



# Estimated annual healthcare costs after acute pulmonary embolism: results from a prospective multicentre cohort study

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## Aims

Patients surviving acute pulmonary embolism (PE) necessitate long-term treatment and follow-up. We estimated, the chronic economic impact of PE on the German healthcare system.

## Methods and results

We calculated the direct cost of illness during the first year after discharge for the index PE, analysing data from a multicentre prospective cohort study in Germany. Main and accompanying readmission diagnoses were used to calculate DRG-based hospital reimbursements; anticoagulation costs were estimated from the exact treatment duration and each drug's unique national identifier; and outpatient post-PE care costs from guidelines-recommended algorithms and national reimbursement catalogues. Of 1017 patients enrolled at 17 centres, 958 (94%) completed  $\geq 3$ -month follow-up; of those, 24% were rehospitalized (0.34 [95% CI 0.30–0.39] readmissions per PE survivor). Age, coronary artery, pulmonary and kidney disease, diabetes, and (in the sensitivity analysis of 837 patients with complete 12-month follow-up) cancer, but not recurrent PE, were independent cost predictors by hurdle gamma regression accounting for zero readmissions. The estimated rehospitalization cost was €1138 (95% CI 896–1420) per patient. Anticoagulation duration was 329 (IQR 142–365) days, with estimated average per-patient costs of €1050 (median 972; IQR 458–1197); costs of scheduled ambulatory follow-up visits amounted to €181. Total estimated direct per-patient costs during the first year after PE ranged from €2369 (primary analysis) to €2542 (sensitivity analysis).

## Conclusion

By estimating per-patient costs and identifying cost drivers of post-PE care, our study may inform decisions concerning implementation and reimbursement of follow-up programmes aiming at improved cardiovascular prevention.

<sup>†</sup> The first two authors contributed equally.

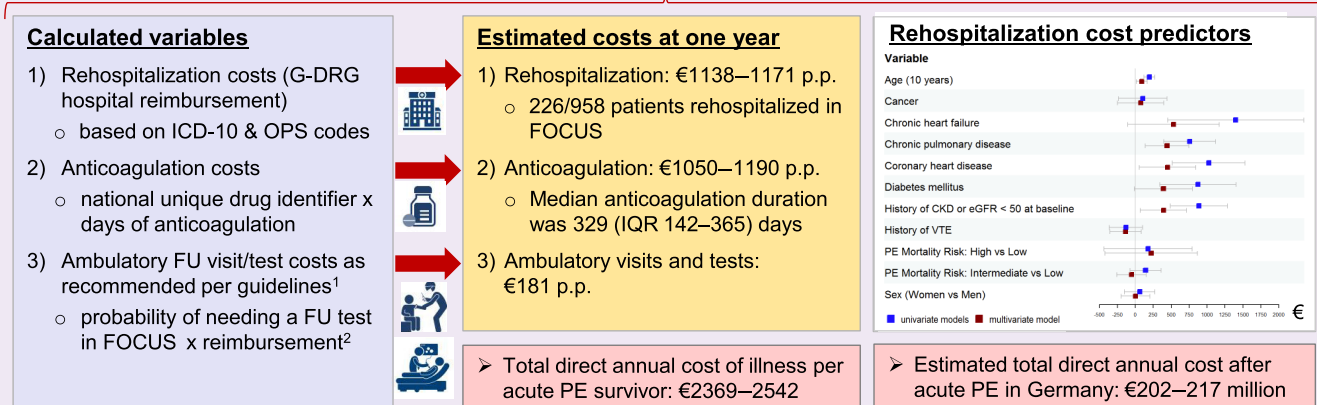
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## Graphical Abstract

Follow-up After Acute Pulmonary Embolism **FOCUS.**

- Prospective observational cohort study
- Unselected patients with acute symptomatic PE, 17 centres in Germany
- Comprehensive follow-up: clinical, imaging, functional, laboratory testing
- Prospectively documented rehospitalizations, anticoagulant medication
- **Cost of illness over 12 months after discharge:  $n=958$  patients in the primary analysis ( $\geq 3$ -month FU);  $n=837$  patients in the sensitivity analysis ( $\geq 12$ -month FU)**



<sup>1</sup> 2019 European Society of Cardiology (ESC) Guidelines for the diagnosis and management of acute pulmonary embolism. *Eur Respir J* 2019; 54(3). doi: 10.1183/13993003.01647-2019.

<sup>2</sup> EBM (ambulatory healthcare services) catalog of the National Association of Statutory Health Insurance Physicians in Germany.

CI: confidence interval; CKD: chronic kidney disease; d: days; eGFR: estimated glomerular filtration rate; FU: follow-up; G-DRG: German version of Diagnosis Related Groups; ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10<sup>th</sup> revision; OPS: *Operationen- und Prozeduren-Schlüssel* (operation and procedure codes in G-DRG); PE: pulmonary embolism; p.p.: per patient; VTE: venous thromboembolism.

