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Early View

Original article

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Take home message: The risk stratification for PAH of the current European PH guidelines may allow survival prediction in medically treated CTEPH patients (136 characters).

Abstract

Abbreviated versions of the ESC/ERS pulmonary hypertension guidelines risk stratification have been recently validated in patients with pulmonary arterial hypertension. We aimed to investigate their prognostic value in medically treated chronic thromboembolic pulmonary hypertension (CTEPH) patients from the COMPERA registry, which collects six variables of interest (WHO functional class, 6-minute walking distance, brain natriuretic peptide, right atrial pressure, cardiac index and mixed venous oxygen saturation).

We included patients with at least one follow-up visit, no pulmonary endarterectomy, and at least three of the six variables available, and classified the patients into low, intermediate and high risk groups. As secondary analysis, the number of non-invasive low risk criteria was counted. The association between risk assessment and survival was evaluated.

Data from inclusion and follow-up (median, 7 months) visits were available for 561 and 231 patients, respectively. Baseline 1- and 5-year survival estimates were significantly different (p<0.0001) in the baseline low (98.6;88.3%), intermediate (94.9;61.8%), and high risk (75.5;32.9%) cohorts. Follow-up data were even more discriminative with, respectively, 100, 92 and 69% 1-year survival. The number of low risk non-invasive criteria was also associated with survival.

These analyses suggest that the ESC/ERS risk assessment may be applicable in patients with medically treated CTEPH.

Key words: chronic thromboembolic pulmonary hypertension, risk stratification, mortality, survival

Introduction

The 2015 ESC/ERS pulmonary hypertension (PH) guidelines [1] recommend to evaluate the severity of patients with pulmonary arterial hypertension (PAH) with a panel of data derived from clinical assessment, exercise tests, biochemical markers and echocardiographic and haemodynamic evaluations, with regular follow-up assessments every 3-6 months in stable patients. The resulting data should be used to categorise patients into risk groups with low risk (estimated 1-year mortality rate < 5%), intermediate risk (5-10%), and high risk (> 10%), and to facilitate treatment decision in a treat to target approach. The accuracy of this risk assessment strategy, at baseline as well as during follow-up, has been recently demonstrated under real life conditions, in three different prospective cohorts: the Swedish Pulmonary Hypertension Registry (SPAHR, [2]), the French Pulmonary Hypertension Registry ([3]), and the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA, [4]).

There is as yet no established risk assessment strategy to guide treatment decisions in patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH). Here, we aimed to investigate whether the ESC/ERS risk stratification strategy could also be applied in patients with CTEPH who were not candidates for surgery, by analysing data from COMPERA, a European-based PH registry that captures data from patients with all forms of PH who receive targeted medical therapy [5, 6]. We applied two sets of analyses, looking at the discriminative value of global low, intermediate and high risk scores, as it had been done in the Swedish registry and the COMPERA analysis [2, 4], and at the number of low risk criteria, following the French strategy [3], to predict long-term prognosis.

Methods

Database

COMPERA (www.COMPERA.org; registered at Clinicaltrials.gov with identifier NCT01347216) is an ongoing web-based PH registry launched in 2007 which collects baseline, follow-up and outcome data from patients who receive PAH medical therapies. Initially, COMPERA included only patients with PAH but since 2009, the registry captured patients with all forms of PH, including CTEPH. Specialised centres in several European countries participate (Austria, Belgium, Germany, Greece, Hungary, Italy, Netherlands, Switzerland and the United Kingdom), with ~80% of the patients coming from German PH centres. COMPERA enrols only patients with newly diagnosed PH, i.e. patients must be entered into the database no later than 6 months after the date of diagnosis. Further methodological details have been published elsewhere [4-6].

Among other variables, WHO functional class (FC), 6-minute walking distance (6MWD), brain natriuretic peptides (BNP or NT-proBNP), right atrial pressure (RAP), cardiac index (CI) and mixed venous oxygen saturation (SvO_2) are captured in COMPERA whenever available. These six variables were used in the present study for the validation of a truncated version of the risk assessment strategy proposed by the European PH guidelines.

Patients

Patients were selected from the COMPERA database according to the following criteria: 1) treatment-naïve patients newly diagnosed with CTEPH or residual PH after pulmonary endarterectomy (PEA) between January 1, 2009 and December 2, 2017 with data from baseline and at least one follow-up visit available; 2) mean pulmonary artery pressure ≥25 mmHg and pulmonary artery wedge pressure ≤15 mmHg at the time of diagnosis; 3) no PEA or balloon pulmonary angioplasty (BPA) during follow up, and 4) at least three of the six listed variables available at baseline.

Risk stratification strategy

An abbreviated version of the 2015 ESC/ERS risk stratification strategy, including the six variables recorded in COMPERA, was used to categorise patients as low, intermediate or high risk. Following a validation strategy proposed by Kylhammar et al. [2], the cut-off values proposed in the guidelines were graded 1–3 (1: low risk, 2: intermediate risk and 3: high risk). For each patient, the sum of all grades was divided by the number of available variables and rounded to the next integer to define the risk group. Calculations were made from baseline assessments and from follow-up assessments between 3 months and 2 years after the initiation of PAH medical therapy.

In a second set of analyses, proposed by Boucly et al. [3], we evaluated the presence of three non-invasive low-risk criteria (risk score-3) which were defined as 1) WHO FC I or II, 2) 6MWD >440 m, and a BNP <50 ng·L^{-1} or NT-proBNP <300 ng·L^{-1}. Patients were classified according to the number of low risk criteria present at inclusion and at the time of follow-up.

Statistical analyses

The primary analysis set consisted of the entire patient population that fulfilled the inclusion criteria listed earlier. Sensitivity analyses were performed with those patients for whom all six risk score variables were available and for the subgroup of patients with surgically inoperable CTEPH. Other subgroups were not assessed because the numbers of patients were considered too low.

For the follow-up risk stratification, patients who underwent their first comprehensive follow-up risk assessment between 3 months and 2 years after treatment initiation were considered. Where available, we chose the first visit that included follow-up haemodynamics. If no haemodynamic follow-up was available during the first 2 years after diagnosis, we selected the follow-up visit that contained most of the data of interest. For all analyses, only patients with at least one further follow-up were included into the analysis.

Continuous data are presented as mean±SD or as median and interquartile range (IQR). In patients who died, investigators were asked to provide the most likely cause of death. There was no independent adjudication of causes of death. Survival was evaluated using Kaplan–Meier analysis and log-rank test, truncated at 5 years. Survival was censored at the last available visit reported for a patient; mortality was recorded with the date of patient's death. Hazard ratios for the single risk-score items were estimated using univariate and multivariate Cox regression analysis, using the respective low-risk group as reference. IBM SPSS Statistics (version 19.0; Armonk, NY, USA) was used for analysis.

