Impact of Catheter-Directed Thrombolysis on the Socio-Economic Burden of Pulmonary Embolism in Germany: A Cost-Effectiveness Analysis

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Running title: Cost-effectiveness of catheter thrombolysis in PE

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Abstract

Background and Aims Catheter-directed treatment has yielded promising results in acute pulmonary embolism (PE), but state-of-the-art health economic evaluation of interventional treatment options is needed for healthcare systems to endorse its integration into clinical practice. We sought to provide an evidence-based comprehensive evaluation of the cost-effectiveness of catheter-directed thrombolysis (CDT) in PE.

Methods A systematic review and meta-analysis were conducted to retrieve outcomes of patients with intermediate- or high-risk PE treated with CDT versus standard of care (SoC). A cost-effectiveness analysis (CEA) model was developed, comparing CDT with SoC from the healthcare provider's (payer's) and the societal perspective in Germany (population of 84 million). A dynamic budget impact analysis (BIA) model was applied, assuming gradually increasing adoption of CDT.

Results Over a 5-year time horizon, CDT resulted in 4.13 life-years (LY) and 3.58 quality-adjusted life years (QALY), compared to 3.90 LY and 3.38 QALY with SoC. From the payer's perspective, the incremental cost-utility ratio (ICUR) for CDT was €27,349 per QALY. From the societal perspective, costs were lower for CDT than for SoC (€33,313 versus €37,501). Cost-effectiveness of CDT was confirmed when focusing on patients with intermediate-risk PE; it also persisted when only randomized controlled trials were considered. Probabilistic analysis confirmed the robustness of the model. BIA showed that, despite the higher upfront treatment costs of CDT in the acute phase, cost savings can be expected in the long term.

Conclusions In selected patients with acute PE, catheter-directed interventions may improve patient outcomes while remaining within the acceptable cost-effectiveness threshold.

Key Words

Pulmonary embolism; catheter-directed therapy; standard medical treatment; cost-effectiveness; cost-utility; budget impact analysis

Key Learning Points

What is already known on this topic:

- In contrast to other frequent cardiovascular syndromes, the socio-economic burden of pulmonary embolism (PE) has not been systematically studied thus far.
- Interventional catheter-directed treatment of PE currently exhibits one of the fastest growth rates of innovative therapies in cardiovascular medicine.

What this study adds:

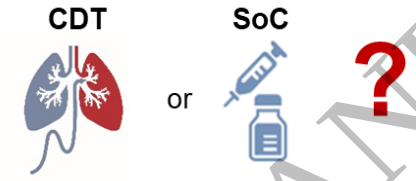
- We conducted a comprehensive evidence-based cost-effectiveness and budget impact analysis comparing catheter-directed thrombolysis (CDT) with the current standard of care for acute intermediate-risk and high-risk PE.
- From the broad societal perspective, CDT was a dominant strategy, yielding better health outcomes at a lower overall cost over a five-year time horizon; from the

payer’s perspective, the incremental cost-utility ratio with CDT was approximately €27,000 per QALY.

- Although CDT is associated with higher initial costs, its benefits in terms of QALYs gained may justify its adoption in appropriately selected patients. A controlled progressive increase in CDT use may help to balance clinical effectiveness with financial sustainability.

Structured Graphical Abstract

Acute intermediate- and high-risk PE:



- **CDT for PE has higher upfront costs, but possible long-term benefits and cost savings**
- **Usage of CDT rising, socio-economic impact unclear**

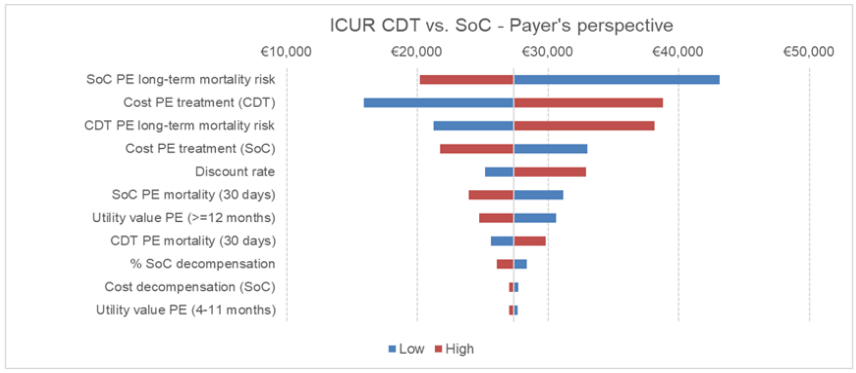
Cost-effectiveness and cost-utility analysis

(German healthcare system; 5-year horizon)

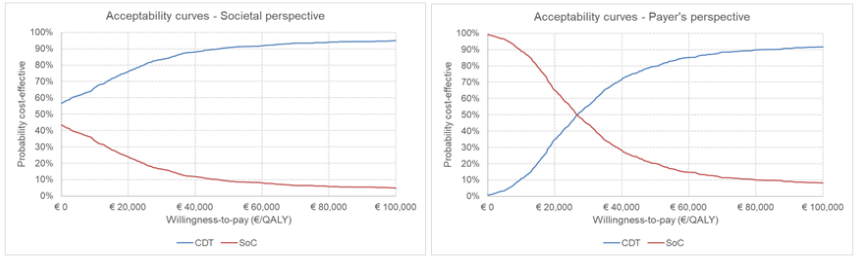
4.13 LY
3.58 QALY
Mean cost per patient:
- €11,657 (payer's perspective)
- €33,313 (societal perspective)

