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The aftermath of acute pulmonary embolism: approach to persistent functional limitations

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A model for estimating the health economic impact of earlier diagnosis of chronic thromboembolic pulmonary hypertension

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ABSTRACT

Background: Diagnostic delay of chronic thromboembolic pulmonary hypertension (CTEPH) exceeds >1 year, contributing to higher mortality. Health-economic consequences of late CTEPH diagnosis are unknown. We aimed to develop a model for quantifying the impact of diagnosing CTEPH earlier on survival, quality-adjusted life years (QALYs) and healthcare costs.

Material and methods: A Markov model was developed to estimate lifelong outcomes, depending on the degree of delay. Data on survival and quality of life were obtained from published literature. Hospital costs were assessed from patient records (n=498) at the Amsterdam UMC - VUmc, which is a Dutch CTEPH referral center. Medication costs were based on a mix of standard medication regimens.

Results: For 63-year-old CTEPH patients with a 14 months diagnostic delay of CTEPH (median age and delay of patients in the European CTEPH Registry), lifelong healthcare costs were estimated at €117,100 for a mix of treatment options. In a hypothetical scenario of maximal reduction of current delay, improved survival was estimated at a gain of 3.01 life years and 2.04 QALYs. The associated cost increase was €44,654, of which 87% was due to prolonged medication use. This accounts for an incremental cost-utility ratio of €21,900/QALY.

Conclusion: Our constructed model based on the Dutch healthcare setting demonstrates a substantial health gain when CTEPH is diagnosed earlier. According to Dutch health-economic standards, additional costs remain below the deemed acceptable limit of €50,000/QALY for the particular disease burden. This model can be used for evaluating cost-effectiveness of diagnostic strategies aimed at reducing the diagnostic delay.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a debilitating and potentially life-threating condition which is mostly established as a consequence of acute pulmonary embolism (PE).[1-4]. The steady progression of symptoms, including exertional dyspnea, negatively impacts functional status of CTEPH patients as well as the daily lives of their relatives.[5,6] Appropriate treatment modalities comprise pulmonary endarterectomy, balloon pulmonary angiography and pulmonary arterial hypertension (PAH) targeted therapy.

It has been demonstrated that CTEPH is often diagnosed after a considerable diagnostic delay that contributes to higher pulmonary artery pressures at diagnosis and impaired survival.[7-9] Nevertheless, strategies for earlier diagnosing CTEPH are usually not part of routine care for patients diagnosed with PE although persistent symptoms merit follow-up according to existing guidelines. Recently, the 2019 ESC/ERS Guidelines on PE have proposed an echocardiography-based algorithm in patients with persistent dyspnoea or predisposing conditions for CTEPH 3-6 months after PE.[10] Alternatively, the InShape II algorithm is aimed at early exclusion of CTEPH following an acute PE while limiting the number of required echocardiograms, and has been evaluated in a prospective management study.[11-14] The diagnostic yield of strategies for early CTEPH diagnosis remains unclear as prospective management studies are currently lacking.[15] Moreover, the economic consequences of clinical algorithms for early CTEPH diagnosis after acute PE are unknown, even though such knowledge is urgently needed to guide policy makers to decide on optimal and cost-effective follow-up after acute PE.

In this study, a model for evaluation of cost-effectiveness depending on the degree of diagnostic delay of CTEPH was constructed and presented allowing evaluation of lifelong outcomes in CTEPH patients. The use of this model is illustrated by comparing two scenarios: the current diagnostic delay as reported in the International CTEPH registry and a hypothetical scenario of no delay.[7,16]

METHODS

Cost-effectiveness model

A Markov model was developed to predict lifelong outcomes of CTEPH patients, depending on the (hypothetical) degree of diagnostic delay for a CTEPH diagnosis (**Figure 1**). Four types of treatment groups were taken into account, i.e. pulmonary endarterectomy (PEA), balloon pulmonary angioplasty (BPA), pulmonary arterial hypertension (PAH) targeted therapy and a no-treatment group. For each separate treatment group, life expectancy, quality of life and healthcare costs were estimated,

