CAMPHOR score

Newnham, Michael; Bunclark, Katherine ; Abraham, Nisha ; Ali, Samantha ; Amaral-Almeida, Liliana ; Cannon, John E ; Doughty, Natalie ; Ng, Choo; Ponnaberanam, Anie ; Sheares, Karen; Speed, Nicola ; Taboada, Dolores; Toshner, Mark; Tsui, Steven; Jenkins, David P ; Pepke-Zaba, Joanna

DOI:
10.1183/13993003.02096-2019

Title page

Full Title: CAMPHOR score: patient-reported outcomes are improved by pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension (CTEPH)

Authors: Michael Newnham,[1,2,3] Katherine Bunclark,[2] Nisha Abraham,[2] Samantha Ali,[2] Liliana Amaral-Almeida,[2] John E Cannon,[2] Natalie Doughty,[2] Choo Ng,[2] Anie Ponnaberanam,[2] Karen Sheares,[2] Nicola Speed,[2] Dolores Taboada,[2] Mark Toshner,[2,3] Steven Tsui,[2] David P Jenkins,[2] Joanna Pepke-Zaba[2]

Affiliations:

[1] University of Birmingham, Institute of Applied Health Research, Birmingham, UK

[2] Royal Papworth Hospital, Cambridge, UK

[3] University of Cambridge, Department of Medicine, Cambridge, UK

Corresponding author:

Dr Joanna Pepke-Zaba, Pulmonary Vascular Disease Unit, Royal Papworth Hospital NHS Foundation Trust, Papworth Road, Cambridge Biomedical Campus, Cambridge, CB2 0AY

+44 (0) 1223 639697

joanna.pepke-zaba@nhs.net

Take-home message:

Patients with CTEPH report significant improvement in patient-reported CAMPHOR scores after pulmonary endarterectomy compared with patients not operated on, but those with clinically significant residual pulmonary hypertension have less benefit.

Journal:

European Respiratory Journal – original research article

Main text, 2916 (max. 3000)

Abstract, 248 (max. 250)

Figures/Tables, 3/4 (max. 8 total)

References 38 (max. 40)

Abstract

Background

Pulmonary endarterectomy (PEA) is the recommended treatment for eligible patients with chronic thromboembolic pulmonary hypertension (CTEPH). The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) score is an internationally-validated patient-reported outcome (PRO) measure for CTEPH. It assesses 3 domains: activity, quality of life (QoL) and symptoms. We assessed PROs in patients with CTEPH undergoing PEA.

Methods

This retrospective observational study of consecutive CTEPH patients undergoing PEA at the UK national PEA centre between 2006 and 2017 assessed change in CAMPHOR score from baseline (pre-PEA) until up to 5 years post-PEA. CAMPHOR scores were compared between (i) those with and without clinically significant residual PH and (ii) those undergoing PEA and propensity-matched CTEPH patients who were not operated on. The minimally clinically important difference (MCID) was calculated using an anchor-based method.

Results

Of 1324 CTEPH patients who underwent PEA, 1053 (80%) had a CAMPHOR score recorded pre-PEA, 934 (71%) within a year of PEA and 784 (60%) had both. There were significant improvements between pre- and post-PEA in all three CAMPHOR domains (median ± interquartile range: activity, −5±7; QoL, −4±8; and symptoms, −7±8; p<0.0001, all). Improvements in CAMPHOR score were greater and more sustained in those without clinically significant residual PH. CTEPH patients undergoing PEA had better CAMPHOR scores than those not operated on. The MCID in CAMPHOR score was -3±5 for activity, -4±7 for QoL, and -6±7 for symptoms.

Conclusions

PROs are markedly improved by PEA in patients with CTEPH, more so in those without clinically significant residual PH.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is an infrequent but important complication of pulmonary embolism. Organisation and fibrosis of thrombotic material leads to obstruction of proximal pulmonary arteries which, together with a secondary small vessel vasculopathy, results in pulmonary hypertension [1]. CTEPH can lead to debilitating symptoms and functional impairment that affects quality of life (QoL) [2]. CTEPH patients who are eligible for surgery should be offered pulmonary endarterectomy (PEA), which involves removing obstructive thromboembolic material from surgically accessible pulmonary arteries [3]. PEA leads to improved symptoms and better survival in CTEPH [4, 5]. However, up to half of patients will have residual pulmonary hypertension (PH) after PEA that is associated with lower post-operative 6-minute walk distance (6MWD) and worse World Health Organization functional class (WHO FC) [6, 7]. Treatment options for residual PH may include licenced drug therapy or balloon pulmonary angioplasty (BPA) [8-11].

Since 2008, the World Symposium on Pulmonary Hypertension (WSPH) has recommended including patient-reported outcome (PRO) measures as secondary endpoints in clinical PH trials to assess health-related quality of life (HRQoL) [12]. However, PROs remain an underutilised outcome measure in clinical trials despite their relevance to patients [2]. This is partly because changes in PROs have often been more modest than other clinical trial endpoints, such as 6MWD and pulmonary haemodynamics [13-15]. There has also been a reliance on generic PRO measures in PH clinical trials that may lack sensitivity in PH including CTEPH [16].

