Journal of the American Heart Association

ORIGINAL RESEARCH

Cost-of-Illness Analysis of Long-Term Health Care Resource Use and Disease Burden in Patients With Pulmonary Embolism: Insights From the PREFER in VTE Registry

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BACKGROUND: As mortality from pulmonary embolism (PE) decreases, the personal and societal costs among survivors are receiving increasing attention. Detailing this burden would support an efficient public health resource allocation. We aimed to provide estimates for the economic and disease burden of PE also accounting for long-term health care use and both direct and indirect costs beyond the acute phase.

METHODS AND RESULTS: This is a cost-of-illness analysis with a bottom-up approach based on data from the PREFER in VTE registry (Prevention of Thromboembolic Events—European Registry in Venous Thromboembolism). We calculated direct (clinical events and anticoagulation) and indirect costs (loss of productivity) of an acute PE event and its 12-month follow-up in 2020 Euros. We estimated a disability weight for the 12-month post-PE status and corresponding disability adjusted life years presumably owing to PE. Disease-specific costs in the first year of follow-up after an incident PE case ranged between 9135 Euros and 10 620 Euros. The proportion of indirect costs was 42% to 49% of total costs. Costs were lowest in patients with ongoing cancer, mainly because productivity loss was less evident in this already burdened population. The calculated disability weight for survivors who were cancer free 12 months post-PE was 0.017, and the estimated disability adjusted life years per incident case were 1.17.

CONCLUSIONS: The economic burden imposed by PE to society and affected patients is considerable, and productivity loss is its main driver. The disease burden from PE is remarkable and translates to the loss of roughly 1.2 years of healthy life per incident PE case.

Key Words: burden of disease ■ cost-of-illness ■ disability weight ■ disability-adjusted life years ■ productivity loss ■ pulmonary embolism

Venous thromboembolism (VTE) and its most severe manifestation, pulmonary embolism (PE), constitute a major burden for health care systems worldwide. The incidence rate of PE is rising in Europe and the United States.[1,2] In 2014, the International Society on Thrombosis and Haemostasis Steering Committee for World Thrombosis Day reported an incidence of PE ranging from 0.15 to 0.95 cases per 1000 population per year in Western Europe.[3] In parallel, annual mortality rates from acute PE are decreasing worldwide, and thus the numbers of patients surviving an episode of PE are projected to increase in the future.[4–6] Patients recovering from acute PE may suffer from decreased physical performance and be faced with permanent or temporary

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.027514

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Pulmonary embolism causes an economic and productivity burden translating to the loss of approximately 1.2 years of healthy life per incident case.
- In the first year after pulmonary embolism, disease-specific costs ranged between 9135 Euros and 10 620 Euros (2020 Euros), of which almost half consisted of indirect costs.
- The economic burden imposed by pulmonary embolism is highest in patients with no active cancer, presumably because of a lower preexisting productivity impairment.

What Are the Clinical Implications?

- The long-term management of patients with acute pulmonary embolism should include specific measures to assess and reduce the loss of productivity, possibly including personalized rehabilitation programs.
- The costs and disadvantages to health care providers and patients of an intensive clinical follow-up after pulmonary embolism should be weighed against the opportunity to timely address or prevent long-lasting financial burden.

Nonstandard Abbreviations and Acronyms

DOAC	direct oral anticoagulants
EQ-5D	European Quality of Life 5-dimension descriptive system
EU	European Union

loss of work, with a substantial percentage displaying objectively documented clinical and functional pulmonary impairment or reporting persistently worse quality of life.[7,8]

These late outcomes can lead to significant personal and societal costs. Dissecting the corresponding economic burden would support efficient priority setting and resource allocation in public health and health care policies. However, European data are lacking, and previous efforts to quantify the annual costs related to a PE event were based on modeling strategies that relied on incidence assumptions rather than individual-level prospectively collected data.[9,10] An analysis of the PREFER in VTE registry (Prevention of Thromboembolic Events—European Registry in Venous Thromboembolism) has studied the health care resource use in relation to PE; however, no cost calculations were performed.[11]

The primary aim of this study was to determine the average costs per PE incident case by using data from a large-scale, thoroughly monitored cohort of patients with PE that was specifically followed to comprehensively estimate health care resource use as well as the direct and indirect burden deriving from PE over 12 months after the incident event. A further aim of the study was to calculate the burden of disease imposed by PE in terms of disability-adjusted life years (DALYs).

METHODS

We used an incidence-based, bottom-up approach to perform a cost-of-illness analysis for PE using patients followed after acute PE in the PREFER in VTE study.[12,13]

Patient Population, Data Collection, and Subgroups

PREFER in VTE was a prospective, observational registry conducted in 7 European countries (Austria, France, Germany, Italy, Spain, Switzerland, and the United Kingdom) between January 2013 and July 2015 with the aim of documenting the epidemiology, real-life management, and outcomes of a large, unselected population with confirmed first-episode or recurrent VTE, accounting for isolated deep vein thrombosis (without a concomitant PE diagnosis) and PE with or without deep vein thrombosis. Briefly, the study investigators collected information regarding sociodemographic and clinical parameters, comorbidities, VTE risk factors, baseline information on the index VTE event, treatment strategies, quality of life and patient satisfaction, resource use, and clinical events during follow-up.[13] For this analysis, we included only patients diagnosed with acute PE as the index event (irrespective of history of prior VTE) and with follow-up data. Before study commencement, the registry protocol was approved by the responsible ethics committees for the participating countries and the relevant hospital-based institutional review boards. All patients enrolled in the registry first provided written informed consent. The outline has been previously described.[12,13] All data from PREFER in VTE have been made available in anonymized form at the Vivli – Center for Global Clinical Research Data repository and can be accessed after approval of a data request by the data contributor at https://vivli.org.[14]

Statistical Analysis

Study Perspective, Time Horizon, and Definition of Costs

This cost analysis was performed from a societal rather than solely a health care perspective and therefore incorporated both direct and indirect costs, for

example, costs paid by insurers, the patients, and costs due to productivity loss. The time horizon over which costs were evaluated was the 12 months after the index event because that was the follow-up duration of the PREFER in VTE study. Direct costs included those related to the management of the index PE event (including initial hospitalization and treatment), anticoagulation, VTE-related ambulatory visits to medical professionals and other health care practitioners, the patient's own contribution toward VTE-related medication or medical supplies such as compression stockings, as well as the costs for formal (by a health or social care professional and nursing help) or informal help (patient's own contribution) and those related to clinical events such as PE recurrence, deep vein thrombosis recurrence, major and minor bleedings, postthrombotic syndrome incidence, heparin-induced thrombocytopenia, and chronic thromboembolic pulmonary hypertension. Indirect costs included costs for productivity loss, international normalized ratio measurement in vitamin-K antagonist users, lost earnings, self-payment and travel costs (patient's own contribution), and domestic assistance made necessary after PE, such as cleaners, shopping, and household services (patient's own contribution). Costs for productivity loss were estimated using the friction cost method, in which hours of work lost due to the index PE event (which were recorded in detail in the PREFER in VTE registry and applied only to patients previously employed and >70 years of age) were multiplied by the average hourly labor cost in the European Union (EU, as described later). We assumed an 80-day friction period for the replacement of subjects who did not return to work.[15] No discounting was applied because of the 12-month time frame of this analysis. We did not estimate a monetary valuation of intangible losses.