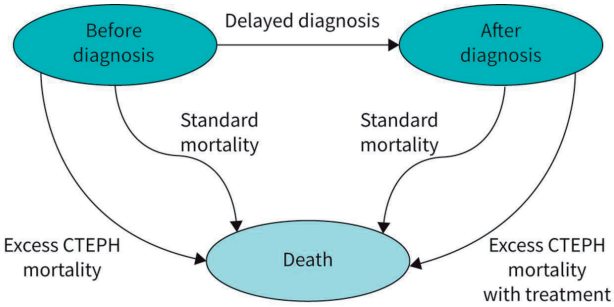

Figure 1: States and transitions in the Markov model
Note: The state 'After diagnosis' is also split up by type of treatment (pulmonary endarterectomy, balloon pulmonary angioplasty, pulmonary arterial hypertension targeted and no treatment). Utilities and costs are modelled depending on health state, treatment and time since diagnosis.

distinguishing the pre- and post-treatment situation if appropriate, as described in more detail below. The Markov model was built up from weekly cycles with a 100-year time horizon, thus evaluating life-long outcome for a predetermined delay range of 0 to 3.0 years until diagnosis. Consistent with Dutch guidelines for economic evaluations in health care, long-term outcomes were given less weight by discounting costs at 4.0% and QALYs at 1.5%.[17] Subsequently, a cost-utility analysis was performed in which the incremental cost-utility ratio (ICUR) was calculated as follows:

$$ICUR = \frac{costs_{no\ delay} - costs_{current}}{QALY_{no\ delay} - QALY_{current}},$$

which relates the change in costs to the change in outcome in terms of QALYs.

To reflect the current care situation, the base-case model assesses a "typical CTEPH patient" who is male in 50% of cases, has a fixed age at diagnosis of 63 years, and a fixed diagnostic delay of 1.2 years in accordance with the International Prospective CTEPH Registry comprising 27 European centers.[7] In this base case grounded on a Dutch healthcare perspective, we have assumed a 60% proportion of cases undergoing PEA, whereas performing BPA was set at 15%.[7,18,19] The PAH targeted therapy group comprised 15% of total, and the remaining 10% received no treatment.[7,18]

Data on life expectancy

All-cause mortality rates after a CTEPH diagnosis were derived from published literature. Data for the PEA, PAH targeted therapy and no-treatment groups were based on the International Prospective CTEPH Registry comprising patients diagnosed with CTEPH between 2007 and 2009, i.e. before the BPA era.[7,14,16] Survival data for patients treated with BPA were derived from the French Pulmonary Hypertension Network Registry, whom were diagnosed between 2013 and 2016.[20] Given the absence of data on life expectancy

in the period before CTEPH patients have been diagnosed correctly ('survival during the diagnostic delay'), survival before diagnosis for all treatment groups was assumed to coincide with survival of the untreated patient group.[7] Excess CTEPH mortality was modelled by subtracting standard Dutch mortality from the mortality reported in these studies, then fitting a two-group mixed-exponential model and extrapolating that model for 10 years.[21] In addition, non-CTEPH mortality was modelled by standard Dutch life-tables obtained from the 'Central Agency for Statistics' (www.cbs.nl, accessed at 1st February 2021).[22]

Data on health-related quality of life

Utility values based on the EuroQol five dimensions questionnaire (EQ-5D) and the Short Form Health (SF-36) Survey retrieved from published literature were used in the model to determine quality-adjusted life expectancy (**Table 1**). Pre-treatment utility of patients in the PEA and PAH targeted therapy groups were based on the value of CTEPH patients before undergoing a PEA approximating an equivalent baseline situation.[23] For the BPA group, comparable pre-treatment utility values were available.[24] Post-treatment values were incorporated in the model for each particular group to best match potential changes in quality of life.[5,23-25] We assumed a stable utility for the no-treatment group equal to the pre-treatment value of the PEA group. Utility values derived from SF-36 questionnaire were converted to EQ-5D values for all treatment groups following the method reported by Rowen et al.[26]

