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Predictors of mortality in inoperable chronic thromboembolic pulmonary hypertension

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Summary
Introduction: Recent studies suggest that medically treated patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) have an improved prognosis. However, only limited data are available concerning predictors of mortality in these patients. The aim of this study was to assess, and to identify, predictors of the long-term outcome of inoperable CTEPH patients.
Methods: We analysed 84 inoperable CTEPH patients referred to our centre between 1999 and 2008. During follow-up (mean 32 months), 17 patients died and one underwent a lung transplantation. The 1-, 3- and 5-year survival rates were 93, 78 and 68%, respectively. Univariate analysis demonstrated that 6-min walking distance (6MWD), mean pulmonary artery pressure (mPAP), right atrial pressure (RAP) and pulmonary vascular resistance (PVR) were predictive factors for survival. In the multivariate analysis only 6MWD was independently related to poor survival (hazard ratio 0.995; 95% CI, 0.991–0.998; $P = 0.003$). Kaplan–Meier curves showed that patients with an mPAP > 40 mmHg, PVR > 584 dyn s cm^{-5} and RAP > 12 mmHg had a very poor prognosis.
Conclusions: Haemodynamic parameters (mPAP, RAP, PVR) and the 6MWD at baseline are predictive factors for mortality of medically treated inoperable CTEPH patients. A subgroup

Abbreviations: 6MWD, 6-min walking distance; AMC, associated medical conditions; CTEPH, chronic thromboembolic pulmonary hypertension; ERA, endothelin receptor antagonist; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro brain natriuretic peptide; PDE-5 inhibitor, phosphodiesterase-5 inhibitor; PVR, pulmonary vascular resistance; PEA, pulmonary endarterectomy; RAP, right atrial pressure; ROC, receiver operating characteristics; RVP, right ventricular pressure; SvO_2, mixed venous oxygen saturation.

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of these patients with good prognostic factors, defined by their haemodynamics and clinical measures, have an improved long-term survival and outcome.
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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is an uncommon, although increasingly diagnosed, disease of the pulmonary artery vasculature characterised by intraluminal thrombus formation and fibrous stenosis or complete obliteration.[1,2] These obstructions are typically distributed in the central pulmonary arteries. As a result patients develop various degrees of pulmonary hypertension, depending on the extent of the vascular obstructions. Left untreated, this leads to right ventricular failure and death.[3] Predictive factors for survival in patients with inoperable CTEPH treated medically have not been sufficiently elucidated.

In recent years medical treatment with proven efficacy in idiopathic pulmonary arterial hypertension (IPAH) and other forms of PAH, such as prostacyclin, phosphodiesterase-5 inhibitors (PDE-5 inhibitors) and endothelin receptor antagonists (ERA), has been tried in patients with inoperable CTEPH[4–11] sometimes as a therapeutic bridge to pulmonary endarterectomy (PEA).[12,13] Although the effect of treatment on long-term survival has never been investigated in a randomised trial, recent data from two large PAH centres show that long-term survival of medically treated CTEPH patients is much better than was reported in earlier studies of untreated patients.[14,15] However, it is unclear which parameters predict long-term survival in this era of PH-specific (oral) medical treatment. Therefore the aim of this study was to identify the determinants of survival in medically treated inoperable CTEPH patients.

Materials and methods

Subjects and study design

This observational cohort study encompassed 84 inoperable CTEPH patients. All patients were referred to the Department of Pulmonary Diseases at the VU Medical Centre (a specialised referral centre for the evaluation and treatment of PH) between May 1999 and February 2008. Cohort entry was defined as the time/date of first right heart catheterisation, to establish the diagnosis of pulmonary arterial hypertension. See Table 1 for baseline patient characteristics.

