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Time Trends and Excess Mortality Compared to Population Controls after a First-Time Pulmonary Embolism or Deep Vein Thrombosis

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Thromb Haemost

Abstract

Background Recent data on temporal trends in excess mortality for patients with pulmonary embolism (PE) and deep vein thrombosis (DVT) compared with the general population are scarce.

Methods A nationwide Swedish register study conducted from 2006 to 2018 including 68,960 PE and 70,949 DVT cases matched with population controls. Poisson regression determined relative risk (RR) for 30-day and 1-year mortality trends while Cox regression determined adjusted hazard ratios (aHRs). A significance level of 0.001 was applied.

Results In PE cases, both 30-day mortality (12.5% in 2006 to 7.8% in 2018, RR: 0.95 [95% CI: 0.95–0.96], $p < 0.0001$) and 1-year mortality (26.5 to 22.1%, RR: 0.98 [0.97–0.98], $p < 0.0001$) decreased during the study period. Compared with controls, no significant change was seen in 30-day (aHR: 33.08 [95% CI: 25.12–43.55] to 24.64 [95% CI: 18.81–32.27], $p = 0.0015$ for interaction with calendar year) or 1-year (aHR: 5.85 [95% CI: 5.31–6.45] to 7.07 [95% CI: 6.43–7.78], $p = 0.038$) excess mortality. The 30-day excess mortality decreased significantly (aHR: 39.93 [95% CI: 28.47–56.00) to 24.63 [95% CI: 17.94–33.83], $p = 0.0009$) in patients with PE without known cancer before baseline, while the excess 1-year mortality increased (aHR: 3.55 [95% CI: 3.16–3.99] to 5.38 [95% CI: 4.85–5.98], $p < 0.0001$) in PE cases surviving to fill a prescription of

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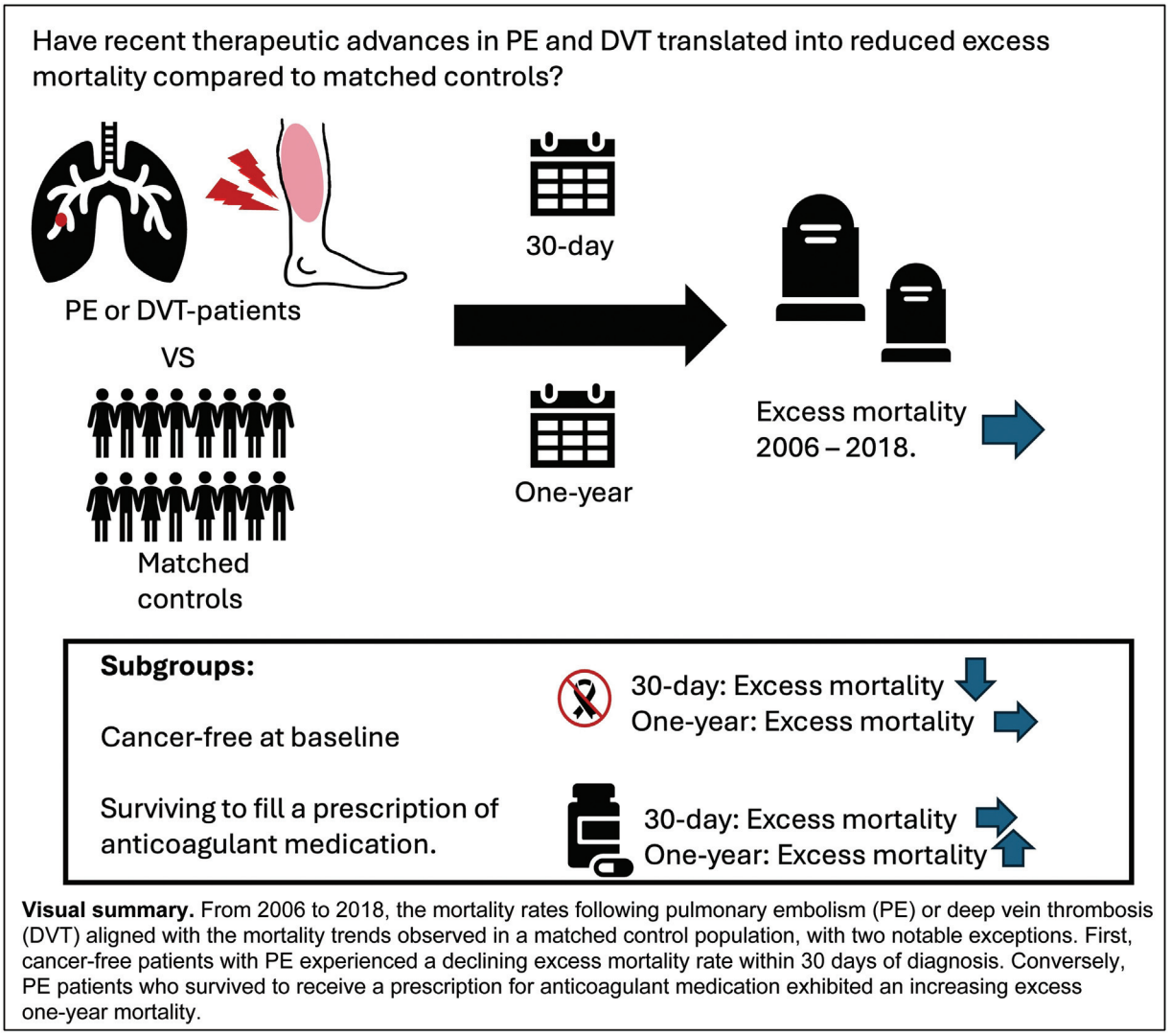

Visual summary. From 2006 to 2018, the mortality rates following pulmonary embolism (PE) or deep vein thrombosis (DVT) aligned with the mortality trends observed in a matched control population, with two notable exceptions. First, cancer-free patients with PE experienced a declining excess mortality rate within 30 days of diagnosis. Conversely, PE patients who survived to receive a prescription for anticoagulant medication exhibited an increasing excess one-year mortality.

anticoagulation. In DVT cases, 30-day and 1-year mortality declined, while excess mortality compared with controls remained stable.

Conclusion In general, the improved mortality following PE and DVT paralleled population trends. However, PE cases without cancer had decreasing excess 30-day mortality, whereas those surviving to fill a prescription for anticoagulant medication showed increasing excess 1-year mortality.