Table 1: EQ-5D utility values for each health state in the Markov model

Utilities	PEA group	BPA group	PAH targeted therapy group	No-treatment group
Pre-treatment	0.504 [23] *	0.504 [23] *	0.504 [23] *	0.504 [23] *
Post-treatment	0.743 [23,25] *	0.705 [24] *	0.73 [5]	0.504 [#]

Note:

* After transforming the known utility values derived from SF-36 questionnaire to estimated EuroQol five dimensions (EQ-5D) values following the method reported by Rowen et al. [26].

[#] Identical to pre-treatment utility in PEA group.

Estimation of hospital, intervention and medication costs

Focusing on the Dutch healthcare setting, healthcare use was retrospectively assessed for all CTEPH patients diagnosed by right heart catheterization (n=498) between January 2012 and January 2019 at the VU Medical Center, which is a Dutch referral center for CTEPH. CTEPH-related hospital and intervention costs were assessed from a third party payer perspective, using prices reported by the 'Dutch Healthcare Authority' (www.opendisdata.nl, accessed at 1st February 2021).[27] These prices include costs of hospital and medical specialist care, and are established by agreements between health insurers

and healthcare providers. Medication costs of PAH targeted therapy were derived from 'Zorginstituut Nederland' (www.medicijnkosten.nl, accessed at 1st February 2021) averaging a mix of standard medication regimens (**Appendix A**).[28] Costs in the PEA group comprised those of one-off surgical intervention and outpatient care. In addition, 25% of patients were assumed to benefit from lifelong PAH targeted therapy because of residual PH after surgery (modelled from one year after diagnosis). Residual PH has been described to occur in 5-35% of patients three months after their PEA.[29-34] Although the most recent study has observed that residual PH prompted subsequent PAH targeted therapy in only a quarter, we have conservatively estimated that all patients with residual PH received a combined therapeutic approach.[30]

Expenses in the BPA group consisted of costs for endovascular interventions, outpatient care, bridging therapy (modelled from 0.5 year after diagnosis) and in 60% lifelong PAH targeted therapy.[20] In the patient group treated with PAH targeted therapy only, lifelong PAH targeted therapy and outpatient care were taken into account. Double therapy (riociguat and an endothelin receptor blocker) was considered relevant in 8% of patients based on available literature, healthcare use in the VU Medical Center and expert opinion.[35,36] For patients in the no-treatment group, only outpatient care was included. Observed hospital and medication costs over time, weighted for the four treatment groups, are plotted in **Figure 2**, and all seem to stabilize after three to five years after diagnosis. Costs are reported in euros, at Dutch price level 2020 (where €1 ≈ USD 1.27 according to purchasing power parity).

Concerning early surveillance, we assumed that 33 echocardiograms are required per CTEPH case given the CTEPH incidence of approximately 3%. Therefore, screening program costs were estimated to be €4125,- per CTEPH case, based on a maximum price of €125 per echocardiography.

Sensitivity analyses

A range of univariate sensitivity analyses were performed to assess the robustness of the model to variations of chosen parameter values. Age at diagnosis was varied over the reported age range derived from the International Prospective CTEPH Registry (51 to 72 year, base case was 63). We analysed the impact of the duration of excess CTEPH mortality (base case 10 years) by varying it from a shorter 4-year duration to a lifetime duration (modelled as 99 years). Survival during delay is evaluated for an alternative more optimistic scenario, i.e. by ignoring the observed initial high mortality in the first 6 months of the no-treatment group (better survival versus base case survival). Given the variations in treatment choices worldwide and the emerging role of BPA as alternative interventional treatment for CTEPH, the proportion of PEA and BPA treatment was varied (ratio 75% vs. 45% to 0% vs. 30%, respectively). Moreover, the percentage of patients in the BPA group using PAH targeted medication is now diverged from 10% to 100%.[7,20,37,38]