Several HRQoL measures have been assessed in CTEPH including generic (e.g. 36-Item Short Form Survey (SF-36) [17-19] and EuroQol- 5 Dimension (EQ-5D) [20, 21]) and PH specific scores (EmPHasis-10 [22] and Living with Pulmonary Hypertension questionnaire [LPH] [23]). Disease-specific PROs for PH/CTEPH may be more effective than generic measures in assessing HRQoL and predicting clinical deterioration [13-15]. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) score is the only PRO that was specifically developed in a cohort that included CTEPH and was validated in an adequate sample size [24]. It assesses 3 domains: activity, QoL and symptoms and is an independent predictor of clinical

deterioration in CTEPH [14]. The minimally clinical important difference (MCID) is the smallest difference in outcome score that patients perceive as important and has not yet been defined for CAMPHOR [2].

The traditional clinical outcome measures in PH and CTEPH (6MWD, WHO FC, pulmonary haemodynamics and mortality) have several limitations. Survival following PEA has substantially improved, with in-hospital mortality <2.5% in some expert centres, limiting its usage as a future outcome measure [6]. Clinical symptoms may be disproportional to resting pulmonary haemodynamics, which is exemplified by chronic thromboembolic disease with an mPAP < 25mmHg [25]. Finally, functional outcome measures in PH may not correlate with meaningful outcomes such as hospitalisation, initiation of rescue therapy and death [26].

Treatment options for managing CTEPH have broadened to include PEA, BPA, riociguat [3, 8, 11], and medical therapies for pulmonary arterial hypertension (PAH) used off-label [4, 27, 28]. Current and future clinical trials will assess combination treatments particularly for residual PH post-PEA. Therefore, there is an increasing need for robust outcome measures that patients deem important including PROs in CTEPH clinical trials.

The aims of this study were to (i) investigate the change in CAMPHOR score in a large cohort of CTEPH patients undergoing PEA, (ii) determine whether this varies in those with and without clinically significant residual pulmonary hypertension post-PEA, (iii) compare CAMPHOR scores in those undergoing PEA with CTEPH patients not operated on, and (iv) determine the minimally clinically important difference (MCID) for CAMPHOR score in CTEPH.

Methods

Study participants

This retrospective study was approved by the Health Research Authority, UK (IRAS project ID: 238805). Consecutive adult patients with CTEPH who underwent PEA at the national PEA centre (Royal Papworth Hospital, UK) from January 2006 to June 2017 were eligible. Study inclusion/exclusion criteria are summarised in **supplementary figure S1**. CTEPH was diagnosed according to international guidelines [29] and PEA was performed as previously described [5, 29]. Following PEA, patients were reviewed at 6 and 12 months at either Royal Papworth Hospital or their local specialist PH centre and annually thereafter for at least 5 years. Data were prospectively collected using a dedicated PH database. Clinical data (not including survival) and CAMPHOR scores were only available for patients at the time of review at Royal Papworth Hospital, Cambridge, UK.

Patient characteristics at baseline and CAMPHOR score

Baseline data for all patients were recorded at the time of diagnostic right heart catheterisation and pre-operatively for patients with CTEPH undergoing PEA. This included CAMPHOR score, demographics, co-morbidities, pulmonary vasodilator therapy, WHO FC, 6MWD, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and haemodynamics. Operative data included type of surgical disease (Jamieson classification [30]), concomitant surgery, complications and length of stay. Outcome data, including CAMPHOR score, were recorded within 1 year of PEA. The CAMPHOR questionnaire assesses symptoms (25 questions), activity (15 questions) and QoL (25 questions). It takes 8-10 minutes to complete and is negatively weighted with higher scores indicating poorer outcome. Symptoms and QoL are both scored out of 25, and activity out of 30.

Clinically significant residual PH post-PEA

To assess the effect of residual PH on longitudinal CAMPHOR score, patients were dichotomised into those with (mPAP ≥30 mmHg) and without (mPAP <30 mmHg) clinically significant residual PH post-PEA and this threshold has been proposed in previous studies [6, 7]. This relationship was further investigated by stratifying the cohort into subgroups (mPAP post-PEA: <25, 25–30, 31–36, 37–42, 43–48 and ≥49

mmHg). Additional analyses were performed by stratifying patients by post-PEA PVR (**supplementary materials**).

CAMPHOR score for operated and not-operated CTEPH

CAMPHOR scores from CTEPH patients undergoing PEA were compared with CTEPH patients who were not operated on between 2005 and 2015 at Royal Papworth Hospital. The groups were propensity matched for baseline CAMPHOR score, mPAP, age, sex and year of diagnosis. Matching was performed using the nearest neighbour method and a ratio of 3:1 (PEA:no-PEA).

Minimally clinically important difference

The MCID in CAMPHOR score was calculated using an anchor-based method. Participants were asked to answer an 'anchor' question that assessed their global change in health status since the last review (7-point scale ranging from 'very much better' to 'very much worse') in addition to completing the CAMPHOR questionnaire. The median change in CAMPHOR score from baseline (pre-PEA) to the first follow-up post-PEA was calculated for each point on this scale. The MCID was defined as the median change in CAMPHOR score associated with a "moderately better" health status change. The MCID was confirmed by statistical distribution methods and additionally by utilising the MCID for 6MWD that has previously been defined for PAH (**supplementary materials**) [31]. Sensitivity analyses were performed in different subsets of operated CTEPH patients to confirm that MCIDs were robust (**supplementary materials**).