Background

In recent decades, significant improvements have been made in the care of patients with venous thromboembolism (VTE), including standardized risk assessment,[1] increased use of indefinite anticoagulation,[1–3] and heightened awareness of thromboprophylaxis.[4]

However, the extent to which these advancements have translated into improved survival for VTE patients remains uncertain. Consequently, several recent large-scale studies investigating trends in pulmonary embolism (PE)-related mortality have emerged, albeit with conflicting findings in different regions.[5–9] However, death certificate data have been reported to have low accuracy,[10] possibly with particularly large difficulties in determining PE-related mortality, given the lack of a clear definition.[11] Accordingly, reporting all-cause mortality data may be more informative. Studies specifically assessing all-cause mortality in PE patients have demonstrated a reduction in both short- and long-term mortality,[12–14] indicating that the advancements in PE patient care have indeed led to improved survival. However, mortality is also decreasing in the general population,[15] and most of these studies lack a comparator group such as the general population. Hence, uncertainty persists as to whether the observed improved survival, in particular in long-term

mortality, reflects a result of improved VTE care or simply an overall increase in survival across the general population. A more precise way to assess time trends in VTE mortality could be to explore if the excess mortality trend in VTE patients increases or decreases compared with the general population.

The PE population is diverse, underscoring the need for subgroup mortality analysis. For instance, while most PE patients survive until filling a prescription of anticoagulant medication, studies specifically exploring mortality within this subgroup are lacking.[12,16] Similarly, patients with cancer-associated VTE constitute a distinct group warranting separate analysis given their considerably higher death rate.[17]

The primary objective of this study was to explore trends in 30-day and 1-year all-cause mortality from 2006 to 2018 in patients with a first-time PE or deep vein thrombosis (DVT) episode, compared with matched controls from the general population. Secondary objectives comprised separate analyses of patients who survived to fill a prescription of anticoagulant medication at the pharmacy and of patients without known cancer at baseline.

Methods

Study Population

This nationwide, Swedish, register-based study included patients with a first-time VTE from 2006 to 2018. The included registers were the National Patient Register, the National Prescribed Drug Register, the National Cause of Death Register, and the Total Population Register.

The National Patient Register has virtually complete coverage of inpatient care.[18] Hospital-based outpatient care (not primary care) has been registered since 2001, with almost complete coverage for all caregivers over the last decade.[18,19] The National Prescribed Drug Register contains data on all dispensed prescription medications in Sweden from July 2005 and onwards.[20] The National Cause of Death Register contains data on underlying and contributing causes of death for inhabitants registered in Sweden.[21] The Total Population Register contains data on all inhabitants in Sweden, including their area of residence.[22]

VTE cases were identified in the National Patient Register, linked with the other registers using the Swedish Personal Identifier Number (a unique number identifying every Swedish citizen), and merged into a pseudonymized dataset, where the Personal Identifier Number was replaced by a serial number. Up to four control persons per case were retrieved from the Total Population Register and matched to VTE cases on age, sex, area of residence, and date of the first VTE diagnosis of cases. Control persons suffering from VTE after matching were censored at that time point and became cases. The yearly number of Swedish inhabitants, used for the calculation of incidence rates, was provided by Statistics Sweden.[23]

Primary and secondary position diagnostic codes from in- and outpatient registers for VTE with the following diagnostic codes were included: ICD-10 (International Classification of Diseases 10th Revision): PE (I26), DVT (I80 except I80.0). Diagnostic codes for pregnancy-associated VTE were not included. The Swedish version of the ICD-10 does not encompass specific codes for upper extremity thrombosis (I82.62), which prevented us from distinguishing cases of upper extremity thrombosis. Additionally, codes for other venous embolism or thrombosis (I82.4X) are also absent. The outpatient and DVT diagnoses in the National Patient Register may have low accuracy.[24,25] Therefore, all diagnoses were confirmed by either (1) a prescription of anticoagulant medication filled within 30 days of the DVT or PE diagnosis (for Anatomical Therapeutic Chemical codes, see ►**Supplementary Table S1**, available in the online version), or (2) in cases the patient died before filling a prescription, a confirmation of the VTE diagnosis in the National Patient Register by a VTE diagnosis as an underlying or contributing cause of death in the National Cause of Death Register. Cases with concomitant diagnosis of both PE and DVT were classified as PE.

Exclusion Criteria

- Cases with prior DVT/PE. International Classification of Diseases Revision 9 (ICD-9): PE (415B, 416W), DVT (451 except 451 A, and 453C); or ICD-10: PE (I26), DVT (I80 except I80.0).
- Dispense of prescription of anticoagulant treatment within 6 months before the VTE diagnoses for cases (6 months before the matching date for controls).
- Age <18 years at the time of first VTE.

See ►**Fig. 1** for the flow chart for study inclusion.

The study was approved by the Swedish Ethical Review Authority (Dnr 2019–01956).

Comorbidities

Baseline comorbidities encompassed registered diagnoses within 7 years preceding the occurrence of the VTE event, with the VTE date in cases serving as the index date for control subjects. The following comorbidities were included: ischemic heart disease, heart failure, peripheral artery disease, ischemic stroke, hemorrhagic stroke, dementia, chronic obstructive pulmonary disease, systemic connective tissue disorders, liver disease, diabetes, hemiparesis, kidney failure, human immunodeficiency virus, psychosis, and cancer.

Additionally, certain comorbidities were defined based on registered diagnoses within 6 months preceding the VTE date, including bleeding, peptic ulcer, surgery, lower extremity fracture, and trauma. Detailed ICD-10 codes for all diagnoses are provided in ►**Supplementary Table S2** (available in the online version). Concomitant medications were determined by prescription fillings within 6 months before the VTE (►**Supplementary Table S2**, available in the online version).