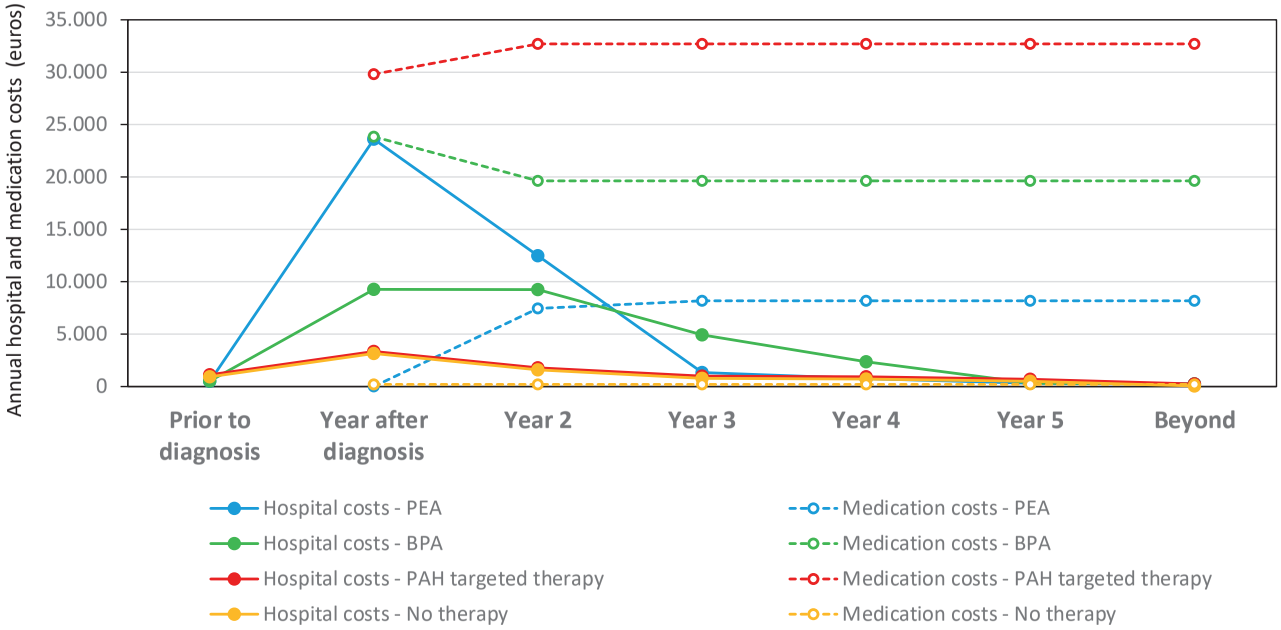

Figure 2: Average healthcare expenses per treatment group in years before and after CTEPH diagnosis for the base case analysis, distinguishing hospital and medication costs

Abbreviations: PEA, pulmonary endarterectomy; BPA, balloon pulmonary angiography; PAH, pulmonary arterial hypertension.

Since our model does not include diagnostic costs of pursuing an earlier diagnosis, fictitious costs of a potential strategy aimed at reducing the diagnostic delay were here taken into account ranging from the base case of €0 to €20,000. The change in utility due to treatment, the medication costs and the hospital costs were increased and decreased by 50%, and the discount rates for costs and QALYs were varied from 0% to 5% (base case was 4.0% and 1.5%, respectively).