Survival analysis

Survival from PEA until a census date of April 2018 was recorded using centralised national records. Multivariable Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals (CIs) and associations were confirmed by multiply imputing missing data (**supplementary materials**). Cox models were checked for proportional hazards assumptions, influential observations, non-linearity.

Statistical analyses

Groups were compared using the Mann-Whitney *U* test for continuous data and the Cochran-Armitage test for WHO FC. A false discovery rate adjusted *p*-value was used to account for multiple testing. Data averages are described as median ± interquartile range (IQR) unless otherwise specified; 95% CIs of the median were calculated using bootstrapping (100 replicates) and the percentile method. Change from baseline (pre-PEA) were calculated as the median of differences. Pearson correlation coefficient described associations between complete pairs of outcomes or CTEPH severity variables including CAMPHOR score. Variables associated with CAMPHOR were assessed using multivariable linear models. Multiple imputation was used for a sensitivity analysis of longitudinal CAMPHOR scores to assess for bias in the complete cases analysis.

Results

In total, 1324 patients with CTEPH underwent PEA and were included in the main analysis. The cohort characteristics are summarised in **table 1**. Of these patients, 1053 (80%) had a CAMPHOR score recorded at baseline (pre-PEA), 934 (71%) at follow-up within a year of PEA and 784 (60%) had scores at both time points. The median ± IQR time to follow-up CAMPHOR score was 139 ± 79 days.

Median ± IQR change from baseline (pre-PEA) to post-PEA follow-up (within 1 year) for the three CAMPHOR sub-scores indicated a significant improvement in all three domains: activity, −5 ± 7; QoL, −4 ± 8; and symptoms, −7 ± 8 (p<0.0001, all; **table 2**). There were also significant improvements in 6MWD, NT-proBNP, WHO FC and haemodynamics (p<0.0001, all; **table 2**). The improvements in CAMPHOR score were sustained for 5 years post-PEA (**figure 1**, **supplementary table S1**). To investigate potential confounding from CTEPH patients with missing pre- and post-PEA CAMPHOR scores, multiple imputation was performed. As the change in CAMPHOR score from baseline in the multiply imputed analysis was consistent with the complete cases analysis there was no significant bias from missingness (**supplementary table S2**).

Clinically significant residual PH post-PEA

Patients were dichotomised into those with (n=369), and those without (n=685) clinically significant residual PH post-PEA. Patient characteristics in these groups are summarised in **supplementary table S3.** There were significant post-operative improvements in CAMPHOR compared with baseline in the no residual PH group (median ± IQR change from baseline: activity, −5 ± 7; QoL, −5 ± 9; symptoms, −8 ± 8; p<0.0001, all) and residual PH group (activity, −4 ± 6; QoL, −3 ± 6; symptoms, −6 ± 7; p<0.0001, all). Patients with no residual PH had greater improvements than those with residual PH (**figure 2a**). Furthermore, the improvements in the no residual PH group were better sustained over 5 years than in those with residual PH, who experienced a worsening trend in CAMPHOR score 2–3 years after PEA (**figure 2a**). When patients were stratified by mPAP or PVR post-PEA, there was a worsening of CAMPHOR scores as mPAP or PVR increased (**figure 2b; supplementary figure S2**).

CAMPHOR score for operated and not-operated CTEPH

There were 198 patients with CTEPH not operated on at Royal Papworth Hospital during 2005–2015. As the PEA and no-PEA CTEPH groups differed in baseline variables, including CAMPHOR score (**supplementary table S4**), propensity matching was performed. This resulted in 132 patients not operated on (no-PEA) matched to 396 patients who underwent PEA. The not operated group was heterogenous and the reasons for not undergoing PEA included: distal, surgically inaccessible disease (n=56), comorbidities (n=31), patient declined the operation (n=19) and other reasons (n=26), including a combination of these factors or limited disease/symptoms. The characteristics of the two groups following propensity matching are summarised in **supplementary table S5**. CAMPHOR scores at follow-up years 1 and 2 were significantly worse in the no-PEA group than in the PEA group (p<0.0001, all domains) (**figure 3**; **supplementary table S5**).

CAMPHOR correlation and association

There was a moderate negative correlation between the change from baseline to 1-year post-PEA in CAMPHOR activity score and 6MWD (Pearson correlation coefficient, −0.4; **supplementary figure S3**). Correlations between the change from baseline to 1 year post-PEA in CAMPHOR score and changes in both WHO FC and haemodynamic parameters were relatively weak. A multivariable linear regression analysis of CAMPHOR domain scores at baseline demonstrated that pre-PEA CAMPHOR score (activity, QoL and symptoms) was associated with age, and the CAMPHOR activity domain was associated with 6MWD, but there was no association with haemodynamics (**supplementary table S6**).