Methods

The diagnosis of CTEPH was made using standard diagnostic criteria.[16,17] All patients were evaluated by a multi disciplinary team of pulmonary physicians, surgeons and radiologists using ventilation/perfusion scintigraphy, CT pulmonary angiography, conventional pulmonary angiography, and right heart catheterisation. CTEPH patients were regarded as inoperable when either distal, surgically inaccessible vascular occlusions were present or when the severity of the PH was greater than predicted from the degree of vascular obliteration. In addition, all patients received a complete work-up to exclude left sided heart disease by means of echocardiography, and pulmonary diseases as an underlying cause of the pulmonary hypertension by means of high resolution computed tomography

Table 1 Baseline parameters between survivors and non-survivors with CTEPH.

Variable	All ($n = 84$)	Survivors ($n = 66$)	Non-survivors ($n = 18$)	P
Age (years)	64 ± 13	64 ± 14	63 ± 12	0.99
Female/male ratio (n)	59/25	47/19	12/6	0.7
Functional class NYHA (%) I, II, III or IV	4, 26, 45, 25	100, 91, 90, 43	0, 9, 10, 57	0.0001
RAP (mmHg)	9.4 ± 6.9	8 ± 6	14 ± 7.9	0.004
Diastolic RVP (mmHg)	12 ± 13	11 ± 14.6	15.9 ± 8.4	0.04
mPAP (mmHg)	45 ± 13	42.9 ± 13.4	53 ± 9.6	0.003
PVR (dyn s cm^{-5})	718 ± 368	631 ± 312	1015 ± 399	0.0001
Cardiac index (L min^{-1} m^{-2})	2.6 ± .9	2.8 ± .9	2.2 ± .9	0.03
SvO_2 (%)	62 ± 11	63 ± 9.6	56 ± 12.8	0.01
SaO_2 (%)	93 ± 6	93 ± 6	92 ± 4	0.34
6MWD (m)	363 ± 135	390 ± 124	264 ± 131	0.0001
NT-proBNP (ng L^{-1})	1702 ± 2278	1566 ± 2238	3206 ± 2420	0.1

Values are presented as mean ± SD. P values refer to comparisons between survivors and non-survivors. NYHA, New York Heart Association; RAP, right atrial pressure; Diastolic RVP, diastolic right ventricular pressure; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; SvO_2, mixed venous oxygen saturation; 6MWD, 6-min walking distance; NT-proBNP, N-terminal pro brain natriuretic peptide; ASD, atrial septal defect; CAD, coronary artery disease; AMC, associated medical conditions (i.e. permanent central intravenous lines, splenectomy, inflammatory bowel disease).

and pulmonary function testing. In the clinical diagnostic work-up all patients were classified according to the NYHA functional class and all patients ($n = 75$) had to perform a 6-min walk test (6MWD), according to current guidelines.[18] Blood was taken from a peripheral vein to assess N-terminal pro brain natriuretic peptide (NT-proBNP) ($n = 60$) analysed on an ELECSYS 1010 bench top analyser (Roche Diagnostics, Netherlands). Since NT-proBNP measurement was not available until the end of 2003, this data could not be obtained in 25 patients. In addition to coumadin (adjusted to a target international normalised ratio between 2.0 and 3.0) oxygen and diuretics CTEPH patients also received PH-specific medications. The pharmacological treatment varied among patients (see Table 2), depending on the clinical condition. The introduction of new drugs during the time course of this study is another source of treatment variability. In the period after 2003 patients in NYHA class III received oral therapy as first line. Choice of oral monotherapy was based on medication availability and clinical data available at that time.

Statistical analyses

Baseline parameters between survivors and non-survivors were compared using independent Student's *t*-tests. Categorical data were compared using χ^2 tests. Univariate analyses based on the proportional hazard model were used to examine the relationships between survival and selected demographic, clinical measures and haemodynamics measured at baseline. Forward stepwise multivariate analysis based on the Cox proportional hazard model was used to examine the independent effect of multiple covariates on survival, controlling for possible confounders. Optimal cut-off values assessed with receiver operating curve (ROC) analysis were used to separate the patients on both sides into two groups. Survival curves were derived by the Kaplan–Meier method. Groups were compared by the log rank test.