Cost Inputs

We updated previous estimates by performing a systematic search of the literature from April 2014 to December 2021 via PubMed.[10] We considered as eligible original articles presenting clinically relevant cost-of-illness VTE-related source data from the 28 countries that formed the EU-28 and were published from 2010 onwards. We selected a single article per country per cost item (the most recent publication) to avoid unit-of-analysis issues in cost calculations. Because some studies mentioned a range of costs for some of the cost input categories, we abstracted high and low estimates of the cost sources of the studies conducted within the EU-28 to derive low and high average PE-associated cost inputs (costs for clinical events, ambulatory visits to other health care practitioners, and anticoagulation). These EU-28 cost inputs were selected because they reflect a general European population and our reference registry, PREFER in VTE, was conducted in 7 European countries, of which 6 (except for Switzerland) were part of the EU at the time the study was conducted (in 2013–2014, the United Kingdom was part of the EU). Data from Eurostat, the EU statistical bureau, were used to derive mean ambulatory costs per visit from a medical professional for each country in the PREFER in VTE and hourly labor costs of the year 2014.[16] Medical costs, costs for formal and informal help and domestic help, and costs for international normalized ratio measurement were obtained directly from the PREFER in VTE data. For the purposes of our study, we adjusted all cost inputs for inflation and purchasing power parity to 2020 Euros (€); the cost inputs are presented in Table 1. See Data S1 for the search string and the results of the systematic review of the literature.[17–29]

Cost Calculations

Total average costs per PE patient comprised 6 general categories: costs for the index PE hospitalization, costs for clinical events during follow-up, costs for anticoagulation after the index event, costs for ambulatory visits during follow-up, the patient's own contribution, and costs related to productivity loss. We calculated the average costs of clinical events during follow-up by multiplying the cost inputs as described by the number of events as recorded in the PREFER in VTE study. Relevant literature sources were identified to populate the incidence of events not recorded in the PREFER in VTE study, such as postthrombotic syndrome, heparin-induced thrombocytopenia, and chronic thromboembolic pulmonary hypertension.[32–34] We used the low averages and the high averages of cost inputs to calculate a lower and higher end of cost estimates. We calculated average costs from sources other than clinical events during follow-up by using data directly collected in the PREFER in VTE study, including the anticoagulation costs for which we used the reported days of anticoagulation prescription. A stratified analysis was performed according to the presence of active cancer, provoked PE (absence of cancer and one of the following: prolonged immobilization, confined to bed >5 days, major trauma or surgery <3 months, and estrogen use), and unprovoked PE.[35] Missing values were assumed to be missing at random and were therefore excluded from the calculation of total costs (complete case analysis). We tested any differences in baseline characteristics between patients who completed the 12-month follow-up and patients who did not. All calculations were performed in R (the R Project for Statistical Computing, version 4.1.1) and Microsoft Office Excel® in a remote computer environment provided by the Vivli data platform and were independent from the registry sponsor.

Table 1. Pulmonary Embolism Associated Cost Inputs Adjusted for Inflation* and Purchasing Power Parity (2020 Euros)

	Baseline – low averages	High averages
PE (index hospitalization), € per event†	2327.6	3532.6
Deep vein thrombosis readmission/recurrence, € per event†	1185.6	1278.1
PE readmission/ recurrence, € per event†	4026.1	4026.1
Minor bleeding, € per event†	211.4	229.0
Major bleeding, € per event†	4195.9	4378.9
Heparin-induced thrombocytopenia, € per event†	3616.1	3616.1
Postthrombotic syndrome, € per year†	1564.0	2725.1
Chronic thromboembolic pulmonary hypertension, € per year†	21 251.0	26 932.2
Low-molecular weight heparin, € per day	7.93	7.93
Vitamin-K agonist, € per day	0.10	0.10
Direct oral anticoagulant, € per day	2.99	3.53
Fondaparinux, € per day	8.52	8.52
Medical ambulatory visits, € per visit‡	Germany 132.2, Italy 57.2, Spain 61.6, France 137.1, Austria 132.2, Switzerland 518.9, United Kingdom 172.4	Germany 132.2, Italy 57.2, Spain 61.6, France 137.1, Austria 132.2, Switzerland 518.9, United Kingdom 172.4
Nonmedical ambulatory visits, € per visit§	29.6	38.2
Hours of work lost, € per hour‡	28.5	28.5

€ indicates Euros; and PE, pulmonary embolism.

Low average depicts the average of the low-end estimate of cost values across the sources of cost inputs, whereas high average depicts the average of the high-end estimate of cost values.

*Inflation was calculated with the use of https://www.inflationtool.com/euro; purchasing power parities were taken from https://ec.europa.eu/eurostat/databrowser/view/prc_ppp_ind/default/table?lang=en.

†Data updated from Barco et al.[10]

‡Based on Eurostat data tables.[16,30]

§Calculated from Hoogendoorn et al.[31]

Disability Weights and DALYs

In order to assess the 12-month disease burden imposed by PE we calculated DALYs. First, we used a multiattribute utility instrument, the European Quality of Life 5-dimension descriptive system (EQ-5D) health questionnaire, to derive a disability weight for the post-PE state 12 months after the index event, which represents the disability imposed by PE.[36,37] The EQ-5D health questionnaire generates a utility index that ranges from <0 (death) to 1 (perfect health). For the calculation of the PE-specific disability weight, the 12-month EQ-5D index scores for the PREFER in VTE population with PE were subtracted from the average index score for an age-matched country-specific general population.[38] Accordingly, the disability weight ranges from <0 (perfect health) to 1 (death). Then, DALYs were calculated as the sum of years living with disability (calculated as the product of years until death and the disability weight) and the years of life lost due to premature mortality (calculated using country- and sex-specific values for life expectancy in 2014).[39] We excluded patients with active cancer from the burden of disease analysis, because of the lack of standardized population norms for this diverse and heavily burdened population. We used bootstrapping to obtain 95% CIs for the disability weight at 12 months and mean DALYs per patient.

RESULTS

Data from 1349 patients diagnosed with PE from the PREFER in VTE registry were analyzed for this study (see Figure S1 for the patient selection flow chart). Of them, 835 (61.9%) were over 60 years of age, and 628 (46.6%) were women. Presence of an active cancer was recorded in 113 patients (8.4%). Baseline characteristics of the included population are shown in Table 2, and characteristics of the index PE event can be seen in Table S1. Clinical events over the 12-month follow-up can be seen in Table S2.

Average 12-Month Costs

On average, each incident PE case generated costs between 9135 and 10 620 € over the first 12 months. Costs for patients with cancer (8274–9752 €) and patients with unprovoked PE (8695 to 9612 €) were lower than costs for patients without cancer with provoked PE (10 423–11 307 €), mainly owing to differences in productivity loss. Figure 1 displays the total 12-month costs per patient with PE in the overall population and specifically in patients with cancer-associated, provoked noncancer, and unprovoked PE.