Minimally clinically important difference

The MCID in CAMPHOR scores associated with a moderately better health status change following PEA were: activity (median ± IQR), −3 ± 5; QoL, −4 ± 7; and symptoms, −6 ± 7 (**table 3**). Importantly, the median change in CAMPHOR score from baseline (pre-PEA) to post-PEA follow-up within a year (described above; **figure 1** and **supplementary table S1**) exceeded these MCID thresholds. The MCIDs were consistent across different subgroups in the sensitivity analyses (**supplementary materials**). The changes in CAMPHOR score at 1 year post PEA among patients with

residual PH (described above; **figure 2** and **supplementary table S2**) exceeded or equalled the MCID threshold for activity and symptoms but not QoL.

Survival

Age was the only variable at baseline (pre-PEA) that was significantly associated with 1 year survival post-PEA (hazard ratio [95% CI]), 1.17 (1.02-1.35) per 5-year age increase (p=0.0288) (**table 4**). The 3 domains of the CAMPHOR score at baseline were not associated with 1 year survival following PEA. The same findings occurred when multiply imputed data were considered with the exception of a nominal association for sex (**supplementary table S7**). Additional survival analyses to investigate if CTEPH patients with greater CAMPHOR improvement post-PEA also had improved long-term survival is presented in the **supplementary materials**.

Discussion

This is the largest study to date of PROs in patients with CTEPH and in patients undergoing PEA. There were significant improvements in the CAMPHOR domains of activity, QoL and symptoms following PEA, and importantly these were sustained for up to 5 years. CTEPH patients with no clinically significant residual PH (mPAP < 30mmHg) had greater improvements in CAMPHOR compared to those with residual PH. CAMPHOR scores were also better in patients who had undergone PEA compared with those who were not operated on. The MCID in each domain of the CAMPHOR score was established as activity −3, QoL −4 and symptoms −6 points.

In contrast to previous findings [32], correlations between CAMPHOR scores and other clinical outcomes (WHO FC, pulmonary haemodynamics) were relatively weak. The only moderate correlation was between an improvement in CAMPHOR activity score and 6MWD. This suggests that improved physiological and functional outcome measures may not translate into improvements deemed important to patients such as QoL. Therefore, the CAMPHOR score provides important additional utility to assessing outcomes for CTEPH patients undergoing PEA.

Previous studies have reported improved PROs following PEA however, they have been limited by reliance on generic PROs, small sample sizes or absence of MCIDs for the PRO tool [18, 33-35]. An advantage of the CAMPHOR score over generic and PH-specific PROs is its development and validation in CTEPH with multiple domains that are specific to CTPEH patients. The present study, in a large cohort of CTEPH patients undergoing PEA demonstrated an improvement in CAMPHOR score that exceeded the defined MCID and was sustained for up to 5 years. Patients with clinically significant PH following PEA had CAMPHOR activity and symptom improvements greater than the MCID. This is consistent with previous smaller studies using generic PROs [18, 34]. However, in the residual PH group the QoL change did not quite exceed the MCID threshold and improvements over 5 years were less sustained. As the improvements in CAMPHOR score following PEA were lower in patients with residual PH, additional treatment modalities including BPA and licenced pulmonary artery vasodilators need consideration in this group [10, 36]. Furthermore, as there was a graduation of worsening CAMPHOR scores with increasing post-PEA

mPAP and PVR, additional treatment modalities following PEA may benefit from a stratified approach.

We have previously reported improved CAMPHOR score in a cohort of CTED patients undergoing PEA and these improvements would exceed the MCID defined in the present study [25]. This confirms that in selected CTED patients, PEA offers significant improvements in PROs including QoL, which is a more meaningful outcome than some traditional measures including haemodynamics. PROs such as CAMPHOR score should be utilised more widely in future studies of CTEPH as recommended by the WSPH [37]. This is particularly relevant in scenarios where more modest improvements in functional, haemodynamic and survival outcome measures are expected, including residual PH post-PEA, CTED and clinical trials of additive and combination therapies in CTEPH.

Patients with CTEPH undergoing PEA had better longitudinal CAMPHOR scores than a propensity matched group of not operated patients. This is consistent with a recent study in CTEPH that reported improved survival in patients undergoing PEA compared to those with operable disease but declining PEA surgery [38]. Our CAMPHOR data further substantiates that PEA is the guideline recommended treatment for patients with CTEPH as it results in improved PROs in addition to the known improved functional, haemodynamic and survival outcomes [4, 5].

This study has a number of strengths including the large sample size, prospective data collection of consecutive patients using a dedicated PH database and is the first study to establish the MCID for the CAMPHOR score in CTEPH. Whilst patients were referred by a number of specialist PH centres, one limitation is that the majority of data included in the study was from a single national PEA centre. This contributed to incomplete longitudinal data for the CAMPHOR score and a different number of patients at each timepoint. This was addressed by multiple imputation that produced results similar to complete case analyses. Another limitation is that the not operated CTEPH group were heterogenous in the reasons that PEA was not undertaken, and the analysis in this group should be considered exploratory. The MCIDs were defined for operated CTEPH patients and may not apply to the not-operated CTEPH cohort. Finally, there was incomplete data on follow-up medications, which limited an

assessment of the effect of pulmonary vasodilator therapy on CAMPHOR score in the operated and not-operated groups.

In conclusion, PROs are markedly improved by PEA in patients with CTEPH, more so in those without clinically significant residual PH or those not operated on. The MCID was established for CTEPH, and PEA resulted in improvements greater than this threshold. This provides a benchmark against which future therapeutic interventions can be assessed and PROs should be utilised more widely in future CTEPH studies.