## Keywords

Pulmonary embolism • Cost of illness • Economic burden • Readmission • Anticoagulation • Long-term care

## Key Learning Points

What is already known on this topic

- The annual incidence of pulmonary embolism is climbing and an increasing number of patients surviving an acute PE episode need chronic treatment and follow-up.
- Data on the long-term impact of PE on European healthcare systems are sparse and still based on pooled analyses of older cohorts and adaptation of US cost models.

What this study adds

- We calculated the direct cost of illness during the first year after acute PE, analysing data from a large multicentre cohort study in Germany with prospective follow-up of consecutive unselected PE survivors.
- Estimated annual costs amounted to €2369–2542 per study patient, which would correspond to approximately €2.5 million per million population; they were mainly related to rehospitalizations and chronic anticoagulation.
- ESC guidelines-recommended outpatient follow-up visits aiming at early detection of chronic complications and general cardiovascular prevention were only a minor contributor to the overall costs of post-PE care.

## Introduction

Survival rates in the acute phase of pulmonary embolism (PE) are improving,<sup>1,2</sup> paralleled by a decrease of PE-related mortality in the population.<sup>3–5</sup> This is related, at least partly, to increased awareness and early diagnosis of the disease, combined with recent advances in antithrombotic treatment.<sup>6–8</sup> On the other hand, the annual incidence of acute PE continues to climb as the population ages worldwide,<sup>1,2</sup> meaning that an ever-increasing number of patients surviving an acute PE episode need chronic treatment and follow-up. The long-term

risk of symptomatic recurrence of venous thromboembolism (VTE) is substantial,<sup>9</sup> and extended anticoagulation beyond the first 3–6 months is often recommended.<sup>10,11</sup> Moreover, the risk of any-cause rehospitalization after a first-time PE may be high as recently suggested by population data in Denmark.<sup>12</sup> Finally, a broad spectrum of clinical and/or functional abnormalities may persist or appear *de novo* after PE,<sup>13,14</sup> directly affecting morbidity and quality of life over the long term<sup>15–17</sup> and supporting the recommendation for structured ambulatory follow-up programmes.<sup>8,18</sup>

In view of the above, patient care after an acute PE episode poses a substantial burden on healthcare systems globally, which, however, has not yet been systematically analysed. Existing models for estimating the annualized cost of illness of VTE in Europe date back to the past decade and were based on pooled data from older cohorts<sup>19</sup> and adaptation of US cost models.<sup>20</sup> This is in contrast to myocardial infarction and stroke, for which estimates at the European level were recently updated.<sup>21</sup>

Aiming to address this gap of knowledge, we analysed in the present study a large multicentre cohort of unselected patients with acute symptomatic PE who were prospectively followed after hospital discharge.<sup>15</sup> We sought to determine the direct cost of illness of PE during the first year after hospital discharge, dissecting it into the costs related to (i) rehospitalizations from any cause, (ii) chronic anticoagulant medication, and (iii) scheduled outpatient follow-up and testing.

## Methods

### Study population

The FOLLOW-up after aCUte pulmonary emboliSm (FOCUS) study (German Clinical Trials registry number: DRKS00005939) was conducted at 17 large-volume centres across Germany and prospectively enrolled consecutive unselected patients (all comers) with confirmed diagnosis of acute symptomatic PE irrespective of clinical severity or thrombus load.<sup>15</sup> Following hospital discharge, patients were followed with a standardized assessment plan; this comprised clinical, functional, imaging, and laboratory testing as well as patient-reported health status and outcomes, at pre-specified visits 3, 12, and 24 months after the index PE episode. Since FOCUS was an observational study, patient treatment was at the investigators' discretion and in adherence to European Society of Cardiology (ESC) guidelines in effect at the time of patient recruitment.<sup>22,23</sup> Detailed demographic and clinical data, diagnostic procedures, and outcomes were prospectively recorded in an electronic case report form (eCRF). FOCUS was approved by the ethics committees of the participating sites and written informed consent was obtained from all patients.

The present study analysed data from FOCUS related to the period between hospital discharge and the end of 1-year follow-up.

### Prospectively collected and calculated variables, cost estimations

At the follow-up visits, the FOCUS investigators documented any rehospitalizations of the study patients since hospital discharge (for the 3-month visit), or since the previous outpatient visit (for the 12-month and 24-month visit). The information included the reason(s) for readmission to the hospital (main and accompanying diagnoses) as well as reimbursement-relevant procedures, and it was obtained from medical reports at hospital discharge; these were provided by the patient or (if not in their possession) by the patient's general practitioner. International Statistical Classification of Diseases (ICD) codes, specifically the 10th revision with German modification (ICD-10-GM), and the German procedure codes (*Operationen- und Prozedurenschlüssel; OPS*) were generated by two of the authors (K.M. and K.C.). Subsequently, the information was entered into an official online German Diagnosis Research Groups (G-DRG) calculator,<sup>24</sup> and the calculated DRG was translated into the amount of hospital reimbursement for the year 2023, assuming the average length of hospital stay for the given indication.