Results

Risk stratification at baseline and mortality

A total of 561 patients met the inclusion criteria of newly diagnosed CTEPH or residual PH after PEA, with at least one follow-up visit, no PEA or BPA during follow-up, and at least three of the six risk score variables available at baseline (**Figure 1**). At the time of inclusion, 44.2% of these patients were inoperable due to peripheral location of the thrombus (surgically inoperable) and 15.0% due to comorbidities (medically inoperable); 8.6% had surgically accessible disease; 13.0% had refused PEA; and 5.3% had persistent PH after pulmonary endarterectomy (post PEA); for 13.9% operability was still under investigation or information was not available (unknown). All patients received PAH medical therapies within 6 months of study inclusion since the start of PAH therapy is an inclusion criterion for COMPERA. Patient characteristics are shown in **Table 1.** Noteworthy, the low risk group was younger and included more post-PEA patients. The increasing mortality risk was accompanied by an increase in comorbidities such as diabetes mellitus and atrial fibrillation, while obstructive sleep apnea and thyroid disease tended to decrease.

Out of the six variables of interest for this study, at least two were available in 568 patients, at least three in 561 (98.8%) patients (baseline analysis set), at least four in 537 (94.5%) patients, at least five in 482 (84.9%) patients and all six variables were available in 318 (56.0%) patients. WHO FC was available in 97.7% of the patients, 6MWD in 79.4%, BNP or NT-proBNP in 80.3%, RAP in 94.4%, CI in 92.8% and SvO_2 in 89.6%.

During the follow-up, up to five years after diagnosis, 132 patients (23.5%) had died, 6 (7.4%) in the low risk cohort, 80 (20.9%) in the intermediate risk cohort, and 46 (46.9%) in the high risk cohort. Right heart failure was reported as the most likely cause of death in 54% of all patients, 50% of the low risk group, 46% of the intermediate risk group, and 67% of the high risk group. Infection (27.4%), cancer (18.3%), and bleeding (13.7%) were other frequent causes of death. Besides, 14 (2.5%) patients were lost to follow-up, 1 (1.2%) in the low risk group, 9 (2.4%) in the intermediate risk group and 4 (4.1%) in the high risk group.

For the entire baseline cohort, the survival estimates at 1, 2, 3, 4, and 5 years were 92.0, 83.9, 74.7, 68.3 and 59.8%, respectively. The corresponding survival estimates for the low, intermediate and high risk groups are presented in **Figure 2**, panel A (p<0.0001 for all groups comparison, with p=0.007 for low vs intermediate group comparison and p<0.0001 for intermediate vs high group comparison; **Figure 2**). The predictive value of each variable at baseline is shown in **Figure 3**.

Similar results were obtained from a sensitivity analysis that included only those 318 patients for whom all six baseline variables were available. Here, the survival differences between the three risk categories were also statistically significant with p<0.0001 for all comparisons, with p=0.032 for low vs intermediate group comparison and p<0.0001 for intermediate vs high group comparison (Supplementary Table S1 and Figure S1). The results of the analysis for the surgically inoperable CTEPH subgroup (n=248) are shown in Supplementary Table S2 and **Figure 4**. The survival differences between all 3 groups were statistically significant (p<0.0001 for all group comparisons, with p=0.011 for low vs intermediate group comparison and p<0.0001 for intermediate vs high group comparison).

Risk stratification at follow-up and mortality

Out of the 496 patients with follow-up data within 2 years of treatment initiation, at least two variables were available in 435 (87.7%) patients, at least three in 253 (51.0%) patients, at least four in 100 (20.2%) patients, at least five in 78 (15.7%) patients, and all six in 44 (8.9%) patients. WHO FC was available in 86.3% of the patients, 6MWD in 72.4%, BNP or NT-proBNP in 68.1%, RAP in 20.8%, CI in 20.8% and SvO_2 in 19.8%.

Follow-up data (between 3 months and 2 years after treatment initiation) with at least three out of the six variables of interest and at least one follow-up thereafter were available for 231 patients (**Figure 1**), with a median duration between inclusion and follow-up risk assessment of 7 months (IQR 4; 10). The characteristics of these patients at the time of follow-up risk assessment are shown in **Table 2 and** Supplementary Table S3.

One (0.4%) patient was lost to follow-up in the intermediate risk group. Within 5 years of follow-up assessment, 61 patients (26.4%) had died, 4 (8.5%) in the low risk group, 43 (27.2%) in the intermediate risk group and 14 (53.8%) in the high risk group. The survival estimates at 1, 2, 3, 4, and 5 years for the low, intermediate and high risk groups are presented in **Figure 2, panel B** (p<0.0001 for all group comparison; p=0.014 for low vs intermediate and p=0.0001 for intermediate vs high group comparisons).

The full risk score analysis at follow-up could not be performed because of too low case numbers, since right heart catheterization was not done regularly at follow-up.

From baseline to follow-up, 50/231 (21.6%) improved their risk category; 152/231 (65.8%) remained stable and 29/231 (12.6%) deteriorated. Changes in the risk category from baseline to follow-up were associated with a shift in the mortality risk (p<0.0001) as shown in **Figure 5**. The group which worsened from "low" to "high risk" (n=1) and the one which improved from "high" to "low risk" (n=3) were omitted from survival analysis.

Risk score-3 approach at baseline and at follow-up

At baseline, the three non-invasive variables, WHO FC, 6MWD and BNP/NT-proBNP, were available in 368 patients, and 64.1%, 23.1%, 9.5%, and 3.3% of them had no, one, two, or three low-risk criteria, respectively. Patient characteristics are presented in Supplementary Table S4. Noteworthy, age progressively decreased with increasing number of low risk criteria; female prevalence also decreased. Comorbidities were randomly distributed among the risk groups. The survival estimates at 1, 2, 3, 4, and 5 years for no, one, two and three low risk criteria are presented in **Figure 6, panel A** (p<0.0001 for all group comparisons, with significant differences between 0 and 1, 0 and 2, and 0 and 3 low risk criteria).

At follow-up, the three variables were available in 199 patients, and 47.7%, 32.2%, 11.6%, and 8.5% of them had no, one, two, or three low risk criteria, respectively. Patient characteristics are presented in Supplementary Table S5. The survival estimates at 1, 2, 3, 4, and 5 years for no, one, two and three low risk criteria are presented in **Figure 6, panel B** (p=0.017 for all group comparisons, with significant differences between 0 and 2, and 0 and 3 low risk criteria).

Discussion

To the best of our knowledge, the present analyses concern one of the largest prospectively collected contemporary population of newly diagnosed CTEPH patients, not operated during follow-up. The main findings can be summarized as follows: i) overall survival estimates of 92, 75, and 60% at 1, 3, and 5 years, respectively; ii) an efficient risk stratification of 5-year mortality at baseline and at follow-up using an abbreviated ESC/ERS risk score assessment; and iii) the confirmation of the risk estimates proposed in the European PH guidelines with 1-year mortality risks of <5%, 5–10% and >10% in patients at low, intermediate or high risk, respectively, for the global cohort of medically treated CTEPH patients, both at baseline as well as at follow-up.