3.90 LY
3.38 QALY
Mean cost per patient:
- €6087 (payer's perspective)
- €37,501 (societal perspective)

- **Payer's perspective: ICUR €27,349 per QALY gained**
- **Societal perspective: CDT "dominant" (less costly than SoC)**



One-way sensitivity analysis: ICUR of CDT changes across each parameter's higher (red bars) and lower (blue bars) values, but remains below €45,000/QALY



Probabilistic sensitivity analysis: CDT becomes cost-effective at willingness to pay of €28,000/QALY *(payer's perspective)*; CDT remains cost effective at any threshold *(societal perspective)*

- **CDT may be cost-effective for selected patients with acute PE**
- **CDT may improve patient outcomes while remaining within the acceptable cost-effectiveness threshold**

CDT, catheter-directed thrombolysis; ICUR, incremental cost-utility ratio; LY, life-years; PE, pulmonary embolism; QALY, quality-adjusted life-years; SoC, standard of care

Introduction

Pulmonary embolism (PE), the third most frequent acute cardiovascular syndrome, is associated with significant morbidity and mortality in the population of Europe and other regions of the world.[1,2] Important factors contributing to the substantial impact of PE on the affected individuals and the society include, (a) its rising annual incidence;[3,4] and (b) the associated long-term disease burden, since acute PE is frequently followed by persisting symptoms and functional impairment which compromise the patients' quality of life[5-7] and generate further healthcare expenditures.[8]

The socio-economic burden of PE has not been systematically studied thus far, in contrast to the detailed country-specific data which already exist for other cardiovascular syndromes.[9] This needs to change however, since PE treatment has now entered a phase of rapid evolution. Specifically, catheter-directed procedures consisting of pharmacologically dissolving or mechanically fragmenting and aspirating pulmonary emboli have emerged as a promising option for patients with acute 'severe' PE in need of advanced treatment.[10-12] In the United States (US), the use of percutaneous catheter interventions for PE has continuously increased in the last decade,[13] whereas many European healthcare systems remain reluctant to reimburse these procedures. Initial procedural costs are higher than standard anticoagulation therapy or systemic thrombolysis, but potential savings from fewer complications, shorter hospitalization, and improved long-term patient outcomes also need to be considered.[14] Consequently, state-of-the-art health economic evaluation of innovations in PE treatment is urgently needed to assess their overall impact on healthcare systems and the society, set the standard for cost-effectiveness assessment in ongoing randomized trials, and

improve the level of evidence for guideline recommendations which remain inconclusive on this topic to date.[15]

To address this priority, the present study aimed at providing an evidence-based systematic evaluation of the costs versus benefits of advanced catheter-directed PE treatment. Our analysis focused on catheter-directed thrombolysis (CDT), the use of which for more than 10 years has permitted the accumulation of a larger volume of data compared to more recently introduced mechanical modalities.

Materials and methods

Overview of methodology

We developed a model to carry out a cost-effectiveness analysis and a budget impact analysis comparing CDT with the current standard of care, and taking into consideration both the payer's (insurance-based) and the societal perspective in the German healthcare system. A two-step approach was followed, linking internationally derived clinical outcomes of patients with PE to country-specific cost and healthcare utilization data. Pooled estimates of outcome parameters were obtained from the published literature and subsequently applied to a hypothetical national patient cohort within the constructed models. Country-specific reimbursement tariffs, productivity losses, and demographic adjustments for background mortality were used to parameterize all cost components and epidemiological inputs.

Data sources and outcomes

A systematic review was conducted to retrieve clinical outcomes on PE patients treated with either CDT or standard of care, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria.[16] Specifically, we searched the electronic

database MEDLINE (via PubMed) covering the period from January 2014 through July 2024. The search syntax and string to identify relevant studies was as follows: *("Pulmonary Embolism"[Mesh]) AND (((((((((Catheter-directed thrombolysis) OR (CDT)) OR (Ultrasound-assisted thrombolysis)) OR (Ultrasound-facilitated thrombolysis)) OR (USAT)) OR ("Anticoagulants"[Mesh])) OR ("Heparin"[Mesh])) OR ("Thrombolytic Therapy"[Mesh])) OR (systemic thrombolysis)).* To complement our search, the references from all studies included in previous meta-analyses were retrieved and manually reviewed according to the snowball effect.[17-21] Full-text observational prospective or retrospective cohort studies, and randomized controlled trials (RCTs) or therapeutic arms of RCTs, including adult patients with intermediate-risk or high-risk PE[15] treated with CDT (with or without ultrasound assistance) or with the current standard of care (mostly heparin anticoagulation), were deemed eligible. Data from studies focusing on mechanical thrombectomy or systemic thrombolysis were eligible only with regards to their control arm, if this was anticoagulation alone or CDT. Exclusion criteria included, 1) study designs other than those specified; 2) studies on different or unspecified PE populations; 3) studies published before 2014 (year of publication of the randomized controlled trial that led to FDA approval of catheter-directed ultrasound-assisted thrombolysis in PE[22]), aiming to focus on modern-era, currently used techniques; 4) studies not differentiating between CDT and mechanical thrombectomy; and 5) studies not reporting outcomes separately for CDT. No restrictions were applied regarding language or sample size. All studies were imported into Rayyan (http://rayyan.qcri.org) and, after duplication removal, two of the authors (KCC and KM) independently screened titles and abstracts, and went through full texts for eligible studies; a third author (LV) was consulted to resolve any disagreement. Subsequently, the two authors independently extracted data regarding study design and the outcomes of interest on a predefined Excel spreadsheet. A pilot test was

performed before initiation to ensure coherence; any disagreement was resolved by consensus. The corresponding authors of studies not reporting outcomes of interest were contacted for data sharing. The primary clinical outcomes of interest were in-hospital or 30-day mortality, haemodynamic decompensation and intracranial bleeding. Extracranial bleeding, length of stay in the hospital and the intensive care unit, one-year recurrence rate and all-cause hospital readmissions were also collected.