A detailed presentation of average costs per cost input category per patient with PE can be seen in Table 3. Costs for clinical events during follow-up ranged from 794 € to 1025 € on average. The indirect costs were mainly driven by productivity losses, and their proportion of total costs was 42% to 49% for the overall population, 28% to 33% for cancer, 52% to 56% for noncancer provoked PE, and 43% to 47% for unprovoked PE (Figure 2). Patient's own out-of-pocket

Table 2. Baseline Characteristics of Patients in the PREFER in VTE

Characteristic	Overall (n=1349)	Patients with ongoing cancer (n=113)	Patients with provoked PE (n=393)	Patients with unprovoked PE (n=843)
Age, y				
10–49	327 (242.%)	10 (8.8%)	149 (37.9%)	168 (19.9%)
50–69	480 (35.6%)	49 (43.4%)	126 (32.1%)	305 (36.2%)
≥70	542 (40.2%)	54 (47.8%)	118 (30.0%)	370 (43.9%)
Sex, female	628 (46.6%)	43 (38.1%)	221 (56.2%)	364 (43.2%)
PE with DVT	630 (46.7%)	67 (59.3%)	182 (46.3%)	381 (45.2%)
Country				
Germany, Austria, Switzerland	231 (17.1%)	6 (5.3%)	72 (18.3%)	153 (18.1%)
France	347 (25.7%)	24 (21.2%)	99 (25.2%)	224 (26.6%)
Italy	315 (23.4%)	40 (35.4%)	105 (26.7%)	170 (20.2%)
Spain	315 (23.4%)	39 (34.5%)	81 (20.6%)	195 (23.1%)
United Kingdom	141 (10.5%)	4 (3.5%)	36 (9.2%)	101 (12.0%)
Risk factors for venous thromboembolism				
Use of estrogen drugs	87 (6.4%)	3 (2.7%)	84 (21.4%)	0 (0.0%)
Prolonged immobilization	234 (17.3%)	18 (15.9%)	216 (55.0%)	0 (0.0%)
>5 days in bed	156 (11.6%)	16 (14.2%)	140 (35.6%)	0 (0.0%)
Surgery or trauma <3 months	186 (13.8%)	17 (15.0%)	169 (43.0%)	0 (0.0%)
Previous DVT	209 (15.5%)	12 (10.6%)	42 (10.7%)	155 (18.4%)
Previous PE	135 (10.0%)	7 (6.2%)	18 (4.6%)	110 (13.0%)
Chronic venous insufficiency	191 (14.2%)	12 (10.6%)	47 (12.0%)	132 (15.7%)
Previous bleeding event	55 (4.1%)	7 (6.2%)	19 (4.8%)	29 (3.4%)
History of thrombophilia	70 (5.2%)	1 (0.9%)	20 (5.1%)	49 (5.8%)
Diabetes	149 (11.0%)	17 (15.0%)	37 (9.4%)	95 (11.3%)
Hypertension	621 (46.0%)	49 (43.4%)	153 (38.9%)	419 (49.7%)
Renal disease*	85 (6.3%)	5 (4.4%)	17 (4.3%)	63 (7.5%)
Cardiovascular disease†	906 (67.2%)	72 (63.7%)	241 (61.3%)	593 (70.3%)

DVT indicates deep vein thrombosis; PE, pulmonary embolism; and PREFER in VTE, Prevention of Thromboembolic Events—European Registry in Venous Thromboembolism.

*Based on estimated glomerular filtration rate <90 mL/min.

†Defined as any of hypertension, vascular disease (peripheral artery disease, coronary artery disease, cerebral vascular disease), congestive heart failure.

contributions accounted for 7% to 8% of the total costs, after excluding the costs of the index event and the costs from hours of work lost. Anticoagulation accounted for 18% to 21% of total costs for patients with cancer, whereas this was only 5% to 6% for patients without cancer and was primarily driven by the use of low-molecular-weight heparins and fondaparinux (Figure 3).

DALYs

After the exclusion of patients with ongoing cancer and patients who had died as detailed in the Methods, there were 591/1196 missing EQ-5D index values (49.4%) at the 12-month follow-up (Table S3). We calculated the disability weight for PE 12 months after the index event to be 0.017 (bootstrapped 95% CI, 0.0002–0.0344; see Figure S2 for the bootstrap replicates plots). The estimated DALYs per patient with incident PE were 1.17 (bootstrapped 95% CI, 0.75–1.59).

DISCUSSION

In this cost-of-illness and burden of disease analysis for PE we report a substantial cost expense for both the index treatment and the 12-month course of a single first or recurrent PE event. By using a detailed record of prospectively collected data from a practice-based study, we found that indirect costs and the patient's own contribution make up a significant part of the total expenses for PE. The economic and societal

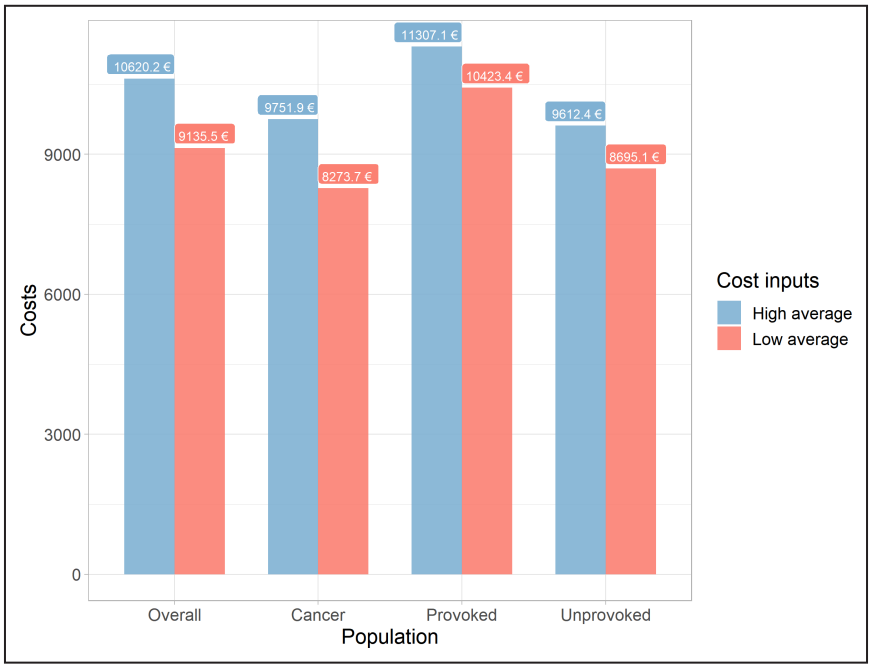

Figure 1. Average total costs (low and high average) per patient profile (overall, cancer, provoked no cancer, unprovoked) in the PREFER in VTE (Prevention of Thromboembolic Events—European Registry in Venous Thromboembolism) registry (absolute costs in 2020 Euros [€]).

burden imposed by PE is not limited to the acute stage but extends into the 12 months following diagnosis as patients experience complications, suffer from decreased productivity, and incur additional costs.