Survival was estimated from the date of initial diagnosis until February 5, 2008, the date of death or that of lung transplantation. A P value <0.05 was considered statistically significant.

Results

The baseline patient characteristics and haemodynamics are summarised in Table 1. The mean age was 64 ± 13 years and the majority of patients were female. The NYHA functional class II, III and IV is also given in the table. The averaged exercise capacity expressed in 6MWD was 363 ± 35 m, indicating moderate exercise intolerance. The haemodynamic parameters showed that patients had significant pulmonary hypertension with increased RV and RA pressures.

Table 2 shows the treatments and comorbidities in the inoperable CTEPH patients. The vast majority of survivors were treated with a PDE-5 inhibitor and in clinically deteriorating patients an ERA was added after initial therapy with a PDE-5 inhibitor. In the non-survivors, prostacyclin was the most commonly used drug, reflecting the clinical severity of the condition in these patients. Prostacyclin was the most commonly used drug before 2003 in contrast to treatment after 2003 (39% vs. 8% respectively).

Associated medical conditions (AMC) and cancer were the most common comorbidities.

Differences in parameters between survivors and non-survivors are also shown in Table 1. The non-survivors had a significantly worse haemodynamic status at baseline than survivors (i.e. significantly higher RAP, diastolic RVP, mean PAP, PVR and significant lower SvO_2). The higher pressures in non-survivors were reflected in a tendency to higher NT-proBNP values but this did not reach significance due to the large standard deviation. As expected non-survivors had a significantly worse NYHA functional class compared to survivors. The performance in 6MWD was also lower in the non-survivors ($P < 0.0001$).

Survival

During a mean observation time of 32 ± 20 months (range 0–87 months) no patients were censored for reasons other

Table 2 Treatment with PH-specific drugs and comorbidities in patients with CTEPH.

Variable	All ($n = 84$)	Survivors ($n = 66$)	Non-survivors ($n = 18$)	*P*
Medication				
PDE-5 inhibitor		33	1	–
ERA		4	1	–
Prostacyclin		3	7	–
Combination PDE-5 + ERA		15	3	–
Combination Pros + PDE-5		0	4	–
Combination Pros + PDE-5 + ERA		1	1	–
Comorbidities				
Congenital heart disease (ASD)	5	5	0	
Cancer	11	7	4	
CAD	6	6	0	
COPD	8	8	0	
Thyroid disease	2	2	0	
Atrial fibrillation	1	1	0	
AMC	10	6	4	

PDE-5 inhibitor, phosphodiesterase-5 inhibitor; ERA, endothelin receptor antagonist; Prost, prostacyclin.

than death. From the 84 patients 17 patients (20%) died from right heart failure ($n = 13$), and respiratory failure in the end stage of right heart failure ($n = 4$). At 2 years one patient had undergone lung transplantation.

The 1-, 3- and 5-year survival for the total cohort was 93, 78 and 68%, respectively.

Although survival was significantly better after 2003 compared with the survival before 2003, with 1-, 3- and 5-year survival rates of 97, 84 and 79% vs. 71, 50 and 43% respectively, patients at clinical presentation in the period before 2003 had more severe disease as reflected by their haemodynamics (mPAP 51 ± 9 vs. 44 ± 14, $P = 0.02$; PVR 924 ± 427 vs. 686 ± 353, $P = 0.03$).

Univariate analysis

Table 3 shows the results of the univariate Cox proportional hazards regression analysis. Of the haemodynamic variables mPAP, RAP and PVR were associated with poor survival, and of the clinical variables only 6MWD was significantly related to an increased risk of death. The hazard ratio for a 50-m difference in 6MWD was 0.779 (95% CI; 0.640–0.947) and for a 100 dyn s cm^{-5} difference in PVR 1.221 (95% CI: 1.004–1.486).