Outcomes

The primary outcome of this study was the time trends in excess mortality in patients with PE or DVT compared with matched controls. Secondary outcomes were time-trend analyses in excess mortality in patients who survived to

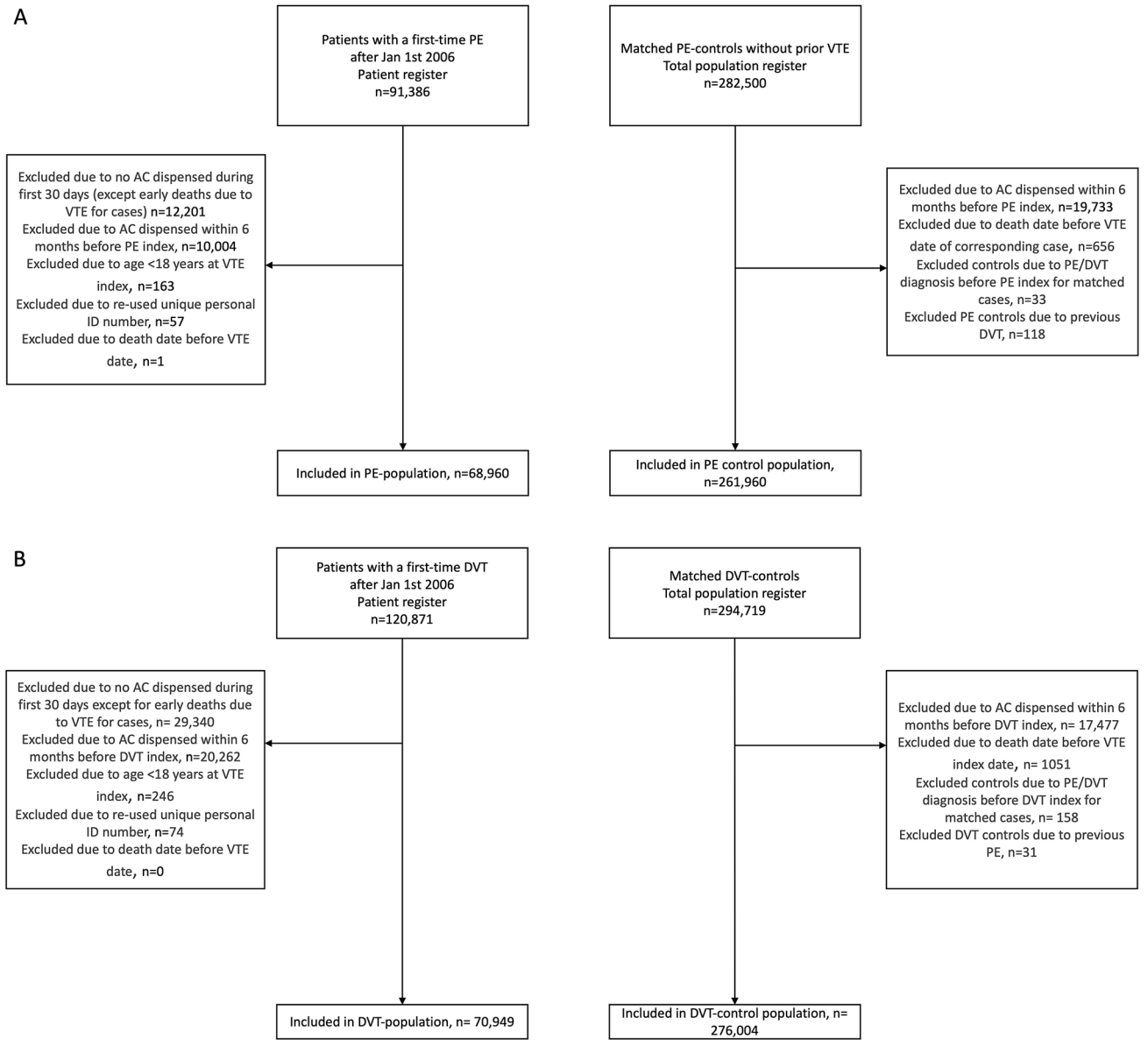

Fig. 1 Flow chart for study inclusion for PE cases and controls (**A**) and DVT cases and controls (**B**). AC, anticoagulant medication; DVT, deep vein thrombosis; PE, pulmonary embolism.

fill a prescription of anticoagulant medication at the pharmacy and in patients without known cancer at baseline, both compared with their respective controls. Cases and controls were followed until death, up to 1 year after the index VTE, or December 31, 2019, whichever came first. Controls were censored at the time of the first VTE during the study follow-up.

Statistical Analysis

Continuous baseline characteristic variables were described by mean, standard deviation, median, and range, as applicable, and categorical variables by frequency and percentage. The incidence rate for PE and DVT was calculated by dividing the number of events each calendar year by the number of inhabitants 18 years and older in Sweden the same year, using population numbers from Statistics Sweden.

Crude event rates were calculated as the number of deaths divided by the number of follow-up years per respective study group and expressed by 1,000 person-years. The 95% confidence interval (CI) for the event rate was estimated using exact Poisson limits. Crude event rates and incidence for 30-day and 1-year (0–365 days) mortality were described for each calendar year. Separate analyses were made for PE cases versus their controls and DVT cases versus their controls. In separate sub-analysis, PE and DVT cases who filled a prescription for anticoagulant medication and PE and DVT cases without diagnosed cancer 7 years prior to baseline were assessed for mortality. Poisson regression was used to determine relative risk (RR) for trends in mortality rates over time. RR with 95% CI was presented.

The Cox proportional hazard regression model was used to calculate hazard ratios (HRs) with 95% CI for mortality for

cases versus controls. We adjusted HR for all comorbidities registered before the index VTE. HR was also adjusted for sex and age since the original age and sex-matching had become unbalanced due to the exclusion of individuals according to predefined exclusion criteria. Additionally, the interaction between the group (cases vs. control) and the year of the first VTE diagnosis was investigated. The proportional hazards assumption was tested by introducing an interaction term between the log(time) and the group (cases and controls), respectively, for PE and DVT.

All tests were two-tailed. Due to the large number of patients included in this study, and the multiple testing performed, a significance level of 0.001 was applied. All analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina, United States).

Results

From January 2006 to December 2018, a total of 68,960 cases (51.4% female, median age 69.0) presenting with first-time PE and 70,949 cases with a first-time DVT (50.4% female, median age 65.7) were identified. PE cases were matched with 261,960 population controls, whereas DVT patients were correspondingly matched with 276,004 population controls. Among the identified cases, 63,424 individuals with PE and 70,577 with DVT survived to fill a prescription for anticoagulant medication at the pharmacy. Furthermore, 49,743 PE cases and 54,895 DVT cases had no history of cancer diagnosis within 7 years preceding the baseline.

The incidence of PE increased from 56.2 per 100,000 inhabitants in 2006 to 78.6 per 100,000 inhabitants in 2018 (►**Table 1**). Conversely, the incidence of DVT was 59.9 per 100,000 in 2006, which increased to 76.3 per 100,000 by 2011 before stabilizing for the remainder of the study period.

Baseline characteristics of patients in 2006 and 2018 are shown in ►**Table 1**. During the study period, outpatient management became more prevalent. Toward the end of the study period, fewer patients had ischemic heart disease or heart failure, while the prevalence of kidney failure increased. In 2006, a larger number of PE patients had cancer compared with 2018, whereas the proportion remained stable in the DVT patient group (►**Table 1**).

