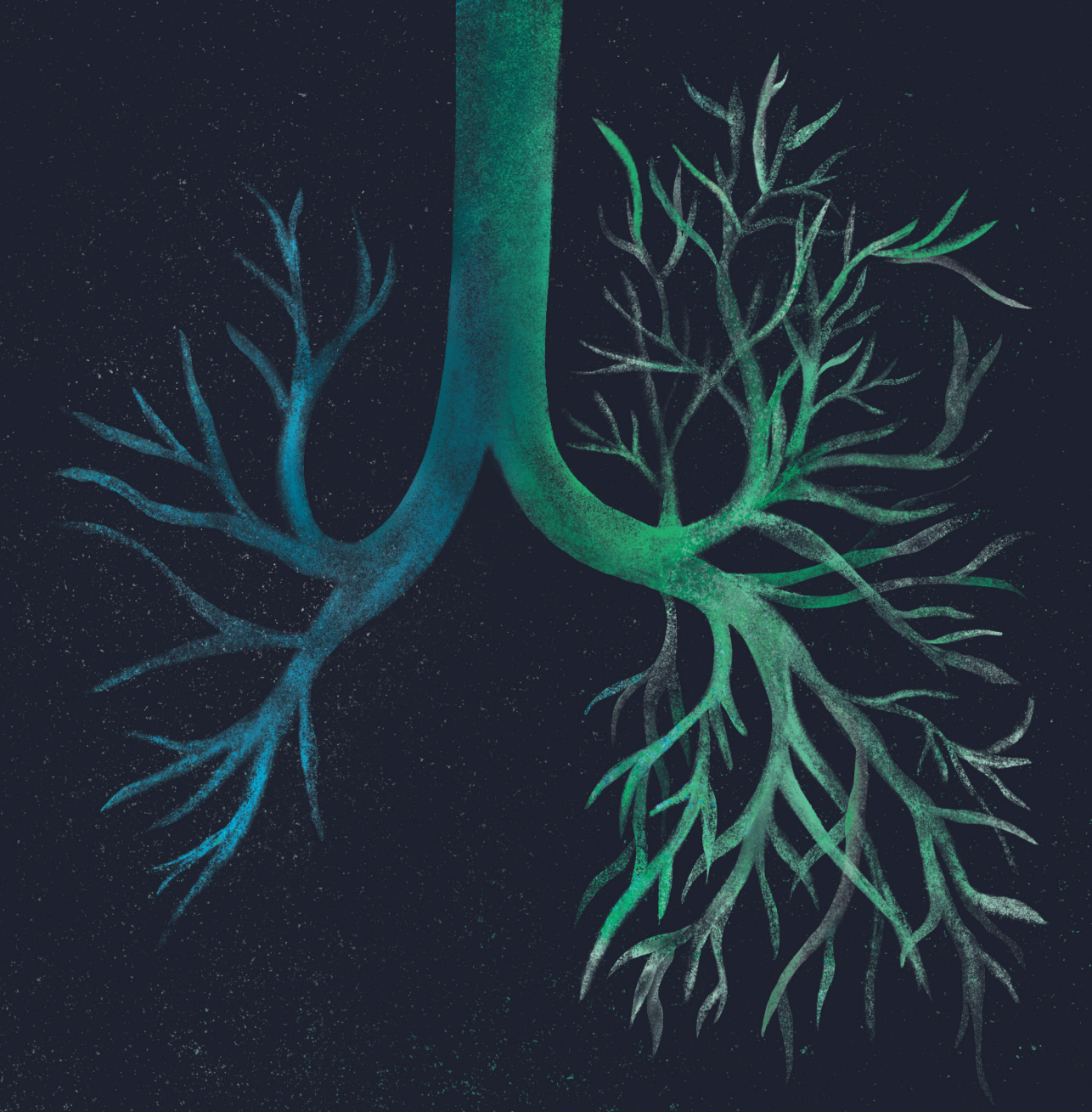

Chronic thromboembolic pulmonary hypertension

clinical outcomes

M.C.J. van Thor

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Chronic thromboembolic pulmonary hypertension
clinical outcomes

Chronische trombo-embolische pulmonale hypertensie
klinische uitkomsten

(met een samenvatting in het Nederlands)

Proefschrift

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Mitch Christian Johan van Thor
geboren op 21 januari 1992
te Maastricht

Promotoren

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Copromotor

Dr. J.J. Mager

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CHAPTER 1

General introduction

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Background

Chronic thromboembolic pulmonary hypertension (CTEPH) is a pulmonary vascular disease, usually due to incomplete resolution of acute pulmonary embolisms[1]. Chronic thromboembolisms cause a macrovascular obstruction in proximal pulmonary arteries and vascular remodelling may subsequently result in microvascular disease[2,3]. The subsequent increase in pulmonary vascular resistance (PVR) and pulmonary artery pressure (PAP) leads to increased right ventricular (RV) afterload and wall stress. Eventually, RV dysfunction and failure will develop, with its associated morbidity and mortality[4,5].
The incidence of acute pulmonary embolism in Europe ranges from 66 to 104 cases per 100.000 population per year, while CTEPH incidence ranges from 3 to 5 cases per 100.000 population per year[6]. However, as CTEPH diagnosis remains challenging due to nonspecific symptoms and the absence of an acute pulmonary embolism in a part of all patients, there may be a diagnostic delay that negatively impacts CTEPH prognosis[7].
All patients are advised to be discussed in a multidisciplinary CTEPH team to establish CTEPH diagnosis and to choose treatment strategy[8]. Pulmonary endarterectomy (PEA) is the preferred treatment in operable patients as it greatly improves outcome and prognosis[9]. Patients with inoperable disease, reluctant to undergo PEA or with recurrent/persistent PH after PEA should be treated with PH-specific medical therapy and, if possible, balloon pulmonary angioplasty (BPA) to improve outcome[10–13].

Pathophysiology and clinical aspects

A previous (symptomatic) pulmonary embolism and deep venous thrombosis occurred in respectively 75% and 56% of all CTEPH patients[14]. Acute pulmonary embolism is treated with anticoagulation therapy, however, in up to two third of patients residual perfusion defects persist after three months of anticoagulation therapy[15]. Over time, complete resolution of thromboembolism will occur in most patients, while in a minority CTEPH will develop. It is unclear why some patients do develop CTEPH and others do not.
There are established risk factors for CTEPH development, which influence the inflammatory, coagulation or fibrinolysis system. For example, an increased risk is observed in patients with a history of malignancy, underlying autoimmune or haematological disease, after splenectomy or thyroid replacement therapy[16–18]. In addition, also large and recurrent pulmonary embolisms and inadequate anticoagulation treatment may promote incomplete resolution of (proximal) thromboembolisms and evolution to organised fibrotic cloths, thereby increasing the risk of CTEPH development[2].
In addition to macrovascular disease, microvascular disease may develop, probably due to redistribution of pulmonary flow and distal thrombus embolization. This may lead to

shear stress and endothelial dysfunction[19]. Although the underlying molecular mechanisms are not completely known, the nitric oxide-soluble guanylate cyclase(sGC)-cyclic guanosine monophosphate pathway may plan an important role[20].

Diagnosis and treatment

Timely CTEPH diagnosis and treatment remains challenging. Most patients present with non-specific symptoms as dyspnoea, oedema, fatigue, chest pain and syncope[14]. However, these symptoms are usually due to RV failure and may therefore already reflect advanced disease. The time between the acute pulmonary embolism and the symptomatic presentation of CTEPH ranges from months to years[4]. In addition, some "acute" pulmonary embolisms are already chronic when diagnosed[21]. As CTEPH is a rare disease, physicians may not recognise CTEPH, with a subsequent delay in CTEPH diagnosis[14,22].

In case of suspected CTEPH disease, work-up starts with a transthoracic echocardiography to assess the probability of pulmonary hypertension[23]. In case of an intermediate or high probability, a ventilation/perfusion scan is necessary[24]. The CTEPH diagnosis is established when pulmonary vessels show evidence of chronic thromboembolisms in the presence of PH after a minimum of 3 months anticoagulation treatment (figure 1). PH is currently defined as a mean PAP (mPAP) of ≥25 mmHg and a wedge pressure ≤15 mmHg on right heart catheterisation.

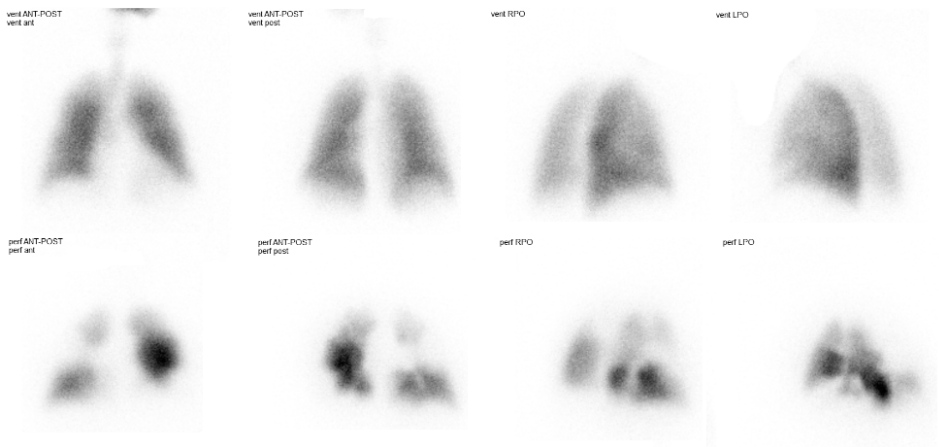

Figure 1. Ventilation/perfusion scan showing mismatched perfusion defects. Top row: normal ventilation scan. Bottom row: Segmental and subsegmental perfusion defects.

Following CTEPH diagnosis, further work up should consist of pulmonary angiography and/or chest computed tomography angiography to assess operability (figure 2). All

test should be reviewed in a multidisciplinary team to select the best treatment for the specific patient[8,25]. In addition, all patients should continue lifelong anticoagulation treatment[23].

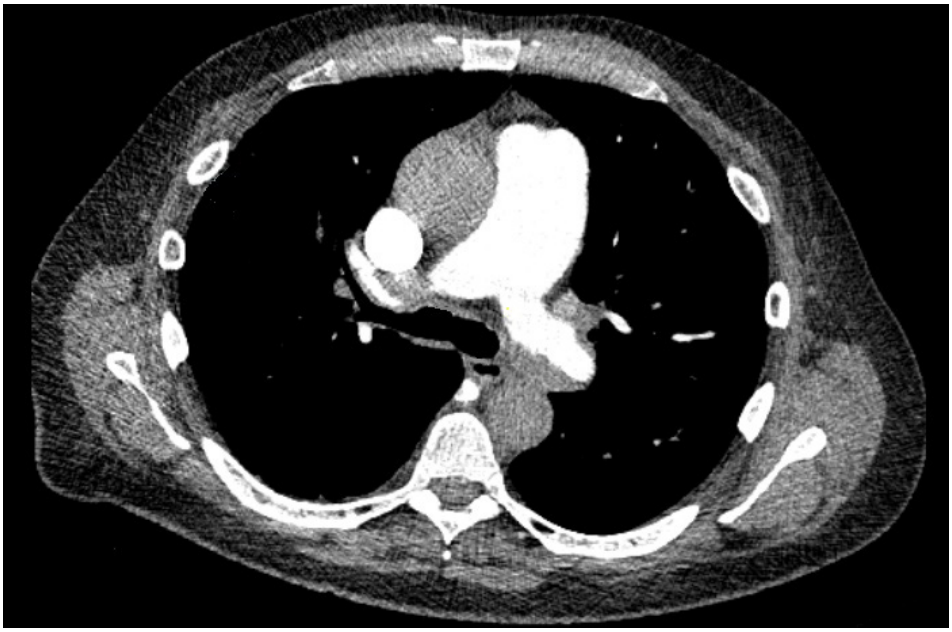

Figure 2. Chest computed tomography angiography with mural thrombus in the left and right pulmonary artery and segmental arteries.