RESULTS

Survival analysis and QALYs

For CTEPH patients diagnosed at an age of 63 years in the base-case analysis, representing current care, our model estimates a life expectancy of 14.3 years and 8.42 QALYs (**Table 2**). The health benefit of a hypothetically optimal situation of no delay between first symptoms and CTEPH diagnosis is represented by an estimated gain in life expectancy of 3.01 years with an associated increase of 2.04 QALYs. Of this increase in QALYs, 0.28 is due to improvement in quality of life during delay, and the remaining 1.76 because of improved life expectancy. The estimated 2-year survival after the first onset of symptoms would increase from 74% for the current delay to 88% without diagnostic delay. **Figure 3** shows the estimated (quality-adjusted) life years, depending on the duration of the delay.

Table 2: Estimated average lifelong healthcare costs and effectiveness

	Base case (i.e. current care)	No delay	Difference
Screening program costs	-	€4125	-
Hospital costs	€21,493	€27,472	€5979
Medication costs (weighted per treatment group)			
PEA (60%)	€40,297	€55,094	€14,797
BPA (15%)	€27,636	€37,619	€9983
PAH targeted therapy (15%)	€27,679	€37,449	€9770
No treatment (5%)	-	-	-
Total lifelong costs	€117,105	€161,759	€ 44,654
Life expectancy (years)	14.3 yr	17.3 yr	3.01 yr
QALYs (years)	8.42 yr	10.45 yr	2.04 yr
Incremental cost-effectiveness ratio	€ 14,853 per life year gained		
Incremental cost-utility ratio	€ 21,910 per QALY gained		

Abbreviations: PEA, pulmonary endarterectomy; BPA, balloon pulmonary angioplasty; PAH, pulmonary arterial hypertension; QALY, quality-adjusted life year.

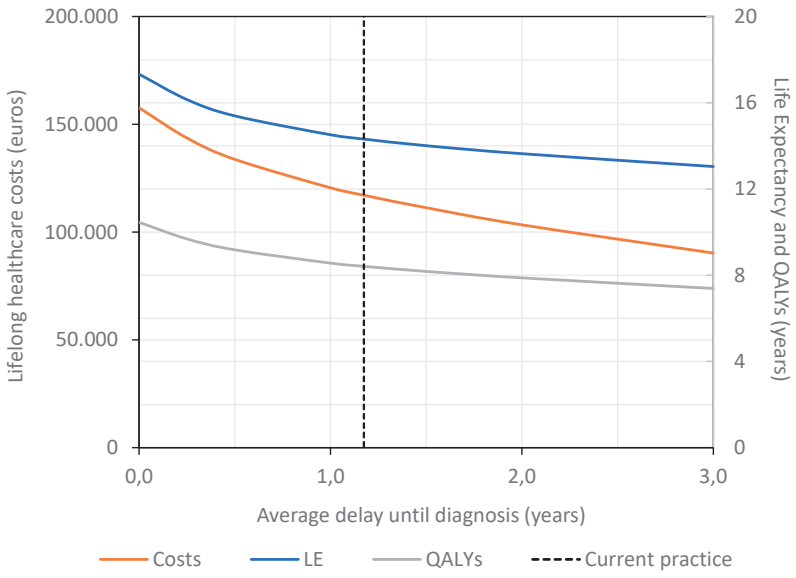

Figure 3: Estimated life expectancy, QALYs and lifelong healthcare costs plotted against diagnostic delay of CTEPH

Abbreviations: LE, life expectancy; QALY, quality-adjusted life year.

Costs and cost-effectiveness analysis

Total lifelong healthcare costs are estimated at €117,105 in the base case for a mix of treatment options (**Table 2**). Reducing the delay from the base case 1.2 years to nil, the model predicts that these total costs would increase to €161,759. This excess in costs of €44,654 represent an increase in healthcare use, of which €38,675 (87%) is attributable to costs of medication use. The ICUR (i.e. costs per QALY gained) was €21,910 per QALY.

