary embolism: a contemporary view of the published literature, Eur. Respir. J. 49 (2017) 1601792.
[4] S.Z. Goldhaber, H. Bounameaux, Pulmonary embolism and deep vein thrombosis, Lancet 379 (2012) 1835–1846.
[5] I.A. Naess, S.C. Christiansen, P. Romundstad, S.C. Cannegieter, F.R. Rosendaal, J. Hammerstrøm, Incidence and mortality of venous thrombosis: a population-based study, J. Thromb. Haemost. 5 (2007) 692–699.
[6] WHO, 10 facts on ageing and health, Available at: http://www.who.int/features/factfiles/ageing/en/ , Accessed date: 18 February 2018.
[7] S.R. Kahn, W. Lim, A.S. Dunn, M. Cushman, F. Dentali, E.A. Akl, D.J. Cook, A.A. Balekian, R.C. Klein, H. Le, S. Schulman, M.H. Murad, Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, Chest 141 (2 Suppl) (2012) e195S–e226S.
[8] S.A. Johannesdottir, E. Horvath-Puho, V. Ehrenstein, M. Schmidt, L. Pedersen, H.T. Sørensen, Existing data sources for clinical epidemiology: the Danish National Database of reimbursed prescriptions, Clin. Epidemiol. 4 (2012) 303–313.
[9] M. Schmidt, L. Pedersen, H.T. Sørensen, The Danish civil registration system as a tool in epidemiology, Eur. J. Epidemiol. 29 (2014) 541–549.
[10] M. Schmidt, S.A. Schmidt, J.L. Sandegaard, V. Ehrenstein, L. Pedersen, H.T. Sørensen, The Danish National Patient Registry: a review of content, data quality, and research potential, Clin. Epidemiol. 7 (2015) 449–490.

[11] M.T. Severinsen, S.R. Kristensen, K. Overvad, C. Dethlefsen, A. Tjønneland, S.P. Johnsen, Venous thromboembolism discharge diagnoses in the Danish National Patient Registry should be used with caution, J. Clin. Epidemiol. 63 (2010) 223–228.
[12] M. Schmidt, S.C. Cannegieter, S.A. Johannesdottir, O.M. Dekkers, E. Horváth-Puhó, H.T. Sørensen, Statin use and venous thromboembolism recurrence: a combined nationwide cohort and nested case-control study, J. Thromb. Haemost. 12 (2014) 1207–1215.
[13] M.E. Charlson, P. Pompei, K.L. Ales, C.R. MacKenzie, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, J. Chronic Dis. 40 (1987) 373–383.
[14] V. Sundararajan, T. Henderson, C. Perry, A. Muggivan, H. Quan, W.A. Ghali, New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality, J. Clin. Epidemiol. 57 (2004) 1288–1294.
[15] T.J. DiCiccio, B. Efron, More accurate confidence intervals in exponential families, Biometrika 79 (1992) 231–245.
[16] M.D. Silverstein, J.A. Heit, D.N. Mohr, T.M. Petterson, W.M. O'Fallon, L.J.3rd. Melton, Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study, Arch. Intern. Med. 158 (1998) 585–593.
[17] J.A. Heit, Venous thromboembolism: disease burden, outcomes and risk factors, J. Thromb. Haemost. 3 (2005) 1611–1617.
[18] W. Huang, R.J. Goldberg, F.A. Anderson, C.I. Kiefe, F.A. Spencer, Secular trends in occurrence of actue venous thromboembolism: the Worcester venous thromboembolism study (1985 to 2009), Am. J. Med. 127 (2014) 829–839.
[19] N. Arshad, T. Isaksen, J.-B. Hansen, S.K. Brækkan, Time trends in incidence rates of venous thromboembolism in a large cohort recruited from the general population, Eur. J. Epidemiol. 32 (2017) 299–305.
[20] D.R. Anderson, D.C. Barnes, Computerized tomographic pulmonary angiography versus ventilation perfusion lung scanning for the diagnosis of pulmonary embolism, Curr. Opin. Pulm. Med. 15 (2009) 425–429.
[21] R.S. Wiener, L.M. Schwartz, S. Woloshin, Time trends in pulmonary embolism in the United States, Arch. Intern. Med. 171 (2011) 831–837.
[22] J.P. Vandenbroucke, T. Koster, F.R. Rosendaal, E. Briët, P.H. Retisma, R.M. Bertina, Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation, Lancet 344 (1994) 1453–1457.
[23] F.R. Rosendaal, Venous thrombosis: a multicausal disease, Lancet 353 (1993) 1167–1173.