In patients with proximal disease, with a proportional PVR and without severe comorbidities, PEA is the treatment of choice as it greatly improves outcome[14,26]. A PEA is performed by a cardiothoracic surgeon and requires a median sternotomy, cardiopulmonary bypass and cooling of the patient's body to 20°C. The pulmonary arteries are opened and dissected to remove thromboembolic material, with patients undergoing intermittent deep hypothermic circulatory arrest to provide a clear and bloodless operating field[9,27]. After successful PEA, improvements in pulmonary hemodynamics, exercise tolerance, symptoms and quality of life are observed[28–30].

Nevertheless, as some patients are inoperable (due to distal disease or comorbidities), are reluctant to undergo PEA or have recurrent or persistent PH after PEA, treatment with PH-specific medical therapy and BPA should be considered (figure 3)[23].

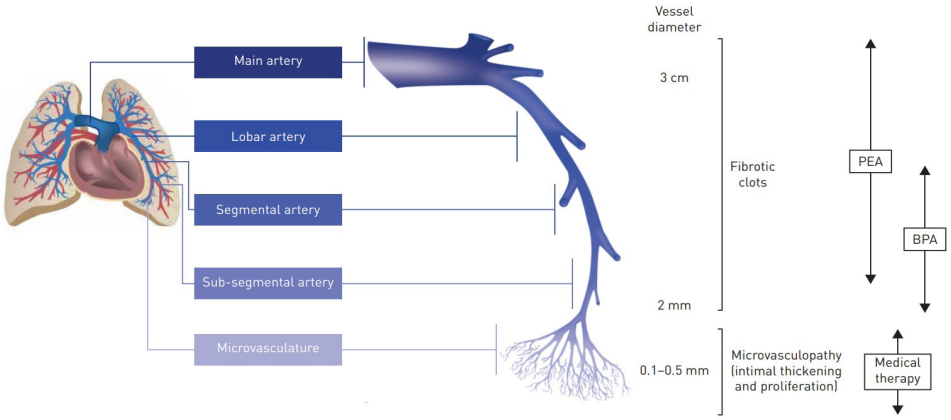

Figure 3. Schematic representation of the pulmonary vascular bed, the different pathogenic manifestations and available treatments. PEA: pulmonary endarterectomy, BPA: balloon pulmonary angioplasty. Adapted from and reproduced with permission of the © ERS 2020: European Respiratory Review Dec 2017, 26 (146) 170105; DOI: 10.1183/16000617.0105-2017 and reproduced with permission of © Elsevier 2020[31].

PART I Pulmonary hypertension-specific medical therapy for chronic thromboembolic pulmonary hypertension

Inoperable patients or patients with recurrent/persistent PH after PEA should receive PH-specific medical therapy to improve exercise capacity and hemodynamics, and to delay clinical worsening[11,23,32,33]. Only riociguat, a sGC-stimulator, is currently approved for CTEPH treatment. Short-term results from the Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase-Stimulator Trial 1 (CHEST-1) showed improvement of 6-minute walking distance (6MWD) and World Health Organization (WHO) functional class (FC), while PVR and N-terminal pro brain natriuretic peptide (NT-proBNP) levels decreased with riociguat[34]. The long-term extension study (CHEST-2) showed that riociguat is efficacious up to one year after treatment initiation and data from the EXPERT registry showed that the use of riociguat in clinical practice was safe[35,36]. Riociguat stimulates and sensitizes sGC with a subsequent increase in cyclic guanosine monophosphate, leading to vasodilatation and altered pulmonary vascular tone.

However, patients using riociguat may experience adverse events or may not achieve maximum dose or treatment goals. Because of resemblance in pathologic pathways between pulmonary arterial hypertension (PAH) and CTEPH, PAH therapy may then be considered[3,25].

Endothelin receptor antagonists (ERAs) have been used in CTEPH before; bosentan significantly improved PVR but had no effect on the 6MWD in the BENEFiT trial, while macitentan, the newest ERA, significantly improved PVR and exercise capacity in the

MERIT-1 trial[37,38]. Macitentan has sustained receptor binding properties and enhanced tissue distribution, and may therefore be superior to other ERAs[39–41].
In PAH, the current clinical practice is to start initial dual combination PH-specific medical therapy to achieve a low-risk status, improve outcome and to reduce the risk of clinical failure[23,42–46]. Combination therapy can be given upfront or sequential. Upfront combination therapy is preferred over sequential combination therapy for PAH, but both strategies were only compared with monotherapy[23,44]. Nevertheless, experience with early combination therapy in CTEPH is limited and is adapted from PAH treatment strategies. In the MERIT-1 trial, 60% of the patients used background PAH therapy combined with macitentan, although these patients did predominantly receive phosphodiesterase type 5 inhibitors and follow-up duration was limited[38]. Other smaller (cohort and case) studies showed improved hemodynamics, WHO FC and 6MWD in patients using combination therapy[47–49].
In the Netherlands we are able to initiate and combine PAH therapy in CTEPH patients, however, this is not possible in all other countries around the world.

PART II Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension

Historically, the first BPA was performed in 1988 in Leiden, the Netherlands[50]. Results of the first series of patients who underwent BPA were reported in 2001, but due to a high percentage of severe complications BPA was not used for years[51]. After several years, however, the technique was reintroduced in Japan. Since then, BPA has gained more interest and is now being used in many countries around the world[13]. The St. Antonius Hospital, Nieuwegein and the Amsterdam UMC, Amsterdam, are the two CTEPH centres in the Netherlands where BPA procedures are performed.
Treatment with BPA aims to restore blood flow in the pulmonary arteries by opening (partially) obstructed vessels leading to improved pulmonary hemodynamics[13]. After gaining vascular access, usually femoral, vascular obstructions are identified by angiography. Then a guide wire is passed across the vascular lesion and balloon dilatation is performed to restore pulmonary blood flow[13]. There are different types of lesions, such as webs, pouch defects, tortuous lesions and total occlusions[52].
Patients require multiple BPA procedures to achieve optimal results and to lower periprocedural complications. However, complications such as vascular injury (with or without haemoptysis), vascular dissection, lung injury and access site complications do occur[25]. Nevertheless BPA technique, patient selection and CTEPH care got more refined nowadays.

PART III Quality of life in patients with chronic thromboembolic pulmonary hypertension

Patients with CTEPH do experience symptoms and impaired exercise tolerance, which can

be measured with WHO FC and 6MWD. However, the impact of disease and treatment on physical, (psycho)social functioning and general wellbeing is also important for quality of life (QoL)[53]. QoL research in CTEPH patients is limited available, but it is known that PH patients experience an impaired QoL due to high disease burden, anxiety and depression[54,55]. Several tools and questionnaires are available to measure QoL, such as general (SF-36) and PH-specific questionnaires (the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) and the EmPHasis-10)[56]. Nevertheless, the use of QoL questionnaires needs validation if translated and used in a specific PH population.
QoL assessment in CTEPH patients after PEA showed improvement of SF-36 and CAMPHOR questionnaires compared to baseline[57–60]. Extensive QoL research in medically treated CTEPH patients is often inconsistent and results of change in QoL after BPA are currently unavailable[53].

AIM OF THIS THESIS

The main aim of this thesis is to describe clinical outcomes of CTEPH patients. Therefore the following goals were defined:

1. To describe the clinical outcome of CTEPH patients using riociguat or macitentan.
2. To describe differences in outcome between CTEPH patients using bosentan and macitentan.
3. To describe the difference in outcome between CTEPH patients using PH-specific medical monotherapy or combination therapy.
4. To describe short-term clinical and hemodynamic results of BPA in CTEPH patients.
5. To describe change in perfusion on perfusion/ventilation scan in CTEPH patients after BPA.
6. To measure (change in) quality of life in CTEPH patients.

OUTLINE OF THIS THESIS

Part I Pulmonary hypertension-specific medical therapy for chronic thromboembolic pulmonary hypertension

- In **chapter 2** we describe survival, clinical worsening and clinical outcome till three-year follow-up in CTEPH patients using riociguat.
- **Chapter 3** describes survival and clinical outcome in technical inoperable and clinical inoperable CTEPH patients using macitentan.
- In **chapter 4** we compare survival and clinical outcome between CTEPH patients using bosentan or macitentan.
- **Chapter 5** describes a comparison of survival and outcome of CTEPH patients using PH-specific monotherapy or combination therapy at one-, three- and five-year follow-up.

Part II Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension

- In **chapter 6** we describe the first results of BPA in CTEPH patients in the Netherlands.
- **Chapter 7** shows change in ventilation/perfusion scan after BPA treatment in CTEPH patients.

Part III Quality of life in patients with chronic thromboembolic pulmonary hypertension

- In **chapter 8** we report and compare QoL outcomes, measured with the CAMPHOR and EmPHasis-10, in CTEPH and pulmonary arterial hypertension patients.

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PART I

Pulmonary hypertension-specific medical therapy for chronic thromboembolic pulmonary hypertension

CHAPTER 2

Long-term clinical value and outcome of riociguat in chronic thromboembolic pulmonary hypertension

M.C.J. van Thor, L. ten Klooster, R.J. Snijder, M.C. Post, J.J. Mager
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ABSTRACT

Background: To improve clinical outcome, patients with inoperable and residual chronic thromboembolic pulmonary hypertension (CTEPH) can be treated with riociguat. The aim of this study is to explore long-term outcomes and to compare our 'real world' data with previous research.

Methods: We included all consecutive patients with technical inoperable and residual CTEPH, in whom riociguat therapy was initiated from January 2014 onwards, with patients followed till January 2019. Survival, clinical worsening (CW), functional class (FC), N-terminal pro brain natriuretic peptide (NT-proBNP) and 6-minute walking distance (6MWD) were described yearly after riociguat initiation.

Results: Thirty-six patients (50% female, mean age 64.9±12.1 years, 54% WHO FC III/IV and 6MWD 337±138m could be included, with a mean follow-up of 2.3±1.2 years. Survival and CW-free survival three years after initiation of riociguat were 94% and 78%, respectively. The 6MWD per 10m at baseline was a significant predictor (HR 0.90 [0.83-0.97], p=0.009) for CW. At three years follow-up the WHO FC and 6MWD improved and NT-proBNP decreased compared to baseline.