Funding

Medical writing support was provided by Victoria Atess, PhD (Watermeadow Medical, an Ashfield Company), funded by Actelion Pharmaceuticals Ltd.

Acknowledgements

We would like to thank the patients and staff at all participating pulmonary hypertension centres: Pulmonary Hypertension Centre and Adult Congenital Heart Centre, Royal Brompton Hospital, London, UK; Pulmonary Hypertension Service, Royal Free Hospital, London, UK; Scottish Pulmonary Vascular Unit, Golden Jubilee Hospital, Glasgow, UK; National Pulmonary Hypertension Service, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK; Pulmonary Vascular Disease Unit, Royal Hallamshire Hospital, Sheffield, UK; Northern Pulmonary Vascular Unit, Freeman Hospital, Newcastle, UK.

References

1. Moser KM, Bloor CM. Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension. *Chest* 1993: 103(3): 685-692.

2. Mathai SC, Ghofrani HA, Mayer E, Pepke-Zaba J, Nikkho S, Simonneau G. Quality of life in patients with chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2016: 48(2): 526-537.

3. Kim NH, Delcroix M, Jais X, Madani MM, Matsubara H, Mayer E, Ogo T, Tapson VF, Ghofrani HA, Jenkins DP. Chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2019: 53(1).

4. Delcroix M, Lang I, Pepke-Zaba J, Jansa P, D'Armini AM, Snijder R, Bresser P, Torbicki A, Mellemkjaer S, Lewczuk J, Simkova I, Barbera JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Jais X, Ambroz D, Treacy C, Morsolini M, Jenkins D, Lindner J, Dartevelle P, Mayer E, Simonneau G. Long-Term Outcome of Patients With Chronic Thromboembolic Pulmonary Hypertension: Results From an International Prospective Registry. *Circulation* 2016: 133(9): 859-871.

5. Jenkins D, Madani M, Fadel E, D'Armini AM, Mayer E. Pulmonary endarterectomy in the management of chronic thromboembolic pulmonary hypertension. *European respiratory review : an official journal of the European Respiratory Society* 2017: 26(143).

6. Cannon JE, Su L, Kiely DG, Page K, Toshner M, Swietlik E, Treacy C, Ponnaberanam A, Condliffe R, Sheares K, Taboada D, Dunning J, Tsui S, Ng C, Gopalan D, Screaton N, Elliot C, Gibbs S, Howard L, Corris P, Lordan J, Johnson M, Peacock A, MacKenzie-Ross R, Schreiber B, Coghlan G, Dimopoulos K, Wort SJ, Gaine S, Moledina S, Jenkins DP, Pepke-Zaba J. Dynamic Risk Stratification of Patient Long-Term Outcome After Pulmonary Endarterectomy: Results From the United Kingdom National Cohort. *Circulation* 2016: 133(18): 1761-1771.

7. Freed DH, Thomson BM, Berman M, Tsui SS, Dunning J, Sheares KK, Pepke-Zaba J, Jenkins DP. Survival after pulmonary thromboendarterectomy: effect of residual pulmonary hypertension. *J Thorac Cardiovasc Surg* 2011: 141(2): 383-387.

8. Ghofrani HA, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH, Mayer E, Simonneau G, Wilkins MR, Fritsch A, Neuser D, Weimann G, Wang C, Group C-S. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med* 2013: 369(4): 319-329.

9. Ghofrani HA, Simonneau G, D'Armini AM, Fedullo P, Howard LS, Jais X, Jenkins DP, Jing ZC, Madani MM, Martin N, Mayer E, Papadakis K, Richard D, Kim NH, investigators Ms. Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1): results from the multicentre, phase 2, randomised, double-blind, placebo-controlled study. *Lancet Respir Med* 2017: 5(10): 785-794.

10. Araszkiewicz A, Darocha S, Pietrasik A, Pietura R, Jankiewicz S, Banaszkiewicz M, Slawek-Szmyt S, Biederman A, Mularek-Kubzdela T, Lesiak M, Torbicki A, Kurzyna M. Balloon pulmonary angioplasty for the treatment of residual or recurrent pulmonary hypertension after pulmonary endarterectomy. *Int J Cardiol* 2019: 278: 232-237.

11. Tanabe N, Kawakami T, Satoh T, Matsubara H, Nakanishi N, Ogino H, Tamura Y, Tsujino I, Ogawa A, Sakao S, Nishizaki M, Ishida K, Ichimura Y, Yoshida M, Tatsumi K. Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension: A systematic review. *Respir Investig* 2018: 56(4): 332-341.

12. McGoon MD, Ferrari P, Armstrong I, Denis M, Howard LS, Lowe G, Mehta S, Murakami N, Wong BA. The importance of patient perspectives in pulmonary hypertension. *Eur Respir J* 2019: 53(1).

13. Favoccia C, Kempny A, Yorke J, Armstrong I, Price LC, McCabe C, Harries C, Wort SJ, Dimopoulos K. EmPHasis-10 score for the assessment of quality of life in

various types of pulmonary hypertension and its relation to outcome. *Eur J Prev Cardiol* 2018: 2047487318819161.