The duration of oral anticoagulant treatment after hospital discharge and the exact anticoagulant drug(s) taken by the patient, including the dose, switch from one anticoagulant to another, date of discontinuation, and resumption of treatment after a discontinuation, all were documented in the eCRF at each follow-up visit. Based on the national central unique drug identifier, including the prices for the year 2023, we calculated the daily costs of treatment with each drug and multiplied them by the respective

duration of treatment in days to obtain the total anticoagulation costs per patient.

Current guidelines recommend a structured schedule of outpatient follow-up visits after acute PE to ensure timely detection of treatment complications and late sequelae.<sup>8,18</sup> This schedule corresponds to an algorithm, in which the diagnostic evaluation and the specific tests to be performed at each step depend on the results of the tests at the previous step.<sup>8</sup> Since all the follow-up examinations included in the ESC guidelines algorithm had been implemented in the FOCUS study,<sup>15</sup> we were able to calculate the probability of necessitating a given visit or test based on the actual results of the preceding examinations. Multiplying this probability by the costs of the visit/test based on the current (January 2024) ambulatory healthcare services reimbursement catalogue of the National Association of Statutory Health Insurance Physicians (*Einheitlicher Bewertungsmaßstab der Kassenärztlichen Bundesvereinigung*) in Germany<sup>25</sup> allowed us to estimate the total current costs of the recommended outpatient post-PE evaluation per study patient.

### Statistical analysis

The primary analysis was conducted in all patients with complete 3-month follow-up data. To assess to what extent the minority of patients with data limited to the first 3 months might have led to underestimation of the 12-month costs, a sensitivity analysis was performed, including only those patients with complete 12-month data. The cumulative incidence of hospital readmissions was plotted with Kaplan-Meier curves accounting for the competing risk of death. Differences between sexes and age groups were analysed with Gray's test.<sup>26</sup>

The number of rehospitalizations over the first year after PE was observed together with a set of baseline variables expected to provide possible risk factors for readmission. We anticipated a substantial proportion of study patients without readmissions, and that the number of rehospitalizations would exhibit a Poisson pattern in the remaining cases. Consequently, we applied a zero-inflated Poisson (ZIP) regression to assess the influence of the risk factors on the number of rehospitalizations; the model provides a parameter for excess zeros (zero process) on top of a Poisson regression model (count process).<sup>27</sup> The zero process was modelled as a binomial with the logit link function, while the count process used the canonical log link. The ZIP regression was applied in a univariable fashion (separately) to each baseline variable; in addition, a multivariable regression was applied to all baseline variables simultaneously.

The number of readmissions per patient included in the analysis is shown as the marginal mean with bootstrapped 95% confidence intervals (CI). The effect estimates of univariable models for each predictor, and of the multivariable model, are displayed as average marginal effects with the corresponding Wald 95% CI. These indicate how strongly the expected value (here, number of readmissions) changes in the model (i) with the increase per age year; (ii) in women (with male sex serving as a reference); (iii) in the presence versus absence of a given categorical baseline variable (for the comorbidities tested); or (iv) in intermediate-risk or high-risk PE, each compared with low-risk PE (the latter being the reference severity category). Of note, the value of the marginal effect is influenced by two factors, a shift in the zero component and a shift in the distribution of readmission numbers. We also report (in the [Supplementary material online](#)) the results of the individual models as incidence rate ratios for the count processes, and as odds ratios for the estimation of excess zeros.

Total rehospitalization-related costs per patient during 1-year follow-up were analysed following a two-step (hurdle) process: In the first step, logistic regression was used to estimate whether costs were higher than zero. In the second, a gamma regression with a log link estimated the effects. The marginal means of the average costs per patient were calculated with the corresponding bootstrapped 95% CI. We additionally calculated these costs employing Bang and Tsiatis' weighted complete case estimator as a control for the possible effect of censoring due to loss to follow-up.<sup>28</sup> Furthermore, we sought to identify predictors of rehospitalization costs, entering the same baseline variables with the same categorization as