Two important probabilistic modeling analyses have depicted the large financial impact of VTE and PE in North America and the EU. First, Mahan et al created a decision tree of all relevant morbidities and mortalities related to PE and estimated that, in the United States, PE accounted for costs that range from $8.5 to $19.8 billion annually.[9] Of those costs, roughly 35% to 50% could be preventable (assuming that 50%–75% of hospital-acquired PE could be prevented applying appropriate hospital-based intervention systems). By applying the same Markov modeling strategies, Barco et al estimated costs attributable to VTE to a range of 1.5 to 13.2 billion € in the EU-28.[10] Both analyses also accounted for prevalent VTE cases beyond the 12-month time point, which is a major difference to our study. Therefore, the costs estimated in our study would be expected to be higher if prevalent PE cases were accounted for. The EU figures are still considerably lower than the corresponding costs in the United States, possibly because of the higher costs entered into the US model, especially the cost of premature death and of the health care cost inflation.[40] Extrapolating our results to the EU-27 adult population of 379 641 992 people in 2020 results in total estimated costs ranging from 520 to 605 million € for an annual PE incidence of 0.15 and from 3.3 to 3.8 billion € for an annual PE incidence of 0.95.[3]

The availability of prospective data now permits a more comprehensive and deterministic rather than probabilistic estimation of the costs related to PE in Europe. In the aforementioned studies, the estimation of indirect costs was limited to the cost owing to premature death and loss of productivity could not be incorporated in the model. Loss of productivity, as reflected by hours of work lost, comprises the largest part of the total PE-related costs; almost half of the total costs in our study. A previous study, based on nationwide Danish registers, calculated that costs from productivity loss comprised 43% of the total costs attributable to PE 1 year after the diagnosis.[41] Although this analysis was also heavily based on estimations rather than observed productivity loss parameters, it generally agrees with the results from our study and underlines the major contribution of productivity loss in the overall estimation of costs attributed to PE. This finding is also in line with the evidence that a great proportion of patients with PE, excluding those who present with objective cardiopulmonary dysfunction, suffer from deconditioning that could hinder their normal transition back to work.[42] Persisting functional limitations are now being increasingly studied and recognized as a frequent complication of acute PE.[43] Investing in safe personalized rehabilitation programs would be a solution to minimize productivity losses.[44] The clinical

Table 3. Average Costs Per Cost Input Category Per Patient With PE in the PREFER in VTE Registry

Cost category			Average costs (overall)	Average costs (cancer)	Average costs (provoked)	Average costs (unprovoked)
Clinical events	PE index event		2327.6–3532.6	2327.6–3532.6	2327.6–3532.6	2327.6–3532.6
	PE recurrence		80.0	138.8	80.8	74.1
	Deep vein thrombosis recurrence		27.0–29.1	61.3–66.1	23.8–25.7	25.4–27.4
	Major bleeding		53.3–55.7	72.3–75.5	55.2–57.6	50.8–53.0
	Minor bleeding		17.0–18.4	10.9–11.8	17.4–18.8	17.3–18.7
	Heparin-induced thrombocytopenia		2.4	2.4	2.4	2.4
	Postthrombotic syndrome		126.4–220.2	160.4–279.5	125.3–218.3	122.3–213.1
	Chronic thromboembolic pulmonary hypertension		488.8–619.4	488.8–619.4	488.8–619.4	488.9–619.4
	Category total		3122–4557	3262–4726	3121–4555	3108–4540
Patient's own contribution	VTE-related ambulatory visits	Physician's office	5.6	1.5	4.9	8.4
		Physician's home	0.2	0	0.1	0.4
		Other HCP's office	3.2	0	10.5	0.2
		Other HCP's home	0.1	0	0.2	0
	Nursing and informal help	Nursing	4.2	58.6	0.5	1.6
		Informal help	21.4	113.9	0	23.8
	Domestic help	Cleaner	18.1	17.1	21.1	16.9
		Shopping	2.3	0	2.6	2.4
		Household	16.2	13.8	10.0	19.4
	Medical costs		37.9	55.3	44.0	33.4
	International normalized ratio	Lost earnings	8.2	0	7.9	8.6
		Self-payment	3.1	0	7.7	1.3
		Travel	20.5	2.8	22.1	20.4
	Compression stockings		31.7	33.8	43.0	26.1
	Hospitalizations		8.4	0	8.5	9.8
	Category total		181	296	182	172
Productivity loss			4436.5	2714.0	5765.6	4047.83
VTE-related ambulatory visits	Physician's office		709.8	276	673.0	784
	Physician's home		34.6	10.5	50.8	30.4
	Other HCP's office		21.3–27.5	3.6–4.6	48.6–62.8	11.2–14.5
	Other HCP's home		14.5–18.7	0.8–1.1	12.7–16.3	17.2–22.2
	Category total		780–790	290–292	785–802	842–851

(*Continued*)

Table 3. (Continued)

Cost category		Average costs (overall)	Average costs (cancer)	Average costs (provoked)	Average costs (unprovoked)
Anticoagulation	Low-molecular-weight heparin	356.4	1479.3	307.1	262.2
	Vitamin-K agonist	20.9	6.9	18.7	23.3
	Direct oral anticoagulant	215.6–254.6	73.4–86.6	226.3–267.2	225.3–265.9
	Fondaparinux	22.4	149.9	16.5	12.3
	Category total	615–654	1709–1722	568–609	523–563

All figures are in 2020 Euros (rounded to first decimal as appropriate). HCP indicates health care practitioner; PE, pulmonary embolism; PREFER in VTE, Prevention of Thromboembolic Events—European Registry in Venous Thromboembolism; and VTE, venous thromboembolism.

efficacy and cost-effectiveness of this practice remain to be further elucidated.

PE was responsible for lower costs in patients with cancer because PE-imposed productivity loss was not as prominent in this population. As cancer, at least in its most severe forms, is a disabling disease by itself, PE does not further decrease the already impaired productivity in patients with cancer as much as it does in patients without cancer. Nevertheless, anticoagulation is a significant economic burden for patients with cancer, mainly because of the large proportion of low-molecular-weight heparins use we observed in this population. However, the publication of studies showing noninferiority of direct oral anticoagulants (DOAC) in cancer-associated PE is likely to also change the economic landscape related to anticoagulation in the populationwith cancer, with an increasing use of DOACs over low-molecular-weight heparins; however, studies on the proportion of contemporary use of DOACs in this population are still lacking.[45]

To the best of our knowledge, this is the first study to estimate a disability weight for the 12-month post-PE status derived from a population without cancer with PE. The seminal 1996 Global Burden of Disease study derived disability weights for a vast array of diseases, but to date, no disability weight for VTE (neither deep vein thrombosis nor PE) has been estimated, even in the most recent 2019 report.[46] Of note, studies have used chronic pulmonary obstructive disease disability weights as proxies for VTE disability weight.[47] In 2014, the International Society on Thrombosis and Haemostasis issued a concern regarding this gap in the literature and urged more data on the global burden of VTE (and subsequently PE) in order to help in the implementation of more efficient resource allocation policies.[3] Previous studies have suggested that although quality of life increases after the acute phase of PE, a substantial percentage of patients experience decreased quality of life 6 and 12 months after the event.[48–50] These data justify the need for the derivation of a disability weight for the post-PE status as an indicator that helps quantify the burden of living after PE. We estimated a disability weight of 0.017, which is comparable to diseases such as mild chronic obstructive pulmonary disease (0.019), long-term mild consequences of stroke (0.019), mild heart failure (0.041), mild angina pectoris (0.033), and worry and daily medication associated with generic uncomplicated disease (0.049).[51] By combining the disability weight with the fatality rates of the PREFER in VTE population, we are able to express the post-12-month PE disease burden in terms of DALYs and estimate a loss of roughly 1.2 years of healthy life per incident PE case. However, it must be acknowledged that there is significant variation in the phenotypes of patients who are post-PE: although most patients are asymptomatic in the follow-up period, a significant proportion of