The survival estimates observed in this series were comparable with findings of the European CTEPH registry [7], in which a 3-year survival of 70% was observed in a cohort of 275 non-operated patients with similar FC, exercise capacity and haemodynamics at diagnosis, of whom only 61% were treated with PAH medical therapy. Independent determinants of survival were FC and RAP at diagnosis, together with the presence of comorbidities such as cancer, coronary disease, left heart failure, and chronic obstructive pulmonary disease. There is further evidence supporting the prognostic relevance of most variables included in COMPERA ESC/ERS abbreviated risk score assessment. FC [8, 9], 6MWD [10-12], RAP [9], and CI [10] were all shown to be independent prognostic factors, while SvO_2 above the median was associated with better survival without being an independent survival predictor [10]. In agreement with current observations, 3-year survival was ranging between 70 and 80% in the above-mentioned non-surgical cohorts. To our knowledge there are no registry data on the value of BNP/NT-proBNP as prognostic indicator in CTEPH. Recently, an analysis of the 237 patients enrolled in CHEST-2 study (open label follow-up of riociguat registration study, [13]) showed that both 6MWD and NT-proBNP concentration at baseline and change from baseline to follow-up (but not absolute value at follow-up) were significantly and independently associated with survival. The association between WHO FC and survival was not significant in that study.

In the present series, 14% of the patients were in the low risk group at baseline, which is similar to the previously PAH data published by the COMPERA investigators [4]. However, this proportion increased only minimally to 20% at follow-up, as opposed to PAH (12 to 24%). This may reflect the older age (69 vs 64 y) and more profound deconditioning of the CTEPH population, as well as the more restrictive use of combination therapy in CTEPH (only 7 vs 19% in PAH at baseline, and 26 vs 41% at follow-up). Lack or limited efficacy of treatments with off-label PAH drugs (in 63% of the patients) should also be considered. As in PAH [2, 4], the highest proportion of the patients was in the intermediate risk group, both at baseline and at follow-up, which questions the need for a more refined approach of the risk stratification. According to Cox regression, 6MWT, WHO-FC and BNP/NT-proBNP were the most discriminative variables, while only BNP/NT-proBNP and WHO-FC were independent predictors of survival (**Figure 3**).

The present study demonstrated that an abbreviated version of the ESC/ERS risk score assessment developed for PAH using at least three out of six selected variables provided accurate distinction between the risk groups in medically treated patients with CTEPH. Survival of the low and intermediate risk groups at baseline overlap

during first 2 years, while the survival curves of the low and intermediate risk groups at follow-up separate immediately, underscoring the notion that risk assessment at follow-up, i.e. when patients receive medical therapies allows for a more accurate prediction of survival than the baseline assessment. It is also possible that cut-off values and stratification strata suggested for PAH, to segregate low and intermediate risk groups, do not perform as well in the CTEPH population. This is further illustrated by the sensitivity analysis involving only surgically inoperable patients which showed better than expected 1-year survival in the low and intermediate risk groups (100 and 98.8%, respectively). While the Swedish approach performed reasonably well in discriminating the risk groups, the French non-invasive risk score-3 at follow-up identified patients with an excellent long-term survival, similar to what has been reported in PAH [3, 14]. Unfortunately, we were not able to perform the French risk score-4 analysis, including WHO FC, 6MWD, RAP, and CI, because too few right heart catheterisations were performed at follow-up (RAP and CI available in only 33 patients).

In the present analysis, variables closely linked to the mortality risk were 6MWD, WHO FC, BNP/NT-proBNP, and SvO_2, whereas RAP and CI performed less well. Changes in the risk category, regardless of the direction, were predictors of long-term survival and may therefore be considered end-points in future clinical trials. In the present series, 34% of the patients with newly diagnosed CTEPH had experienced a change in the risk category from baseline to follow-up, determined mainly by changes in WHO FC, 6MWD and BNP/NT-proBNP. Using this approach in CTEPH, we could also move from the short-term 6MWD/pulmonary vascular resistance trial design [15-17] to longer term studies determining the net benefit, i.e. the ratio of patients who improve or worsen their risk category.

One of the most important limitations of our study was the fact that not all variables included in the risk stratification strategy proposed by the ESC/ERS PH guidelines were available. Information on clinical signs of right heart failure, progression of symptoms, syncope, cardio-pulmonary exercise test, and echocardiography were missing. Further limitations include missing values, especially haemodynamics at follow-up. When comparing risk assessment at baseline and at follow-up, we may argue that very severe patients might have died, and very mild patients might have dropped out during the follow-up, however there does not seem to be a significant selection bias as shown by the overlap of patient characteristics between baseline and follow-up cohorts (Table S3). No statistical measure was applied to account for the immortal time bias during the follow-up time window of 3-24 months (median, 7 months), which would potentially even have enhanced the differences between the risk groups. Additionally, this study does not take into account the potential effects of BPA in inoperable CTEPH patients, since the technique has only recently been implemented in a limited number of European centres [18]. Still in 2016, only 25% of the newly diagnosed inoperable CTEPH patients in Germany underwent BPA [19]. Even if we anticipate a further generalisation of the procedure, risk assessment is a dynamic concept and if BPA improves risk it will also improve outcomes with a better risk stratification at follow-up than at diagnosis similarly to what is observed in medically treated patients.

In conclusion, the current study shows that an abbreviated version of the ERS/ESC risk stratification may be applicable to medically treated CTEPH patients, with 1-year mortality rates conform to the prediction (<5% for low risk; 5-10% for intermediate risk; and >10% for high risk). However, with the current therapeutic strategy

largely based on monotherapy with off-label use of drugs not approved for the treatment of CTEPH, low risk is achieved in only one in five patients.

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Tables

Table 1. Characteristics of the patients included in the baseline risk stratification group (n=561)