Mortality and Time Trends Compared with Matched Controls

Pulmonary Embolism and 30-Day Mortality

The 30-day mortality for patients with PE decreased from 12.5% in 2006 to 7.8% in 2018 (►**Fig. 2A**; detailed in ►**Supplementary Table S3**, available in the online version). Time-trend analysis revealed a reduction in event rates, with an annual 5% decrease (RR: 0.95, 95% CI: 0.95–0.96, $p < 0.0001$). Conversely, the controls showed no significant change in mortality ($p = 0.026$). The adjusted HR (aHR) compared with matched controls demonstrated a numerical decrease, albeit not statistically significant, from 33.08 (95% CI: 25.12–43.55) in 2006 to 24.64 (95% CI: 18.81–32.27) in 2018 ($p = 0.0015$ for interaction with calendar year).

Among PE patients who filled a prescription for anticoagulant medication, 30-day mortality was 1.9% in 2006 and 2.0% in 2018 (►**Fig. 2B**; detailed in ►**Supplementary Table S4**, available in the online version). Time-trend analysis showed stable mortality in cases (RR: 1.01, 95% CI: 0.99–1.02, $p = 0.41$) as well as controls ($p = 0.016$). The aHR did not change significantly, 4.03 (95% CI: 2.76–5.90) in 2006 and 6.42 (95% CI: 4.57–9.02) in 2018 ($p = 0.075$).

In patients with PE without a history of cancer before baseline, the 30-day mortality declined from 11.1% in 2006 to 6.5% in 2018 (►**Fig. 2C**; detailed in ►**Supplementary Table S5**, available in the online version). Time-trend analysis revealed an annual decrease in event rates (RR: of 0.95, 95% CI: 0.95–0.96, $p < 0.0001$) for cases, but no significant change for controls ($p = 0.06$). The aHR declined significantly from 39.93 (95% CI: 28.47–56.00) to 24.63 (95% CI: 17.94–33.83, $p = 0.0009$).

Pulmonary Embolism and One-Year Mortality

The 1-year all-cause mortality among patients with PE declined from 26.5% in 2006 to 22.1% in 2018 (►**Fig. 2D**; detailed in ►**Supplementary Table S3**, available in the online version). Time-trend analysis revealed an annual decrease of 2% in event rates (RR of 0.98, 95% CI: 0.97–0.98, $p < 0.0001$) for cases as well as a decline in controls ($p < 0.0001$). The aHR did not change significantly, 5.85 (95% CI: 5.31–6.45) in 2006 and 7.07 (95% CI: 6.43–7.78) in 2018 ($p = 0.038$).

When considering only PE patients who filled a prescription for anticoagulation, the 1-year mortality was 17.5% in 2006 and 17.2% in 2018 (►**Fig. 2E**; detailed in ►**Supplementary Table S4**, available in the online version). Time-trend analysis showed no significant change in cases (RR: 1.00, 95% CI: 0.99–1.00, $p = 0.20$), but a decrease in controls ($p < 0.0001$). The aHR increased from 3.55 (95% CI: 3.16–3.99) in 2006 to 5.38 (95% CI: 4.85–5.98) in 2018 ($p < 0.0001$).

In PE patients without a history of cancer, the 1-year mortality was 20.0% in 2006 and 15.6% in 2018 (►**Fig. 2F**; detailed in ►**Supplementary Table S5**, available in the online version). Time-trend analysis showed an annual decrease in event rates (RR: 0.97, 95% CI: 0.97–0.98, $p < 0.0001$) in cases, accompanied by a decline in controls ($p < 0.0001$). The aHR did not change significantly, 5.32 (95% CI: 4.73–5.99) in 2006 and 6.12 (95% CI: 5.44–6.88) in 2018 ($p = 0.51$).

Deep Vein Thrombosis and 30-Day Mortality

For patients with a DVT diagnosis, the 30-day mortality was 2.4% in 2006 and 1.8% in 2018 (►**Fig. 3A**; detailed in ►**Supplementary Table S6**, available in the online version). Time-trend analysis showed an annual decrease in event rates (RR: 0.97, 95% CI:, 0.96–0.97, $p < 0.0001$) in cases, as well as in controls ($p < 0.0001$). The aHR did not change significantly, 6.06 (95% CI: 4.32–8.50) in 2006 and 5.17 (95% CI: 3.70–7.24) in 2018 ($p = 0.29$).

Among DVT patients who filled a prescription for anticoagulant medication, the 30-day mortality was 1.6% in 2006

Table 1 Baseline characteristics of PE cases and controls and DVT cases and controls during calendar years 2006 and 2018 of the study period