Conclusion: Our study confirms that riociguat is an effective treatment in patients with technical inoperable and residual CTEPH at long-term follow-up. Although our results are consistent with previous studies, more 'real world' research is necessary to confirm long-term results.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a disease of progressive pulmonary artery remodelling with high morbidity and mortality[1–3]. Pulmonary endarterectomy (PEA) is the preferred treatment, as it has a good prognosis and outcome in operable patients[4,5]. Inoperable patients and patients with persistent pulmonary hypertension after PEA (residual PH) are treated with PH pharmacologic therapy to improve exercise capacity and hemodynamics, and to delay clinical worsening (CW)[5–7]. The soluble guanylate cyclase (sGC) stimulator riociguat is currently the only officially registered treatment for CTEPH. Short-term results from the Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase-Stimulator Trial 1 (CHEST-1)[8] showed improvement of 6-minute walking distance (6MWD) and World Health Organization (WHO) functional class (FC), decreased pulmonary vascular resistance (PVR) and N-terminal pro brain natriuretic peptide (NT-proBNP) levels. The long-term extension study (CHEST-2)[9] showed that the use of riociguat is safe and efficacious up to one year after treatment initiation. However, long-term follow-up data and experiences from 'real world' data are both limited available.

In this article, we describe the long-term clinical outcome of technical inoperable and residual CTEPH patients on riociguat therapy. Furthermore we try to identify predictors for death and CW and we compare our 'real world' data with the previous (randomized, controlled) riociguat studies.

2. Methods

2.1 Study population

We retrospectively included all consecutive technical inoperable CTEPH and residual PH patients who started with riociguat treatment and were discussed in our multidisciplinary CTEPH team from January 2014 onwards and were followed till January 2019. Our expert team consists of pulmonologists, cardiologists, radiologists, cardiothoracic surgeons and specialised nurse practitioners. The date of the final CTEPH multidisciplinary team meeting was used as date of diagnosis. We collected patient characteristics at time of diagnosis and additional test results performed within 3 months of diagnosis. Imaging tests (transthoracic echocardiography, ventilation/perfusion scans, chest computed tomography scan and pulmonary angiography), right heart catheterisation, blood tests and (cardiopulmonary) exercise testing were performed according to the current guideline to establish CTEPH diagnosis and to asses operability[10]. PH was defined as a mean pulmonary artery pressure (mPAP) of ≥25 mmHg and a wedge pressure ≤15 mmHg. The diagnosis of CTEPH was made when a considerable amount of pulmonary vessels showed evidence of chronic thromboembolisms in the presence of PH after a minimum

of 3 months anticoagulation treatment, using two different imaging techniques. Patients were considered inoperable if they had peripheral (i.e. predominantly subsegmental or more distal) thromboembolic disease. Residual PH was defined as a persistent elevated (≥ 25 mmHg) mPAP after PEA.
Both technical inoperable and residual CTEPH patients started with riociguat therapy. If the patient remained symptomatic or had severe hemodynamic impairment at baseline, pharmacologic therapy was extended to off-label pulmonary arterial hypertension (PAH) oral combination therapy. In case of disease progression under combination therapy, triple therapy using intravenous prostanoids was initiated.
All patients, including stable disease, were systematically evaluated for balloon pulmonary angioplasty (BPA) treatment to improve hemodynamics and consequently symptoms and outcomes. Patients were accepted for BPA treatment by the multidisciplinary CTEPH team, if they had accessible thromboembolic lesions and did not have severe contraindications for BPA.

2.2 Outcome, events and follow-up

Patients were annually followed from initiation of riociguat treatment till the last known date of riociguat use or until death, lost to follow-up or end of study. WHO FC, 6MWD, NT-proBNP and (adverse) events were collected at regular outpatients visits, which were scheduled every 3 months.
Time of death and time to clinical worsening (CW) were noted. Death was defined as all-cause mortality and CW was defined as a combination of death, or non-elective hospitalisation for CTEPH or disease progression. We defined disease progression as the initiation of intravenous prostanoids or a reduction in 6MWD by 15% compared to baseline combined with worsening WHO FC, except for patients already in functional class IV. Only the first event of CW was noted in patients with multiple events. Maximum riociguat dose and adverse events (AEs) during treatment were noted.

2.3 Statistical analyses

All statistical analyses were performed with SPSS (IBM SPSS statistics version 24). Distribution of continuous data was visually assessed and normally distributed data were presented as mean ± standard deviation (SD) and not normally distributed data as median (interquartile range (IQR)). Categorical data were presented as number and percentage. Change to baseline in WHO FC, NT-proBNP and 6MWD, was assessed with a paired t-test or Wilcoxon signed rank test. Differences between riociguat patients with and without events were assessed with student t-tests, Mann-Whitney U test, Pearson Chi-Square and Fisher exact tests. Kaplan-Meier curves were used for assessment of survival and CW-free survival in the overall population and to assess (CW-free) survival with patients censored

at start of BPA treatment. Cox proportional hazards regression analyses were used to identify predictors. All tests were 2-tailed and were considered statistically significant if the p-value was below 0.05. The time between diagnosis and the start of riociguat was corrected with a time-dependent covariate. The study was approved by the local ethical commission (number W17.132).

3. Results

3.1 Study population

We included 36 consecutive inoperable and residual CTEPH patients (50% female, mean age 64.9±12.1 years) on riociguat therapy. Baseline characteristics are presented in table 1. The majority of patients had inoperable disease (92%), only 3 patients had residual CTEPH. Most patients had a history of thromboembolic event (89%) and at least one concomitant comorbidity (69%). There were no patients with a history of chronic osteomyelitis, ventriculoatrial shunt or inflammatory bowel disease. At the time of diagnosis patients were predominantly in WHO FC III/IV (54%). Patients had a mean pulmonary arterial pressure of 38.1±9.3 mmHg and a PVR of 6.1±3.7 WU. At baseline 17 patients (47%) started combination therapy. At the end of the follow up period, however, 27 patients (75%) received combination or triple therapy. During follow-up twelve patients (33%) underwent concomitant balloon pulmonary angioplasty (BPA).

Table 1. Baseline patient characteristics and medication strategy for patients with or without CW

	All patients (n=36) (Mean ± SD)	**No CW (n=29)** (Mean ± SD)	**CW (n=7)** (Mean ± SD)	**P-value**
Demographic characteristics				
Age (years)	64.9 ± 12.1	65.1 ± 12.2	64.3 ± 12.8	0.879
Female gender, n (%)	18 (50.0)	13 (44.8)	5 (71.4)	0.402
Inoperable / residual CTEPH, n (%)	33 (91.7) / 3 (7.3)	27 (93.1) / 2 (6.9)	6 (85.7) / 1 (14.3)	0.488
History taking				
Smokers (ever), n (%)	21 (58.3)	16 (55.2)	5 (71.4)	0.674
COPD, n (%)	11 (30.6)	9 (31)	2 (28.6)	1.000
Hypertension, n (%)	9 (25.0)	7 (24.1)	2 (28.6)	1.000
Diabetes, n (%)	4 (11.1)	3 (10.3)	1 (14.3)	1.000
Hyperlipidemia, n (%)	1 (2.8)	1 (3.4)	0	1.000
Thyroid dysfunction, n (%)	1 (2.8)	0	1 (14.3)	0.194
Hematologic disease, n (%)	14 (38.9)	11 (37.9)	3 (42.9)	1.000
Cardiac device, n (%)	1 (2.8)	0	1 (14.3)	0.189
Venous thrombosis, n (%)	6 (16.7)	5 (17.2)	1 (14.3)	1.000

Acute pulmonary embolism, n (%)	32 (88.9)	26 (89.7)	6 (85.7)	1.000
Clinical characteristics				
WHO FC I/II/III/IV (%)	0/46/51/3	0/46/50/4	0/43/57/0	1.000
NT-proBNP (pg/mL), median (IQR)	382 (186-2220)	364 (178-2188)	1345 (189-2418)	0.983
6MWD (m)	337 ± 138	363 ± 130	237 ± 128	**0.027**
Right-sided heart catheterization				
CO (L/min)	5.2 ± 1.6	5.2 ± 1.6	4.9 ± 1.7	0.693
RAP mean (mmHg)	7.9 ± 3.1	7.8 ± 3.3	8.0 ± 2.5	0.897
PAP mean (mmHg)	38.1 ± 9.3	38.6 ± 10.0	36.2 ± 5.4	0.391
PVR (WU)	6.1 ± 3.7	6.1 ± 4.0	5.9 ± 2.8	0.881
Treatment start follow-up				
VKA/NOAC/LMWH (%)	89/8/3	90/7/3	86/14/0	0.733
Riociguat, n (%)	17 (47.2)	13 (44.8)	4 (57.1)	0.684
Riociguat + ERA, n (%)	19 (52.8)	16 (55.2)	3 (42.9)	0.684
Treatment last follow-up				
Riociguat, n (%)	6 (16.7)	6 (20.7)	0	0.317
Riociguat + ERA, n (%)	26 (72.2)	20 (69.0)	6 (85.7)	0.645
Riociguat + ERA + prostanoid	1 (2.8)	0	1 (14.3)	0.194
Switch to PDE5 inhibitor	3 (8.3)	3 (10.3)	0	1.000
Concomitant BPA treatment				
BPA, n (%)	12 (33.3)	9 (31.0)	3 (42.9)	0.664

SD: standard deviation, CTEPH: chronic thromboembolic pulmonary hypertension, COPD: chronic obstructive pulmonary disease, WHO FC: World Health Organisation functional class, NT-proBNP: N-terminal pro brain natriuretic peptide, 6MWD: 6-min walking distance, 6MWT: 6-min walking test, CO: cardiac output, RAP: right atrial pressure, PAP: pulmonary arterial pressure, PVR: pulmonary vascular resistance, ERA; endothelin receptor antagonist, PDE5 inhibitor: phosphodiesterase type 5 inhibitor; BPA: balloon pulmonary angioplasty.

3.2 Safety and adverse events

We achieved the maximum riociguat dose (2.5 mg three times daily) in 30 (83%) patients, a dose of 2.0 mg three times daily in 3 (8%) patients and a dose of 1.5 mg three times daily in 3 (8%) patients. These last 3 patients got other PAH medication prescribed, as they received suboptimal riociguat dose and had adverse events. Mean riociguat treatment duration was 2.3±1.2 years.

Twenty-four (67%) patients experienced at least one AE during treatment. Serious AEs of hypotension and severe dyspnoea occurred in respectively 6 (17%) and 1 (3%) of the patients, of which 2 (6%) discontinued riociguat treatment for these reasons. One patient discontinued treatment due to upper respiratory tract infection after riociguat initiation.

Common AEs were dyspepsia (25%), headache (22%), diarrhoea (19%), upper respiratory tract symptoms (17%), dizziness (14%) and anaemia (11%). Individual patients could experience multiple (adverse) events. None of the patients experienced syncope, haemoptysis, acute renal or acute right ventricular failure (see supplemental table 1).

3.3 Survival and freedom from clinical worsening

In total 7 (19%) patients experienced CW during follow-up. Two (5%) patients died, both experienced CW prior to death. Five (14%) patients alive experienced CW, three (8%) of them needed intravenous prostanoids. The 3 patients with CW and BPA treatment had experienced CW before the start of BPA treatment.