Data synthesis and statistical analysis

Meta-analyses were performed on numerical outcome data to synthesize the clinical outcomes for the two treatment strategies. To incorporate all available evidence from both comparative and single-arm studies, analyses were conducted separately for CDT and anticoagulation alone, the latter to be referred to from now on as current standard of care. The methodology adhered to the Cochrane Guidelines for Systematic Reviews.[23] Statistical analyses were carried out using STATA17 software, applying a random-effects maximum likelihood model to the clinical outcomes analysed, and taking into account possible heterogeneity across studies.

Construction of the model

A cost-effectiveness analysis model was developed in MSExcel to compare CDT versus standard of care from the perspective of the national healthcare service and the society in Germany. The analysis followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines.[24]

A Markov model (Supplementary Figure S1) was constructed to simulate potential clinical pathways of patients and estimate life-years, quality-adjusted life years (QALYs), and

associated costs for CDT versus standard of care in an adult population with acute PE. The model incorporated key health states including intracranial haemorrhage, haemodynamic decompensation and death. Rates of events obtained from the meta-analysis were used to populate the model. Acknowledging in-hospital case-fatality rates of 30% for subarachnoid haemorrhage and 45% for intracerebral bleeding,[25,26] and considering an equal distribution between these two clinical manifestations of intracranial haemorrhage,[27,28] a weighted 37.5% in-hospital mortality rate from this complication was calculated for the sake of the present analysis. Early deaths from acute PE and its complications were assumed to happen within the first month of the process. Long-term PE-related mortality over 3.8-year follow-up (14.5% for CDT, 20.9% for standard of care) was extracted from a dedicated observational study[29] and extrapolated to 5 years using an exponential survival function, assuming a constant monthly hazard. A summary of the model input data is provided in Table S1.

A time horizon of 5 years was applied for the baseline analysis considering a population with a mean age of 57 years (58% men) as derived from the meta-analysis. Mortality rates were further adjusted for age and gender according to mortality tables for the German population, taking into account deaths caused by other comorbidities.[30] A discount rate of 3% was applied to QALYs and costs,[31] and one-month Markov cycle length was chosen. As the reference studies reported, in general, frequency of complications over limited time horizons, we assumed that no additional outcomes directly related to the index acute PE occurred beyond the early phase (30 days or until hosital discharge); late sequelae were incorporated into the model through post-acute survival and health-related quality-of-life effects.

Healthcare resource utilization and costs

From the payer's perspective, costs of in-hospital treatment of acute PE were calculated based on the German Diagnosis Related Groups (G-DRG) reimbursement system.[32] All assumptions made for calculation of costs related to acute-phase complications, notably haemodynamic decompensation and intracranial haemorrhage, are explained in Table S2. From the societal perspective, productivity losses due to premature mortality were considered; for this purpose, a mean monthly wage of €3667[33] was applied in case of death occurring before the retirement age, currently at 64.4 years in Germany;[34] this was adjusted to the current unemployment rate (6.1%) in this country.[35]

Quality-of-life estimates

Utility coefficients for the model health states were obtained from the literature. In particular, we used the data from a large multicentre study with prospective long-term follow-up in a German cohort of acute PE survivors.[5] In that study, which assessed the patients' quality of life 3 and 12 months after the acute event, the utility weight measured by the EuroQoL 5D 5L[36] increased from 0.85 (standard deviation [SD], 0.22) to 0.87 (SD, 0.20). We did not assume additional chronic disutility in patients who survived in-hospital haemodynamic decompensation, since the severity of the acute event has not been reported to independently affect quality of life or healthcare resource utilization over the long term.[5,8] For survivors of intracranial haemorrhage we used the previously reported utility value of 0.15 (range 0.0-0.65).[6]

Cost-effectiveness analysis

The incremental cost-effectiveness ratio (ICER) was estimated as the difference in the mean expected costs between CDT and standard of care divided by the difference in the mean expected life-years between these treatment options. We particularly focused on the incremental cost-utility ratio (ICUR) by considering effectiveness expressed in QALYs. Willingness-to-pay thresholds vary considerably among different countries;[37] for Germany, it has been estimated that a threshold value of approximately €90,000 per life-year gained for innovative health technologies may not deteriorate the efficiency of the healthcare system, and that adjusting life-years for the quality of life does not change this threshold.[38] Accordingly, we applied a willingness-to-pay threshold of €90,000 per QALY in the base-case scenario.

Deterministic and probabilistic sensitivity analyses (PSA) were conducted to assess the robustness of the model. For the PSA, model parameters were extracted from assigned probability distributions to reflect uncertainty; a beta distribution was applied for utilities and the proportions of patients experiencing complications, whereas a gamma distribution was used for costs. Parameter variability was derived from 95% confidence intervals (CI), standard deviation (SD), or ranges reported in meta-analyses and other reference studies. In cases in which variation data were unavailable (mainly costs), a ±20% deviation from the baseline value was assumed. Parameters were then randomly sampled from their respective distributions over 10,000 Monte Carlo simulations. Results were graphically represented using cost-effectiveness acceptability curves and scatterplots for the incremental cost-utility ratio. Additionally, one-way sensitivity analyses were carried out using the same parameter variations as in PSA, except for the discount rate which varied from 0 to 10%.