Mortality was not associated with patient age, NT-proBNP, mixed venous oxygen saturation, cardiac index, NYHA functional class and associated medical conditions (AMC).

Receiver-operating characteristics (ROC)

To distinguish survivors from non-survivors according to baseline parameters, an ROC analysis was performed with the significant predictors from the univariate analysis. Groups were created based on the optimal cut-off values determined by ROC analysis and Kaplan–Meier curves were compared for the different groups.

Table 3 Univariate Cox proportional hazard analysis of variables associated with mortality in inoperable CTEPH ($n = 84$).

Variable	Hazard ratio	95% CI	*P*
Age (years)	0.996	0.963–1.030	0.82
6MWD (m) [per 50 m increase in distance]	0.779	0.640–0.947	0.003
NT-proBNP (ng L^{-1})	1.000	1.000–1.000	0.22
NYHA I, II vs. III, IV	3.044	0.700–13.226	0.14
mPAP (mmHg)	1.038	1.003–1.074	0.034
PVR (dyn s cm^{-5}) [per 100 dyn increase in resistance]	1.221	1.004–1.486	0.004
SvO_2 (%)	0.974	0.938–1.012	0.18
CI (L min^{-1} m^{-2})	0.599	0.322–1.116	0.11
RAP (mmHg)	1.072	1.009–1.140	0.025
AMC	2.307	0.740–7.187	0.149

NYHA class is dichotomised comparing classes I and II with classes III and IV. CI, confidence interval; AMC, associated medical conditions (i.e. splenectomy, permanent central intravenous lines, and inflammatory disorders).

Patients with a 6MWD less than 298 m had a significantly lower survival rate than those with a 6MWD more than 298 m (log rank test, $P < 0.009$; Fig. 1a). Separation of the groups using the median 6MWD of 386 m was significantly less predictive than when using the optimal cut-off value of 298 m determined by the ROC analysis (data not shown). The same Kaplan–Meier curves showed that patients with an mPAP > 40 mmHg, RAP > 12 mmHg and, PVR > 584 dyn s cm^{-5} were at a significantly higher risk of death compared with patients who had an mPAP < 40 mmHg ($P < 0.02$), RAP < 12 mmHg ($P = 0.009$), and PVR < 584 dyn s cm^{-5} ($P = 0.002$) respectively (Fig. 1b,c,d).

Multivariate analysis

In the forward stepwise multivariate analysis, we examined the effect on mortality of each independent baseline variable in the presence of others. All independent variables found to be significant in the univariate analysis were included. Only 6MWD was independently related to poor survival (hazard ratio 0.995; 95% CI, 0.991–0.998; $P = 0.003$). Backward multivariate analysis showed the same outcome.

Discussion

We found that haemodynamic parameters (i.e. mPAP, RAP, PVR) and the 6MWD at baseline are strongly related to long-term outcome and survival in CTEPH patients with inoperable disease.

Survival

Data on long-term survival in inoperable CTEPH patients before modern vasoactive treatment were very poor. The only two studies describing survival in medically untreated CTEPH patients showed that the 3-year survival rate was as low as 10% in patients with a mean PAP > 30 mmHg[19] and the 5 year survival 14% in patients with a mean PAP > 50 mmHg.[3] In our present study, with modern treatment, the overall 1-, 3- and 5-year survival was 93, 78 and 68%, respectively. These survival rates are comparable with recently published studies of Bonderman and Condliffe et al.[14,15] In the study of Bonderman et al. 1-, 3- and 5-year survival was 88, 65 and 65% respectively, although these were patients without associated medical conditions. With associated medical conditions these inoperable CTEPH patients had poorer 1-, 3- and 5-year survivals of 74, 45 and 15%. Condliffe et al. showed in a national study of medically treated inoperable CTEPH patients from the United Kingdom 1-, 3- and 5-year survival of 82, 70 and 55% respectively.[15]