	N	All n=561	Low risk n=81 (14%)	Intermediate risk n=382 (68%)	High risk n=98 (18%)
Age (years)		69 ± 13	63 ± 12	70 ± 12	71 ± 12
Gender, % female		54%	49%	55%	52%
BMI (kg/m^2)	530	28 ± 6	28 ± 5	28 ± 7	28 ± 5
CTEPH status (n; %)					
Post PEA		*30 (5%)*	*9 (11%)*	*20 (5%)*	*1 (1%)*
Surgically inoperable		*248 (44%)*	*37 (46%)*	*176 (46%)*	*35 (36%)*
Medically inoperable		*84 (15%)*	*13 (16%)*	*53 (14%)*	*18 (18%)*
Accessible		*48 (9%)*	*6 (7%)*	*31 (8%)*	*11 (11%)*
Refused surgery		*73 (13%)*	*6 (7%)*	*51 (13%)*	*16 (16%)*
Operability unknown		*78 (14%)*	*10 (12%)*	*51 (13%)*	*17 (17%)*
WHO FC Class I/II/III/IV, %	550	0/15/72/13	0/51/49/0	1/11/81/7	0/0/52/48
6MWD (m)	449	302 ± 126	420 ± 106	304 ± 115	185 ± 90
NTproBNP (ng/L) Median (Q1; Q3)	377	1,402 (352; 3,565)	111 (75; 270)	1,326 (416; 2,654)	3,898 (2,745; 6,216)
BNP (ng/L)	81	186 (53; 486)	31 (22; 49)	187 (65; 382)	681 (499; 769)
Haemodynamics					
RAP (mmHg)	533	*8 ± 5*	*5 ± 3*	*8 ± 5*	*13 ± 5*
PAPm (mmHg)		*42 ± 11*	*36 ± 9*	*42 ± 11*	*48 ± 11*
PAWP (mmHg)		*9 ± 4*	*9 ± 3*	*9 ± 4*	*10 ± 3*
CI (l/min/m2)	525	*2.2 ± 0.8*	*3.0 ±0.7*	*2.2 ± 0.7*	*1.6 ± 0.3*
PVR (dyn·s·cm-5)	547	*734 ± 387*	*411 ± 177*	*702 ± 315*	*1,135 ± 442*
SvO2 (%)	508	*63 ± 9*	*71 ± 5*	*63 ± 8*	*53 ± 7*
Comorbidities					
Any comorbidities	478	*91%*	*90%*	*91%*	*93%*
CHD	449	*20%*	*11%*	*21%*	*23%*
AHT	460	*59%*	*55%*	*61%*	*56%*
DM	462	*16%*	*9%*	*16%*	*23%*
OSAS	418	*9%*	*14%*	*9%*	*4%*
VTE	447	*72%*	*67%*	*72%*	*74%*
Thyroid disease	426	*20%*	*25%*	*20%*	*14%*
Atrial fibrillation	559	*8%*	*1%*	*9%*	*13%*
Initial therapy (within 6 months after diagnosis)					

ERA		24%	20%	24%	31%
PDE5i		42%	44%	41%	46%
sGCs		37%	40%	38%	31%
PCA		1%	0%	1%	3%
Monotherapy		93%	93%	95%	90%
Combination therapy		7%	7%	5%	10%
Anticoagulation		97%*	98%	96%	97%

Categorical data are shown as n and % of the respective population. Continuous data are depicted as mean ± SD unless stated otherwise. N is specified when data are not available for the whole population.

Abbreviations: BMI, body mass index; CTEPH, chronic thromboembolic pulmonary arterial hypertension; PEA, pulmonary endarterectomy; WHO FC, World Health Organization Functional Class; 6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; RAP, right atrial pressure; PAPm, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; SvO_2, mixed-venous oxygen saturation; CHD, coronary heart disease; AHT, arterial hypertension; DM, diabetes mellitus; OSAS, obstructive sleep apnea; VTE, venous thromboembolism; ERA, endothelin receptor antagonists (87% bosentan); PDE5i, phosphodiesterase-5 inhibitors (72% sildenafil); sGCs, stimulator of soluble guanylate cyclase; PCA, prostacyclin analogues; * 26% direct oral anticoagulants

Table 2. Variables obtained between 3 months and 2 years after treatment initiation of the patients included into the follow-up risk stratification group (n=231)

	N	All n=231	Low risk n=47 (20%)	Intermediate risk n=158 (68%)	High risk n=26 (11%)
Age (years)		69 ± 14	60 ± 14	71 ± 13	74 ± 8
Gender, % female		55%	47%	57%	54%
BMI (kg/m^2)	167	28 ± 6	28 ± 5	29 ± 7	28 ± 3
CTEPH status (n; %)					
Post PEA		*17 (7%)*	*5 (11%)*	*12 (8%)*	*0*
Surgically inoperable		*107 (46%)*	*25 (53%)*	*72 (46%)*	*10 (39%)*
Medically inoperable		*32 (14%)*	*2 (4%)*	*25 (16%)*	*5 (19%)*
Accessible		*15 (7%)*	*5 (11%)*	*10 (6%)*	*0*
Refused surgery		*35 (15%)*	*7 (15%)*	*20 (13%)*	*8 (31%)*
Operability unknown		*25 (11%)*	*3 (6%)*	*19 (12%)*	*3 (12%)*
WHO FC Class I/II/III/IV, %	211	4/31/61/4	20/61/20/0	0/28/71/1	0/0/71/29
6MWD (m)	208	318 ± 132	464 ± 125	298 ± 97	168 ± 96
NTproBNP (ng/L) Median (Q1; Q3)	175	867 (227; 2,082)	128 (77; 250)	1,133 (400; 2,002)	4,083 (2,736; 4,819)
BNP (ng/L)	34	145 (70; 324)	11 (5; 18)	136 (71; 203)	388 (337; 1,033)
Haemodynamics					
RAP (mmHg)	94	*8 ± 6*	*5 ± 3*	*8 ± 4*	*17 ± 6*
PAPm (mmHg)	97	*40 ± 10*	*34 ± 12*	*41 ± 9*	*46 ± 6*
PAWP (mmHg)	93	*9 ± 4*	*7 ± 3*	*9 ± 4*	*12 ± 4*
CI (l/min/m2)	89	*2.3 ± 0.8*	*3.0 ± 0.8*	*2.2 ± 0.7*	*1.7 ± 0.4*
PVR (dyn·s·cm-5)	93	*654 ± 374*	*381 ± 227*	*670 ± 310*	*1,043 ± 470*
SvO2 (%)	90	*63 ± 8*	*70 ± 4*	*64 ± 6*	*52 ± 8*
Comorbidities (from inclusion)					
Any comorbidities	182	*90%*	*73%*	*93%*	*100%*
CHD	170	*23%*	*3%*	*26%*	*35%*
AHT	177	*57%*	*53%*	*58%*	*56%*
DM	176	*13%*	*6%*	*13%*	*28%*
OSAS	149	*11%*	*14%*	*9%*	*21%*
VTE	165	*69%*	*61%*	*70%*	*73%*
Thyroid disease	154	*25%*	*24%*	*27%*	*19%*
Atrial fibrillation	225	*10%*	*2%*	*8%*	*31%*
Therapy (at time of FU risk evaluation)					

ERA		40%	23%	44%	50%
PDE5i		49%	36%	53%	50%
sGCs		28%	34%	25%	31%
PCA		2%	4%	2%	0%
no therapy		3%	8%	2%	0%
Monotherapy		71%	77%	70%	69%
Combination therapy		26%	15%	28%	31%
Anticoagulation		97%	98%	97%	96%

Categorical data are shown as n and % of the respective population. Continuous data are depicted as mean ± SD unless stated otherwise. N is specified when data are not available for the whole population.