14. McCabe C, Bennett M, Doughty N, MacKenzie Ross R, Sharples L, Pepke-Zaba J. Patient-reported outcomes assessed by the CAMPHOR questionnaire predict clinical deterioration in idiopathic pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. *Chest* 2013: 144(2): 522-530.

15. Mehta S, Sastry BKS, Souza R, Torbicki A, Ghofrani HA, Channick RN, Delcroix M, Pulido T, Simonneau G, Wlodarczyk J, Rubin LJ, Jansa P, Hunsche E, Galie N, Perchenet L, Sitbon O. Macitentan Improves Health-Related Quality of Life for Patients With Pulmonary Arterial Hypertension: Results From the Randomized Controlled SERAPHIN Trial. *Chest* 2017: 151(1): 106-118.

16. Twiss J, McKenna S, Ganderton L, Jenkins S, Ben-L'amri M, Gain K, Fowler R, Gabbay E. Psychometric performance of the CAMPHOR and SF-36 in pulmonary hypertension. *BMC Pulm Med* 2013: 13: 45.

17. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992: 30(6): 473-483.

18. Archibald CJ, Auger WR, Fedullo PF, Channick RN, Kerr KM, Jamieson SW, Kapelanski DP, Watt CN, Moser KM. Long-term outcome after pulmonary thromboendarterectomy. *Am J Respir Crit Care Med* 1999: 160(2): 523-528.

19. Kamenskaya O, Klinkova A, Loginova I, Chernyavskiy A, Lomivorotov VV, Karaskov A. Factors affecting the quality of life before and after surgery in patients with chronic thromboembolic pulmonary hypertension. *Qual Life Res* 2018: 27(3): 747-754.

20. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990: 16(3): 199-208.

21. Ivarsson B, Hesselstrand R, Rådegran G, Kjellström B. Health-related quality of life, treatment adherence and psychosocial support in patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension. *Chron Respir Dis* 2019: 16: 1479972318787906-1479972318787906.

22. Yorke J, Corris P, Gaine S, Gibbs JS, Kiely DG, Harries C, Pollock V, Armstrong I. emPHasis-10: development of a health-related quality of life measure in pulmonary hypertension. *Eur Respir J* 2014: 43(4): 1106-1113.

23. Bonner N, Abetz L, Meunier J, Sikirica M, Mathai SC. Development and validation of the living with pulmonary hypertension questionnaire in pulmonary arterial hypertension patients. *Health Qual Life Outcomes* 2013: 11: 161.

24. McKenna SP, Doughty N, Meads DM, Doward LC, Pepke-Zaba J. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR): a measure of health-related quality of life and quality of life for patients with pulmonary hypertension. *Qual Life Res* 2006: 15(1): 103-115.

25. Taboada D, Pepke-Zaba J, Jenkins DP, Berman M, Treacy CM, Cannon JE, Toshner M, Dunning JJ, Ng C, Tsui SS, Sheares KK. Outcome of pulmonary endarterectomy in symptomatic chronic thromboembolic disease. *Eur Respir J* 2014: 44(6): 1635-1645.

26. Sitbon O, Gomberg-Maitland M, Granton J, Lewis MI, Mathai SC, Rainisio M, Stockbridge NL, Wilkins MR, Zamanian RT, Rubin LJ. Clinical trial design and new therapies for pulmonary arterial hypertension. *Eur Respir J* 2019: 53(1).

27. Pepke-Zaba J, Jais X, Channick R. Medical Therapy in Chronic Thromboembolic Pulmonary Hypertension. *Ann Am Thorac Soc* 2016: 13 Suppl 3: S248-254.

28. Charalampopoulos A, Gibbs JS, Davies RJ, Gin-Sing W, Murphy K, Sheares KK, Pepke-Zaba J, Jenkins DP, Howard LS. Exercise physiological responses to

drug treatments in chronic thromboembolic pulmonary hypertension. *J Appl Physiol (1985)* 2016: 121(3): 623-628.

29. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016: 37(1): 67-119.

30. Thistlethwaite PA, Mo M, Madani MM, Deutsch R, Blanchard D, Kapelanski DP, Jamieson SW. Operative classification of thromboembolic disease determines outcome after pulmonary endarterectomy. *J Thorac Cardiovasc Surg* 2002: 124(6): 1203-1211.

31. Mathai S, Puhan M, Lam D, Wise R. The minimal important difference in the 6-minute walk test for patients with pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2012: 186(5): 428-33.

32. Reis A, Santos M, Vicente M, Furtado I, Cruz C, Melo A, Carvalho L, Goncalves F, Sa-Couto P, Almeida L. Health-Related Quality of Life in Pulmonary Hypertension and Its Clinical Correlates: A Cross-Sectional Study. *Biomed Res Int* 2018: 2018: 3924517.

33. Thakrar M, Hall A, Crackett R, al. e. Functional and Quality of Life Improvements in Treated Patients with Chronic Thromboembolic Pulmonary Hypertension. *J Heart Lung Transplant* 2013: 32: Suppl: S304.

34. Yoshimi S, Tanabe N, Masuda M, Sakao S, Uruma T, Shimizu H, Kasahara Y, Takiguchi Y, Tatsumi K, Nakajima N, Kuriyama T. Survival and quality of life for

patients with peripheral type chronic thromboembolic pulmonary hypertension. *Circ J* 2008: 72(6): 958-965.