Prognostic factors

In IPAH, cardiac index, degree of RAP and PAP elevation are associated with survival.[20] In CTEPH few data are available about prognostic factors of survival with modern vasoactive therapy. In previous studies of medically untreated CTEPH patients the degree of mPAP was a strong predictor of mortality.[3,19] In our present study of inoperable CTEPH

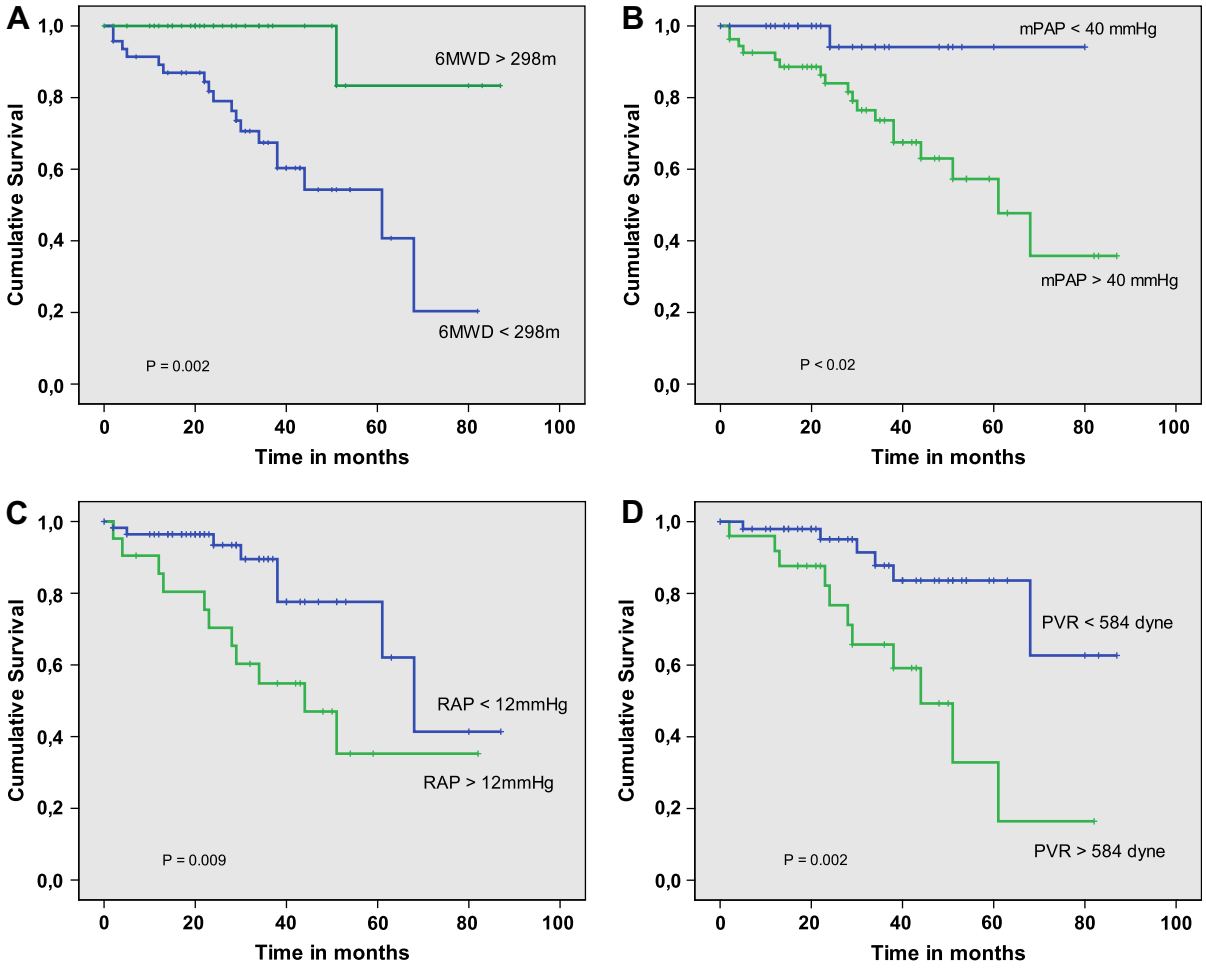

Figure 1 Kaplan–Meier curves according to the optimal cut-off value derived by ROC analysis for 6-min walking distance (6MWD; panel A); mean pulmonary artery pressure (mPAP, panel B); right atrial pressure (RAP, panel C); and pulmonary vascular resistance (PVR, panel D).