Abbreviations: BMI, body mass index; CTEPH, chronic thromboembolic pulmonary arterial hypertension; PEA, pulmonary endarterectomy; WHO FC, World Health Organization Functional Class; 6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; RAP, right atrial pressure; PAPm, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; SvO_2, mixed-venous oxygen saturation; CHD, coronary heart disease; AHT, arterial hypertension; DM, diabetes mellitus; OSAS, obstructive sleep apnoea; VTE, venous thromboembolism; ERA, endothelin receptor antagonists; PDE5i, phosphodiesterase-5 inhibitors; sGCs, stimulator of soluble guanylate cyclase; PCA, prostacyclin analogues.

Table S1. Characteristics of the patients included into the baseline risk stratification group (analysis included only patients for whom all risk score variables were available, n=318)

	N	All n=318	Low risk n=37 (12%)	Intermediate risk n=229 (72%)	High risk n=52 (16%)
Age (years)		71 ± 11	62 ± 11	71 ± 11	73 ± 10
Gender, % female		53%	49%	54%	54%
BMI (kg/m^2)	296	29 ± 6	28 ± 5	29 ± 7	28 ± 5
CTEPH status (n; %)					
Post PEA		*17 (5%)*	*5 (14%)*	*12 (5%)*	*0 (0%)*
Surgically inoperable		*155 (49%)*	*17 (46%)*	*119 (52%)*	*19 (37%)*
Medically inoperable		*48 (15%)*	*3 (8%)*	*37 (16%)*	*8 (15%)*
Accessible		*23 (7%)*	*4 (11%)*	*10 (4%)*	*9 (17%)*
Refused surgery		*47 (15%)*	*5 (14%)*	*31 (14%)*	*11 (21%)*
Operability unknown		*28 (9%)*	*3 (8%)*	*20 (9%)*	*5 (9%)*
WHO FC Class I/II/III/IV, %		1/15/72/12	0/62/38/0	1/10/82/7	0/0/54/46
6MWD (m)		300 ± 129	445 ± 101	304 ± 115	183 ± 88
NTproBNP (ng/L) Median (Q1; Q3)	258	1379 (344; 3,413)	108 (73; 249)	1275 (383; 2,586)	3975 (3411; 6,444)
BNP (ng/L)	60	140 (53; 450)	31 (22; 59)	152 (57; 382)	603 (482; 699)
Haemodynamics					
RAP (mmHg)		*8 ± 6*	*4 ± 3*	*8 ± 6*	*12 ± 5*
PAPm (mmHg)		*41 ± 10*	*36 ± 9*	*40 ± 10*	*47 ± 10*
PAWP (mmHg)		*9 ± 4*	*8 ± 3*	*9 ± 4*	*10 ± 3*
CI (l/min/m2)		*2.2 ± 0.8*	*2.9 ± 0.6*	*2.3 ± 0.8*	*1.6 ± 0.4*
PVR (dyn·s·cm-5)	316	*698 ± 365*	*400 ± 167*	*656 ± 298*	*1104 ± 419*
SvO2 (%)		*63 ± 9*	*71 ± 5*	*64 ± 8*	*54 ± 6*
Comorbidities					
Any comorbidities	265	*92%*	*97%*	*91%*	*93%*
CHD	251	*18%*	*13%*	*19%*	*17%*
AHT	256	*62%*	*56%*	*63%*	*61%*
DM	259	*16%*	*0%*	*17%*	*24%*
OSAS	231	*11%*	*23%*	*10%*	*5%*
VTE	249	*75%*	*78%*	*75%*	*73%*
Thyroid disease	237	*22%*	*30%*	*22%*	*13%*
Atrial fibrillation	317	*10%*	*0%*	*11%*	*14%*
Initial therapy (within 6 months after diagnosis)					

ERA		28%	27%	27%	35%
PDE5i		39%	38%	38%	40%
sGCs		36%	46%	36%	27%
PCA		0.3%	0%	0%	2%
Monotherapy		96%	86%	97%	96%
Combination therapy		4%	14%	3%	4%
Anticoagulation		97%	100%	97%	98%

Table S2. Characteristics of the patients with surgically inoperable CTEPH included into the baseline risk stratification group (n=248)

	N	All n=248	Low risk n=37 (15%)	Intermediate risk n=176 (71%)	High risk n=35 (14%)
Age (years)		68 ± 12	64 ± 10	69 ± 12	67 ± 14
Gender, % female		53%	46%	53%	57%
BMI (kg/m^2)	226	28 ± 6	28 ± 4	29 ± 6	28 ± 7
WHO FC Class I/II/III/IV, %	247	0/14/73/13	0/49/51/0	1/9/82/8	0/0/50/50
6MWD (m)	209	307 ± 130	421 ± 105	306 ± 117	167 ± 88
NTproBNP (ng/L) Median (Q1; Q3)	172	1,366 (356; 3,438)	110 (67; 270)	1,334 (432; 2,970)	3,855 (2,644; 7,528)
BNP (ng/L)	37	207 (57; 456)	31 (22; 45)	208 (78; 444)	536 (486; 670)
Haemodynamics					
RAP (mmHg)	236	8 ± 6	4 ± 3	8 ± 6	14 ± 5
PAPm (mmHg)		41 ± 12	35 ± 9	41 ± 11	49 ± 13
PAWP (mmHg)		9 ± 4	9 ± 3	9 ± 4	10 ± 3
CI (l/min/m2)	236	2.3 ± 0.9	3.0 ± 0.5	2.3 ± 0.9	1.6 ± 0.3
PVR (dyn·s·cm-5)	243	700 ± 411	367 ± 136	675 ± 322	1,188 ± 553
SvO2 (%)	229	64 ± 9	71 ± 5	64 ± 9	54 ± 6
Comorbidities					
Any comorbidities	202	93%	94%	93%	87%
CHD	196	19%	9%	21%	23%
AHT	197	59%	62%	61%	48%
DM	198	16%	9%	16%	19%
OSAS	186	9%	14%	9%	0%
VTE	199	77%	69%	79%	77%
Thyroid disease	183	15%	17%	16%	7%
Atrial fibrillation		10%	3%	11%	11%
Initial therapy (within 6 months after diagnosis)					
ERA		28%	19%	27%	40%
PDE5i		47%	43%	47%	51%
sGCs		29%	38%	30%	20%
PCA		0.4%	0%	0%	3%

Monotherapy		93%	92%	94%	86%
Combination therapy		7%	8%	6%	14%
Anticoagulation		98%	100%	97%	100%

Table S3. Variables obtained at baseline for the baseline risk stratification group (n=561), and at baseline and at 3 months to 2 years follow up for the follow-up risk stratification group (n=231)