Budget impact analysis

A dynamic budget impact analysis (BIA) model was developed to compare the standard of care scenario for managing patients with acute PE to hypothetical future scenarios assuming a gradual increase in the adoption of CDT at the national level in Germany. Starting from an observed CDT penetration rate of 1.44% among all PE-related hospitalizations in Year 1,[39] the annual CDT rate might increase linearly to 3.1% (95% CI 3.0-3.2%) by year 5 applying a conservative model, and to 8.7% (8.3-9.2%) applying a maximal model, based in both cases on recent US trends.[13] These proportions refer to the total annual number of hospitalizations (approximately 100,000) for acute PE in Germany.[39] The total costs for both the current and future years were calculated by multiplying the annual cost per treatment strategy (CDT versus standard of care) by the eligible population, incorporating successive yearly incident cohorts to maintain a dynamic model. Financial projections were presented as undiscounted costs, as the analysis focused on the expected budget impact at each time point.[40]

Results

Literature search

The initial literature search yielded 3596 reports, screened by reviewing the title or abstract. Out of 124 studies in the full-text evaluation, 74 were ultimately found eligible, including a total of 11,043 patients (Figure 1); of these, 4763 patients were treated with CDT (ultrasound-assisted in the majority of cases) and 5665 received SoC. The complete list of the studies included in the meta-analysis is shown in the Supplement. Among them were 17 randomized controlled trials as well as 6 prospective and 51 retrospective observational cohort studies, yielding a total of 54 study arms with CDT and 35 with standard of care. Intermediate-risk PE

patients were included in 54 treatment arms, intermediate- and high-risk patients in 33, and high-risk patients alone in two.

Clinical data

The population considered in the systematic literature review had an average age of 57 years; 58% of the patients were men. Mortality at 30 days was 2.02% and 4.96% for CDT and standard of care, respectively. Haemodynamic decompensation occurred in 0.4% of the patients who underwent CDT compared to 5.04% of those treated with the standard of care (Table S1). Intracranial haemorrhage was very rare in both treatment arms. Figures S2, S3 and S4 display the Forest plots for standard of care and CDT, showing the effect size of each study with the corresponding 95% CI, the overall effect size of all selected studies, and the degree of heterogeneity (quantified using the I^2 metric from 0% to 100%: the higher the value, the larger the heterogeneity).

Cost-effectiveness analysis

Over a 5-year time horizon, CDT resulted in 4.13 life-years and 3.58 QALY, compared to 3.90 life-years and 3.38 QALY for the standard of care. From the payer's perspective, the mean cost per patient was €11,657 for CDT and €6087 for standard of care. The incremental cost-effectiveness ratio was €23,721 per life-year, while the incremental cost-utility ratio was €27,349 per QALY. One-way sensitivity analyses performed from the payer's perspective revealed that early mortality and the costs of treating haemodynamic decompensation complicating acute PE were the parameters most impacting the model results (Figure 2). Viewed from the societal perspective, CDT resulted in costs of €33,313 per patient, whereas a higher cost of €37,501 was calculated for the current standard of care. Consequently, CDT

may be considered a dominant strategy in this setting, being associated with less expenditures and more life-years or QALY compared to the standard of care.

In a sensitivity analysis focusing only on those studies that included patients with intermediate-risk PE, CDT appeared to be even more cost-effective compared to anticoagulation alone as the current SoC, with an incremental cost-effectiveness ratio of € 21,771 per life-year and an incremental cost-utility ratio of €25,087 per QALY from the payer's perspective; CDT remained a dominant strategy from the societal perspective.

Another sensitivity analysis, considering only the results of randomized controlled trials (and excluding observational studies) for early mortality and complications, confirmed the robustness of the model. The calculated 5-year incremental cost-utility ratio was only slightly higher (€29,343 per QALY) from the payer's perspective, while CDT remained dominant from the societal perspective.

Further support for cost-effectiveness of CDT was provided by probabilistic sensitivity analyses. As shown in Figure 3, upper panels, simulations showing incremental cost and QALYs of CDT compared to the current standard of care lay largely below the willingness-to-pay threshold, particularly when viewed from the societal perspective. The acceptability curves from these analyses (Figure 3**,** lower panels) highlight that, from the payer's perspective, CDT becomes cost-effective starting at a willingness-to-pay threshold of about €28,000 per QALY. On the other hand, when viewed from the societal perspective, CDT appears cost-effective at any threshold. The only parameter impacting result variation from the societal perspective was the retirement age, resulting in an incremental cost-utility ratio of €27,349 per QALY at the lower extreme (53 years) and thus effectively aligning the analysis with the payer's perspective.

Budget impact analysis

BIA was first performed from the payer's perspective, considering a conservative gradual increase in CDT use from 1.44% to 3.10% of the therapy mix in the entire hospitalized PE population over the next five years,[13] i.e., increasing by 0.42% annually. This estimate yielded additional spending of €63,222,340 over a 5-year horizon in the German healthcare system, corresponding to costs of approximately €126 per PE patient. On the other hand, BIA from the *societal* perspective yielded a considerably lower additional cost of €12,104,069 for the same time horizon, corresponding to a per-patient cost of 'only' €24. Thus, although the higher upfront treatment cost of CDT may not be compensated over the short term, substantial savings could be expected over the long term. In contrast, when the BIA from the payer's perspective considered a model of steeper increase in CDT use from 1.44% to 8.7% over the following five years[13] (average annual increase of 1.82%), it yielded additional costs of €141,205,844 or €282 per PE patient. In this latter scenario, the estimate from the societal perspective was €42,541,566, with a per-patient cost of €85. Detailed budget impact estimates for both scenarios and perspectives are provided in Figure 4.