	2006					2018				
Variable	**PE cases**	**PE controls**		**DVT cases**	**DVT controls**	**PE cases**	**PE controls**		**DVT cases**	**DVT controls**	
	***N* = 4,034**	***N* = 15,636**		***N* = 4,328**	***N* = 17,306**	***N* = 6,345**	***N* = 23,310**		***N* = 5,993**	***N* = 22,637**	
Incidence per 100,000 inhabitants	56.2	NA		60.3	NA	78.6	NA		74.2	NA	
Demographics											
Age (y)	69.0 ± 16.0	68.6 ± 16.2		67.0 ± 16.8	66.6 ± 17.0	69.0 ± 15.4	68.0 ± 15.5		65.3 ± 16.6	64.2 ± 16.6	
	72 (18–100)	71 (18–100)		69 (18–103)	68 (18–103)	72 (18–103)	71 (18–103)		68 (18–103)	66 (18–103)	
	n = 4,034	*n* = 15,636		*n* = 4,328	*n* = 17,306	*n* = 6,345	*n* = 23,310		*n* = 5,993	*n* = 22,637	
Age categories (y)											
18 to <30	92 (2.3%)	380 (2.4%)		118 (2.7%)	495 (2.9%)	163 (2.6%)	662 (2.8%)		181 (3.0%)	754 (3.3%)	
30 to <40	169 (4.2%)	681 (4.4%)		186 (4.3%)	813 (4.7%)	204 (3.2%)	821 (3.5%)		324 (5.4%)	1,309 (5.8%)	
40 to <50	249 (6.2%)	1,004 (6.4%)		400 (9.2%)	1,645 (9.5%)	333 (5.2%)	1,331 (5.7%)		576 (9.6%)	2364 (10.4%)	
50 to <60	451 (11.2%)	1,792 (11.5%)		560 (12.9%)	2,271 (13.1%)	721 (11.4%)	2,900 (12.4%)		873 (14.6%)	3,530 (15.6%)	
60 to <70	848 (21.0%)	3,357 (21.5%)		968 (22.4%)	3,901 (22.5%)	1,321 (20.8%)	5,101 (21.9%)		1,281 (21.4%)	5,000 (22.1%)	
70 to <80	1,001 (24.8%)	3,827 (24.5%)		920 (21.3%)	3,614 (20.9%)	1,957 (30.8%)	7,103 (30.5%)		1,530 (25.5%)	5,600 (24.7%)	
≥80	1,224 (30.3%)	4,595 (29.4%)		1,176 (27.2%)	4,567 (26.4%)	1,646 (25.9%)	5,392 (23.1%)		1,228 (20.5%)	4,080 (18.0%)	
Sex											
Male	1,895 (47.0%)	7,299 (46.7%)		2,078 (48.0%)	8,182 (47.3%)	3,100 (48.9%)	11,223 (48.1%)		3,066 (51.2%)	11,559 (51.1%)	
Female	2,139 (53.0%)	8,337 (53.3%)		2,250 (52.0%)	9,124 (52.7%)	3,245 (51.1%)	12,087 (51.9%)		2,927 (48.8%)	11,078 (48.9%)	
In-/out-patient visit for index VTE											
In-patient	3,785 (93.8%)	NA		1,888 (43.6%)	NA	5,306 (83.6%)	NA		1,341 (22.4%)	NA	
Out-patient	249 (6.2%)	NA		2,440 (56.4%)	NA	1,039 (16.4%)	NA		4,652 (77.6%)	NA	
Medical history before baseline											
Ischemic heart disease	569 (14.1%)	1,580 (10.1%)	[a]	411 (9.5%)	1,538 (8.9%)	673 (10.6%)	1,804 (7.7%)	[a]	399 (6.7%)	1,455 (6.4%)	
Heart failure	386 (9.6%)	755 (4.8%)	[a]	231 (5.3%)	774 (4.5%)	442 (7.0%)	629 (2.7%)	[a]	221 (3.7%)	497 (2.2%)	[a]
Peripheral artery disease	69 (1.7%)	270 (1.7%)		88 (2.0%)	235 (1.4%)	117 (1.8%)	292 (1.3%)	[a]	84 (1.4%)	245 (1.1%)	
Ischemic stroke	222 (5.5%)	645 (4.1%)	[a]	217 (5.0%)	647 (3.7%)	[a] 245 (3.9%)	555 (2.4%)	[a]	190 (3.2%)	442 (2.0%)	[a]
Hemorrhagic stroke	52 (1.3%)	109 (0.7%)	[a]	56 (1.3%)	124 (0.7%)	[a] 82 (1.3%)	158 (0.7%)	[a]	61 (1.0%)	129 (0.6%)	[a]
Dementia	104 (2.6%)	434 (2.8%)		167 (3.9%)	422 (2.4%)	[a] 220 (3.5%)	543 (2.3%)	[a]	207 (3.5%)	388 (1.7%)	[a]

Table 1 (*Continued*)

	2006						2018					
Variable	PE cases	PE controls		DVT cases	DVT controls		PE cases	PE controls		DVT cases	DVT controls	
	N = 4,034	*N* = 15,636		*N* = 4,328	*N* = 17,306		*N* = 6,345	*N* = 23,310		*N* = 5,993	*N* = 22,637	
Chronic obstructive pulmonary disease	243 (6.0%)	404 (2.6%)	[a]	141 (3.3%)	444 (2.6%)		492 (7.8%)	663 (2.8%)	[a]	246 (4.1%)	538 (2.4%)	[a]
Systemic connective tissue disorders	123 (3.0%)	218 (1.4%)	[a]	100 (2.3%)	205 (1.2%)	[a]	228 (3.6%)	360 (1.5%)	[a]	167 (2.8%)	300 (1.3%)	[a]
Peptic ulcer	29 (0.7%)	32 (0.2%)	[a]	26 (0.6%)	26 (0.2%)	[a]	27 (0.4%)	24 (0.1%)	[a]	23 (0.4%)	22 (0.1%)	[a]
Liver disease	32 (0.8%)	79 (0.5%)		39 (0.9%)	71 (0.4%)	[a]	63 (1.0%)	131 (0.6%)	[a]	76 (1.3%)	116 (0.5%)	[a]
Diabetes mellitus	317 (7.9%)	1,073 (6.9%)		311 (7.2%)	1,064 (6.1%)		674 (10.6%)	1,787 (7.7%)	[a]	521 (8.7%)	1,512 (6.7%)	[a]
Hemiparesis	16 (0.4%)	34 (0.2%)		18 (0.4%)	36 (0.2%)		99 (1.6%)	149 (0.6%)	[a]	67 (1.1%)	123 (0.5%)	[a]
Kidney failure	91 (2.3%)	173 (1.1%)	[a]	71 (1.6%)	179 (1.0%)	[a]	284 (4.5%)	510 (2.2%)	[a]	257 (4.3%)	398 (1.8%)	[a]
Cancer	987 (24.5%)	1,680 (10.7%)	[a]	943 (21.8%)	1,688 (9.8%)	[a]	1,783 (28.1%)	2,978 (12.8%)	[a]	1,301 (21.7%)	2,475 (10.9%)	[a]
HIV	4 (0.1%)	5 (0.0%)		1 (0.0%)	5 (0.0%)		3 (0.0%)	14 (0.1%)		5 (0.1%)	17 (0.1%)	
Bleeding	103 (2.6%)	141 (0.9%)	[a]	119 (2.7%)	146 (0.8%)	[a]	206 (3.2%)	208 (0.9%)	[a]	132 (2.2%)	176 (0.8%)	[a]
Psychosis	5 (0.1%)	28 (0.2%)		11 (0.3%)	23 (0.1%)		26 (0.4%)	30 (0.1%)	[a]	12 (0.2%)	29 (0.1%)	
Surgery	624 (15.5%)	634 (4.1%)	[a]	655 (15.1%)	675 (3.9%)	[a]	789 (12.4%)	766 (3.3%)	[a]	605 (10.1%)	721 (3.2%)	[a]
Lower extremity fracture	129 (3.2%)	116 (0.7%)	[a]	217 (5.0%)	149 (0.9%)	[a]	139 (2.2%)	107 (0.5%)	[a]	237 (4.0%)	80 (0.4%)	[a]
Trauma	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Dispensed medication within 6 months before baseline												
Oral contraceptives or hormone replacement therapy	365 (9.0%)	1,359 (8.7%)		402 (9.3%)	1,454 (8.4%)		486 (7.7%)	1,521 (6.5%)		396 (6.6%)	1,332 (5.9%)	
Antiplatelet treatment	1,145 (28.4%)	3,861 (24.7%)	[a]	916 (21.2%)	3,887 (22.5%)		1,339 (21.1%)	4,536 (19.5%)		897 (15.0%)	3,642 (16.1%)	
Proton pump inhibitors	902 (22.4%)	1,738 (11.1%)	[a]	815 (18.8%)	1,834 (10.6%)	[a]	1,667 (26.3%)	3,341 (14.3%)	[a]	1,307 (21.8%)	2,964 (13.1%)	[a]
Statins	551 (13.7%)	2,353 (15.0%)		432 (10.0%)	2,209 (12.8%)	[a]	1,273 (20.1%)	5,138 (22.0%)	[a]	1,024 (17.1%)	4,308 (19.0%)	[a]
Selective serotonin reuptake inhibitor	516 (12.8%)	1,248 (8.0%)	[a]	453 (10.5%)	1,443 (8.3%)	[a]	755 (11.9%)	1,706 (7.3%)	[a]	500 (8.3%)	1,619 (7.2%)	