	Baseline group at baseline n=561	Follow up group at baseline n=231	Follow up group at follow up N=231
Age (years)	69 ± 13	68 ± 14	69 ± 14
Gender, % female	54%	55%	-
BMI (kg/m^2)	28 ± 6	28 ± 6	28 ± 6
CTEPH status (n; %)			
Post PEA	*30 (5%)*	*17 (7%)*	-
Surgically inoperable	*248 (44%)*	*107 (46%)*	-
Medically inoperable	*84 (15%)*	*32 (14%)*	-
Accessible	*48 (9%)*	*15 (7%)*	-
Refused surgery	*73 (13%)*	*35 (15%)*	-
Operability unknown	*78 (14%)*	*25 (11%)*	-
WHO FC Class I/II/III/IV, %	0/15/72/13	0/18/69/13	4/31/61/4
6MWD (m)	302 ± 126	319 ± 129	318 ± 132
NTproBNP (ng/L) Median (Q1; Q3)	1,402 (352; 3,565)	1,266 (284; 3,477)	867 (227; 2,082)
BNP (ng/L)	186 (53; 486)	166 (52; 465)	145 (70; 324)
Haemodynamics			
RAP (mmHg)	*8 ± 5*	*9 ± 6*	*8 ± 6*
PAPm (mmHg)	*42 ± 11*	*42 ± 11*	*40 ± 10*
PAWP (mmHg)	*9 ± 4*	*9 ± 4*	*9 ± 4*
CI (l/min/m2)	*2.2 ± 0.8*	*2.2 ± 0.7*	*2.3 ± 0.8*
PVR (dyn·s·cm-5)	*734 ± 387*	*727 ± 380*	*654 ± 374*
SvO2 (%)	*63 ± 9*	*62 ± 9*	*63 ± 8*
Comorbidities (from inclusion)			
Any comorbidities	*91%*	*90%*	-
CHD	*20%*	*23%*	-
AHT	*59%*	*57%*	-
DM	*16%*	*13%*	-
OSAS	*9%*	*11%*	-
VTE	*72%*	*69%*	-
Thyroid disease	*20%*	*25%*	-
Atrial fibrillation	*8%*	*10%*	-
Therapy (at baseline and at time of FU risk evaluation)			

ERA	24%	36%	40%
PDE5i	42%	41%	49%
sGCs	37%	27%	28%
PCA	1%	1%	2%
no therapy	0%	0%	3%
Monotherapy	93%	92%	71%
Combination therapy	7%	8%	26%
Anticoagulation	97%	98%	97%

Table S4. Characteristics of the patients with 0 to 3 low risk criteria at baseline (n=368)

	N	All n=368	Low risk criteria = 0 n=236 (64%)	Low risk criteria = 1 n=85 (23%)	Low risk criteria = 2 n=35 (10%)	Low risk criteria = 3 n=12 (3%)
Age (years)		70 ± 12	73 ± 10	68 ± 11	62 ± 14	57 ± 12
Gender, % female		52%	56%	54%	34%	17%
BMI (kg/m^2)	346	28 ± 6	28 ± 6	29 ± 7	27 ± 6	26 ± 4
CTEPH status (n; %)						
Post PEA		*21 (6%)*	*11 (5%)*	*3 (4%)*	*5 (14%)*	*2 (17%)*
Surgically inoperable		*173 (47%)*	*108 (46%)*	*42 (49%)*	*17 (49%)*	*6 (50%)*
Medically inoperable		*54 (15%)*	*39 (17%)*	*13 (15%)*	*2 (6%)*	*0 (0%)*
Accessible		*30 (8%)*	*21 (9%)*	*4 (5%)*	*4 (11%)*	*1 (8%)*
Refused surgery		*53 (14%)*	*35 (15%)*	*11 (13%)*	*6 (17%)*	*1 (8%)*
Operability unknown		*37 (10%)*	*22 (9%)*	*12 (14%)*	*1 (3%)*	*2 (17%)*
WHO FC Class I/II/III/IV, %		1/15/73/12	0/0/84/16	0/21/72/7	6/69/23/3	0/100/0/0
6MWD (m)		298 ± 131	248 ± 98	335 ± 115	467 ± 97	552 ± 80
NT-proBNP (ng/L) Median (Q1; Q3)	300	1385 (343; 3,436)	2503 (1121; 4,173)	290 (124; 1,547)	263 (88; 687)	94 (75; 130)
BNP (ng/L) Median (Q1; Q3)	69	140 (51; 456)	226 (105; 499)	40 (17; 96)	139 (23; 630)	22 (22; 22)
Haemodynamics						
RAP (mmHg)		*8 ± 6*	*9 ± 6*	*7 ± 4*	*6 ± 5*	*7 ± 5*
PAPm (mmHg)		*41 ± 11*	*43 ± 10*	*38 ± 10*	*36 ± 9*	*34 ± 10*
PAWP (mmHg)		*9 ± 4*	*9 ± 4*	*9 ± 4*	*8 ± 4*	*8 ± 4*
CI (l/min/m2)		*2.2 ± 0.8*	*2.1 ± 0.8*	*2.5 ± 0.8*	*2.4 ± 0.7*	*2.9 ± 0.6*
PVR (dyn·s·cm-5)		*708 ± 366*	*805 ± 379*	*566 ± 290*	*522 ± 216*	*380 ± 144*
SvO2 (%)		*63 ± 9*	*61 ± 8*	*68 ± 7*	*64 ± 12*	*73 ± 4*
Comorbidities (from inclusion)						
Any comorbidities	310	*93%*	*93%*	*93%*	*86%*	*91%*
CHD	292	*19%*	*19%*	*19%*	*17%*	*18%*
AHT	298	*63%*	*67%*	*63%*	*48%*	*46%*
DM	302	*16%*	*18%*	*17%*	*7%*	*0%*
OSAS	270	*11%*	*9%*	*13%*	*14%*	*14%*
VTE	293	*73%*	*71%*	*76%*	*72%*	*82%*
Thyroid disease	277	*21%*	*18%*	*28%*	*23%*	*20%*
Atrial fibrillation	310	*9%*	*13%*	*2%*	*0%*	*0%*

Initial therapy (within 6 months after diagnosis)						
ERA		28%	28%	28%	31%	17%
PDE5i		39%	43%	34%	26%	33%
sGCs		36%	32%	39%	46%	58%
PCA		1%	1%	0%	0%	0%
Monotherapy		95%	95%	95%	97%	92%
Combination therapy		5%	5%	5%	3%	8%
Anticoagulation		97%	98%	92%	100%	100%

Table S5. Characteristics of the patients with 0 to 3 low risk criteria at 3 months to 2 years follow-up (n=199)