Discussion

In the present study, we conducted a comprehensive cost-effectiveness and budget impact analysis comparing CDT with the current standard of care for the management of acute PE. We considered a large volume of data derived from randomized controlled trials and observational studies published in the past 10 years. We estimated both direct (treatment- and complication-related) and indirect (productivity loss-related) costs, aiming to assess the overall socio-economic impact of PE and its treatment on the healthcare system and the society in Germany, a country with a population of approximately 84 million. The analysis from

the broad societal perspective suggested that CDT is a dominant strategy, yielding better health outcomes at a lower cost over a five-year time horizon. When the analysis was restricted to the payer's perspective, CDT was associated with an incremental cost-utility ratio of approximately €27,000 per QALY. Analysis considering only randomized controlled trials as well as probabilistic sensitivity analyses yielded consistent results and thus confirmed the robustness of the model. Thus, CDT may represent 'good value for money' from the payer's perspective in the German healthcare system,[38] and it might also lie below the willingness-to-pay threshold in a number of further countries.[37] However, confirmation of the latter hypothesis will require analyses with country-specific data, both with regards to reimbursement of healthcare services and to the costs resulting from loss of productivity.

Analysis of the budget impact of an anticipated growing use of CDT demonstrated increases in healthcare expenditures from both perspectives over the first five years. However, the total cost from the societal perspective exhibited a decreasing trend, meaning that the initial increase in costs due to the treatment may be followed by cost savings over the long term. Consequently, reimbursement of medically validated catheter-directed treatment options may be an investment able to provide future benefits for the society as a whole, allowing for continuous improvement of the patients' management according to the value-based healthcare paradigm.[41]

In the literature there is paucity of health economic evaluations of CDT, and catheter-directed treatments in general, in the setting of acute PE. A recently published preliminary assessment, from the societal perspective, of the cost-effectiveness of CDT versus anticoagulation alone for intermediate-risk PE in the US considered a short-term horizon of one month.[42] The cost associated with CDT was estimated at $22,353 with a 0·984 probability of survival at one month, whereas the cost with anticoagulation alone was $25,060 and the

probability of survival 0·958. The authors suggested that catheter-directed thrombolysis may result in savings of $104,089 per death averted. Although the results of health economic analyses performed in different countries are not directly comparable, our findings support the notion that use of CDT may, apart from clinical benefits, be a cost-saving strategy for the society when applied to selected patients with acute PE.

In the present study, cost-effectiveness of CDT was influenced by various factors including patient characteristics, complication rates, and healthcare costs. While CDT may overall be cost-effective for patients with intermediate - and high-risk PE, further evidence is needed to optimize patient selection criteria and consequently the allocation of resources for this treatment modality. In this context, the majority of the existing studies which provided the input data for our analysis, did not explicitly distinguish between intermediate-high- and intermediate-low-risk PE. It is, however, crucial to remind that CDT, and any form of advanced catheter-directed treatment, should be reserved for patients at truly elevated risk of haemodynamic collapse and death.[10,11] A large randomized trial currently comparing CDT with anticoagulaton alone requires, beyond the standard definition of intermediate-high risk,[15] additional inclusion criteria of cardiorespiratory distress and threatening decompensation.[43] This and other ongoing trials (summarized in[14]) with specified PE severity criteria are investigating both early and late outcomes; they will thus help to assess the entire spectrum of possible benefits of CDT for the patients' prognosis and quality of life, with possible implications for further cost savings over the long term. Continuous real-world data collection and monitoring is equally crucial for generating more robust evidence, since medical device assessment presents unique challenges due to rapid innovation, user training and competence, and dynamic pricing.[44] For example, clinical outcomes associated with new technologies such as CDT are often influenced by the operators' learning curve,[45] and centres

with higher procedure volumes may achieve better overall device performance and health outcomes at lower procedure costs.[45]

Despite the strengths of our analysis, some limitations need to be acknowledged. First, although our model was developed using the best available evidence to this date, some parameters derived from observational data may introduce uncertainty; for example, this may be the case for CDT-related reduction of case-fatality. To address this issue, multiple sensitivity analyses were performed, demonstrating that the results were robust and resistant to variations in key assumptions; nevertheless, selection bias cannot be excluded.

This study was conducted from the perspective of the German healthcare system, which may limit generalizability to other countries with different reimbursement structures. Nevertheless, the transparent, detailed explanation of all assumptions made and all input data considered in the analysis fulfils the requirements of the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER)[46] and the European Network for Health Technology Assessment (EUnetHTA) guidelines.[47] Because of this, our study may facilitate health economic analyses exploring CDT cost-effectiveness and budget impact across healthcare systems in different countries; these will permit assessment of its broader applicability and economic sustainability.

Third, our cost effectiveness and budget impact analysis did not include the still unknown impact of CDT on late PE sequelae, particularly on chronic thromboembolic pulmonary disease and hypertension. As mentioned above, ongoing randomized trials evaluating various modalities of advanced treatment include up to two-year patient follow-up[14] which will hopefully allow further insights into the socioeconomic impact of potential long-term effects.