Note: Data are presented as mean ± standard deviation, median (range) and number of observations, or number (percentage). For test between two groups with respect to dichotomous variables, a Chi-square test was used; for ordered categorical variables, the Mantel–Haenszel Chi-square trend test was used; and for continuous variables, a two-sample *t*-test was used.
[a]Significant difference between case and control, $p < 0.001$.

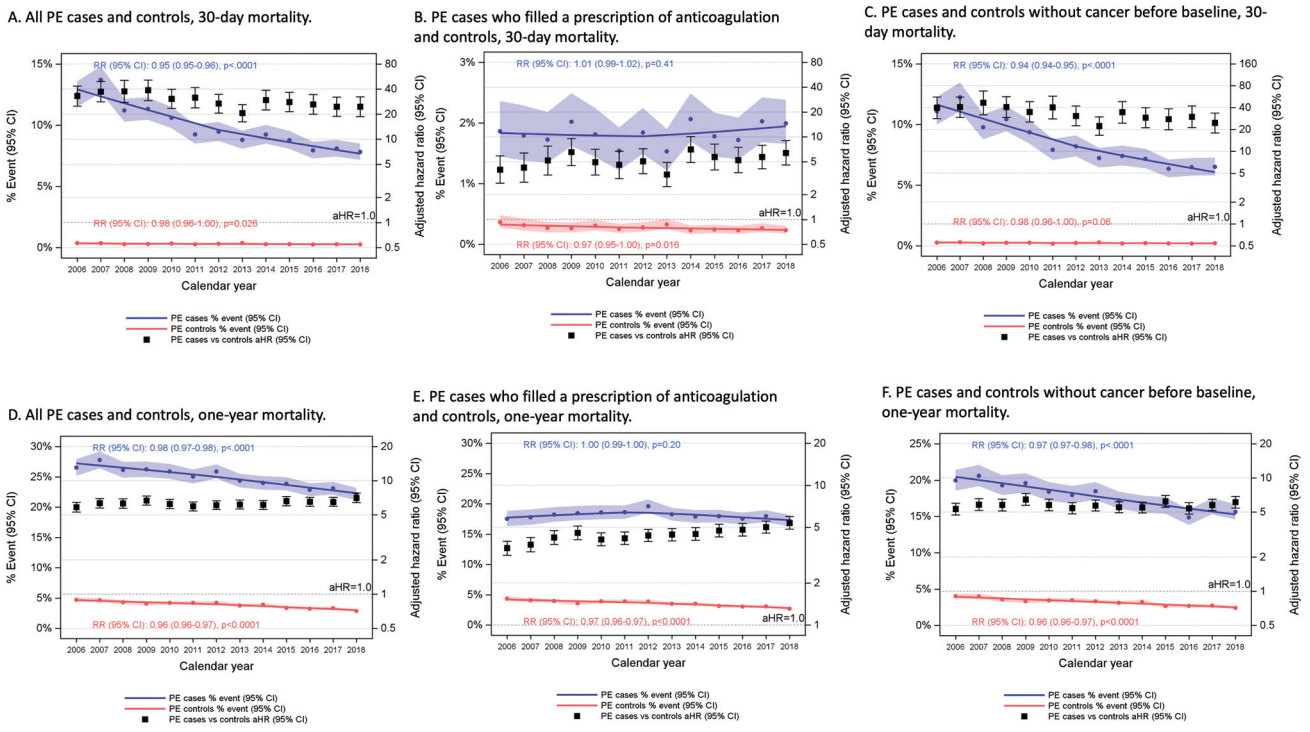

Fig. 2 (**A**) Thirty-day mortality, relative risk (RR) over time, and adjusted hazard ratios (aHRs) for PE cases versus controls over calendar years. (**B**) Thirty-day mortality, RR over time, and aHR for PE patients who filled a prescription for anticoagulant medication. (**C**) Thirty-day mortality, RR over time, and aHR for PE cases and controls without cancer before baseline. (**D**) One-year mortality, RR over time, and aHR for PE cases versus controls over calendar years. (**E**) One-year mortality, RR over time, and aHR for PE patients who filled a prescription for anticoagulant medication. (**F**) One-year mortality, RR over time, and aHR for PE cases and controls without cancer before baseline. PE, pulmonary embolism.