Kaplan-Meier curves for overall survival and CW-free survival are shown in figure 1. Survival was 100%, 94%, and 80% at two, three and four years after riociguat initiation, respectively. One patient died in the third year and 1 in the fourth year after therapy initiation. If patients were censored at start of BPA treatment, survival at three and four years decreased to 92% and 79% respectively. Cox proportional hazards regression for survival showed no significant hazard ratios (HR) for baseline characteristics.

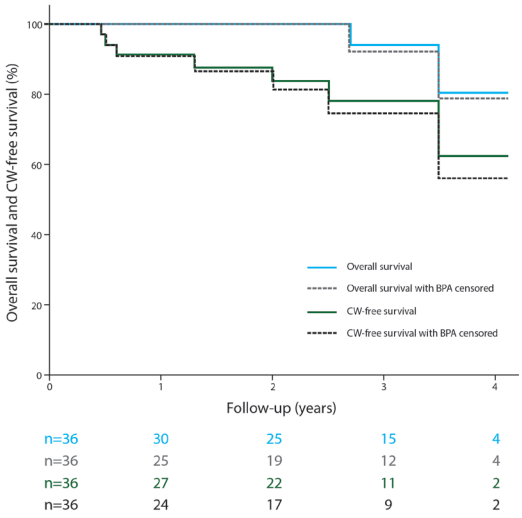

Figure 1. Kaplan-Meier overall survival and CW-free survival curves and numbers at risk for riociguat patients after therapy initiation. Overall survival and CW-free survival with BPA patients censored are shown with dashed lines.

Most CW occurred in the first year, with a CW-free survival of 88%, 78% and 63% at two, three and four years after riociguat initiation. These numbers decreased to 87%, 75% and 56% respectively if patients were censored at the start of BPA treatment. A significant baseline predictor for CW was 6MWD per 10m with HR 0.90 [0.83-0.97] (see supplemental table 2).

A comparison of baseline values between patients with or without CW showed a significant lower 6MWD in the CW group. Furthermore, all patients who experienced CW received combination therapy at the last follow-up compared to only 75% of the patients without CW.

3.4 Follow-up

Overall, WHO FC improved during the first year compared to baseline and stabilised afterwards in our study population. Most patients were in WHO FC I and II during follow-up. Results are shown in figure 2.

Median NT-proBNP decreased significantly in the overall population with -67 pg/mL (-1355-49) at one year (p=0.04) and stabilised afterwards. A comparison between patients with and without CW showed no significant difference between changes to baseline in NT-proBNP (see supplemental figure 1).

During follow-up the mean6MWD significantly increased for the overall population with 55±72m at year 1 (p=0.0003), with 60±65m at year 2 (p=0.0002) and with 89±61m at year 3 (p=0.001) compared to baseline (see supplemental figure 2).

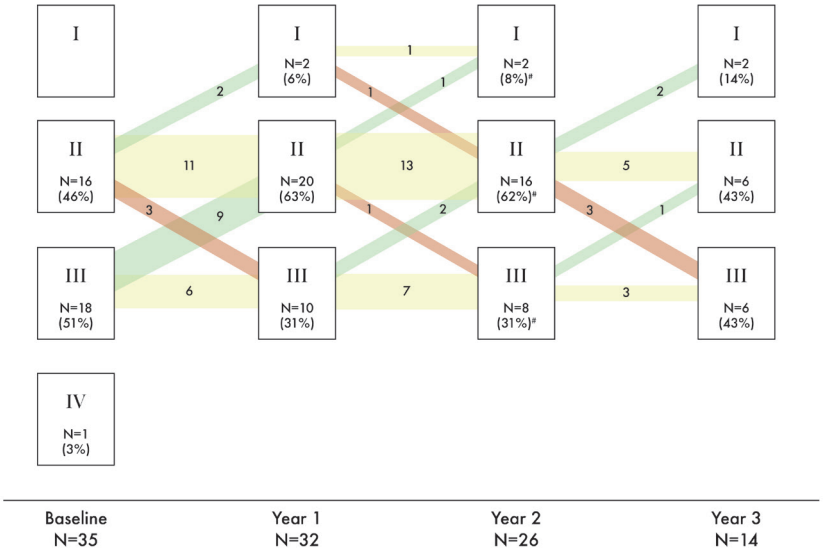

Figure 2. WHO FC at baseline and follow-up. Number and percentage of patients at risk for each time point and change of patients between time points. Patients who got lost to follow-up or who died between time points were not noted at the next time point. #Data do not add up to 100% due to rounding.

4. Discussion

In this article we report an effective and safe clinical outcome up to three years after the initiation of riociguat, in inoperable and residual CTEPH patients.

Previous (randomized) research showed safe and effective short-term results of riociguat treatment for CTEPH[6,11–13]. Riociguat stimulates and sensitizes sGC with a subsequent increase in cyclic guanosine monophosphate, leading to vasodilatation, altered pulmonary vascular tone and eventually to improved clinical functioning. Riociguat is currently the only registered CTEPH therapy for patients with inoperable or residual PH after PEA[10].

Although these controlled trials provide excellent evidence about treatment effectivity, generalizability may be low for patients seen in daily practice where treatment adherence and comorbidities differ[14]. Our 'real-world' data from our clinical care settings may add value to overcome this disadvantage, but should be used with care, as findings may be confounded[14].

We achieved the recommended riociguat dose in 83% of our patients, which is consistent with results reported in the CHEST studies[8,9,15] or a multicentre, non-randomized observational study by Halank et al[16], including 41 inoperable CTEPH patients. We did not identify new safety issues nor any haemoptysis or pulmonary haemorrhage in our study population. In general, adverse events were limited in our cohort and were in line with results from the CHEST studies[15].

Patients in the CHEST-1 were excluded if they had received other PAH medications within 3 months before study entry[8]. In our cohort we also included patients with a longer CTEPH disease history or who were already on other PAH medication, as patients in daily practise often switch between therapies to achieve maximal treatment effect or due to adverse events. In addition, a recent study reported improved WHO FC and pulmonary hemodynamics after a switch from sildenafil to riociguat [17], although another research showed that a switch may not be as effective as direct initiation of riociguat[18]. However, the patients in this transition group were older and had more severe CTEPH disease[18]. It is possible that patients in our cohort with a longer disease duration or who switched to riociguat had worse results compared to those in whom riociguat was immediate initiated, but this was not the focus of our current research.

The percentage of patients with combination therapy was low (7-10%) in the CHEST-1[9,15] and was not separately specified for CTEPH patients by Halank et al[16]. Research in PAH patients showed that combination therapy, e.g. with endothelin receptor antagonists, may delay CW and improve exercise capacity[19,20]. In our cohort we frequently treated patients with combination therapy, up to 75% at latest follow-up. Our hospital is a tertiary care centre for CTEPH, therefore we are able to start off-label PAH specific combination therapy

in CTEPH patients. We initiate combination therapy if the patient remains symptomatic or has severe hemodynamic impairment at baseline, despite being clinically stable. The same applies for BPA treatment, as we try to improve hemodynamics and eventually outcome. However, as the guidelines recommend extension to combination therapy in symptomatic patients and BPA treatment in inoperable patients, we expect that our cohort is a good reflection of the current clinical (treatment) course in inoperable and residual CTEPH patients.

We found a survival of 100% during the first two years, with a decrease to 80% four years after initiation of riociguat. For CW-free survival this was 89% at two and 63% at four years respectively. Our values correspond with results reported in the CHEST[9,15] and were better than reported by Halank et al[16]. However, definitions for CW differed between the studies; the CHEST combined PEA, hospitalisation due to PH, start of new PH treatment, decreased 6MWD, persistent worsening of WHO FC and death. Whereas Halank et al combined PEA, the use of other PH medication and death in their observational study. In our study, we combined death, rescue intravenous prostanoid treatment, hospitalisation due to PH, or a decreased 6MWD combined with worsened WHO FC. As our definition of CW was stricter, our percentages of CW-free survival may be slightly different. However, there were no patients who underwent PEA after riociguat initiation in our cohort and the number of patients who had CW due to decreased 6MWD or WHO FC was low in the other studies. We decided to only note (rescue) prostanoid treatment as CW, as we extended treatment to combination therapy in accordance to the guideline[10]. Our patients were also systematically evaluated for BPA treatment to optimise treatment and disease control. As BPA improves outcome, it consequently may prevent or delay CW in our cohort and may result in a slightly overestimated treatment effect of riociguat[21]. However, censoring of BPA patients at their first BPA did not change outcomes significantly, probably because some of these patients had already experienced CW before the start of their BPA treatment.
An updated and uniform definition for (time to) CW in CTEPH is needed to improve the ability to compare (future) study results.

Fortunately, due to the low number of deaths, we were unable to identify predictors for survival. We did find that baseline 6MWD was a significant predictor for CW, what is consistent with previous publications of a worse prognosis and CW-free survival in CTEPH patients with low 6MWD[15,22–24]. However, as baseline 6MWD was already significant lower in patients with CW, less improvement and a shorter time to CW may be expected.

Overall, WHO FC improved and eventually stabilised in most of our patients. However, our results are less profound compared to the other studies[15,16]. A worse WHO FC at baseline and a longer disease duration in our cohort might explain this finding. The

decrease in NT-proBNP one year after initiation of riociguat was consistent with results from the CHEST-2[9]. The decrease in NT-proBNP persisted up to 3 years, although the decrease became less profound during follow-up.

Mean 6MWD increased with riociguat therapy during follow-up. As we also initiated riociguat treatment in patients with a 6MWD below 150m, which were excluded in the CHEST-trial[9], a less profound increase in 6MWD may be expected. However, our overall results were comparable and during follow-up slightly better than results from the other studies[9,15,16].

4.1 Limitations

As our population was small, the mean follow-up time was limited and numbers of patients at risk differed at each time point, results should be interpret with caution. Nevertheless our results were largely consistent with previous studies. We performed a cohort study, what predisposes for bias and confounds result interpretation. Although we included all consecutive patients, patients who died prior to riociguat treatment are not included and this selection bias may result in an overestimated (CW-free) survival. Unfortunately we do not have data of quality-of-life measurements.

5. Conclusion

Long-term follow-up of riociguat therapy in our 'real world' CTEPH patients showed an effective long-term treatment effect, with a reasonable (CW-free) survival and significantly improved clinical parameters. The baseline 6MWD is a significant predictor for CW. Although WHO FC improvement was less profound, our results are largely consistent with other studies. More 'real world' research is necessary to establish more clinical long-term results.