Lastly, the societal perspective of our analysis focused solely on productivity losses due to premature death related to acute PE. Future research should expand data collection to include out-of-pocket expenses as well as costs for formal and informal care,[9] permitting more comprehensive assessment of the cost-effectiveness of CDT in this clinical setting.

Conclusion

Our analysis supports the cost-effectiveness of CDT compared to the current standard of care in the management of intermediate- and high-risk PE, highlighting the potential of catheter-directed interventions to improve patient outcomes while remaining within the cost-effectiveness thresholds accepted in various countries.[48,49] Although CDT is associated with higher initial costs, its benefits in terms of QALYs gained may justify its adoption in appropriately selected patients. From a budgetary perspective, a controlled progressive increase in CDT utilization may represent a wise strategy for healthcare systems seeking to balance clinical effectiveness with financial sustainability. Upcoming randomized trial results and further accumulation of real-world data will be valuable in validating these results across different healthcare settings and patient populations.

Contributors' Statement

K. Mohr was responsible for conceptualization, investigation, data curation, project administration, visualization, and writing of the original manuscript draft; K. Christodoulou, for investigation, data curation, formal analysis, methodology, and validation; S. Barco and L. Valerio, for conceptualization, methodology, investigation, and validation; T. Neusius, for conceptualization, methodology, and supervision; K. Keller, L. Hobohm and M. Vosseler, for investigation, methodology, formal analysis and visualization; T. Uphaus and M. Hahn, for investigation, methodology, and visualization; F.A. Klok, for investigation, methodology, and validation; H. Binder, for methodology, validation, and supervision; S. Konstantinides, for conceptualization, funding acquisition, investigation, methodology, project administration, supervision, and validation; C, Rognoni, for conceptualization, investigation, methodology, formal analysis, supervision, and writing of the original draft. All authors critically reviewed and made edits to the manuscript draft, and approved its final version for submission to the *European Heart Journal*.

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Data availability

Proposals for data access may be addressed to the corresponding author (KM), and will be considered in accordance with the data access policy of the University Medical Centre of the Johannes Gutenberg University Mainz, Germany.

Disclosure of interests

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Figure Legends

Figure 1 PRISMA flowchart of the study selection process.

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.[16]

Figure 2 Tornado diagram reporting one-way sensitivity analyses on the ICUR (baseline value, €27,349 per QALY) from the payer's perspective. Displayed is the ICUR variation according to each parameter's higher (red horizontal bars) and lower (blue bars) values.

CDT, catheter-directed thrombolysis; ICUR, incremental cost-utility ratio; PE, pulmonary embolism; QALY, quality-adjusted life-year(s); SoC, standard of care.

Figure 3 Cost-effectiveness of catheter-directed thrombolysis versus standard of care from the payer's (left panels) and the societal (right panels) perspective over a five-year time horizon. *Upper panels,* Change in QALYs (x-axis) plotted against the change in costs (y-axis), analysed from the payer's (left) and societal (right) perspective. The latter also takes into account indirect costs due to productivity loss. Points falling below the diagonal line are considered cost-effective at a willingness-to-pay (maximum cost considered acceptable for payers) threshold of €90,000 per QALY gained. *Lower panels,* Acceptability curves derived from the probabilistic sensitivity analyses. From the payer's perspective (left), CDT becomes cost-effective starting at a willingness-to-pay threshold of €28,000 per QALY. From the societal perspective (right), CDT was cost-effective at any threshold.

CDT, catheter-directed thrombolysis; QALY, quality-adjusted life-year(s); SoC, standard of care; WTP, willingness to pay.

Figure 4 Budget impact analysis of CDT adoption in acute PE treatment. *A***,** conservative CDT growth scenario; *B,* maximal CDT growth scenario. Treatment costs (light blue boxes) increase with time as the therapy mix changes in favour of CDT. From the payer's perspective (upper panels in scenario *A* and *B*), the budget impact (dark blue boxes) increases in parallel to the treatment costs; the increase is more pronounced in the scenario of maximal CDT growth (*B*). From the societal perspective (lower panels), budget impact starts falling after Year 1 in scenario A, and after Year 3 in scenario *B*, as the importance of cost savings related to productivity loss (green boxes) grows over time. Costs related to ICH (red label) were also considered, but they are not visible in the graphs because ICH was very rare, both in patients undergoing CDT and in those treated with the standard of care.

CDT, catheter-directed thrombolysis; ICH, intracranial haemorrhage; PE, pulmonary embolism.