	N	All n=199	Low risk criteria = 0 n=95 (48%)	Low risk criteria = 1 n=64 (32%)	Low risk criteria = 2 n=23 (12%)	Low risk criteria = 3 n=17 (9%)
Age (years)		69 ± 14	72 ± 11	72 ± 14	58 ± 17	60 ± 13
Gender, % female		55%	59%	58%	44%	35%
BMI (kg/m^2)	140	29 ± 7	29 ± 6	29 ± 8	28 ± 6	27 ± 4
CTEPH status (n; %)						
Post PEA		*15 (8%)*	*4 (4%)*	*6 (9%)*	*2 (9%)*	*3 (18%)*
Surgically inoperable		*91 (46%)*	*49 (52%)*	*22 (34%)*	*12 (52%)*	*8 (47%)*
Medically inoperable		*29 (15%)*	*16 (17%)*	*12 (19%)*	*0*	*1 (6%)*
Accessible		*13 (7%)*	*4 (4%)*	*5 (8%)*	*1 (4%)*	*3 (18%)*
Refused surgery		*30 (15%)*	*15 (16%)*	*7 (11%)*	*6 (26%)*	*2 (12%)*
Operability unknown		*21 (11%)*	*7 (7%)*	*12 (19%)*	*2 (9%)*	*0*
WHO FC Class I/II/III/IV, %		4/33/59/4	0/0/93/7	0/58/41/2	13/70/17/0	29/71/0/0
6MWD (m)		320 ± 131	255 ± 94	307 ± 92	459 ± 107	540 ± 82
NTproBNP (ng/L) Median (Q1; Q3)	166	997 (207; 2,194)	1948 (997; 3,967)	505 (186; 1,385)	257 (128; 838)	87 (71; 106)
BNP (ng/L) Median (Q1; Q3)	34	145 (71; 324)	176 (112; 337)	113 (27; 324)	63 (48; 84)	11 (-; -)
Haemodynamics						
RAP (mmHg)	29	*8 ± 5*	*9 ± 5*	*5 ± 3*	*7 ± 1*	*5 ± 1*
PAPm (mmHg)	31	*38 ± 9*	*41 ± 7*	*35 ± 10*	*28 ± 11*	*30 ± 15*
PAWP (mmHg)	30	*9 ± 4*	*10 ± 4*	*7 ± 3*	*13 ± 0*	*9 ± 1*
CI (l/min/m2)	31	*2.1 ± 0.6*	*1.9 ± 0.6*	*2.2 ± 0.5*	*2.4 ± 0.6*	*2.8 ± 0.4*
PVR (dyn·s·cm-5)	31	*708 ± 430*	*843 ± 424*	*540 ± 190*	*205 ± 86*	*309 ± 221*
SvO2 (%)	29	*62 ± 9*	*61 ± 10*	*68 ± 3*	*71 ± 1*	*-*
Comorbidities (from inclusion)						
Any comorbidities	163	*90%*	*94%*	*95%*	*73%*	*73%*
CHD	153	*25%*	*25%*	*33%*	*14%*	*7%*
AHT	160	*58%*	*57%*	*62%*	*47%*	*60%*
DM	159	*14%*	*19%*	*13%*	*7%*	*0%*
OSAS	135	*11%*	*8%*	*15%*	*7%*	*18%*
VTE	146	*69%*	*72%*	*71%*	*64%*	*47%*
Thyroid disease	139	*25%*	*25%*	*24%*	*23%*	*31%*
Atrial fibrillation	195	*10%*	*14%*	*8%*	*0%*	*6%*

Therapy (at time of FU risk evaluation)						
ERA		36%	47%	20%	44%	24%
PDE5i		49%	53%	52%	44%	29%
sGCs		28%	23%	31%	17%	53%
PCA		1%	0%	2%	4%	0%
No therapy		3%	0%	5%	4%	6%
Monotherapy		78%	73%	83%	83%	82%
Combination therapy		20%	27%	13%	13%	12%
Anticoagulation		97%	95%	98%	96%	100%

Figures

Figure 1. Patient disposition. CTEPH, chronic thromboembolic pulmonary hypertension; FU, follow-up; PEA, pulmonary endarterectomy; BPA, balloon pulmonary angioplasty.

Figure 2. 5-year survival (at least 3 variables available): A. from baseline; B. from follow-up

Figure 3. Hazard ratios for the risk-score items at baseline, estimated by A) univariate and B) multivariate Cox regression analysis, using the respective low-risk group as reference. IR: intermediate risk group; HR: high risk group; 6MWD: 6-min walking distance; WHO FC: World Health Organization functional class; BNP, brain natriuretic peptide; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; SvO_2: mixed venous oxygen saturation; RAP: right atrial pressure; CI: cardiac index.

Figure 4. 5-year survival from baseline of surgically inoperable CTEPH (at least 3 variables)

Figure 5. 5-year survival according to change in risk category from baseline to follow-up (at least 3 variables available)

Figure 6. 5-year survival according to the number of low risk criteria: A. from baseline; B. from follow-up