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Appendix

Supplemental table 1. Adverse events

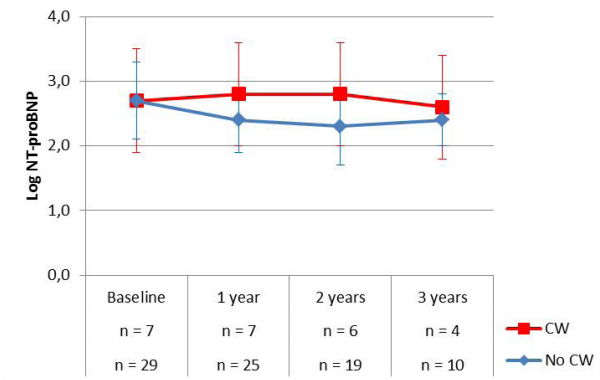
	All patients (n=36)
Serious adverse events, n (%)	**6 (16.7)** [#]
Hypotension, n (%)	6 (16.7)
Severe dyspnea, n (%)	1 (2.8)
Adverse events, n (%)	**24 (66.7)**[#]
Dyspepsia, n (%)	9 (25.0)
Headache, n (%)	8 (22.2)
Diarrhea, n (%)	7 (19.4)
Upper respiratory tract symptoms, n (%)	6 (16.7)
Dizziness, n (%)	5 (13.8)
Anemia, n (%)	4 (11.1)
Oedema, n (%)	3 (8.3)
Back pain, n (%)	3 (8.3)
Nausea, n (%)	3 (8.3)
Vomiting, n (%)	2 (5.6)
Changed taste, n (%)	2 (5.6)
Increased INR, n (%)	2 (5.6)
Epistaxis, n (%)	2 (5.6)
Constipation, n (%)	2 (5.6)
Cough, n (%)	1 (2.8)

INR: international normalized ratio. # Unique patients, individual patients could experience multiple (adverse) events.

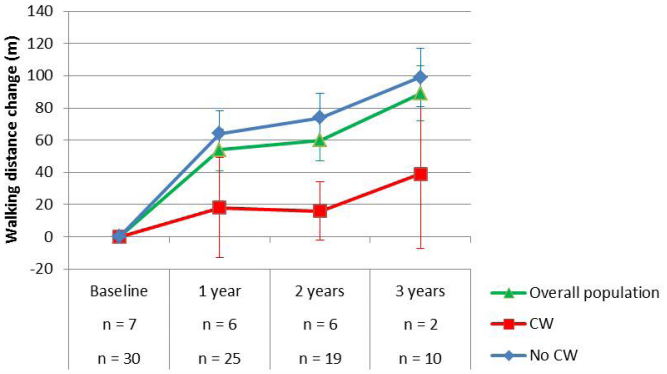
Supplemental table 2. Baseline characteristics and cox proportional hazards regression for CW

	HR (univariate)	**P-value**
Age	1.01 [0.95-1.07]	0.794
Male	0.22 [0.04-1.22]	0.083
Smokers	1.56 [0.29-8.38]	0.602
WHO FC	-	0.940
6MWD per 10 m	0.90 [0.83-0.97]	**0.009**
NT-proBNP per 1 log	1.08 [0.32-3.65]	0.896
CO	0.85 [0.52-1.37]	0.497
RAP mean	1.03 [0.78-1.37]	0.822
PAP mean	0.99 [0.91-1.08]	0.815
PVR (WU)	1.02 [0.83-1.26]	0.832

HR: hazard ratio, WHO FC: World Health Organisation functional class, 6MWD: 6-min walking distance, 6MWT: 6-min walking test, NT-proBNP: N-terminal pro brain natriuretic peptide, CO: cardiac output, RAP: right atrial pressure, PAP: pulmonary arterial pressure, PVR: pulmonary vascular resistance



Supplemental figure 1. Log NT-proBNP ± standard error and number of patients at risk at baseline and annual follow-up for riociguat patients with or without clinical worsening.



Supplemental figure 2. Mean ± standard error 6MWD change and number of patients at risk at baseline and annual follow-up for riociguat patients with or without clinical worsening.

CHAPTER 3

Long-term real world clinical outcomes of macitentan therapy in chronic thromboembolic pulmonary hypertension

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ABSTRACT

Background: Macitentan treatment for chronic thromboembolic pulmonary hypertension (CTEPH) in the routine clinical setting is increasing. However, 'real world' macitentan experience is scarce and is needed to differentiate from controlled clinical trial settings. We describe our outcomes and clinical 'real world' experience of macitentan mono- and combination therapy with riociguat or sildenafil in CTEPH.

Methods: We included all consecutive CTEPH patients, either non-operated or with residual PH after pulmonary endarterectomy (PEA), treated with macitentan in the St. Antonius hospital in Nieuwegein, the Netherlands, between 01-2014 and 11-2019. We describe clinical outcomes and adverse events (AEs) until 2 years after macitentan initiation.

Results: In total 73 CTEPH patients on macitentan were included, of which 18 patients were clinically inoperable (n=7 declined PEA, n=11 nonacceptable risk-benefit) and 55 had technically inoperable CTEPH (n=48)/residual PH (n=7). Clinically inoperable patients (mean age 72.4±10.2 years, 61% female, 28% macitentan monotherapy, observation period 2.0 (1.9-2.0) years) had a survival of 100% and clinical worsening (CW)-free survival of 88% at 2-year follow-up respectively, with a significant increased 6-min walking distance (6MWD). Technically inoperable/residual PH patients (mean age 62.1±14.1 years, 60% female, 27% macitentan monotherapy, observation period 2.0 (1.0-2.0) years) had a 2-year survival and CW-free survival of 86% and 68% respectively, with significant improved 6MWD and NT-proBNP. Nonsevere AEs were reported in 30% of all patients.

Conclusion: Macitentan mono- and combination therapy in non-operated CTEPH and residual PH is safe and improves clinical outcomes till 2-year follow-up.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is due to a chronic thromboembolic obstruction of the pulmonary arteries. Subsequent distal arteriopathy impairs hemodynamics and results eventually in heart failure and death[1].

All patients should be evaluated for pulmonary endarterectomy (PEA) as this greatly improves symptoms and prognosis and cures part of all patients[2,3]. Inoperable patients and patients with residual - persistent or recurrent - PH after PEA should be treated with PH-specific medication, to improve symptoms and hemodynamics[3,4], and should be evaluated for balloon pulmonary angioplasty (BPA). BPA restores blood flow in the pulmonary arteries by opening (partially) obstructed vessels, leading to improved pulmonary hemodynamics[5,6].

Riociguat is currently the only licensed PH-specific therapy for inoperable or persistent/recurrent CTEPH, improving 6-min walking distance (6MWD), World Health Organization functional class (WHO FC) and pulmonary vascular resistance (PVR)[3,7–9]. The off-label use of pulmonary arterial hypertension (PAH) drugs may also be effective in symptomatic CTEPH patients, due to a resemblance in pathologic pathways[1,10]. In clinical practice, CTEPH expert centres often switch or combine PH-specific therapy due to intolerance, adverse events (AEs) and to optimise treatment.

The recent MERIT-1 trial, a prospective randomized trial investigating macitentan in inoperable CTEPH, showed improved hemodynamics and exercise capacity[11]. Real-world experience of macitentan use in routine clinical setting of CTEPH is needed to differentiate from controlled clinical trial settings.

As our CTEPH expert centre is allowed to use macitentan for CTEPH treatment, due to previous promising results of endothelin receptor antagonists in CTEPH[11,12], we do have clinical experience on macitentan both as mono- and combination therapy with riociguat or sildenafil.

In this study, we aim to highlight the potential role of macitentan therapy in CTEPH and describe patient clinical 'real world' outcomes and AEs until 2 years after treatment initiation.

2. Methods

2.1 Study population

In this retrospective observational cohort study, we included all consecutive CTEPH patients, either non-operated or with residual PH after PEA, treated with macitentan in the St. Antonius Hospital in Nieuwegein, the Netherlands, between 01-2014 and 11-2019. The diagnosis was established, and operability was assessed, according to the guideline[3], in a multidisciplinary team, including cardiologists, pulmonologists, radiologists, cardiotho-

racic surgeons and specialised nurse practitioners. PH was defined as a mean pulmonary artery pressure (mPAP) of ≥25 mmHg and a wedge pressure ≤15 mmHg at right heart catheterisation (RHC). The diagnosis of CTEPH was made when mismatched perfusion defects on lung scan were seen with signs of CTEPH on multidetector CT angiography or conventional pulmonary angiography in the presence of PH after a minimum of 3 months anticoagulation treatment. Patient characteristics, history and additional tests were collected if performed within 3 months of diagnosis.

2.1.1 Patient subgroups

Patients with operable disease (i.e. central or segmental thromboembolic disease with a proportional PVR), but a nonacceptable risk-benefit for surgery due to severe comorbidities (e.g. severe lung or renal disease) or who declined PEA were considered *clinically inoperable*. Patients with predominantly subsegmental or more distal thromboembolic disease were considered as *technically inoperable*. Patients with persistent or recurrent PH after PEA were considered as *residual PH after* PEA. We combined *technically inoperable* patients with *residual PH* patients, as both groups have arteriopathy and may benefit from PH-specific therapy[13].

2.1.2 PH-specific therapy strategies and adverse events

Riociguat monotherapy was initiated in all symptomatic, inoperable CTEPH patients. Treatment was extended to combination therapy with macitentan (10 mg) if the patient was not in the low risk group of the risk stratification strategy of the European Society of Cardiology / European Respiratory Society guideline[14]. In case of intolerance for riociguat, patients were switched to macitentan monotherapy or in case of combination therapy to sildenafil-macitentan. In case of patients on combination therapy with worsening risk stratification group, therapy was extended to triple therapy by addition of prostacyclin therapy. Baseline was defined as date of start of macitentan therapy. Time from diagnosis till baseline was noted. All patients were systematically evaluated for concomitant BPA treatment if they had accessible thromboembolic lesions and did not have severe contraindications (i.e. right-sided valvular endocarditis or mechanical heart valve or a thrombus or myxoma in the right atrium). Date of first BPA was noted, to provide follow-up and outcome with time and event censored after start of BPA separately.

Operable patients received bridging therapy with monotherapy (in case of low risk group) or combination therapy (in case of intermediate-high risk group) with riociguat-macitentan or sildenafil-macitentan. Baseline was set as date of PEA in patients with *persistent* PH after PEA, while this was the date of RHC confirming PH in patients with *recurrent* PH after PEA. Waiting time from diagnosis till PEA was noted. AEs during macitentan treatment were collected.

2.2 Survival, clinical worsening and clinical outcomes

Patients were followed from baseline up till 2 years after macitentan initiation or to last available information (latest date of macitentan use in follow-up, death or end of the observation period for the study: 11-2019). Follow-up consisted of regular outpatient clinic visits alternating between a pulmonologist and cardiologist every 3 months.

Death was defined as all-cause mortality, and clinical worsening (CW) as a combined outcome of death, disease progression or non-elective hospitalisation for CTEPH. Disease progression was considered as a reduction ≥15% of 6MWD from baseline to last available information plus worsening WHO FC (except for patients already in FC IV) or the use of prostacyclin rescue therapy. Only the first event of CW was noted in patients with multiple events during observation period.

WHO FC, 6MWD and N-terminal pro brain natriuretic peptide (NT-proBNP) were determined at the outpatient visits. Follow-up assessments for this study were collected annually (from baseline) from the outpatient visit closest to 1- and 2-year follow-up dates.

2.3 Statistical analyses

All statistical analyses were performed with SPSS (IBM SPSS statistics version 24). Tests were two-tailed and were considered statistically significant if the p-value was below 0.05. Continuous data were presented as mean ± standard deviation or as median with inter-quartile range. Categorical data were presented as number and percentage. Differences in clinical outcomes were analysed with the Wilcoxon signed rank test and linear-by-linear association. Survival and time to CW were analysed with Kaplan-Meier method. The study was approved by the local ethical commission (number W17.132).