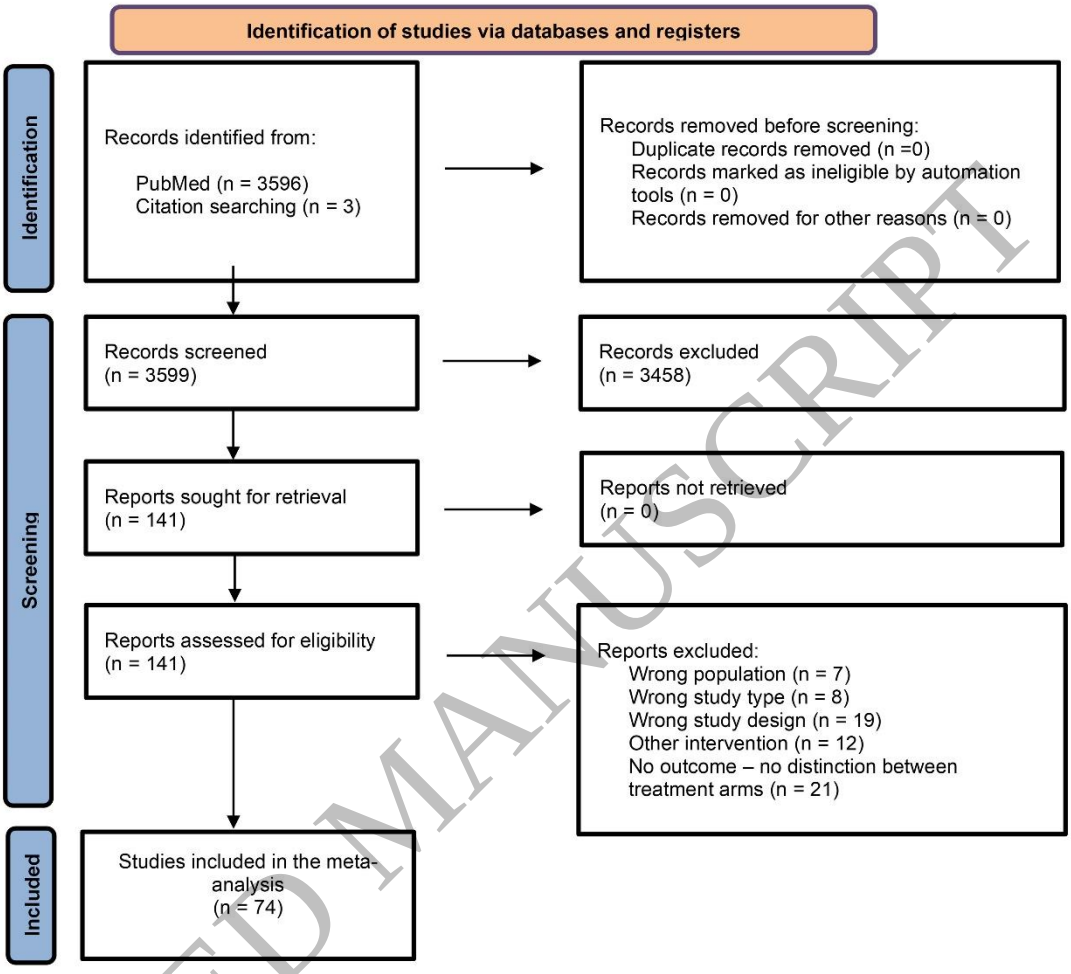

Figure 1
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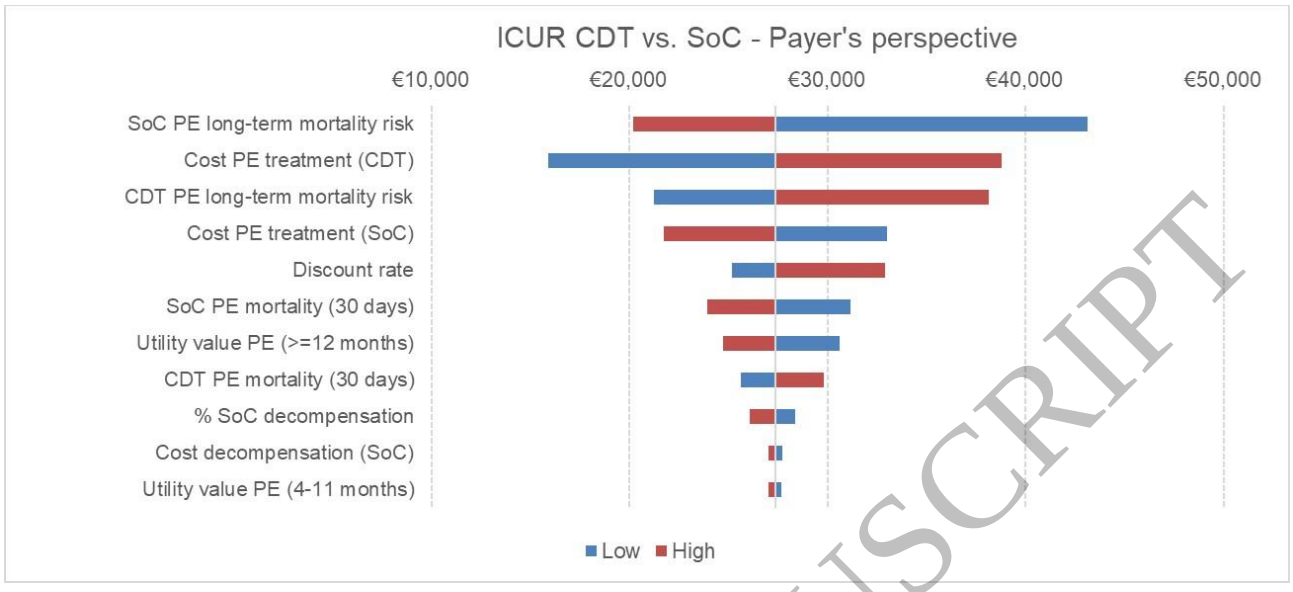