**Table 1** Baseline characteristics of the study patients (n = 958)

Patient demographics	
Women, n	435 (45%)
Age (years), median (IQR)	64 (51–74)
Comorbidities and other risk factors, n	
Heart failure	45 (4.7%)
Coronary artery disease	85 (8.9%)
Chronic pulmonary disease	149 (16%)
Cancer	92 (9.6%)
Chronic kidney disease or eGFR <50 mL/min/1.73 m <sup>2</sup>	157 (16%)
Diabetes mellitus	104 (11%)
History of VTE	237 (25%)
Risk class of index PE	
Low	497 (52%)
Intermediate	433 (45%)
High	28 (2.9%)

eGFR, estimated glomerular filtration rate; IQR, interquartile range; PE, pulmonary embolism; VTE, venous thromboembolism.

for the model analysing the number of readmissions (see above). The effect estimates of univariable models, and of the multivariable model, are reported as average marginal effects with Wald 95% CI. In analogy to the approach presented in the previous paragraph, we also report (Supplementary material online) the results of the individual models as change in log costs on the condition of costs being greater than zero in the gamma regression with log link, and as odds ratios to predict that costs were zero in the logistic regression.

All analyses were performed using R version 4.3.2, package *cmprsk* for cumulative incidences, and packages *pscl* and *glmmTMB* for ZIP and hurdle regression models, respectively. Marginal effects were calculated with the package *marginalEffects*. Cost estimation accounting for censored data was performed using the *ccostr* package.

## Results

### Baseline characteristics and clinical outcomes

A total of 1017 patients were analysed in the FOCUS study; their baseline characteristics have been described previously.<sup>15</sup> Of those, 958 (94.2%) completed at least the first (3-month) follow-up visit and were included in the primary analysis. Out of the latter patients, 837 (82.3% of the entire study population) also had complete 12-month follow-up data and were included in the sensitivity analysis. The key baseline characteristics of the population are shown in Table 1; the patients' median age was 64 years (interquartile range [IQR] 51–74 years), 45% were women, and acute PE belonged to the intermediate-risk or high-risk class in 48% of the cases. A comparison of the patients included in the primary and sensitivity analyses is displayed in Supplementary material online, Table S1 of the Online Supplement; no differences in baseline characteristics were observed, with the exception of cancer which was more frequent in the primary analysis population. A total of 40 (4.2%) deaths occurred within the first 12 months after discharge. Of these, 16 occurred before the 3-month follow-up visit, and 24 between 3 and 12 months.

Overall, 226 (23.6%) patients were readmitted to the hospital at least once, for an estimated average of 34 (95% CI 30–39) readmissions per 100 acute PE survivors. The total number of readmissions was 325, as 70/226 (31%) patients were rehospitalized more than

once. As shown in Figure 1, the cumulative incidence of readmissions was independent from the patient's sex, whereas it differed between age groups. Leading causes of readmission were cardiovascular disease (mostly decompensated heart failure and coronary artery disease) in 54 cases (16.6%), cancer in 36 (11.1%), infectious or other acute inflammatory disease in 34 (10.5%), pulmonary disease in 28 (8.6%), bleeding in 14 (4.3%), and VTE recurrence in 12 (3.7%); in 147 cases (45.2%), the readmission was symptom-related.

### Costs related to rehospitalizations

Table 2 (left columns) shows the marginal effects of the patients' baseline clinical characteristics on the number of hospital readmissions over the first 12 months; the results of the individual models (Poisson regression for count and logistic regression for estimation of excess zeros) are shown in Supplementary material online, Table S2. In the simple (univariable) model, increasing age, coronary heart disease, chronic heart failure, chronic pulmonary disease, chronic kidney disease, diabetes, and cancer all were associated with a larger number of hospitalizations; in the adjusted (multivariable) model, only age, coronary artery disease, and chronic pulmonary disease remained independent predictors. The sensitivity analysis conducted in the patients with complete 12-month follow-up added cancer to the list of independent predictors of readmissions (Supplementary material online, Table S4; left columns).