3. Results

3.1 Study population

There were 236 prevalent CTEPH patients in the observation period, of whom 73 were non-operated or had residual PH and were receiving macitentan therapy. There were 18 (24.7%) *clinically inoperable* patients and 48 (65.8%) *technically inoperable* patients plus 7 (9.6%) patients with *residual PH after PEA*. Total macitentan observation period was 2.0 (1.1-2.0) years and 1.8 (0.7-2.0) years with time censored after first BPA. Baseline characteristics are shown in table 1 and figure 1.

Table 1. Characteristics at diagnosis

Total: n=73	**Clinically inoperable (n=18)**	**Technically inoperable / residual PH after PEA (n=55)**
Demographic characteristics, n (%)		
Age (years), mean±SD	72.4±10.2	62.1±14.1
Female	11 (61)	33 (60)
Caucasian / black	17 (94) / 1 (6)	53 (96) / 2 (4)
Medical History, n (%)		
Coronary artery disease	1 (6)	3 (6)
Deep venous thrombosis	7 (39)	14 (26)
Acute pulmonary embolism	14 (78)	44 (80)
Chronic obstructive pulmonary disease	6 (33)	11 (20)
Obstructive sleep apnoea syndrome	2 (11)	5 (9)
Thyroid dysfunction	0	4 (7)
Splenectomy	0	1 (2)
Hematologic disease	3 (17)	11 (20)
Malignancy	4 (22)	9 (16)
Smoker (ever)	9 (50)	32 (58)
Hypertension	11 (61)	11 (20)
Clinical and hemodynamic characteristics, mean±SD		
WHO FC I/II/III/IV (%)	0/50/50/0	0/36/60/4
NT-proBNP (pg/mL), median (IQR)	319 (197-1357)	1409 (291-2785) [1]
6MWD (m), median (IQR)	310 (211-396)	330 (218-427) [1]
CO (l/min)	4.8±1.1 [2]	5.1±1.8 [4]
RAP (mmHg)	6.5±3.3 [3]	9.3±3.9 [5]
mPAP (mmHg)	38.7±9.8	42.9±11.2 [5]
PAWP (mmHg)	10.1±6.4	12.8±7.7 [6]
PVR (WU), median (IQR)	6.1 (4.7-8.5) [2]	6.5 (3.9-10) [7]
Treatment at baseline, n (%)		
Macitentan monotherapy	5 (28)	15 (27)
Macitentan + riociguat	8 (44)	24 (44)
Macitentan + sildenafil	5 (28)	16 (29)
BPA	3 (17)	19 (35)
VKA/NOAC/LMWH	83/17/0	85/13/2
Time from diagnosis to baseline (years), median (IQR)	0.3 (0-0.7)	0.5 (0.3-6.8)
Macitentan observation period (years), median (IQR)	2.0 (1.9-2.0)	2.0 (1.0-2.0)
Macitentan observation period BPA censored (years), median (IQR)	2.0 (1.9-2.0)	1.4 (0.6-2.0)

PH: pulmonary hypertension, PEA: pulmonary endarterectomy, WHO FC: World Health Organisation functional class, NT-proBNP: N-terminal pro brain natriuretic peptide, 6MWD: 6-min walking test distance, CO: cardiac output, RAP: right arterial pressure, mPAP: mean pulmonary arterial pressure, PAWP: pulmonary artery wedge pressure PVR: pulmonary vascular resistance, BPA: balloon pulmonary angioplasty, VKA: Vitamin K antagonists, NOAC: novel oral anticoagulant, LMWH: low molecular weight heparin, SD: standard deviation, IQR: interquartile range.
[1] n=52; [2] n=16; [3] n=17; [4] n=47; [5] n=49; [6] n=48; [7] n=44

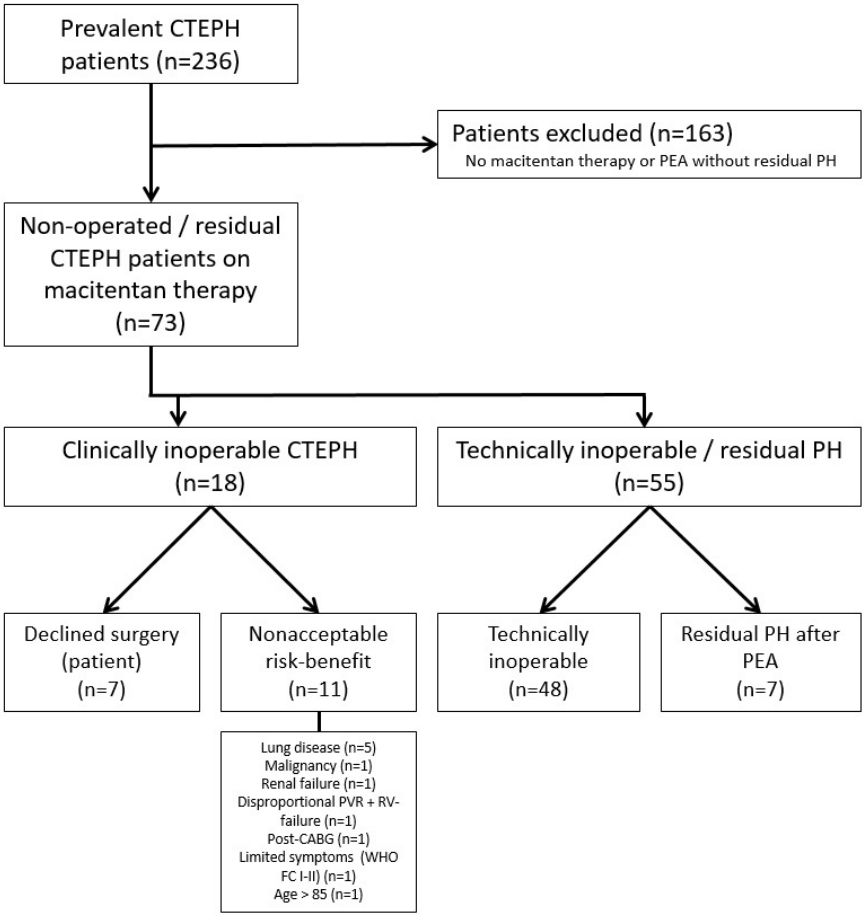

Figure 1. Flowchart patient selection and classification. CTEPH: Chronic thromboembolic pulmonary hypertension, PEA: pulmonary endarterectomy, PH: pulmonary hypertension, PVR: pulmonary vascular resistance, RV: right ventricle, CABG: coronary artery bypass graft, WHO FC: World Health Organization functional class.

3.1.1. Patient subgroups

Clinically inoperable patients did not receive PEA due to a nonacceptable risk-benefit for PEA (n=11, 61%) or due to patient choice to decline surgery (n=7, 39%). Mean age at diagnosis was 72.4±10.2 years, 61% were female and 50% were in WHO FC III/IV. Many patients had comorbidities (61% hypertension, 33% chronic obstructive pulmonary disease, 22% malignancy) at diagnosis.

Patients belonging to the *technically inoperable /residual PH after PEA* group had a mean age of 62.1±14.1 years, 60% were female, 64% were severely symptomatic (WHO FC III/IV) and many had severe haemodynamic impairment (mPAP 42.9±11.2 mmHg and PVR 6.5 WU (3.9-10)). Subgroups characteristics are shown in supplemental table 1.

3.1.2 PH-specific therapy strategies and adverse events

Overall, most patients were on macitentan combination therapy (73%) with riociguat or sildenafil, and vitamin K antagonists (85%).

Clinically inoperable patients had frequent (72%) macitentan combination therapy with riociguat (44%) or sildenafil (28%) and 3 (17%) patients followed concomitant BPA procedures. Total macitentan observation period with and without BPA censored was 2.0 (1.9-2.0) years, with median time between diagnosis and baseline 0.3 (0-0.7) years.

Technically inoperable/residual PH patients also frequently (73%) used macitentan combination therapy with riociguat (44%) or sildenafil (29%) and 19 (35%) patients followed concomitant BPA. Total macitentan observation period was 2.0 (1.0-2.0) years and 1.4 (0.6-2.0) years with BPA censored. Median time between diagnosis and baseline was 0.5 (0.3-6.8) years.

AEs were reported in 30% of all patients, with upper respiratory tract symptoms (10%), headache (5%), fatigue (4%), anaemia (4%) and nausea (4%) as most common AEs. AEs are shown in supplemental table 2.

3.2 Survival, clinical worsening and clinical outcomes

No *clinically inoperable* patient died during the observation period. Two (11.1%) patients with a nonacceptable risk-benefit experienced CW, resulting in a CW-free survival of 88% at two-year follow-up, shown in figure 2. One of these two patients experienced CW after start of BPA treatment, resulting in a two-year CW-free survival of 93% with time after BPA censored.

WHO FC was improved/stabilised for 13 (81%) and 14 (93%) patients at 1- and 2-year follow-up, respectively. Median 6MWD significantly improved +33m (3-102, p=0.008) and +48m (18-88, p=0.001) and median NT-proBNP decreased -72 pg/mL (-754-17) and -81 pg/mL (-1017-28) at one- and two-year follow-up, respectively.

Six (11%) *technically inoperable/residual PH* patients died, all been *technically inoperable*

(n=2 macitentan monotherapy, n=4 riociguat-macitentan combination therapy). Proportion of patients in this group surviving at one- and two-year follow-up were 94% and 86%, respectively, and with BPA censored 93% and 83%, respectively. In total 15 patients experienced CW (n=3 macitentan monotherapy, n=6 riociguat-macitentan combination, n=6 sildenafil combination therapy), with a CW-free survival of 83% and 68% at one- and two-year follow-up, respectively, and 85% and 66% with BPA censored, respectively (figure 2). At one- and two-year follow-up, respectively, 40 (93%) and 19 (83%) of the *technically inoperable /residual PH* patients had improved/stabilised WHO FC compared to baseline. 6MWD significantly improved +66m (9-114, p=0.0001) and +33m (27-109, p=0.001), and NT-proBNP decreased -314pg/mL (-1743-76, p=0.005) and -324pg/mL (-1269-42) at one- and two-year follow-up respectively (table 2, supplemental table 3).