In a plausible situation of decreasing the current delay to 0.5 year, estimated life expectancy and QALYs would increase with 1.08 and 0.76 years, respectively, compared to current situation. This profit is achieved at the expense of total additional costs with an ICUR of €27,199 (**Figure 3**).

Sensitivity analyses

The sensitivity analyses show that costs are most affected by the difference in overall medication costs, rather than by hospital costs (**Figure 4**), as medication forms the largest share (83%) of the total costs. Increasing these medication costs by 50% increases the estimated ICUR to €30,400/QALY. Assuming a higher proportion of patients in the BPA group treated with medical therapy could increase the ICUR to €25,000/QALY. A more equal ratio of PEA to BPA treatments affects the ICUR even more since this would lead to a greater increase in medication use. Better survival during the delay resulted in

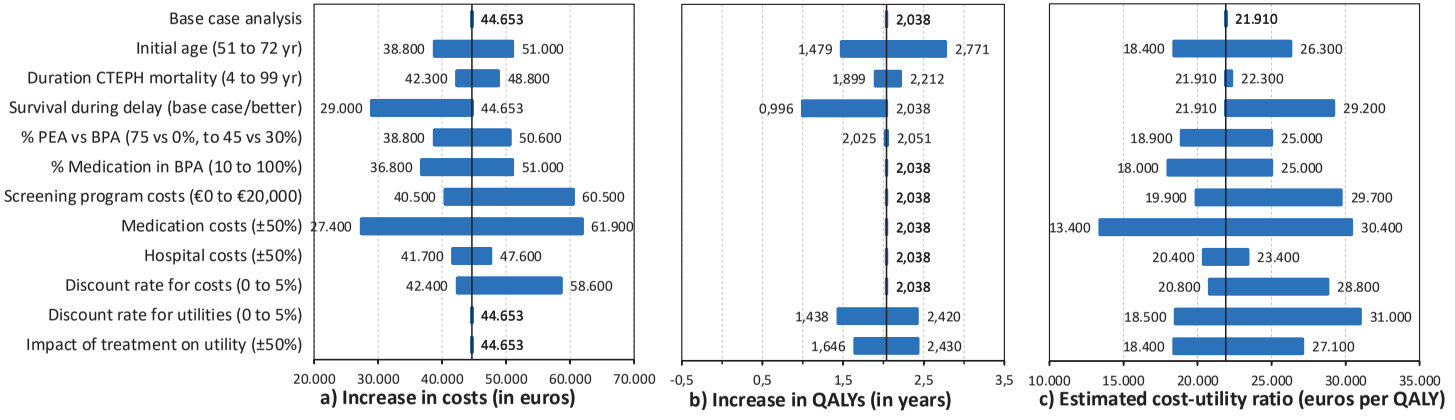

Figure 4: Tornado diagram showing the impact of maximal reduction of delay on costs (panel a), QALYs (panel b) and costs-per-QALY (panel c), depending on model assumptions (compared to current delay)

Abbreviations: PEA, pulmonary endarterectomy; BPA, balloon pulmonary angiography; QALY, quality-adjusted life year.

a smaller QALY difference and an ICUR of €29,200/QALY. If the excess CTEPH mortality would last a lifetime, this would only have a limited impact on both healthcare costs and QALYs. A younger age at diagnosis is beneficial for the life expectancy, lowering the ICUR to €18,400/QALY. Moreover, if we model a more positive impact of treatment on utility, the ICUR would also decrease. If we would increase the screening program costs associated with a fictitious strategy to establish the reduced delay to €20,000, that would increase the ICUR to €29,700/QALY. Finally, if discount rates of costs and utilities would have a greater influence, the estimated ICUR would increase at most to €31,000/QALY.