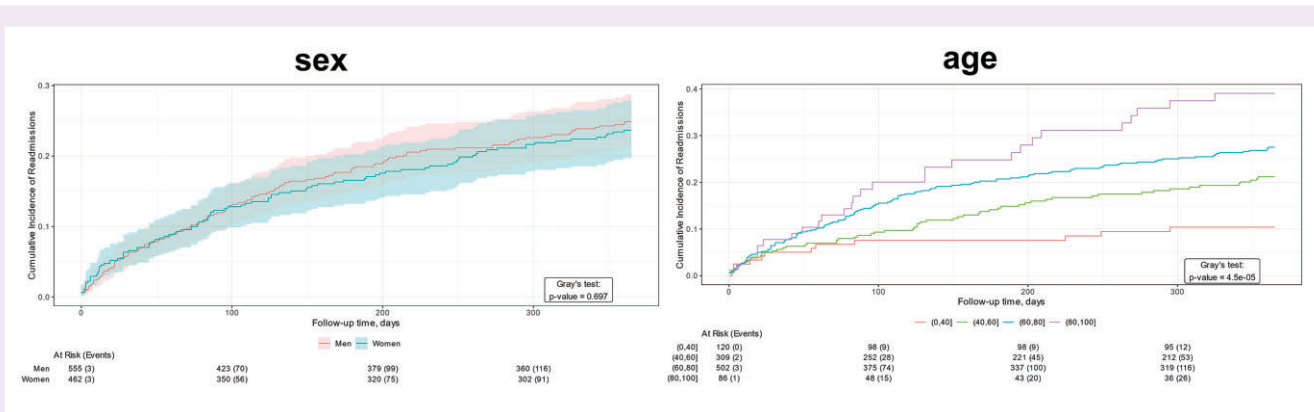
The estimated average total rehospitalization cost was €1138 (95% CI 896–1420) per patient included in the main analysis. Table 2 (right columns) shows the marginal effects of the patients' baseline clinical characteristics on excess hospital readmissions over the first 12 months after acute PE; the results of the individual models (conditional gamma regression for cost count and logistic regression for the excess zeros) are shown in Supplementary material online, Table S3. The predictors of costs in both the univariable and the adjusted (multivariable) models largely overlapped with those of the number of readmissions. The sensitivity analysis of patients with complete 12-month follow-up, shown in Supplementary material online, Table S4, right columns, estimated an overall slightly higher total rehospitalization cost of €1171 (908–1479); analysis using the weighted complete case estimator was consistent with these results, yielding a total cost of €1172.

### Costs related to anticoagulation and ambulatory care

After hospital discharge for the index PE, patients remained on anticoagulation for a median duration of 329 (IQR 142–365) days. The total days and the median duration (in days, with the corresponding IQR) of treatment on each anticoagulant are shown in Table 3; Supplementary material online, Table S5 shows the results of the sensitivity analysis in the patients with a complete 12-month follow-up. From these data and based on current daily costs as per each drug's central unique identifier, we calculated a total of anticoagulant treatment costs amounting to an average of €1050 per patient (median 972; IQR 458–1197) included in the primary analysis and €1190 (median 1168; IQR 931–1197) per patient in the sensitivity analysis.

Costs of scheduled ambulatory visits and tests were calculated based on the decision tree recommended by current guidelines<sup>9</sup> and the actual results of the tests in the FOCUS study population.<sup>15</sup> The calculated probability and current reimbursement (in euros) of each visit and test are shown in Figure 2. Total costs amounted to €181 per patient.

Taking into consideration all the above categories and calculations, the sum of direct per-patient costs during the first year after acute PE was estimated at €2369. The estimate based on the sensitivity analysis was slightly higher, €2542.



**Figure 1** Kaplan-Meier estimator of the cumulative incidence of readmissions in the entire FOCUS population of survivors of acute pulmonary embolism, stratified by sex (left panel; same-colour shaded areas surrounding each curve denote the corresponding 95% confidence interval) and by age group (right panel). Differences between subgroups were analysed with Gray's test.<sup>26</sup> FOCUS: Follow-up after aCUte pulmonary emboliSm study.

**Table 2** Association of the patients' baseline clinical characteristics with the number of hospital readmissions as well as with total rehospitalization costs over the first 12 months of follow-up after acute pulmonary embolism (n = 958 patients)

Predicting variable	Number of excess readmissions (95% CI)		Excess rehospitalization cost in euros (95% CI)	
	Zero-inflated Poisson regression		Hurdle gamma regression	
	Univariable	Multivariable	Univariable	Multivariable
Age (per year increase)	<b>0.008 (0.004–0.011)</b>	<b>0.005 (0.001–0.009)</b>	<b>36 (23–49)</b>	<b>15 (3–28)</b>
Sex (women vs. men)	−0.05 (−0.14 to 0.04)	−0.03 (−0.12 to 0.06)	99 (−257 to 455)	−50 (−373 to 274)
Coronary heart disease	<b>0.43 (0.23–0.63)</b>	<b>0.20 (0.03–0.38)</b>	<b>1939 (964–2914)</b>	<b>684 (48–1321)</b>
Chronic heart failure	<b>0.39 (0.08–0.70)</b>	0.12 (−0.10 to 0.35)	<b>2786 (873–4700)</b>	891 (−170 to 1953)
Chronic pulmonary disease	<b>0.38 (0.22–0.54)</b>	<b>0.26 (0.12–0.41)</b>	<b>1414 (745–2084)</b>	<b>721 (222–1221)</b>
Chronic kidney disease	<b>0.29 (0.14–0.44)</b>	0.13 (0.00–0.27)	<b>1782 (1020–2543)</b>	<b>760 (206–1315)</b>
Diabetes mellitus	<b>0.22 (0.04–0.41)</b>	0.08 (−0.07 to 0.23)	<b>1946 (864–3028)</b>	<b>875 (120–1631)</b>
Cancer	<b>0.23 (0.02–0.43)</b>	0.17 (−0.01 to 0.35)	483 (−205–1170)	558 (−113 to 1230)
Previous VTE	−0.06 (−0.16 to 0.04)	−0.04 (−0.14 to 0.06)	−106 (−511 to 298)	−171 (−528 to 185)
Risk class of index PE				
Low	Ref.	Ref.	Ref.	Ref.
Intermediate	0.02 (−0.07 to 0.11)	−0.07 (−0.16 to 0.02)	321 (−44 to 687)	−35 (−367 to 297)
High	0.07 (−0.18 to 0.31)	0.05 (−0.24 to 0.34)	5 (−794 to 805)	52 (−794 to 897)