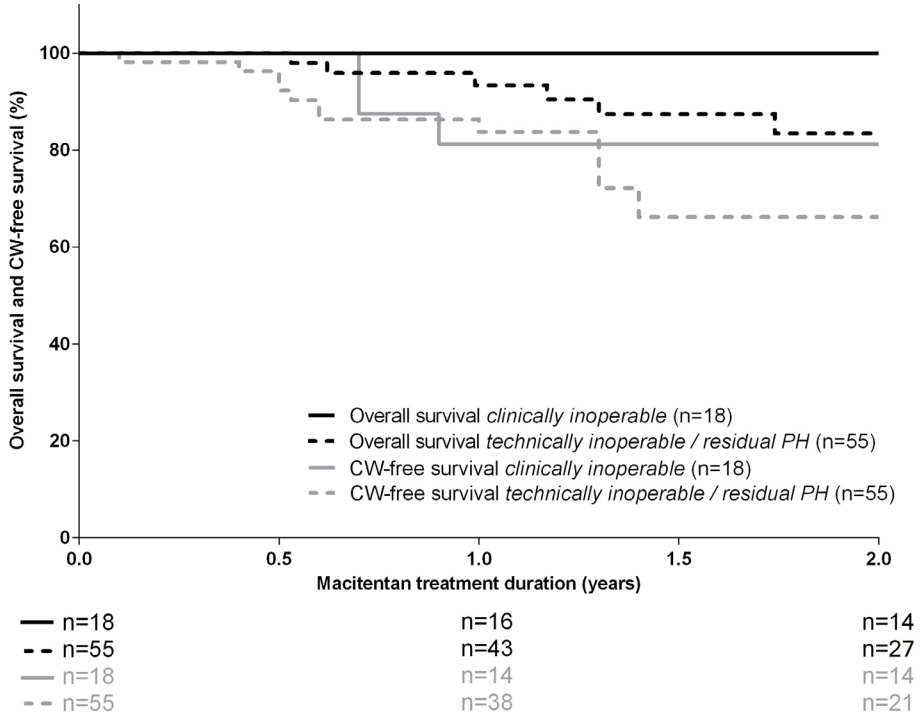

Fig 2. Kaplan-Meier overall survival and CW-free survival and numbers at risk for clinically inoperable and technically inoperable/residual PH patients.

Table 2. Outcomes

Total: n=73	**Clinically inoperable (n=18)**	**Technically inoperable / residual PH after PEA (n=55)**
Clinical outcomes, n (%)		
Deceased	0	6 (11)
Lost-to-follow up	0	2 (4)
Hospitalisation	1 (6)	9 (16)
Prostacyclin rescue therapy	0	4 (7)
Worsened WHO FC + 6MWD	1 (6)	1 (2)
Clinical worsening[#]	2 (11)	15 (27)
Year 0 (at baseline)		
WHO FC I/II/III/IV (%)	0/50/50/0	0/36/60/4
NT-proBNP (pg/mL), median (IQR)	319 (197-1357)	1409 (291-2785) [1]
6MWD (m), median (IQR)	310 (211-396)	330 (218-427) [1]
Year 1		
WHO FC I/II/III/IV (%)	0/50/50/0 [2]	7/60/33/0 [3]
NT-proBNP (pg/mL), median (IQR)	260 (152-419) [2]	330 (192-1731) [4]
6MWD (m), median (IQR)	332 (236-412) [2]	397 (283-486) [5]
Year 2		
WHO FC I/II/III/IV (%)	7/60/33/0 [6]	13/39/39/9 [8]
NT-proBNP (pg/mL), median (IQR)	299 (200-496) [6]	361 (111-1127) [9]
6MWD (m), median (IQR)	339 (240-420) [6]	378 (236-471) [10]

[#] Unique patients, individual patients could experience multiple clinical worsening events. PH: pulmonary hypertension, PEA: pulmonary endarterectomy, WHO FC: World Health Organisation functional class, 6MWD: 6-min walking test distance, TtCW: time to clinical worsening, NT-proBNP: N-terminal pro brain natriuretic peptide, IQR: interquartile range.
[1] n=52 ; [2] n=16; [3] n=43; [4] n=41; [5] n=39; [6] n=14; [8] n=23; [9] n=22; [10] n=20.

There was no significant difference in CW-free survival between patients having followed BPA treatment and those without in the overall population and in the *technically inoperable/residual PH* group (p=0.42 and p=0.09 respectively). There was also no significant difference in 6MWD, NT-proBNP and NYHA FC at one- and two-year follow-up between patients having followed BPA treatment and those without.
A comparison between patients receiving combination therapy with riociguat and combination therapy with sildenafil showed no significant difference in survival and CW-free survival (p=0.07 and p=0.99, respectively).

Desaturations during 6MWD at one- and two-year follow-up did not significantly change compared to baseline in the overall population (p=0.07 and p=0.18), nor in the subgroups separately.

4. Discussion

In this study we present the first real-world data of clinical outcomes and AEs of macitentan mono- or combination therapy (with riociguat or sildenafil) in CTEPH patients. Our main findings are that macitentan therapy in CTEPH improves exercise capacity and is safe with only non-severe AEs.

PH-specific therapy including macitentan mono- and combination therapy with riociguat or sildenafil stabilised patient's symptoms and significantly increased 6MWD in *clinically inoperable* CTEPH.

The *clinically inoperable* CTEPH patients in our cohort were older and less symptomatic compared to the *technically inoperable/residual PH* patients, what is consistent with characteristics reported by Quadery et al in their cohort[15]. Older patients may have more comorbidities resulting in a nonacceptable risk-benefit profile for PEA. None of these patients in our cohort died, while Quadery et al described a worse survival prognosis (±73% survival at 2 years)[15]. However, baseline hemodynamics of the *clinically inoperable* patients in our cohort were slightly better than the patients in their cohort (mPAP 39 vs 43 mmHg, PVR 6.1 vs 7.0 WU), probably partly explaining our better outcomes[15,16]. Our results may indicate that PH-specific therapy may also be valuable in patients with proximal, operable CTEPH.

Patients not eligible for PEA or with residual PH after PEA should receive PH-specific medication to improve symptoms and hemodynamics[3,4]. However, limited studies are available about long-term outcomes of patients receiving macitentan therapy. In our cohort, 6 out of 55 *technically inoperable/residual PH* patients died and 15 patients experienced CW during the 2-year follow-up.

The *technically inoperable/residual PH* patients in our study were slightly older than patients in the MERIT-1 trial (mean age 62 vs 58 years)[11], what may have negatively influenced baseline (6MWD) and outcomes. Especially *technically inoperable* patients in our cohort had severe hemodynamic impairment at baseline, what may result in an increased risk of death during follow-up[17]. However, the mPAP of these patients was slightly lower compared to the MERIT-1 trial (mPAP 43 vs 50 mmHg), and so was the PVR due to a higher cardiac output as well[11].

Most of our patients were on combination therapy (73%), with a higher percentage reported than in previous randomized research in the MERIT-1 and CHEST trials (7-10%) [7,8,11,17] and in the large prospective, cohort of Quadery et al (7% of medically treated

patients)[15]. Furthermore, patients in our cohort were treated with BPA, even in absence of CW. Both differences in treatment may increase (CW-free) survival [5,6,18], although an analysis between patients with and without BPA showed no significant difference in outcomes. The combination of macitentan therapy and BPA in CTEPH patients may be an interesting topic for future research.
In comparison, our survival results for the *technically inoperable* patients were comparable with results reported by Delcroix et al in their multicentre, international prospective registry (86 vs 79% at 2-year follow-up)[19]. However, in this registry outcomes from both *technically* and *clinically* inoperable patients were combined, while we reported outcomes separately. In the cohort of Quadery et al, outcomes for patients were separately reported, however they did use sildenafil instead of riociguat for mono- and combination therapy and their percentage of patients with combination therapy of sildenafil and macitentan was low[15]. It would be interesting to compare the effect of macitentan monotherapy with the different other monotherapies and combination therapies with macitentan, although survival did not differ in our study between patients receiving combination therapy with riociguat or with sildenafil.
The *technically inoperable/residual PH* patients showed significantly improved WHO FC (93% stabilised/improved) and 6MWD (+66m) at 1 year after macitentan initiation with a sustainable result at 2-year follow-up. These long-term results are comparable with the short-term results found in the MERIT-1 trial[11].

Thirty percent of patients treated with macitentan reported an AE, but without necessity to discontinue treatment. No new safety concern was identified and the AE rate was lower than in the MERIT-1 trial (75%)[11] and recent data from the OPUS registry (71%)[20].

4.1 Limitations

Study result interpretations are limited by the small sample size of the cohort described. Although real-world data cannot supplant traditional clinical trials, authors consider that this research may provide valuable insights in a context of a rare disease like CTEPH, with currently, sparse real-world data on macitentan.
As there are no recommendations for PH-specific combination therapy strategies in CTEPH patients yet, results should be interpreted with caution. In addition, results and (adverse) events may be underreported due to the retrospective nature of this study and may be confounded by the different patient and medication (sub)groups. In addition, unfortunately no treatment adherence data are available.

5. Conclusion

PH-specific therapy with macitentan monotherapy and macitentan combination therapy with riociguat or sildenafil is safe and shows improved clinical outcomes in 'real world'

inoperable and residual CTEPH patients. Combinations of different PH-specific therapies may be promising as future CTEPH treatment.

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Appendix

Supplemental table 1. Baseline characteristics subgroups technically inoperable CTEPH and residual PH patients

Total: n=55	**Technically inoperable (n=48)**	**Residual PH after PEA (n=7)**
Demographic characteristics, n (%)		
Age (years), mean±SD	63.3±13.9	53.7±13.9
Female	29 (60) / 19 (40)	4 (57) / 3 (43)
Caucasian / black	47 (98) / 1 (2)	6 (86) / 1 (14)
History taking, n (%)		
Coronary artery disease	3 (6)	0
Deep venous thrombosis	14 (29)	0
Acute pulmonary embolism	37 (77)	7 (100)
Chronic obstructive pulmonary disease	10 (21)	1 (14)
Thyroid dysfunction	4 (8)	0
Splenectomy	1 (2)	0
Hematologic disease	14 (29)	2 (29)
Smoker (ever)	28 (58)	5 (71)
Hypertension	11 (23)	0
Clinical characteristics, mean±SD		
WHO FC I/II/III/IV (%)	0/38/60/2	0/29/57/14
NT-proBNP (pg/mL), median (IQR)	1487 (263-2791) [1]	463 (297-1981)
6MWD (m), median (IQR)	328 (240-416) [2]	338 (195-630)
CO (l/min)	5.0±1.9 [3]	5.4±1.5
RAP (mmHg)	9.7±3.9 [4]	7.1±3.6
mPAP (mmHg)	43.0±11.2 5	41.2±12.2
PAWP (mmHg)	13.0±8.2 [4]	12.0±2.5
PVR (WU), median (IQR)	7.0 (3.9-10) [6]	4.9 (2.9-9.8)
Treatment, n (%)		
Macitentan monotherapy	14 (29)	1 (14)
Macitentan + riociguat	19 (40)	5 (71)
Macitentan + sildenafil	15 (31)	1 (14)
BPA	18 (38)	1 (14)
VKA/NOAC/LMWH (%)	85/13/2	86/14/0
Time from diagnosis to baseline (years), median (IQR)	0.8 (0.3-6.9)	-
Macitentan observation period (years), median (IQR)	1.9 (1.0-2.0)	2.0 (0.8-2.0)

PH: pulmonary hypertension, PEA: pulmonary endarterectomy, WHO FC: World Health Organisation functional class, NT-proBNP: N-terminal pro brain natriuretic peptide, 6MWD: 6-min walking test distance, CO: cardiac output, RAP: right arterial pressure, mPAP: mean pulmonary arterial pressure, PAWP: pulmonary artery wedge pressure PVR: pulmonary vascular resistance, BPA: balloon pulmonary angioplasty, VKA: Vitamin K antagonists, NOAC: novel oral anticoagulant, LMWH: low molecular weight heparin, SD: standard deviation, IQR: interquartile range.
[1] n=45; [2] n=46; [3] n=41; [4] n=42; [5] n=43; [6] n=38

Supplemental table 2. Adverse events

Adverse events	Total (n=73)	Clinically inoperable (n=18)	Technically inoperable / residual PH after PEA (n=55)
Adverse events, n (%)#	**22 (30)**	**6 (33)**	**16 (29)**
Upper respiratory tract symptoms, n (%)	7 (10)	3 (17)	4 (7)
Headache or dizziness, n (%)	4 (6)	0	4 (7)
Anemia, n (%)	3 (4)	0	3 (6)
Fatigue, n (%)	3 (4)	0	3 (6)
Nausea, n (%)	3 (4)	1 (6)	2 (4)
Peripheral edema, n (%)	2 (3)	0	2 (4)
Sleeplessness, n (%)	1 (1)	1 (6)	0
Hair loss, n (%)	1 (1)	1 (6)	0
Joint pain, n (%)	1 (1)	0	1 (2)
Skin problems, n (%)	1 (1)	0	1 (2)
Increased creatinine, n (%)	1 (1)	0	1 (2)
Increased liver enzymes, n (%)	1 (1)	0	1 (2)

PH: pulmonary hypertension, PEA: pulmonary endarterectomy. # Unique patients, individual patients could experience multiple adverse events.