35. Vuylsteke A, Sharples L, Charman G, Kneeshaw J, Tsui S, Dunning J, Wheaton E, Klein A, Arrowsmith J, Hall R, Jenkins D. Circulatory arrest versus cerebral perfusion during pulmonary endarterectomy surgery (PEACOG): a randomised controlled trial. *Lancet* 2011: 378(9800): 1379-1387.

36. Ghofrani HA, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH, Mayer E, Simonneau G, Wilkins MR, Fritsch A, Neuser D, Weimann G, Wang C. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med* 2013: 369(4): 319-329.

37. Galie N, McLaughlin VV, Rubin LJ, Simonneau G. An overview of the 6th World Symposium on Pulmonary Hypertension. *Eur Respir J* 2019: 53(1).

38. Quadery SR, Swift AJ, Billings CG, Thompson AAR, Elliot CA, Hurdman J, Charalampopoulos A, Sabroe I, Armstrong IJ, Hamilton N, Sephton P, Garrad S, Pepke-Zaba J, Jenkins DP, Screaton N, Rothman AM, Lawrie A, Cleveland T, Thomas S, Rajaram S, Hill C, Davies C, Johns CS, Wild JM, Condliffe R, Kiely DG. The impact of patient choice on survival in chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2018: 52(3).

Tables

TABLE 1

Patient demographics and characteristics at baseline (n=1324)

	n	CTEPH PEA
Age at PEA, years	1324	61 ± 21
Women, n (%)	1324	619 (46.8)
Year of PEA	1324	2013 ± 5
Comorbidities, n (%)		
Atrial fibrillation/flutter	1079	98 (9.1)
COPD	1144	81 (7.1)
Diabetes	1146	99 (8.6)
Systemic hypertension	873	326 (37.3)
Ischaemic heart disease	1142	134 (11.7)
Malignancy	1077	113 (10.5)
Pulmonary vasodilator medication, n (%)	1184	346 (29)
CAMPHOR score		
Activity	1053	11 ± 9
Quality of life	1053	11 ± 11
Symptoms	1053	13 ± 10
WHO FC, n (%)	1265	
1		0 (0)
2		161 (12.7)
3		997 (77.8)
4		107 (8.5)
6MWD, metres	1117	297 ± 190
NT-proBNP, pg/mL	448	660 ±1796
Haemodynamics		
mPAP, mmHg	1225	45 ± 15
CI, L/min/m^2	1171	2.14 ± 0.79
PVR, WU	1192	8.49 ± 6.01
RAP, mmHg	744	9 ± 8
PCWP, mmHg	933	11 ± 5
Type of surgical disease[a], n (%)	1225	

1		184 (15)
2		720 (58.8)
3		319 (26)
4		2 (0.2)
Cardiac bypass time, minutes	1136	321 ± 67
Arrest time[b], minutes	999	37 ± 15.5
Concomitant surgery, n (%)	1299	
ASD / PFO closure		44 (3.4)
AVR		13 (1)
CABG		95 (7.3)
MVR		12 (0.9)
Complications, n (%)		
Renal replacement therapy	1025	57 (5.6)
ECMO	1158	64 (5.5)
Pneumonia	1102	138 (12.5)
Re-intubation	1114	104 (9.3)
Return to theatre	1096	84 (7.7)
Tracheostomy	1109	67 (6)
Length of stay, days		
Intensive care unit	1075	4 ± 3
Total hospital	1196	14.5 ± 10
In-hospital mortality, n (%)	1313	49 (3.7)

Data are median ± IQR unless stated otherwise. Data were recorded closest to the time of diagnosis and pre-PEA for 6MWD, NT-proBNP, pulmonary haemodynamics, WHO FC, CAMPHOR score and pulmonary vasodilator medication. N=1324 total cohort.

6MWD: 6-minute walk distance; AVR: aortic valve replacement; CABG: coronary artery bypass graft; CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review score; CI: cardiac index; ECMO: extracorporeal membrane oxygenation; IQR: interquartile range; mPAP: mean pulmonary arterial pressure; MVR: mitral valve replacement; PFO/ASD: patent foramen ovale / atrial septal defect; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; WHO FC: World Health Organization functional class; WU: Wood units.

[a]Jamieson classification – intraoperative surgical disease classification preceding the 6th World Pulmonary Hypertension Symposium update [30].

[b]arrest time refers to deep hypothermic circulatory arrest.

TABLE 2

Outcome measures pre-PEA, post-PEA and change from baseline in patients with CTEPH