DISCUSSION

Our study presents the first Markov model for quantifying the impact of reducing the diagnostic delay of CTEPH on lifelong costs and QALYs without shaping strategies aimed at earlier CTEPH diagnosis itself. Considering the "typical CTEPH patient", a maximal reduction of delay compared to the current diagnostic delay of 1.2 years was shown to result in 2.04 more QALYs against an ICUR of €21,900 per QALY. The additional healthcare expenses primarily consisted of a substantial increase in medication rather than hospital costs: forwarding surgery does not alter the associated costs, whereas forwarding the start of medication treatment does. By performing sensitivity analyses on key parameters of the model, ICUR was demonstrated to be at most €31,000 per QALY. This compares favorably to the willingness-to-pay threshold of €50,000 per QALY that applies to CTEPH care according to Dutch health-economic standards [39].

This cost-effectiveness analysis provides relevant information on the potential value of strategies for earlier diagnosis of CTEPH, which has been addressed in the recommendations on follow-up of patients with acute PE in the 2019 ESC/ERS Guidelines.[10] Although CTEPH greatly affects quality of life and is potentially curable, only few screening approaches have been studied.[10,11,40,41] Of note, we deliberately have constructed the base-case model without regard to the costs of algorithms for earlier CTEPH diagnosis, so the estimated cost-effectiveness ratio applies if -hypothetically- the decrease in delay would be realized without additional costs. Diagnostic strategies to actually reduce delay may require additional costs not yet included in our base-case model, depending on the nature of the strategies and the test characteristics of the chosen clinical algorithm, i.e. both costs associated with the strategy itself and those with false positive and false negative test results. However, if signs of CTEPH are sought for as part of state-of-the-art outpatient care in the course after an acute PE, additional diagnostic costs may even be negligible. Based on our sensitivity analyses, we argue that

a screening approach that reduces the diagnostic delay to nil is allowed to comprise up to €20,000 per patient.

Our model estimates that 2-year survival improves by reducing the diagnostic delay of CTEPH, suggesting that premature deaths from undiagnosed patients can be prevented. This was shown to be associated with higher costs, which may seem contradicting. These higher costs are caused by an increase in PAH targeted medication use. In view of the societal context this excess in costs is counterbalanced by a presumable cost reduction due to increased productivity. Although this has been illustrated by some studies among VTE patients, we have disregarded this in our analysis since no data specifically on labor productivity among CTEPH patients has been published.[42,43] Of note, the impact of disease burden on caregivers has not been taken into account either, and might further favor health benefits.[44]

We acknowledge that our model is based on a Dutch perspective, and that patient characteristics and standard clinical practice may differ internationally. Although Western countries and Japan all recommend PEA as the first-line treatment in patients with operable CTEPH[45-47], it has been argued that BPA treatment in Japan results in better outcomes compared to Western countries.[2,48] In fact, BPA is an emerging treatment modality worldwide which will likely influence the cost-effectiveness analysis over time towards increased costs.[2] As such, after increasing the proportion of patients treated with BPA in our sensitivity analysis to 30% while lowering the proportion of PEA treatment to 45%, we found a marginal increase in ICUR of €3091. Besides, medication costs in particular have a great impact on the ICUR and may vary between regions. Even if these costs would be 50% higher than in the base case analysis, the ICUR would still remain below €30,400 per QALY, which is deemed highly acceptable for pursuing delay reduction in CTEPH patients. Our data needs to be confirmed for health care systems outside of the Netherlands, and will also need to be complemented, in the future, by prospective data showing the impact of early diagnosis on quality of life. Also, in future cost-effectiveness studies, data on survival, adverse events and corresponding costs from RCTs comparing different treatment strategies for CTEPH are required to elucidate the most optimal treatment strategy.