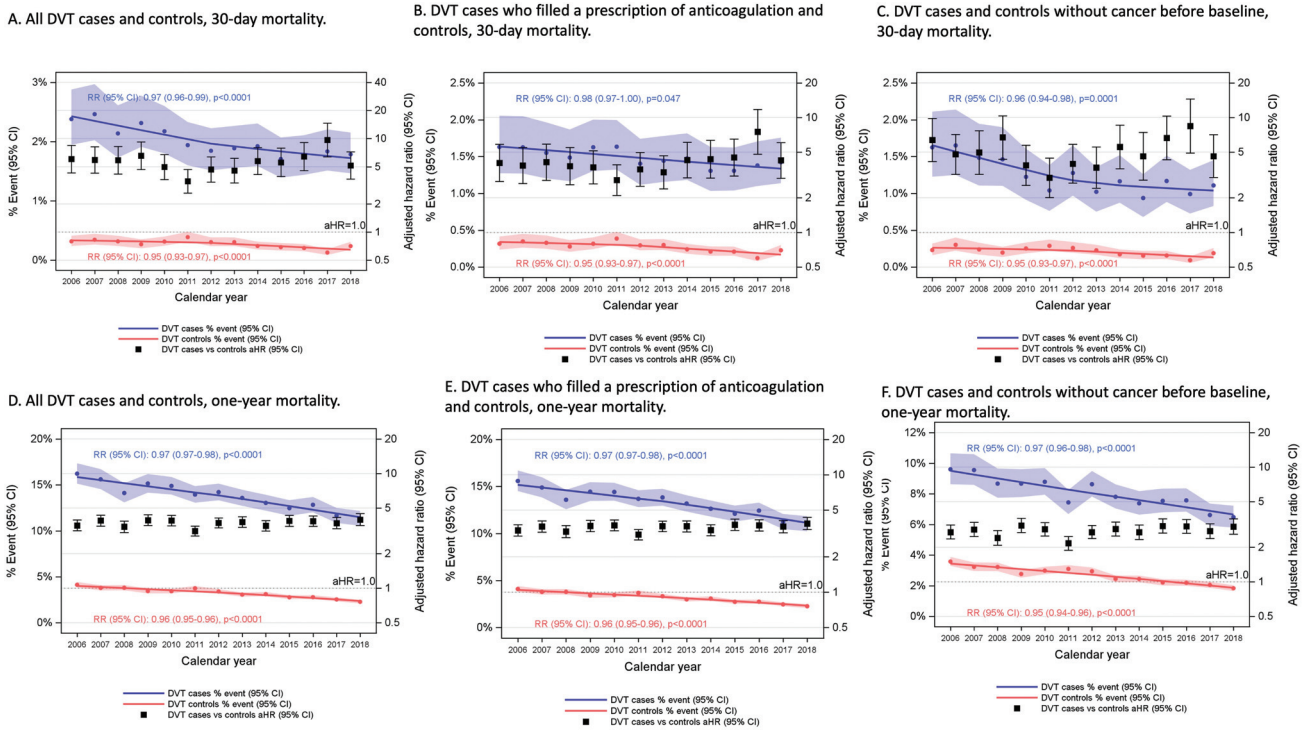

Fig. 3 (**A**) Thirty-day mortality, relative risk (RR) over time, and adjusted hazard ratios (aHRs) for DVT cases versus controls over calendar years. (**B**) Thirty-day mortality, RR over time, and aHR for DVT patients who filled a prescription for anticoagulant medication. (**C**) Thirty-day mortality, RR over time, and aHR for DVT cases and controls without cancer before baseline. (**D**) One-year mortality, RR over time, and aHR for DVT cases versus controls over calendar years. (**E**) One-year mortality, RR over time, and aHR for DVT patients who filled a prescription for anticoagulant medication. (**F**) One-year mortality, RR over time, and aHR for DVT cases and controls without cancer before baseline. DVT, deep vein thrombosis.

and 1.4% in 2018 (►**Fig. 3B**; detailed in ►**Supplementary Table S7**, available in the online version). Time-trend analysis showed no significant trend (RR: 0.98, 95% CI: 0.97–1.00, $p = 0.047$) in cases, but a decline in controls ($p < 0.0001$). The aHR did not change significantly, 4.04 (2.78–5.86) in 2006 and 4.24 (2.96–6.07) in 2018 ($p = 0.028$).

In DVT patients without a history of cancer, the 30-day mortality was 1.6% in 2006 and 1.1% in 2018 (►**Fig. 3C**; detailed in ►**Supplementary Table S8**, available in the online version). Time-trend analysis showed an annual decrease in event rates (RR: 0.96, 95% CI: 0.94–0.98, $p = 0.0001$) in cases, accompanied by a decline in controls ($p < 0.0001$). The aHR did not change significantly, 6.38 (4.15–9.83) in 2006 and 4.62 (3.02–7.08) in 2018 ($p = 0.68$).

Deep Vein Thrombosis and One-Year Mortality

The 1-year mortality in DVT cases was 16.2% in 2006 and 11.3% in 2018 (►**Fig. 3D**; detailed in ►**Supplementary Table S6**, available in the online version). Time-trend analysis showed an annual decrease in event rates by 3% (RR: 0.97, 95% CI: 0.97–0.98, $p < 0.0001$) in cases, accompanied by a decrease in controls ($p < 0.0001$). The aHR did not change significantly, 3.53 (95% CI: 3.17–3.93) in 2006 and 3.97 (95% CI: 3.53–4.47) in 2018 ($p = 0.049$).

When considering only patients filling a prescription for anticoagulant medication, the 1-year mortality was 15.6% in 2006 and 11.0% in 2018 (►**Fig. 3E**; detailed in ►**Supplementary Table S7**, available in the online version). Time-trend analysis showed an annual decrease in event rates (RR: 0.97, 95% CI: 0.97–0.98, $p < 0.0001$) in cases, accompanied by a decrease in controls ($p < 0.0001$). The aHR did not change significantly, 3.36 (95% CI: 3.01–3.76) in 2006 and 3.85 (95% CI: 3.42–4.34) in 2018 ($p = 0.010$).

For patients without a history of cancer before baseline, the 1-year mortality was 9.6% in 2006 and 6.5% in 2018 (►**Fig. 3F**, detailed in ►**Supplementary Table S8**, available in the online version). Time-trend analysis showed an annual decrease in event rates (RR: 0.97, 95% CI: 0.96–0.98, $p < 0.0001$) in cases, accompanied by a decrease in controls ($p < 0.0001$). The aHR did not change significantly, 2.72 (95% CI: 2.37–3.13) in 2006 and 3.03 (95% CI: 2.60–3.54) in 2018 ($p = 0.025$).

Discussion

In the present study, the 30-day and 1-year all-cause mortality rates revealed a significant decrease over time among both PE and DVT patients. However, the excess mortality compared with matched controls remained largely unchanged over time, except for a reduction in 30-day excess mortality among PE cases without a history of cancer. When considering only PE patients surviving to fill a prescription for anticoagulants at the pharmacy, mortality remained unchanged over time, leading to an increase in the 1-year excess mortality compared with matched controls.

Recent studies evaluating mortality trends in VTE patients have reported a decline in mortality rates over time,[12–14] but few studies have compared these declining mortality rates to mortality trends in matched population controls. One recent Danish study reporting time trends in excess mortality in PE showed a significantly decreased 30-day mortality in PE patients relative to population controls matched for sex, age, and cancer, but an increased 31- to 365-day mortality.[12] However, to study excess mortality was not among the study's aims and it was only mentioned briefly in the results, making it difficult to compare with our study.