Figure S1. 5-year survival from baseline (all 6 variables)

```
                              ┌──────────────────┐
                              │ Incident CTEPH with │
                              │  at least 3 variables │
                              │      available       │
                              │       (n=723)        │
                              └──────────┬───────────┘
                                         │
  ┌─────────────────────────┐           │
  │ Only inclusion visit (n=91) │        │      ┌──────────────────────────────────────────────┐
  │ PEA or BPA at FU (n=71      ├─────────┤      │ no FU risk assessment within 3-24 months (n=308) │
  └─────────────────────────┘           │      │ no further FU after the FU risk assessment (n=22) │
                                         │      └──────────────────────────────────────────────┘
                              ┌──────────┴───────────┐                          ┌──────────────┐
                              │   Baseline cohort     ├──────────────────────────┤  FU cohort   │
                              │       (n=561)         │                          │   (n=231)    │
                              └──────────┬───────────┘                          └──────────────┘
                   ┌─────────────────────┼─────────────────────┐
        ┌──────────┴────────┐  ┌─────────┴────────┐  ┌──────────┴───────────┐
        │    Post PEA        │  │   Inoperable      │  │ Accessible (n=48),    │
        │     (n=30)         │  │    (n=332)        │  │  refused (n=73),      │
        └────────────────────┘  └─────────┬────────┘  │  unknown (n=78)       │
                                          │           └──────────────────────┘
                          ┌───────────────┴──────────────┐
               ┌──────────┴─────────┐        ┌───────────┴──────────┐
               │ Surgically inoperable │      │ Medically inoperable  │
               │      (n=248)         │       │      (n=84)           │
               └─────────────────────┘        └──────────────────────┘
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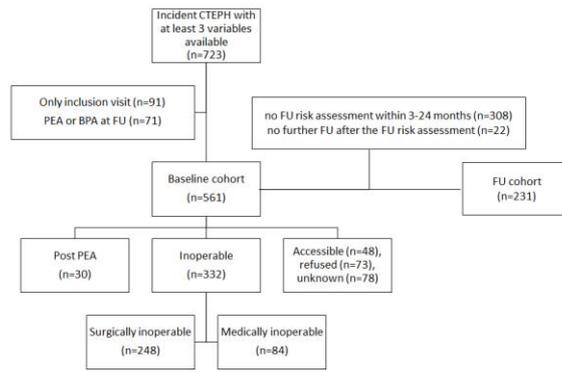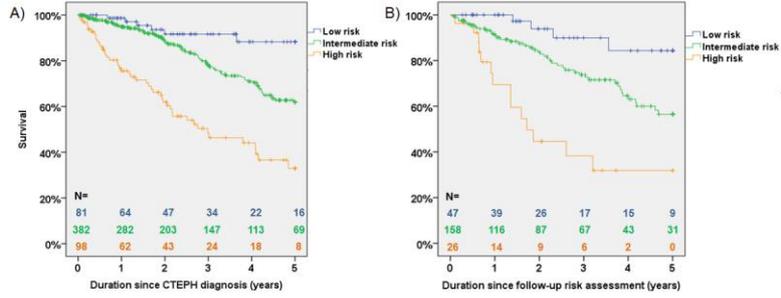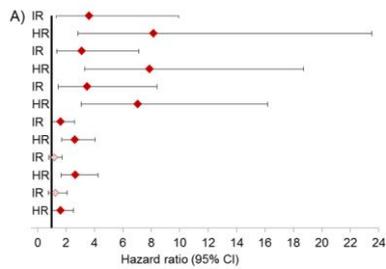
Survival	Years after enrolment					
	0	1	2	3	4	5
Low risk	100%	98.6%	91.7%	91.7%	88.3%	88.3%
Intermediate risk	100%	94.9%	88.2%	78.4%	71.0%	61.8%
High risk	100%	75.5%	61.9%	48.3%	44.1%	32.9%

Survival	Years after enrolment					
	0	1	2	3	4	5
Low risk	100%	100.0%	93.9%	90.0%	84.3%	84.3%
Intermediate risk	100%	91.6%	83.8%	73.8%	63.1%	56.5%
High risk	100%	69.4%	44.6%	38.3%	31.9%	.

A)

6-MWD	IR	3.63 (1.33;9.93)
	HR	8.17 (2.84;23.50)
WHO FC	IR	3.11 (1.36;7.12)
	HR	7.87 (3.31;18.70)
NT pro-BNP/ BNP	IR	3.51 (1.46;8.40)
	HR	7.05 (3.07;16.17)
SvO₂	IR	1.62 (1.01;2.59)
	HR	2.61 (1.69;4.04)
RAP	IR	1.17 (0.79;1.72)
	HR	2.65 (1.65;4.25)
CI	IR	1.25 (0.75;2.07)
	HR	1.62 (1.04;2.52)

B)
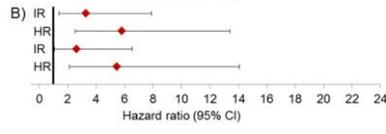
NT pro-BNP/ BNP	IR	3.29 (1.37;7.90)
	HR	5.82 (2.53;13.41)
WHO FC	IR	2.64 (1.07;6.54)
	HR	5.46 (2.12;14.07)
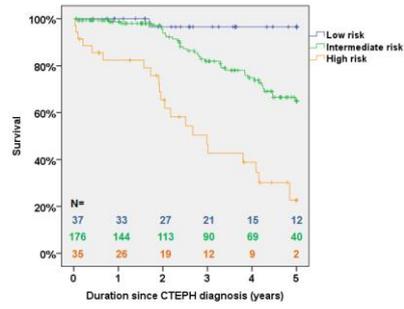
Survival	Years after enrolment					
	0	1	2	3	4	5
Low risk	100%	100%	96.6%	96.6%	96.6%	96.6%
Intermediate risk	100%	98.8%	93.9%	81.9%	74.9%	64.9%
High risk	100%	82.4%	65.4%	46.5%	38.8%	22.6%
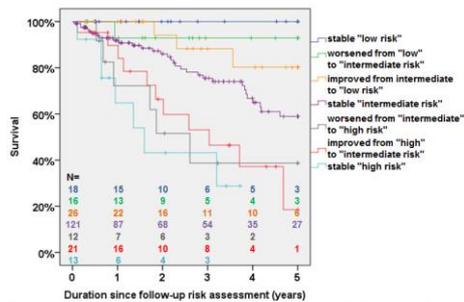
Survival	Years after enrolment					
	0	1	2	3	4	5
stable "low risk"	100%	100%	100%	100%	100%	100%
worsened from "low" to "intermediate risk"	100%	92.9%	92.9%	92.9%	92.9%	92.9%
improved from intermediate to "low risk"	100%	100%	94.1%	88.2%	80.2%	80.2%
stable "intermediate risk"	100%	91.8%	86.0%	75.4%	64.9%	58.9%
worsened from "intermediate" to "high risk"	100%	72.2%	51.6%	38.7%	38.7%	
improved from "high" to "intermediate risk"	100%	89.6%	66.4%	53.1%	37.2%	18.6%
stable "high risk"	100%	64.7%	43.2%	43.2%		

A)

Survival	Years after enrolment					
	0	1	2	3	4	5
3 criteria	100%	100.0%	100.0%	100.0%	100.0%	.
2 criteria	100%	100.0%	95.8%	90.8%	90.8%	90.8%
1 criterion	100%	95.7%	92.3%	87.9%	82.4%	79.0%
no criteria	100%	89.6%	81.4%	69.3%	59.9%	46.2%

B)

Survival	Years after enrolment					
	0	1	2	3	4	5
3 criteria	100.0%	100.0%	100.0%	100.0%	100.0%	.
2 criteria	100.0%	100.0%	94.7%	88.4%	81.6%	81.6%
1 criterion	100.0%	91.6%	84.8%	70.5%	65.8%	61.1%
no criteria	100.0%	90.6%	75.9%	65.3%	50.2%	47.7%
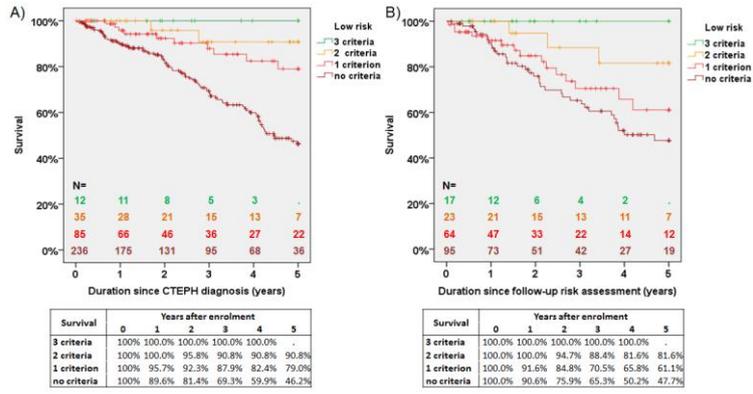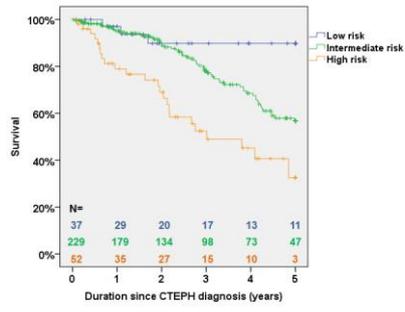
Survival	Years after enrolment					
	0	1	2	3	4	5
Low risk	100%	97.1%	89.8%	89.8%	89.8%	89.8%
Intermediate risk	100%	95.1%	88.9%	78.1%	68.6%	56.7%
High risk	100%	79.0%	69.1%	52.4%	45.2%	32.5%