Our model has limitations, firstly because we had to make several modelling assumptions. For instance, data on quality of life and non-CTEPH related healthcare costs were not sufficiently available in published data for all specific treatment groups. Also, our model was constructed for a "typical CTEPH patient", relying on average parameter values. Our analysis does not provide sufficient information on the impact of earlier diagnosis in specific subgroups. Second, costs related to BPA are inherent to the number of interventional sessions, which may vary widely. A median of 4 sessions per patient was reported in a meta-analysis including 17 studies on BPA, however, with a wide range of 1.8 to 18.6 sessions.[49] In Dutch CTEPH expert centers, a mean of 4.5

(SD 13) BPA sessions per patient are carried out, which likely applies to input data of the model.[50] Also, lifelong anticoagulant therapy is an essential part of treatment in all CTEPH patients, which will be initiated earlier if CTEPH is diagnosed earlier. However, a large proportion of PE patients in whom CTEPH is ruled out will also have these expenses related to increased anticoagulation prescriptions, and, thus, this will likely result in only a limited increase in total costs. Third, in our analysis, gains in survival especially result from curtailing the assumed high mortality before diagnosis. Although many studies have reported mortality data on CTEPH patients, the mortality rate among CTEPH patients who are not yet diagnosed remains unknown. Moreover, it has been demonstrated that patients with the highest delays are associated with worse pulmonary artery pressures and higher mortality.[9] As such, given the lack of data we might have underestimated the positive impact of an earlier diagnosis on progression of disease, and thus the mortality during delay. In contrast, the degree of delay was shown not to affect operability -i.e. treatment choice-, nor NYHA classification which strongly relates to quality of life.[9] Fourth, the survival data were extracted from 2 different studies performed in different years, i.e. the International CTEPH Registry and the French Pulmonary Hypertension Network Registry, which may not be fully comparable.[16,20] Of note, the decision to use both mortality rates without adjustment in our model is supported by several similarities between the study cohorts: age, gender and median diagnostic delay. We may even have underestimated the survival in the different treatment groups given the increased experience with PEA and BPA and its technical improvements in the years after publication of the aforementioned studies. Finally, excess CTEPH mortality was assumed to end 10 years after the diagnosis. Large studies report data of up to 4 years only, however, in our model we observed a stabilized survival curve after 10 year. This pattern is supported by a recent study including 100 operated CTEPH patients which were followed up for a median of 7.2 and maximum of 22 years.[51] A limited impact of longer CTEPH excess mortality has been confirmed in our sensitivity analysis.

In conclusion, this cost-effectiveness analysis based on a Dutch healthcare perspective is the first major effort to start focusing on quantitative assessment of the economic burden of reducing the diagnostic delay of CTEPH versus the benefits for health care systems, and - thus - for society as a whole. Our results indicate beneficial lifelong patient-relevant outcomes against acceptable additional costs after accomplishing an earlier CTEPH diagnosis. Our model can be used for evaluation of the cost-effectiveness of strategies for earlier CTEPH diagnosis, by taking into account the costs associated with reducing the diagnostic delay.

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Appendix A: PAH targeted therapy related costs in the base-case analysis

Therapy type	Dosage	Price per person per year	Weighting factor according to proportional use
Riociguat	3 dd 1-2.5 mg	€ 34,055	0.4
Macitentan	1 dd 10 mg	€ 38,121	0.4
Sildenafil	3 dd 20 mg	€ 4,679	0.2
Weighted price for the mix of treatment groups *	-	**€ 32,693**	-

Note: Assumptions made concerning use of PAH targeted therapy: 1) PEA group: 25% of cases receive lifelong therapy two years after diagnosis[30-34]; 2) BPA group: 0.5 year of therapy in all patients (until first endovascular intervention), as well as in 60% of cases lifelong therapy; 3) PAH targeted therapy group: 100% of cases receive lifelong therapy; 4) no-treatment group: no therapy. Treatment with intravenous prostacyclin analogs has been left out of the cost-effectiveness model given the rare prescriptions in this setting. All costs were determined in euros for the year 2020.

* Including double therapy (riociguat and macitentan) in 8% of patients after 2 years of treatment based on available literature, healthcare use in the VU Medical Center, and expert opinion.[35,36]