patients various haemodynamic variables derived at baseline are able to predict long-term survival. A low mPAP, PVR and RAP at baseline (all below the cut-off value determined by ROC analysis) were beneficial in prognosis for these patients. Of the clinical variables a relatively high 6MWD of 298 m was associated with a better long-term survival. It is somewhat unexpected that mPAP is a predictive factor for survival in PH, since in the end stage of the disease mPAP decreases while the disease progresses. However, our data are in agreement with those reported by Riedel et al.[3] and Lewczuk et al.[19] that also showed an association between mPAP and mortality. Other survival studies in patients with PH have also shown an association between mPAP and mortality.[20,21] It can be expected that patients in NYHA class 3 or 4 with a low mPAP (indicating very severe or end-stage disease) have a worse survival than patients in NYHA class 1 or 2 with a high mPAP (indicating less advanced disease). We did an additional analysis to check this and, surprisingly, the hazard ratio for mPAP when adjusted for the dichotomised NYHA class 1 and 2 versus class 3 and 4 (HR 1.040; 95% CI 1.000–1.081), is the same as the hazard ratio for mPAP alone (HR 1.038; 95% CI 1.003–1.074). This finding indicates that the stage of the disease is not a confounder in this study.

Bonderman et al. showed that associated medical conditions (AMC) are related to increased mortality.[14] In our present study four of the 10 patients with AMC (40%) died. The reason that AMC was found not to be significant in the univariate analysis is probably due to the low number of deaths in the total cohort of patients. Although univariate analysis showed that survival is worse in the period before 2003 at the time when only prostacycline was available, multivariate analysis showed that this variable was not significant, most probably since patients diagnosed with CTEPH had more severe disease reflected by their haemodynamics in comparison to the patient group diagnosed after 2003.

In the ''survivor'' group, 10 of the 66 patients did not receive PH-specific drug therapy because of mild symptoms and/or pulmonary haemodynamics, and only one of the 18 ''non-survivors'' did not receive this drug therapy because it was contraindicated in this patient. Hence, it seems that these medications were not necessarily more beneficial for survival as those patients who did not receive these drugs were not more likely to die during follow-up. However, due to the low number of events in the non-survivor group a relationship between drug therapy and survival could not

be reliably tested in the univariate analysis. Therefore, it was unlikely that our present study would demonstrate a survival benefit from PH-specific drug therapy, even if such a benefit exists. This is in agreement with the recent article by Condliffe et al.[22]

The present study demonstrates that the 6MWD is the only independent factor that predicts survival. Patients with a 6MWD more than 298 m had a significantly better long-term survival than patients walking less. This finding is in accordance with the study by Myamoto in IPAH showing that 6MWD is a strong independent factor associated with mortality.[23] Miyamoto et al. assessed the cut-off value by the median and found that IPAH patients walking more than 332 m had a significantly better survival. Another study showed that with ROC analysis a preoperative 6MWD $\leq$ 345 m was able to predict death in patients who had undergone pulmonary endarterectomy with a sensitivity of 100% and specificity of 36%.[24] Using the cut-off value of 298 m in our study, as determined by ROC analysis, provided the best discrimination between survivors and non-survivors.