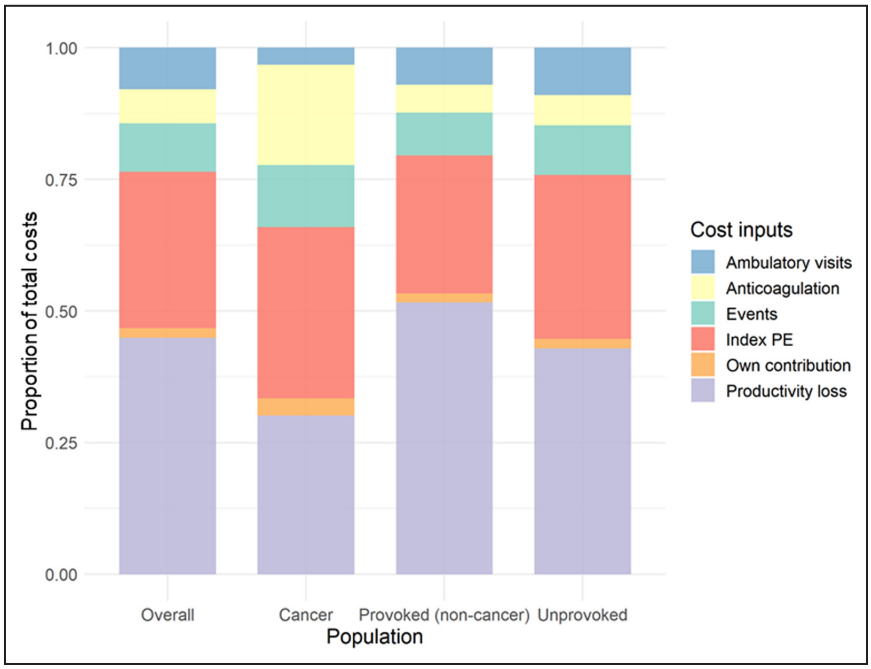

Figure 2. Proportion of each cost input category to the total average costs per incident pulmonary embolism patient in the PREFER in VTE (Prevention of Thromboembolic Events—European Registry in Venous Thromboembolism) registry. PE indicates pulmonary embolism.

patients may suffer from post-PE impairment and a small fraction of them from chronic thromboembolic pulmonary disease or chronic thromboembolic pulmonary hypertension.[42] It is evident that a single disability weight does not fit all these phenotypes.

Future Perspectives

The changing landscape and constantly evolving evidence in PE suggest that our cost calculations may not be valid for long. New emerging management based on refined risk stratification, such as the early discharge and home treatment of patients with low-risk PE, may significantly reduce costs for the index hospitalization.[52,53] On the other hand, the use of advanced interventional therapies, such as ultrasound-assisted thrombolysis in intermediate high-risk PE, may shift costs upwards.[54] Last but not least, the higher COVID-19 associated risk for PE may increase the prevalence of patients post-PE and, thus, increase the overall burden of disease for the population. Future studies should refine the economic and disease burden implications of PE to better fit the different phenotypes of patients post-PE.

Strengths and Limitations

Overall, this study complements and advances previous efforts to quantify the economic, resource use, and overall burden of PE and attempts to describe the societal impact of PE.[11,41,55,56] A novelty of our study is the use of a multicenter, multinational bottom-up approach to calculate PE-related costs. In contrast to top-down approaches, it requires individual patient-level data; however, it is regarded as more accurate, as it helps to elucidate individual cost drivers with no reliance on assumptions.[57] However, some limitations of our study need to be mentioned. First, the countries included were high-income ones that may not reflect the lower-income countries of EU, as well as countries outside the EU. A gap in the evidence is apparent regarding the influence of social determinants of health in VTE, and this study could not adjust for social inequities. In addition, no estimation of intangible losses was possible; however, this is a common limitation of cost-of-illness analyses that is traditionally difficult to address. Also, costs concerning medical supplies related to PE were based on individual patient reporting and, thus, are subject to cognitive bias and under-reporting; if anything, however, this may have led to cost underestimation. The calculated disability weight should be considered as an estimate, as no EQ-5D index values in PREFER in VTE were recorded before the index PE event; instead, age- and country-specific population norms were used as reference. Also, approximately half of patients had a missing 12-month EQ-5D questionnaire, which may have introduced a selection bias in the disability weight calculation. However, the comparison of patients with and without

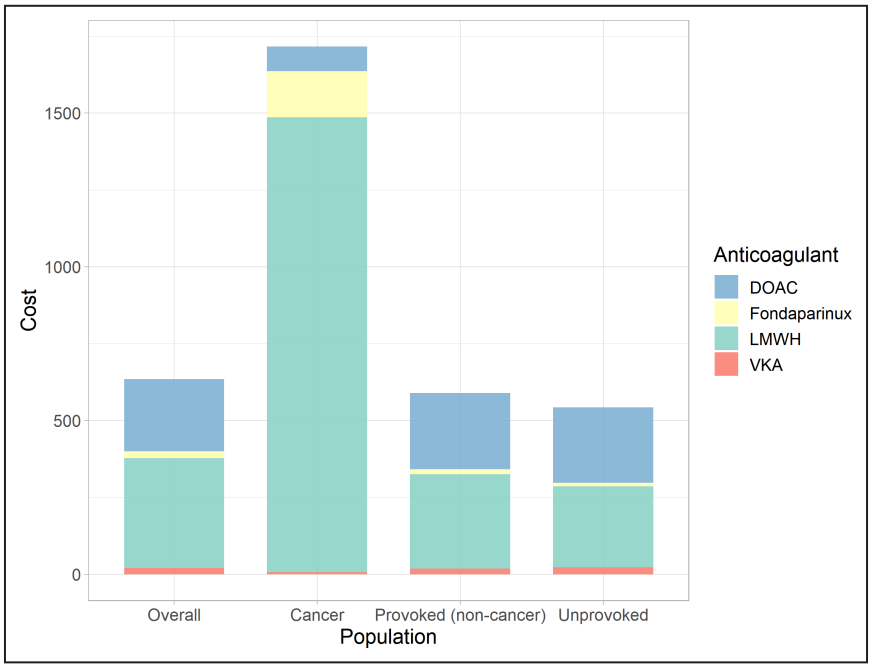

Figure 3. Contribution of each category of anticoagulant in the costs attributed to anticoagulation during follow-up of patients in the PREFER in VTE (Prevention of Thromboembolic Events—European Registry in Venous Thromboembolism) registry (absolute costs in 2020 Euros).
DOAC indicates direct oral anticoagulant; LMWH, low-molecular-weight heparin; and VKA, vitamin K antagonist.

missing values did not show any major differences in baseline characteristics. In addition, the PREFER in VTE registry was conducted between 2013 and 2015, when vitamin-K antagonists were still used in a considerable proportion of patients. Given that the use of DOACs over vitamin-K antagonists in the management of PE is the current standard of care, and because of the higher costs of DOACs (most of which are still covered by primary and secondary patents), we expect the actual current anticoagulation cost for each individual and the society to be higher than those we calculated. The opposite is likely to apply to patients with cancer, with greater proportional use of DOACs and lesser use of low-molecular-weight heparins. Lastly, the variation in the reported population incidences of PE allow for only rough estimations for the EU-level costs.

CONCLUSIONS

PE constitutes a considerable economic and personal burden for society and affected patients. Productivity loss is the main driver of costs in most patients. Each incident PE case is associated with the loss of roughly 1.2 years of healthy life. Future interventions should focus on rehabilitation to support the recovery of productivity after an episode of acute PE.