In both regression models (univariable and multivariable analysis of the number of readmissions [left columns], and of total rehospitalization costs [right columns] per patient), the effect estimates of are displayed as average marginal effects with the corresponding Wald 95% CI. Statistically significant effects ( $P < 0.05$ ) appear in bold. In the zero-inflated Poisson regression (left columns), the estimated number of readmissions per patient is always below 1 because the majority of patients in the FOCUS study had no readmissions at all during the first year of follow-up. For the same reason, the additive rehospitalization costs per patient appear 'low' in the hurdle gamma regression. CI, confidence interval; PE, pulmonary embolism; Ref, reference; VTE, venous thromboembolism.

## Discussion

We calculated the chronic cost of illness of PE during the first year after the index acute event, analysing prospectively collected data from a large prospective multicentre cohort study in Germany. Our results can be summarized as follows: (1) An average of 34 hospital readmissions per 100 survivors of acute PE occurred; (2) the estimated average total rehospitalization cost per patient was €1138–1172, with

age, coronary artery disease, chronic pulmonary disease, and (in the sensitivity analysis of patients with complete 12-month follow-up) cancer being independent cost drivers; (3) average chronic anticoagulation costs over one year amounted to €1050–1190 per patient; and (4) the ambulatory post-PE care recommended by current guidelines (€181 per patient) was only a minor contributor to chronic costs. Accordingly, the total direct per-patient costs during the first year after acute PE were estimated at €2369–2542.

**Table 3** Total patient-days after discharge and median duration of treatment with each anticoagulant drug during the study period (n = 958 patients)

Anticoagulant	Total patient-days per anticoagulant in FOCUS during the first follow-up year <sup>a</sup>	Median duration of treatment (IQR)
Low molecular weight heparin	14 437	48 (42–181)
Fondaparinux	135	135 (135–135)
Rivaroxaban	141 772	365 (213–365)
Apixaban	69 917	365 (220–365)
Edoxaban	9866	324 (220–365)
Dabigatran	10 597	316 (164–365)
VKA—Phenprocoumon	33 566	322 (187–365)
VKA—Warfarin	707	149 (136–154)
Other	229	229 (229–229)
<b>Any anticoagulant</b>	<b>281 541</b>	<b>329 (142–365)</b>

IQR, interquartile range; VKA, vitamin K antagonist.

<sup>a</sup> The FOLlow-up after aCUte pulmonary emboliSm (FOCUS) study prospectively collected data on the type and duration of anticoagulant treatment in each patient, including switches from one anticoagulant to another, the exact date of discontinuation, and any resumption of anticoagulant treatment after discontinuation.

Data on the chronic cost of illness of PE are sparse. A study published in 2016 built decision trees populating them with data from a total of 25 studies of various designs conducted in different European countries.<sup>19</sup> Estimated direct chronic costs concentrated on known complications of VTE and its treatment, notably recurrent events and bleedings. Medication and post-PE care costs were not included.<sup>19</sup> A more recent study based on a European registry analysed prospectively collected data on cost drivers, also focusing, within the direct costs, (only) on those presumed to be 'directly' PE-related.<sup>29</sup> A similar approach was followed in a cohort study which, in contrast to FOCUS, included only patients with low-risk PE.<sup>30</sup> Importantly, however, we found in the present study that recurrent VTE or bleeding was the primary diagnosis in only a minority (3.7 and 4.3%, respectively) of hospital readmissions. Instead, we identified chronic heart, lung and kidney disease, diabetes, and (in the sensitivity analysis) cancer as key predictors of the number and cost of rehospitalizations. These findings are generally in agreement with those of a nationwide registry-based study, although our estimated annual readmission rate is below the 49% absolute risk reported for the Danish population.<sup>12</sup> Importantly however, our study went beyond the description of readmissions and their predictors, calculating current DRG-based hospital reimbursement in the healthcare system of Germany, a country with a population of approximately 84 million. This allowed us to quantify the contribution of hospital readmissions to the direct annual costs after PE and dissect cost predictors among the patients' demographic data and comorbidities. In doing so, we employed zero-inflated statistical models to take into account that these costs were generated by only a minority of the study patients and did not follow a normal distribution.