Figure 2
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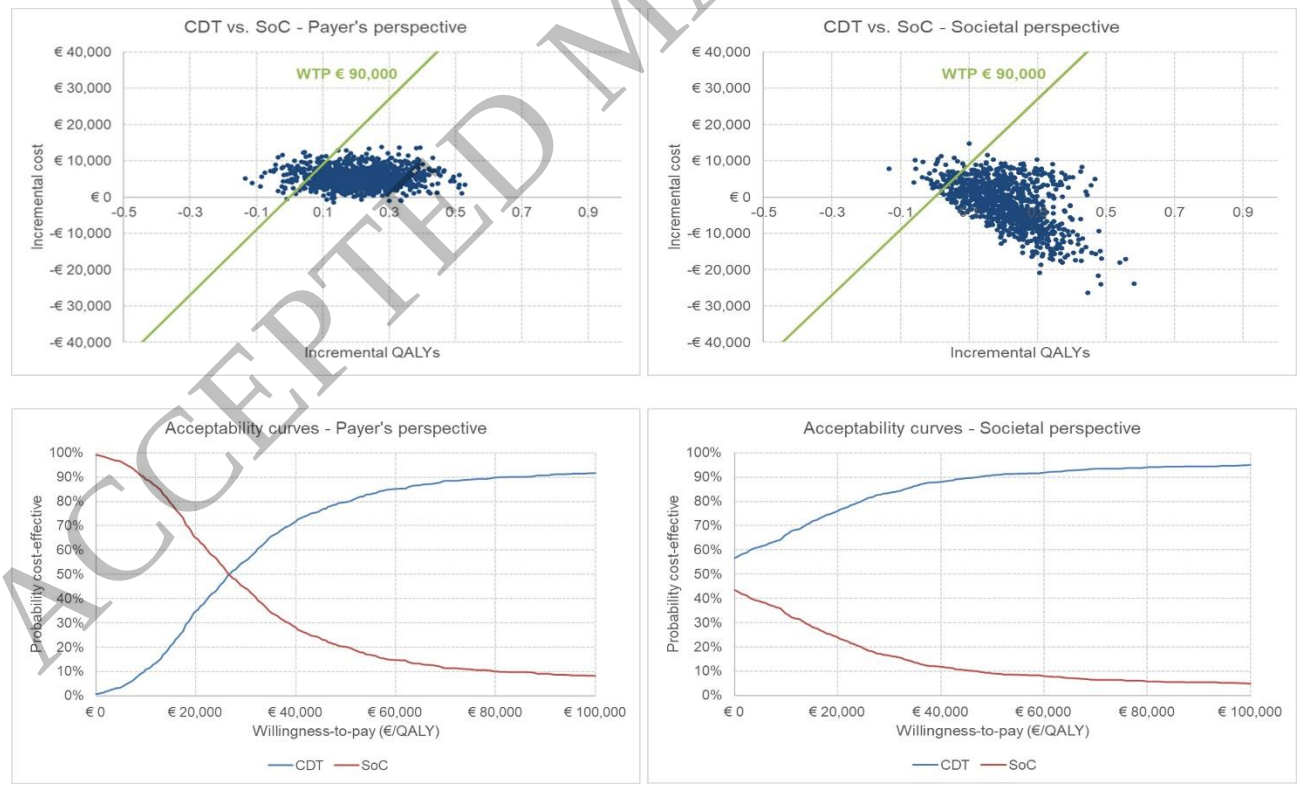

Figure 3
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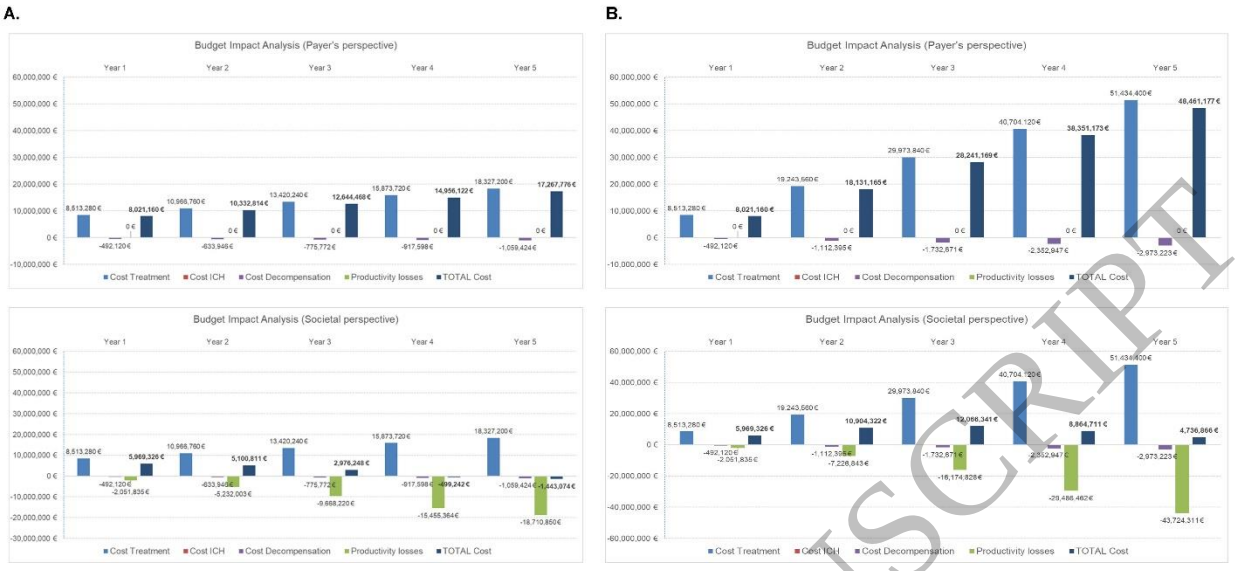

Figure 4
170x76 mm (DPI)