Clinical implication

We have tried to provide a profile of the survivors and non-survivors with both clinical measures and haemodynamics evaluated at baseline. Although it is clear that the treatment of choice is pulmonary endarterectomy (PEA) in patients with CTEPH suitable for surgery, the indications for surgery are not always so clear since the degree of vascular obstruction on angiography is often not correlated to haemodynamic and clinical severity. The prognostic haemodynamic (mPAP, PVR and RAP) and clinical (6MWD) factors in our present study can be used for risk stratification in CTEPH patients with inoperable disease for the decision-making process regarding the treatment options.

The main limitation of this study is its retrospective observational design. As a result of this we miss some NT-proBNP data. This study concerns only inoperable CTEPH patients and therefore results cannot be applied to patients with operable CTEPH patients. Another limitation is the small number of events, therefore the results of the multivariate analysis should be interpreted with caution. Nonetheless, 6MWD remains a strong independent predictor for mortality. Finally, our patients were very heterogeneously treated, according to newly introduced drugs over the years, and the available clinical insights. Since it was not the aim of this study to prove that medical treatment is beneficial in CTEPH, nor to study the differences in efficacy between treatment strategies, no conclusions can be drawn on the optimal treatment schedule. Due to the observational nature of this study, a suggestion for improvements in survival cannot be given. Prospective research with the aim of investigating the optimal treatment scheme in these patients with inoperable disease is needed.

Conclusions

Long-term survival and outcome of medically treated CTEPH patients with inoperable diseases is much improved in this therapeutic era compared with untreated patients and is comparable with recently reported survival rates. Severity at baseline, assessed by haemodynamics and clinical measures, predicts the survival of these patients. A 6MWD above 298 m at baseline is associated with a favourable long-term survival and is simple to determine.

Conflict of interest statement

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References

1. Auger WR, Kim NH, Kerr KM, Test VJ, Fedullo PF. Chronic thromboembolic pulmonary hypertension. *Clin Chest Med* 2007;**28**(1):255—69 [x].
2. Hoeper MM, Mayer E, Simonneau G, Rubin LJ. Chronic thromboembolic pulmonary hypertension. *Circulation* 2006;**113**(16): 2011—20.
3. Riedel M, Stanek V, Widimsky J, Prerovsky I. Longterm follow-up of patients with pulmonary thromboembolism. Late prognosis and evolution of hemodynamic and respiratory data. *Chest* 1982;**81**(2):151—8.
4. Bonderman D, Nowotny R, Skoro-Sajer N, Jakowitsch J, Adlbrecht C, Klepetko W, Lang IM. Bosentan therapy for inoperable chronic thromboembolic pulmonary hypertension. *Chest* 2005;**128**(4):2599—603.
5. Bresser P, Pepke-Zaba J, Jais X, Humbert M, Hoeper MM. Medical therapies for chronic thromboembolic pulmonary hypertension: an evolving treatment paradigm. *Proc Am Thorac Soc* 2006;**3**(7):594—600.
6. Cabrol S, Souza R, Jais X, Fadel E, Ali RH, Humbert M, Dartevelle P, Simonneau G, Sitbon O. Intravenous epoprostenol in inoperable chronic thromboembolic pulmonary hypertension. *J Heart Lung Transplant* 2007;**26**(4):357—62.
7. Ghofrani HA, Schermuly RT, Rose F, Wiedemann R, Kohstall MG, Kreckel A, Olschewski H, Weissmann N, Enke B, Ghofrani S, Seeger W, Grimminger F. Sildenafil for long-term treatment of nonoperable chronic thromboembolic pulmonary hypertension. *Am J Respir Crit Care Med* 2003;**167**(8):1139—41.
8. Hoeper MM, Kramm T, Wilkens H, Schulze C, Schafers HJ, Welte T, Mayer E. Bosentan therapy for inoperable chronic thromboembolic pulmonary hypertension. *Chest* 2005;**128**(4): 2363—7.
9. Hughes RJ, Jais X, Bonderman D, Suntharalingam J, Humbert M, Lang I, Simonneau G, Pepke-Zaba J. The efficacy of bosentan in inoperable chronic thromboembolic pulmonary hypertension: a 1-year follow-up study. *Eur Respir J* 2006; **28**(1):138—43.
10. Reichenberger F, Voswinckel R, Enke B, Rutsch M, El FE, Schmehl T, Olschewski H, Schermuly R, Weissmann N,