ARTICLE INFORMATION

Received August 10, 2022; accepted September 19, 2022.

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Acknowledgments

The authors are grateful to Daiichi Sankyo and the PREFER in VTE investigators for being allowed to use the data. This publication is based on research using data from data contributors Daiichi Sankyo that has been made available through Vivli, Inc. Vivli has not contributed to or approved, and is not in any way responsible for, the contents of this publication.

Sources of Funding

This study was supported by an unrestricted grant from Daiichi Sankyo (Title: "Filling the gaps of knowledge on health care outcomes during long-term anticoagulant treatment of pulmonary embolism," grant number DSE-DE-CV-20001).

Disclosures

Dr Barco received lecture/consultant fees from Bayer HealthCare, Concept Medical, BTG Pharmaceuticals, INARI, Boston Scientific, and LeoPharma; institutional grants from Boston Scientific, Bentley, Bayer HealthCare, INARI, Medtronic, Concept Medical, Bard, and Sanofi; and economic support for travel/congress costs from Daiichi Sankyo, BTG Pharmaceuticals, and Bayer

HealthCare, outside the submitted work. Dr Giannakoulas reports personal lecture/advisory fees from Bayer HealthCare, Pfizer and LeoPharma. Dr Mahan is on the speakers bureau for Astra-Zeneca and Janssen. Dr Konstantinides reports institutional grants and personal lecture/advisory fees from Bayer AG, Daiichi Sankyo, and Boston Scientific; institutional grants from Inari Medical; and personal lecture/advisory fees from MSD and Bristol Myers Squibb/Pfizer. The remaining authors have nothing to declare.

Data Availability Statement

Access to the registry data sets was provided by Daiichi Sankyo.

Supplemental Material

Data S1
Table S1
Table S2
Table S3
Figure S1
Figure S2

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SUPPLEMENTAL MATERIAL

Data S1. Search string and literature review results

Search string

PubMed accessed at 16/12/2021

((((((((((((((((((((((((((((European Union) OR (Europe)) OR (Austria)) OR (Belgium)) OR (Bulgaria)) OR (Cyprus)) OR (Czech Republic)) OR (Denmark)) OR (Estonia)) OR (Finland)) OR (France)) OR (Germany)) OR (Greece)) OR (Hungary)) OR (Ireland)) OR (Italy)) OR (Latvia)) OR (Lithuania)) OR (Luxembourg)) OR (Malta)) OR (Netherlands)) OR (Poland)) OR (Portugal)) OR (Romania)) OR (Slovakia)) OR (Slovenia)) OR (Spain)) OR (Great Britain)) AND ((((Venous Thromboembolism) OR (Venous Thrombosis)) OR (Pulmonary embolism)) OR ((((Venous Thromboembolism) OR (Venous Thrombosis)) OR (Pulmonary embolism)) AND ((((Hemorrhage) OR ((Thrombocytopenia) AND (Heparin))) OR (Pulmonary Hypertension)) OR (Postthrombotic syndrome))))) AND ("Health Care Economics and Organizations"[Mesh])

(("european union"[MeSH Terms] OR ("european"[All Fields] AND "union"[All Fields]) OR "european union"[All Fields] OR ("europe"[MeSH Terms] OR "europe"[All Fields] OR "europes"[All Fields] OR "europes"[All Fields]) OR ("austria"[MeSH Terms] OR "austria"[All Fields] OR "austria s"[All Fields]) OR ("belgium"[MeSH Terms] OR "belgium"[All Fields] OR "belgiums"[All Fields]) OR ("bulgaria"[MeSH Terms] OR "bulgaria"[All Fields]) OR ("cyprus"[MeSH Terms] OR "cyprus"[All Fields]) OR ("czech republic"[MeSH Terms] OR ("czech"[All Fields] AND "republic"[All Fields]) OR "czech republic"[All Fields]) OR ("denmark"[MeSH Terms] OR "denmark"[All Fields] OR "denmark s"[All Fields]) OR ("estonia"[MeSH Terms] OR "estonia"[All Fields]) OR ("finland"[MeSH Terms] OR "finland"[All Fields] OR "finland s"[All Fields]) OR ("france"[MeSH Terms] OR "france"[All Fields] OR "france s"[All Fields]) OR ("germanies"[All Fields] OR "germany"[MeSH Terms] OR "germany"[All Fields] OR "germany s"[All Fields] OR "germanys"[All Fields]) OR ("greece"[MeSH Terms] OR "greece"[All Fields] OR "greece s"[All Fields]) OR ("hungary"[MeSH Terms] OR "hungary"[All Fields] OR "hungary s"[All Fields]) OR ("ireland"[MeSH Terms] OR "ireland"[All Fields] OR "ireland s"[All Fields] OR "irelands"[All Fields]) OR ("italy"[MeSH Terms] OR "italy"[All Fields] OR "italy s"[All Fields]) OR ("latvia"[MeSH Terms] OR "latvia"[All Fields]) OR ("lithuania"[MeSH Terms] OR "lithuania"[All Fields] OR "lithuania s"[All Fields]) OR ("luxembourg"[MeSH Terms] OR "luxembourg"[All Fields] OR "luxembourg s"[All Fields]) OR ("malta"[MeSH Terms] OR "malta"[All Fields] OR "malta s"[All Fields]) OR ("netherlands"[MeSH Terms] OR "netherlands"[All Fields] OR "netherland"[All Fields]) OR ("poland"[MeSH Terms] OR "poland"[All Fields]) OR ("portugal"[MeSH Terms] OR "portugal"[All Fields] OR "portugal s"[All Fields]) OR ("romania"[MeSH Terms] OR "romania"[All Fields] OR "romania s"[All Fields]) OR ("slovakia"[MeSH Terms] OR "slovakia"[All Fields]) OR ("slovenia"[MeSH Terms] OR "slovenia"[All Fields] OR "slovenia s"[All Fields]) OR ("spain"[MeSH Terms] OR "spain"[All Fields] OR "spain s"[All Fields]) OR ("united kingdom"[MeSH Terms] OR ("united"[All Fields] AND "kingdom"[All Fields]) OR "united kingdom"[All Fields] OR ("great"[All Fields] AND "britain"[All Fields]) OR "great britain"[All Fields])) AND ("venous thromboembolism"[MeSH Terms] OR ("venous"[All Fields] AND "thromboembolism"[All Fields]) OR "venous thromboembolism"[All Fields] OR ("venous thrombosis"[MeSH Terms] OR ("venous"[All Fields] AND "thrombosis"[All Fields]) OR "venous thrombosis"[All Fields]) OR ("pulmonary embolism"[MeSH Terms] OR ("pulmonary"[All Fields] AND "embolism"[All