The results of the present study, conducted in unselected patients (all-comers) with PE, highlight changes across the broader spectrum of management and cost drivers after the acute phase. In the era of effective and safe direct oral anticoagulants,<sup>8,11</sup> VTE recurrence or

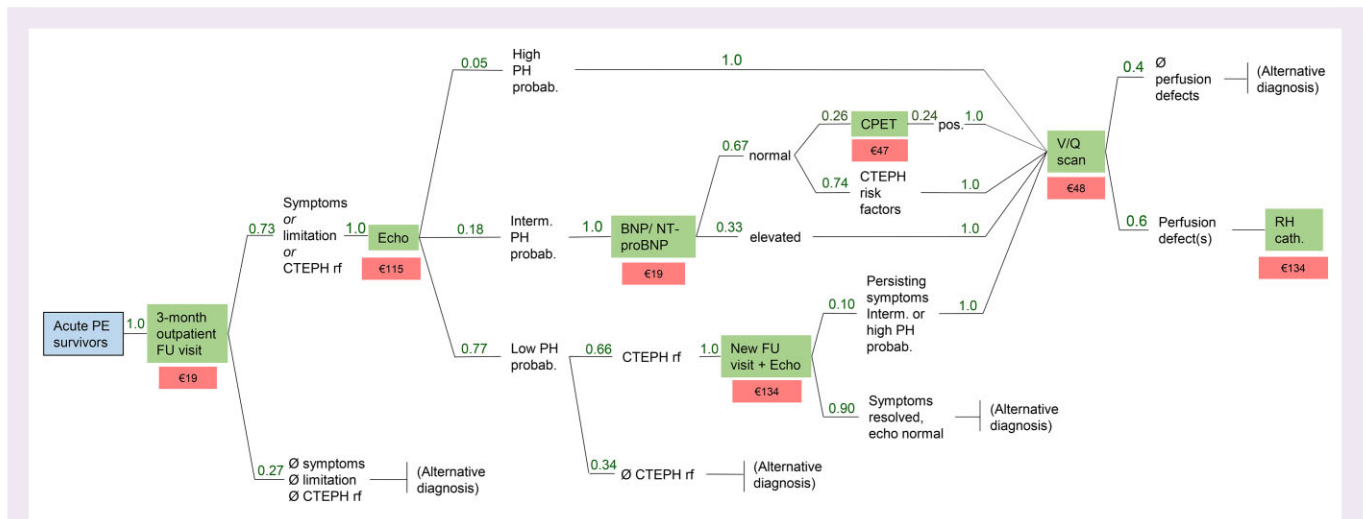
bleeding no longer appear to be major determinants of the direct chronic economic burden of PE. Of course, treatment with these drugs is still costly, affecting costs to a similar extent as rehospitalizations in our study. However, anticoagulant prices are expected to fall in the coming years as generic oral anticoagulants will become available.

Our findings further suggest that structured post-PE follow-up programmes as recommended by current guidelines<sup>8,18</sup> have only a minor impact on the total annual costs after PE in Germany. In fact, such programmes may contribute to direct and indirect cost savings via early detection and treatment of a broad spectrum of persisting clinical and functional abnormalities comprising the so-called 'post-PE syndrome'.<sup>15,16,31–33</sup> Moreover, by identifying the most frequent causes of (co)morbidity in the general population as key drivers of direct costs after PE, our study underlines the need for integration of broader cardiovascular prevention and lifestyle modification in post-PE care.<sup>13</sup> Outpatient cardiopulmonary rehabilitation programmes<sup>34,35</sup> may, if successfully tested in future randomized trials, improve the patients' well-being and quality of life, also offering the potential for reduction of the cost of illness of PE over the long term.

Based on our results and considering an annual incidence of 98 000 hospitalizations for acute PE in Germany along with a 13% in-hospital case fatality for the most recent years available,<sup>36</sup> total annual direct costs after acute PE might be expected to range between €202 and €217 million in Germany, corresponding to €2.4–2.6 million per million population. Clearly, this estimate is to be interpreted with caution, since the analysis of a multicentre cohort such as that of the FOCUS study cannot be directly extrapolated to the population of an entire country. On the other hand, the per-patient costs reported in the present study were generated after the acute phase of PE in the 'real world' of the German healthcare system and based on European and national guideline recommendations. Therefore, they may provide at least a partial insight into the total estimated annual burden of this disease. Of note, these costs do not include the diagnosis and treatment of chronic thromboembolic pulmonary hypertension.