Ghofrani HA, Grimminger F, Mayer E, Seeger W. Long-term treatment with sildenafil in chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2007;**30**(5):922—7.
11. Vizza CD, Badagliacca R, Sciomer S, Poscia R, Battagliese A, Schina M, Agati L, Fedele F. Mid-term efficacy of beraprost, an oral prostacyclin analog, in the treatment of distal CTEPH: a case control study. *Cardiology* 2006;**106**(3):168—73.
12. Kerr KM, Rubin LJ. Epoprostenol therapy as a bridge to pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension. *Chest* 2003;**123**(2):319—20.
13. Nagaya N, Sasaki N, Ando M, Ogino H, Sakamaki F, Kyotani S, Nakanishi N. Prostacyclin therapy before pulmonary thromboendarterectomy in patients with chronic thromboembolic pulmonary hypertension. *Chest* 2003;**123**(2):338—43.
14. Bonderman D, Skoro-Sajer N, Jakowitsch J, Adlbrecht C, Dunkler D, Taghavi S, Klepetko W, Kneussl M, Lang IM. Predictors of outcome in chronic thromboembolic pulmonary hypertension. *Circulation* 2007;**115**(16):2153—8.
15. Condliffe R, Kiely DG, Gibbs JS, Corris PA, Peacock AJ, Jenkins DP, Hodgkins D, Goldsmith K, Hughes RJ, Sheares K, Tsui SS, Armstrong IJ, Torpy C, Crackett R, Carlin CM, Das C, Coghlan JG, Pepke-Zaba J. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. *Am J Respir Crit Care Med* 2008;**177**(10): 1122—7.
16. Klepetko W, Mayer E, Sandoval J, Trulock EP, Vachiery JL, Dartevelle P, Pepke-Zaba J, Jamieson SW, Lang I, Corris P. Interventional and surgical modalities of treatment for pulmonary arterial hypertension. *J Am Coll Cardiol* 2004;**43**(12 Suppl. S):73S—80S.
17. Simonneau G, Galie N, Rubin LJ, Langleben D, Seeger W, Domenighetti G, Gibbs S, Lebrec D, Speich R, Beghetti M, Rich S, Fishman A. Clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2004;**43**(12 Suppl. S):5S—12S.
18. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;**166**(1):111—7.
19. Lewczuk J, Piszko P, Jagas J, Porada A, Wojciak S, Sobkowicz B, Wrabec K. Prognostic factors in medically treated patients with chronic pulmonary embolism. *Chest* 2001;**119**(3):818—23.
20. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM. Kernis JT, Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991;**115**(5):343—9.
21. Fuster V, Steele PM, Edwards WD, Gersh BJ, McGoon MD, Frye RL. Primary pulmonary hypertension: natural history and the importance of thrombosis. *Circulation* 1984;**70**(4):580—7.
22. Condliffe R, Kiely DG, Gibbs JS, Corris PA, Peacock AJ, Jenkins DP, Goldsmith K, Coghlan JG, Pepke-Zaba J. Prognostic and aetiological factors in chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2008 [Epub ahead of print].
23. Miyamoto S, Nagaya N, Satoh T, Kyotani S, Sakamaki F, Fujita M, Nakanishi N, Miyatake K. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2000;**161**(2 Pt 1):487—92.
24. Suntharalingam J, Goldsmith K, Toshner M, Doughty N, Sheares KK, Hughes R, Jenkins D, Pepke-Zaba J. Role of NT-proBNP and 6MWD in chronic thromboembolic pulmonary hypertension. *Respir Med* 2007;**101**(11):2254—62.