The previous studies on time trends in all-cause mortality following PE report varying mortality rates. Notably, studies with higher mortality rates included only inpatients,[12,13,16] possibly leading to the inclusion of more severe PE cases.[26] Additionally, no verification of diagnoses with anticoagulation was employed in the previous studies, allowing for the inclusion of both false-positive cases[25] and patients not receiving anticoagulant treatment, a group previously shown to have a high mortality.[26] Indeed, in one previous study, 46% of patients in 2000 and 31.5% in 2020 did not receive oral anticoagulation, with no mention of the use of low-molecular-weight heparin.[12] Conversely, another study on time trends reporting lower mortality rates included only patients who were able to provide informed consent, possibly selecting less severe PE cases.[14]

Patients with PE without a history of cancer before baseline had decreasing 30-day mortality compared with controls. This could be a result of improved inpatient treatment, increased awareness of PE, and increased access to computed tomographic pulmonary angiogram, which simplifies the diagnosis of PE, but also leads to the identification and treatment of more subsegmental PEs.[27] In this context, it is important to acknowledge that PE is still associated with a substantial risk of short-term all-cause mortality. For instance, our reported 30-day mortality in patients without preceding cancer of 6.5% in 2018 exceeds the 30-day mortality in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention in Denmark in 2018 (30-day mortality of 5.1%).[28] Hence, the mortality improvement seen in this study is a very positive indication of possible VTE-care improvement in a patient population at high risk of death.

The vast majority of PE cases survived the initial hospitalization and filled a prescription for anticoagulant medication (63,424 out of 68,960 patients during the study period). No improvement was observed in either 30-day (1.9% in 2006 and 2.0% in 2018) or 1-year mortality (17.5% in 2006 and 17.2% in 2018). In contrast, the matched population controls experienced a decrease in mortality, resulting in increasing excess mortality for PE cases over time. During the study period, direct oral anticoagulants were introduced, which may have impacted the results. However, the change of treatment practice from warfarin and the increased use of indefinite treatment in Sweden were not fully implemented at the end of the study period, with European guidelines changing first in 2019,[1] making it difficult to evaluate. The trend of increasing excess mortality compared with controls was not seen in patients with DVT with a filled prescription, where excess mortality was stable. A possible explanation for the difference between PE and DVT patients is the increasing

use of thoracic computed tomography scans for cancer follow-up. This could lead to incidental findings of PE in patients with cancer, which could impact mortality.

To address the high long-term mortality, with a relative increase compared with the time trends in the population, information on mortality causes in different subgroups of PE patients is needed. However, studies on specific mortality causes in patients after suffering a PE are scarce. One recent German single-center study reported that the most prevalent 1-year mortality causes in PE patients were PE-related complications, cancer, cardiovascular diseases, and infections.[29] Additional large-scale studies on recent mortality data are needed.

Strengths and Limitations

The main strength of this study is the large population, with national registers including all Swedish inhabitants. Sweden offers universal health care to all inhabitants, meaning there is no selection of patients based on socioeconomic background, which is a potential problem in health care insurance databases.

Similar to many register-based studies, this study has several inherent limitations.[30] One notable limitation is that the use of extensive datasets can yield statistically significant results that may be influenced primarily by the large sample, rather than reflecting meaningful effects. To address this issue, a low significance level has been employed. An additional limitation is that diagnostic coding from clinical practice may be erroneous for various reasons. The validity of VTE diagnoses in the Swedish Patient Register has previously been questioned, in particular for outpatients and patients with DVT.[24,25] We addressed this by validating the VTE diagnosis with either the filling of a prescription of anticoagulant medication within 30 days of the VTE diagnosis (excluding all patients with anticoagulant medication within 6 months prior to the VTE) or a registration of VTE as an underlying or contributing cause of death in the Cause of Death Register for patients who did not survive to fill a prescription of anticoagulant medication at the pharmacy. One limitation of this approach is that it might have led to the exclusion of patients who suffer a VTE after receiving prophylactic outpatient anticoagulation.

The results are likely generalizable to populations with similar thrombotic risk and similar access to high-quality health care as in Sweden. The generalizability to other groups might be lower. Since diagnostic codes for pregnancy-associated VTE were not included in the study, and this group differs from the majority of VTE patients, the generalizability to this group is likely to be low.

Conclusions

We found no significant improvement in excess mortality over time compared with matched controls except for 30-day mortality in PE patients without cancer. In patients with PE who survived to fill a prescription of anticoagulant medication, the excess 1-year mortality compared with controls actually increased. These findings suggest uncertainty regarding whether the advancements in VTE care have effectively translated into improved mortality rates.

What is known about this topic?

- Previous studies indicate a decreasing trend in 30-day and 1-year all-cause mortality rates following pulmonary embolism (PE).
- However, there are limited data on mortality trends associated with deep vein thrombosis (DVT).
- Additionally, minimal research has been conducted into how these trends correlate with overall changes in population mortality.

What does this paper add?

- While 30-day and 1-year mortality decreased over time in patients with PE and DVT, it was parallel to the mortality trends in the population, rendering excess mortality stable over time.
- A sub-analysis showed two exceptions: 30-day mortality in patients with PE without known cancer at baseline decreased over time. One-year mortality in patients with PE who survived to fill a prescription for anticoagulant treatment was unchanged over time, with increasing excess mortality compared with matched controls.

Data Availability Statement

The data that support the findings of this study are available from The National Board of Health and Welfare and Statistics, Sweden, but restrictions apply to the availability of these data, so they are not publicly available.

Authors' Contribution

K.G.S. planned the study. All authors, particularly M.T. and K.G.S., made important contributions to the design of this study. A.P. preformed statistical analyses. All authors were involved in interpreting the data. K.G.S. wrote the first draft of the manuscript. K.G.S., M.T., J.P., S.S., K.S., and C.J.S. provided clinical input at all stages of the project. All authors, particularly M.T. and K.G.S., reviewed and edited the manuscript. All authors approved the final draft.

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Conflict of Interest

K.G.S. has received speaker's honoraria from Bristol-Myers Squibb, Pfizer, Bayer, and Leo Pharma. S.S. has received research grant from Octapharma and honoraria from Alexion, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Regeneron, Sanofi, Servier, Takeda, and Hemostasis Reference Laboratory. K.S. has received speaker's honoraria from Leo Pharma. J.P. has received speaker's honoraria from Pfizer. M.T. has received speaker's honoraria from Viatris. C.J.S. and A.P. report no conflict of interest.

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