The present study has some limitations. First, we did not obtain actual costs after PE from administrative databases, nor did we record unscheduled outpatient healthcare resource utilization.<sup>29,30</sup> However, we consider our estimates to be robust, since we relied on prospectively collected data, (i) on the date as well as the main and accompanying diagnoses of rehospitalizations; (ii) on the type, duration, and switches of anticoagulant medication over 1 year; and (iii) on the probability of needing follow-up tests in post-PE care based on established algorithms. Second, our estimates focused on direct costs after PE; costs due to loss of productivity may also be substantial.<sup>19,29</sup> Third, our primary analysis included the vast majority (94%) of the patients enrolled in FOCUS, but 'only' for 82% of all patients was complete 1-year follow-up information available. Our sensitivity analysis of these latter patients indicates that some shifts in cost drivers, notably cancer, may occur. Finally, we consider the inclusion of all readmissions (instead of only those traditionally ascribed to PE, such as VTE recurrence or major bleeding) and their costs to be a strength of our analysis. However, it is likely that at least some of these rehospitalizations would have occurred in the study patients even if they had not suffered acute PE. To directly address the issue of excess PE-inflicted healthcare costs, as recently attempted in patients with atherosclerotic cardiovascular disease,<sup>37</sup> future studies will need to compare the clinical course of PE survivors with that of appropriately matched individuals from large population cohorts.

In conclusion, the present study provides an estimate of the direct per-patient costs in the first year after acute PE, identifying and dissecting cost drivers. Our results may stimulate health economic research on post-PE care in further countries. They may further inform decisions by policymakers concerning the implementation and



**Figure 2** Decision tree-based outpatient follow-up visits and tests after acute pulmonary embolism (green boxes), with the respective reimbursement in euros (red boxes). The sequence of visits and tests correspond to the pulmonary embolism follow-up algorithm recommended by current European guidelines.<sup>8,18</sup> The standard outpatient follow-up visit includes clinical examination, an electrocardiogram, and a 6-min walking test, followed by specific functional, imaging and/or laboratory tests as indicated. Numbers in green indicate the probability of needing a specific visit or test based on the findings at the previous visit or test as documented in the FOCUS study population. The amounts in euros below each visit/test are based on the current ambulatory healthcare services reimbursement catalogue of the National Association of Statutory Health Insurance Physicians (*Einheitlicher Bewertungsmaßstab der Kassenärztlichen Bundesvereinigung*) in Germany.<sup>25</sup> The indicated echocardiogram reimbursement is for a test performed by a board-certified cardiologist. BNP, brain natriuretic peptide; CPET, cardiopulmonary exercise testing (spirometry); CTEPH, chronic thromboembolic pulmonary hypertension; Echo, outpatient transthoracic echocardiogram including Doppler examination; FOCUS: Follow-up after aCUTE pulmonary embolism study; FU, follow-up; interm. PH probab., intermediate echocardiographic probability for (chronic) pulmonary hypertension as defined by the 2022 European Guidelines on Pulmonary Hypertension;<sup>18</sup> low PH probab., low echocardiographic probability for (chronic) pulmonary hypertension;<sup>18</sup> NT-proBNP, N-terminal pro brain natriuretic peptide; PE, pulmonary embolism; PE survivors, all patients who survived the acute phase of the index PE event and were discharged alive; PH, pulmonary hypertension; pos, positive; rf, risk factor(s); RH cath., right heart catheterization; V/Q scan, ventilation-perfusion lung scintigraphy.

reimbursement of improved follow-up programmes aiming at broader cardiovascular prevention and lifestyle modification.

## Supplementary material

Supplementary material is available at *European Heart Journal—Quality of Care and Clinical Outcomes* online.

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## Data availability

Proposals for data access will be considered by the FOCUS Steering Committee in accordance with the data access policy of the academic study sponsor (University Medical Centre Mainz, Germany).

## Authors' contribution

K.M., P.M., I.S., S.V.K., H.B., and L.V. conceived and planned the study. K.M., P.M., and K.C.C. extracted the data and performed the statistical analysis with guidance and supervision by H.B. and L.V. T.N., K.K. (Kaier), C.A., and I.S. provided expert advice and support in statistics and health economic analysis, both of which were crucial for meeting the objectives of this study. S.B., F.A.K., L.H., I.F., and K.K. (Keller) provided expert input into the analysis of events documented during long-term follow-up after pulmonary embolism. D.B., L.B., R.E., S.R., P.S.W., and S.V.K. were responsible for the integrity of the data in the FOCUS study, representing the entire FOCUS investigator team. S.V.K., P.S.W., and S.R. obtained the funding for conducting the FOCUS study. K.M., P.M., and L.V. provided the first draft of the manuscript. All authors interpreted the data, made critical revisions of the manuscript for important intellectual content, and gave final approval for its submission.

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