Fields]) OR "pulmonary embolism"[All Fields]) OR (("venous thromboembolism"[MeSH Terms] OR ("venous"[All Fields] AND "thromboembolism"[All Fields]) OR "venous thromboembolism"[All Fields] OR ("venous thrombosis"[MeSH Terms] OR ("venous"[All Fields] AND "thrombosis"[All Fields]) OR "venous thrombosis"[All Fields]) OR ("pulmonary embolism"[MeSH Terms] OR ("pulmonary"[All Fields] AND "embolism"[All Fields]) OR "pulmonary embolism"[All Fields])) AND ("blood"[MeSH Subheading] OR "blood"[All Fields] OR "blood"[MeSH Terms] OR "bloods"[All Fields] OR "haematology"[All Fields] OR "hematology"[MeSH Terms] OR "hematology"[All Fields] OR "haematoma"[All Fields] OR "hematoma"[MeSH Terms] OR "hematoma"[All Fields] OR "haemorrhage"[All Fields] OR "hemorrhage"[MeSH Terms] OR "hemorrhage"[All Fields] OR "haemorrhages"[All Fields] OR "hemorrhages"[All Fields] OR "haemorrhagic"[All Fields] OR "haemorrhaging"[All Fields] OR "hematologies"[All Fields] OR "haematomas"[All Fields] OR "hematomas"[All Fields] OR "hematoma s"[All Fields] OR "hematomae"[All Fields] OR "hemorrhaged"[All Fields] OR "hemorrhagic"[All Fields] OR "hemorrhagical"[All Fields] OR "hemorrhaging"[All Fields] OR (("thrombocytopaenia"[All Fields] OR "thrombocytopenia"[MeSH Terms] OR "thrombocytopenia"[All Fields] OR "thrombocytopenias"[All Fields]) AND ("heparin"[MeSH Terms] OR "heparin"[All Fields] OR "heparine"[All Fields] OR "heparins"[All Fields] OR "heparin s"[All Fields] OR "heparinate"[All Fields] OR "heparinated"[All Fields] OR "heparines"[All Fields] OR "heparinic"[All Fields] OR "heparinisation"[All Fields] OR "heparinised"[All Fields] OR "heparinization"[All Fields] OR "heparinize"[All Fields] OR "heparinized"[All Fields] OR "heparinizing"[All Fields])) OR ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All Fields])) OR ("postthrombotic syndrome"[MeSH Terms] OR ("postthrombotic"[All Fields] AND "syndrome"[All Fields]) OR "postthrombotic syndrome"[All Fields])))) AND "Health Care Economics and Organizations"[MeSH Terms]) AND (2014/4/1:3000/12/12[pdat])

Literature search – Included studies and costs

Source	Population	Currency	Cost inputs (Euro 2020)
NHS [45]	UK	Pound (2014)	A: 672 - 2966, I: 1126-3610
Monreal et al. [46]	France	Euro (2012)	A: 1262, C: 419, E: 2799, H: 2453, I: 3641, J: 2194, L: 7.3, N: 2.8
Monreal et al. [46]	Italy	Euro (2012)	A: 396, C: 2028, E: 3414, G: 8233, H: 2893, I: 899, J:5173, L: 3.6, N: 3.9
Monreal et al. [46]	Spain	Euro (2012)	A: 1880, C: 1761, E: 1122, G: 6120, H: 4952, I: 3957, J: 5396, L: 3.1, N: 2.1-2.3
Santos et al. [47]	Portugal	Euro (2012)	A: 2025, B: 2222, G: 48096, H: 118-567, I: 4811, L: 13.5, M: 0.06, N: 2.8
Zindel et al. [48]	Germany	Euro (2010)	A: 1281-1473, B: 181, I: 2420-2716, K: 180-400, L: 11.5, M: 0.2,
Postma et al. [49]	Netherlands	Euro (2010)	F: 3616, O: 8.9
Migliaccio-Walle et al. [50]	UK	Pound (2008)	B: 745, H: 55-5132, J: 2490, K: 349, L: 4.4, N: 4-5.1

Capri et al. [51]	Italy	Euro (2007)	O: 8.1
Gustafsson et al. [52]	Denmark	Euro (2016)	E: 8812
Gourzoulidis et al. [53]	Greece	Euro (2017)	A: 465, D: 187, E: 1004-1308, G: 14480, H: 276-499, I: 1109, L: 7.9, M: 0.05, N: 1.8-3.5
Heisen et al. [54]	Netherlands	Euro (2015)	A: 3768, B: 411, D: 278, E: 10838, H: 182-826
Browne et al. [55]	UK	Pound (2015)	C: 448-758, D: 141-186, E: 1156-1976
Motte et al. [56]	Belgium	Euro (2010)	I: 2631-8830
Schweikert et al. [57]	Europe	Euro (2014)	G: 46173
Boon et al. [58]	Netherlands	Euro (2020)	G: 4404-38491
Hendriks et al. [59]	Netherlands	Euro (2018)	I: 355-2220, L: 10.7, M: 0.09, N: 2.3-2.5

Abbreviations: A: deep venous thrombosis (inpatients); B: deep venous thrombosis (outpatients); C: recurrent deep venous thrombosis; D: minor bleeding; E: major bleeding; F: heparin-induced thrombocytopenia; G: chronic thromboembolic pulmonary hypertension; H: post-thrombotic syndrome; I: pulmonary embolism (inpatients); J: recurrent pulmonary embolism; K: pulmonary embolism (outpatients), L: low molecular weight heparin, M: vitamin K antagonist, N: direct oral anticoagulant, O: fondaparinux.

Costs are expressed either as “cost per event” (A, B, C, D, E, F, I, J, K, L, M, N) or as “annual costs” (G, H).

Table S1. Characteristics of the acute pulmonary embolism event

Characteristic	Overall (n=1349)	Patients with ongoing cancer (n=113)	Patients with provoked PE (n = 393)	Patients with unprovoked PE (n = 843)
Clinical presentation				
Systolic blood pressure, mmHg	130 (23)	127 (30)	130 (24)	132 (28)
Diastolic blood pressure, mmHg	80 (15)	75 (12)	78 (13)	80 (15)
Heart rate, bpm	83 (24)	82 (30)	84 (24)	83 (24)
Dyspnoea	1020 (75.6%)	79 (69.9%)	288 (73.3%)	653 (77.5%)
Chest pain	618 (45.8%)	32 (28.3%)	194 (49.4%)	392 (46.5%)
Cough	227 (16.8%)	20 (17.7%)	58 (14.8%)	149 (17.7%)
Hemoptysis	47 (3.5%)	2 (1.8%)	12 (3.1%)	33 (3.9%)
Syncope	109 (8.1%)	8 (7.1%)	36 (9.2%)	65 (7.7%)
Palpitations	104 (7.7%)	9 (8.0%)	36 (9.2%)	59 (7.0%)
Fever	104 (7.7%)	7 (6.2%)	33 (8.4%)	64 (7.6%)
Cyanosis	28 (2.1%)	4 (3.5%)	8 (2.0%)	16 (1.9%)
Tachypnoea	215 (15.9%)	18 (15.9%)	63 (16.0%)	134 (15.9%)
Tachycardia	223 (16.5%)	20 (17.7%)	72 (18.3%)	131 (15.5%)
Cardiogenic shock	18 (1.3%)	2 (1.8%)	6 (1.5%)	10 (1.2%)
Diagnostic procedures				
CT/MRI	1100 (81.5%)	91 (80.5%)	329 (83.7%)	680 (80.7%)
Ventilation scan	69 (5.1%)	4 (3.5%)	17 (4.3%)	48 (5.7%)
Perfusion scan	127 (9.4%)	10 (8.8%)	31 (7.9%)	86 (10.2%)