Outcome	n	Pre-PEA (baseline)	Post-PEA (follow-up within 1 year)	Change from baseline	*P* value
CAMPHOR score					
Activity	784	11 ± 9 (11,12)	6 ± 9 (5,6)	−5 ± 7 (−5, −4)	<0.0001
QoL	784	11 ± 11 (10,12)	3 ± 10 (3, 4)	−4 ± 8 (−5, −4)	<0.0001
Symptoms	784	13 ± 10 (12,14)	4 ± 7 (3,4)	−7 ± 8 (−8, −7)	<0.0001
6MWD, metres	676	309 ± 170 (300, 320)	366 ± 159 (356, 380)	50 ± 109 (40, 56)	<0.0001
NT-proBNP, pg/mL	326	678 ± 1832 (491, 783)	227 ± 411 (182, 260)	−210 ± 1358 (−398, −98)	<0.0001
WHO FC, n (%)	1058				<0.0001
1		0 (0%)	291 (28%)	–	
2		134 (13%)	473 (45%)	–	
3		822 (79%)	272 (26%)	–	
4		90 (9%)	10 (1%)	–	
Haemodynamics					
CI, L/min/m^2	949	2.17 ± 0.76 (2.1, 2.2)	2.3 ± 0.68 (2.26, 2.34)	0.14 ± 0.87(0.1, 0.19)	<0.0001
mPAP, mmHg	994	45 ± 15 (45, 46)	25 ± 13 (24, 26)	−17 ± 17 (−18, −16)	<0.0001
PVR, WU	963	8.36 ± 5.93 (7.91, 8.79)	3.18 ± 2.8 (3.01, 3.29)	−4.29 ± 5.71 (−4.69, −3.94)	<0.0001
RAP, mmHg	624	9 ± 7 (9, 10)	7 ± 4 (6, 7)	-2 ± 7 (-3, -2)	<0.0001
PCWP, mmHg	677	11 ± 5 (11, 12)	10 ± 5 (10, 11)	-1 ± 6 (-1, 0)	<0.0001

Data are median ± IQR (95% CI) or n (%) unless otherwise stated. n is the number of individuals with results *both* pre- and post-PEA from an overall cohort of n=1324. *P*-values were adjusted by false-discovery rate and calculated using the Mann-Whitney *U* test for continuous data and the Cochran-Armitage test for WHO FC. Change from baseline is the median of differences.

6MWD: 6-minute walk distance; CI: cardiac index; CTEPH: chronic thromboembolic pulmonary hypertension; IQR: interquartile range; mPAP: mean pulmonary arterial pressure; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PCWP: pulmonary capillary wedge pressure; PEA: pulmonary endarterectomy; PVR: pulmonary vascular resistance; RAP: right atrial pressure; WHO FC: World Health Organization Functional Class; WU: Wood units.

TABLE 3

Minimally clinically important difference in CAMPHOR score for patients with CTEPH undergoing PEA

		CAMPHOR domain		
Health status change	**n**	**Activity**	**QoL**	**Symptoms**
Very much better	336	−6 ± 8 (−6, −5)	−5 ± 8 (−6, -5)	−8 ± 8 (−9, −8)
Moderately better	158	−3 ± 5 (−4, −2)	−4 ± 7 (−5, −3)	−6 ± 7 (−7, −6)
A little better	90	−3 ± 4 (−4, −2)	−2 ± 6 (−3, −1)	−5 ± 8 (−6, −3)
Not changed	34	−2 ± 6 (−4, 0)	−1 ± 4 (−2, 0)	−2 ± 6 (−5, 0)
A little worse	20	1 ± 6 (−1, 3)	2 ± 8 (−7, 0)	−2 ± 5 (−3, 2)
Moderately worse	13	1 ± 6 (−3, 3)	−1 ± 4 (−4, 0)	0 ± 5 (−3, 2)
Very much worse	4	−4 ± 20 (−14, 19)	1 ± 12 (−6, 15)	−3 ± 7 (−13, 11)

Data are median ± IQR (95% CI). The change from baseline (pre-PEA) in CAMPHOR score at 1 year post PEA, in relation to ratings to a global health status change question. A “moderately better” change in health status was used to define the MCID. Of 784 with a change from baseline CAMPHOR score, 655 (84%) also had a global health status change recorded and were included in the MCID analysis. A very limited number of patients had worse global health status changes (“A little worse”, “Moderately worse” or “Very much worse”) following PEA resulting in large confidence intervals. CI: confidence interval; IQR: interquartile range; QoL: quality of life.

TABLE 4

Cox proportional hazards model of baseline variables and survival 1 year post-PEA in CTEPH using complete cases

	Unit change	HR	95% CI	*P* value
CAMPHOR				
Activity	1 point	1.03	0.95, 1.11	0.493
QoL	1 point	1.05	0.96, 1.14	0.272
Symptoms	1 point	0.96	0.88, 1.05	0.400
Age	5 years	1.17	1.02, 1.35	0.0288
Sex: Male		0.53	0.27, 1.04	0.0632
6MWD	10 metres	0.97	0.94, 1.00	0.0867
Haemodynamics				
Cardiac index	0.1 L/min/m^2	0.98	0.90, 1.06	0.564
mPAP	5 mmHg	0.97	0.78, 1.2	0.769
PVR	1 WU	1.03	0.92, 1.15	0.603

The association between baseline, pre-PEA variables and 1 year survival following PEA was assessed. CAMPHOR score, 6MWD and haemodynamics are baseline, pre-PEA. Complete cases data was used for this cox proportional hazard model, which included 657 individuals and 38 deaths (667 observations were removed due to incomplete data). 6MWD: 6-minute walk distance; CI: confidence interval; CTEPH: chronic thromboembolic pulmonary hypertension; HR: hazard ratio; mPAP: mean pulmonary arterial pressure; PEA: pulmonary endarterectomy; PVR: pulmonary vascular resistance; QoL: quality of life; WU: Wood units.