Pulmonary angiography	109 (8.1%)	5 (4.4%)	31 (7.9%)	73 (8.7%)
Echocardiography	226 (16.8%)	12 (10.6%)	77 (19.6%)	137 (16.3%)
Venous study	125 (9.3%)	9 (8.0%)	49 (12.5%)	67 (7.9%)
In-hospital therapeutic considerations				
Thrombolysis	55 (4.1%)	1 (0.9%)	23 (5.9%)	31 (3.7%)
Heparin	1143 (84.7%)	94 (83.2%)	332 (84.5%)	717 (85.1%)
Fondaparinux	113 (8.4%)	10 (8.8%)	37 (9.4%)	66 (7.8%)
VKAs	779 (57.7%)	14 (12.4%)	230 (58.5%)	535 (63.5%)
Antiplatelets	30 (2.2%)	3 (2.7%)	8 (2.0%)	19 (2.3%)
DOACs	287 (21.3%)	7 (6.2%)	103 (26.2%)	177 (21.0%)
Embolectomy	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Catheter fragmentation	4 (0.3%)	1 (0.9%)	1 (0.3%)	2 (0.2%)
Vena cava filter	10 (0.7%)	3 (2.7%)	4 (1.0%)	3 (0.4%)
Any invasive therapy	18 (1.3%)	4 (3.5%)	6 (1.5%)	8 (0.9%)
Compression stockings	321 (23.8%)	24 (21.2%)	100 (25.4%)	197 (23.4%)

*Continuous variables are reported as median (interquartile range).

Table S2. Clinical events incidence in the PREFER in VTE

	Overall (n = 1349)	**No cancer (n = 1236)**	**Cancer (n = 113)**	**Provoked no cancer (n = 393)**	**Unprovoked (n = 843)**
DVT readmission/ recurrence	23/1010 (2.2%)	20/952 (2.1%)	3/58 (5.2%)	6/299 (2.0%)	14/653 (2.1%)
PE readmission/ recurrence*	20/1007 (2.0%)	18/951 (1.9%)	2/56 (3.6%)	6/299 (2.0%)	12/652 (1.8%)
Major bleeding	13/1023 (1.3%)	12/965 (1.2%)	1/58 (1.7%)	4/304 (1.3%)	8/661 (1.2%)
Minor bleeding	82/1023 (8.0%)	79/965 (8.2%)	3/58 (5.2%)	25/304 (8.2%)	54/661 (8.2%)
Death	83/1349 (6.2%)	40/1236 (3.2%)	43/113 (38.1%)	14/393 (3.5%)	26/843 (3.1%)

DVT = Deep Venous Thrombosis. PE = Pulmonary Embolism

*Two fatal events

Table S3. Baseline characteristics of patients with missing EQ-5D values at 12 months

Characteristic	Overall (n=1196)	Missing (n=591)	Non-missing (n=605)
Age			
• 10-19	11 (0.9%)	8 (1.4%)	3 (0.5%)
• 20-29	45 (3.8%)	22 (3.7%)	23 (3.8%)
• 30-39	100 (8.4%)	61 (10.3%)	39 (6.4%)
• 40-49	159 (13.3%)	93 (15.7%)	66 (10.9%)
• 50-59	167 (14.0%)	93 (15.7%)	74 (12.2%)
• 60-69	256 (21.4%)	115 (19.5%)	141 (23.3%)
• 70-79	275 (23.0%)	118 (20.0%)	157 (26%)
• 80-89	168 (14.0%)	74 (12.5%)	94 (15.5%)
• 90-99	15 (1.3%)	7 (1.2%)	8 (1.3%)
Sex, female	563 (47.1%)	287 (48.6%)	276 (45.6%)
PE with DVT	540 (45.2%)	238 (40.3%)	302 (49.9%)
Country			
• DACH	222 (18.6%)	135 (22.8%)	87 (14.4%)
• France	318 (26.6%)	149 (25.2%)	169 (27.9%)
• Italy	252 (21.1%)	64 (10.8%)	188 (31.1%)
• Spain	269 (22.5%)	135 (22.8%)	134 (22.1%)
• UK	135 (11.3%)	108 (18.3%)	27 (4.5%)

Excluding patients with ongoing cancer and dead patients

Figure S1. Patient selection flowchart

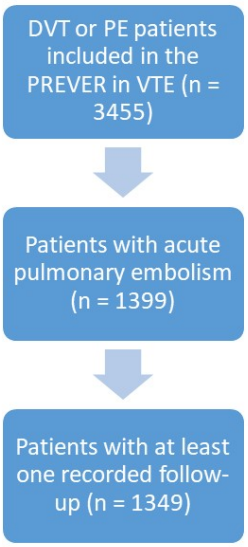
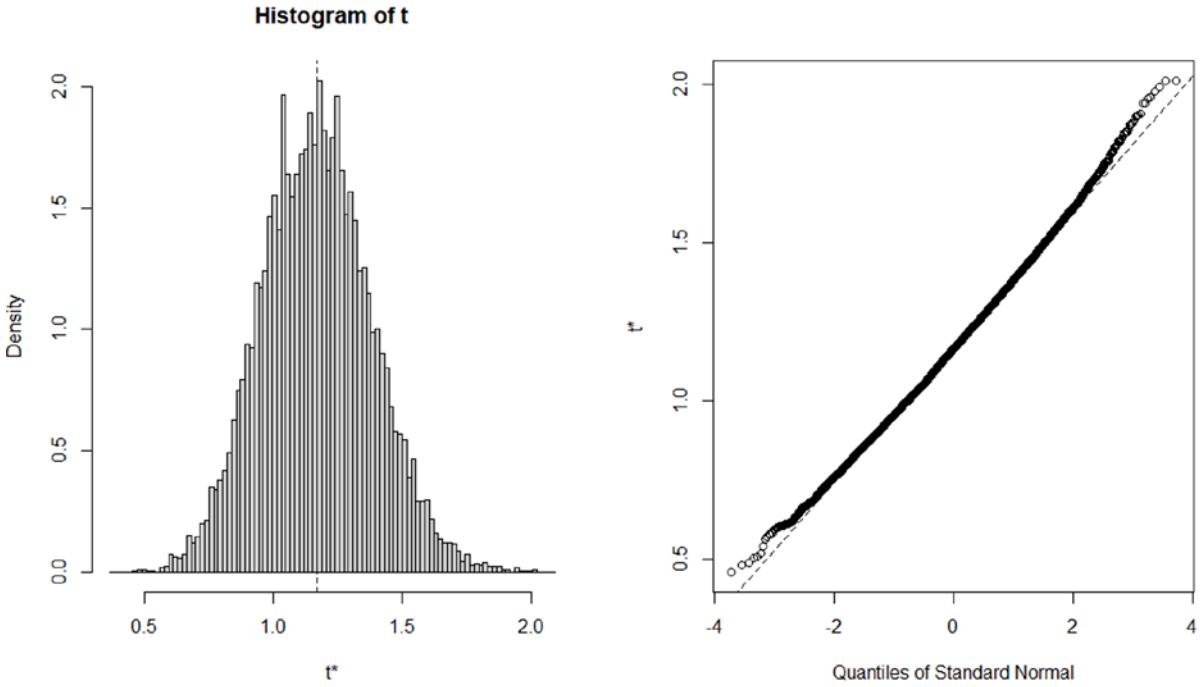


Figure S2. Bootstrap replicates plots

Bootstrapping of mean disability weight at 12 months post pulmonary embolism



Bootstrapping of mean disability adjusted life years post pulmonary embolism