Supplemental table 3. Follow-up outcomes subgroups technically inoperable CTEPH and residual PH patients

Total: n=55	**Technically inoperable (n=48)**	**Residual PH after PEA (n=7)**
Clinical outcomes, n (%)		
Deceased	6 (12.5)	0
Lost-to-follow up	2 (4.2)	0
Hospitalisation	9 (18.8)	0
Prostacyclin rescue therapy	3 (6.3)	1 (14.2)
Worsened WHO FC + 6MWD	1 (2.1)	0
Clinical worsening#	14 (29.2)	1 (14.2)
TtCW (years), median (IQR)	0.85 (0.5-1.4)	-
Year 0 (at diagnosis)		
WHO FC I/II/III/IV (%)	0/38/60/2	0/29/57/14
NT-proBNP (pg/mL), median (IQR)	1487 (263-2791) [1]	463 (297-1981)
6MWD (m), median (IQR)	328 (240-416) [2]	338 (195-630)
Year 1		
WHO FC I/II/III/IV (%)	5/63/32/0 [3]	20/40/40/0 [6]
NT-proBNP (pg/mL), median (IQR)	342 (197-2023) [4]	209 (130-616) [6]
6MWD (m), median (IQR)	391 (301-480) [5]	404 (199-585) [6]
Year 2		
WHO FC I/II/III/IV (%)	10/45/35/10 [7]	-
NT-proBNP (pg/mL), median (IQR)	381 (115-1318) [8]	-
6MWD (m), median (IQR)	380 (263-468) [8]	-

Unique patients, individual patients could experience multiple clinical worsening events. PH: pulmonary hypertension, PEA: pulmonary endarterectomy, WHO FC: World Health Organisation functional class, 6MWD: 6-minu walking test distance, TtCW: time to clinical worsening, NT-proBNP: N-terminal pro brain natriuretic peptide, IQR: interquartile range.
1 n=45; 2 n=46; 3 n=38; 4 n=36; 5 n=34; 6 n=5; 7 n=20; 8 n=19. – too low number of patients at risk to present valuable results

CHAPTER 4

Bosentan or macitentan therapy in chronic thromboembolic pulmonary hypertension?

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ABSTRACT

Background: Research comparing bosentan and macitentan in chronic thromboembolic pulmonary hypertension (CTEPH) is scarce, although macitentan might have superior pharmacologic properties. We present the first real-world, two-year follow-up results and compare clinical outcomes of both drugs in CTEPH.

Methods: All consecutive, technical inoperable or residual CTEPH patients receiving bosentan or macitentan, diagnosed in our multidisciplinary team between January 2003 and January 2019, were included. We report and compare survival, clinical worsening (CW), adverse events, WHO FC, NT-proBNP and 6-minute walking test (6MWT) until two years after medication initiation.

Results: In total 112 patients receiving bosentan or macitentan (58% female, mean age 62±14 years, 68% WHO FC III/IV, 51% bosentan) could be included. Mean treatment duration was 1.9±0.4 years for bosentan and 1.2±0.6 years for macitentan. Two-year survival rate was 91% for bosentan and 80% for macitentan (HR mortality macitentan 1.85 [0.56-6.10], p=0.31). Two-year CW-free survival was 81% and 58% respectively (HR CW macitentan 2.16 [0.962-4.87], p=0.06). Right atrial pressure, cardiac output (for mortality alone) and 6MWT lowest saturation were multivariate predictors at baseline. Overall adverse event rates were comparable and WHO FC, NT-proBNP and 6MWT distance improved similar for both drugs till two-year follow-up.

Conclusion: CTEPH patients receiving bosentan or macitentan have improved clinical outcomes till two-year follow-up, without significant differences in outcomes between both therapies.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH), a progressive pulmonary vascular disease, results in secondary distal arteriopathy and eventually in hemodynamic and functional impairment[1]. Pulmonary endarterectomy (PEA) is the preferred treatment as it improves World Health Organization functional class (WHO FC) and prognosis[2]. Technical inoperable patients and patients with recurrent/persistent PH after PEA (residual PH) should be treated with riociguat[3,4]. Riociguat, a soluble guanylate cyclase stimulator, decreases pulmonary vascular resistance (PVR) and NT-proBNP levels, and improves 6-minute walking distance (6MWD) and WHO FC up to 3 years and is currently the only registered pharmacologic CTEPH therapy[3–6]. However, patients may experience adverse events (AEs) or do not achieve maximum dose or treatment goals. Because of resemblance in pathologic pathways between pulmonary arterial hypertension (PAH) and CTEPH, PAH therapy may then be considered[1,7]. Endothelin receptor antagonists (ERAs) have been used in CTEPH before; bosentan significantly improved PVR but had no effect on 6MWD in the BENEFiT trial, while macitentan, the newest ERA, significantly improved PVR and exercise capacity in the MERIT-1 trial[8,9]. Macitentan has sustained receptor binding properties and enhanced tissue distribution, and may therefore be superior to other ERAs[10–12]. However, clinical experience with ERAs in CTEPH is still limited.

Our CTEPH expert centre is allowed to use ERAs for CTEPH, due to the trial results, and so we do have real-world experience of both bosentan (2003 onwards) and macitentan (2014 onwards). Nevertheless, comparative research between bosentan and macitentan on clinical outcomes in CTEPH patients has not been established. In this study, we focus on clinical outcomes in CTEPH till two years after treatment initiation and compare bosentan and macitentan therapy results.

2. Methods

2.1 Study population and treatment strategies

All consecutive technical inoperable CTEPH and residual PH patients between January 2003 and January 2019 receiving bosentan or macitentan in the St. Antonius Hospital in Nieuwegein, the Netherlands, were included in our retrospective cohort study. Diagnosis was established and operability was assessed, based on the CTEPH guidelines[3], in our CTEPH multidisciplinary team, including cardiologists, pulmonologists, radiologist, cardiothoracic surgeons and nurse practitioners.

PH was defined as mean pulmonary artery pressure (mPAP) ≥25 mmHg and wedge pressure ≤15 mmHg at right heart catheterisation (RHC). CTEPH was diagnosed when mismatched perfusion defects on lung scan were seen with signs of CTEPH on multide-

tector CT angiography or conventional pulmonary angiography in the presence of PH, after at least three months anticoagulation treatment.
Patients with predominantly subsegmental or more distal thromboembolic disease were classified as technical inoperable. Residual PH was defined as persistent elevated mPAP ≥25 mmHg immediately post-PEA by Swan-Ganz measurement and persistent elevated on RHC six months after PEA or the need for PH-specific therapy to achieve mPAP <25 mmHg.
All symptomatic patients between 2003 and 2014 were initiated on bosentan monotherapy, most as part of the BENEFiT[8] trial and in accordance with their inclusion criteria. From 2014 onwards, riociguat was initiated in newly diagnosed CTEPH patients. In case of suboptimal riociguat dose or AEs leading to discontinuation (e.g. hypotension or severe dyspnoea), riociguat was switched to macitentan monotherapy or replaced by sildenafil for combination therapy. Patients with clinical worsening (CW) or without clinical improvement, switched to combination therapy (with ERA and sildenafil/riociguat/prostacyclin). From 2016 onwards, upfront combination therapy was initiated (riociguat/sildenafil plus ERA) in severely symptomatic patients, as later was postulated by the risk stratification strategy of the European Society of Cardiology / European Respiratory Society guideline[13]. In case of patients on combination therapy with worsening risk stratification group, therapy was extended to triple therapy with intravenous prostacyclin or selexipag. Balloon pulmonary angioplasty (BPA) was introduced in our expert centre in 2016. Patients were systematically reviewed for BPA to stabilise or improve hemodynamics and exercise tolerance[14], even if clinically stable. Patient follow-up was censored from the first BPA onwards, to differentiate between ERA and BPA effect.

2.2 Baseline and follow-up

Baseline was defined as start of ERA. Patient characteristics, time from diagnosis till baseline, medical history and additional tests were collected if performed within three months of diagnosis. Outpatient follow-up visits alternated between a pulmonologist and cardiologist every three months.

2.3 Outcomes

Patients were followed from baseline till two years after ERA initiation or last available information before (latest date ERA use, death, start BPA or end of study observation period (01-2019)). Death was defined as all-cause mortality and CW as a combined outcome of death, disease progression or non-elective hospitalisation for CTEPH. Disease progression was considered a reduction ≥15% of 6MWD from baseline to last available information plus worsening WHO FC (except patients already in FC IV) or the use of intravenous prostacyclin or selexipag therapy. Only the first event of CW during the

observation period was noted. All treatment AEs were noted.
WHO FC, 6MWD and NT-proBNP were determined at baseline and follow-up. Follow-up assessments were collected annually (from baseline) from outpatient visits closest to one- and two-year follow-up dates.

2.4 Statistical analyses

Statistical analyses were performed with SPSS software (IBM SPSS statistics version 24). Tests were 2-tailed with $p<0.05$ considered statistically significant. Normally distributed continuous variables were presented as mean ± standard deviation (SD), not normally distributed variables as median (interquartile range (IQR)). Categorical data were presented as number and percentage. Differences between bosentan and macitentan were assessed with student t-tests, Mann-Whitney U, Pearson Chi-Square and Fisher exact tests. Difference between follow-up and baseline were assessed with paired t-test, Wilcoxon signed rank and McNemar tests. Survival and time to CW were analysed with Kaplan-Meier curves and predictors with Cox proportional hazards regression (HR) analyses. Weighted regression with inverse probability of treatment weighting (IPTW) using propensity score was used to adjust baseline differences. Waiting time from diagnosis to baseline was corrected with a time-dependent covariate. The study was approved by the local ethical commission (number W17.132).

3. Results

3.1 Study population

In total 302 CTEPH patients were screened for this study, of which 111 patients were accepted for PEA and 45 for BPA. One hundred ninety patients were excluded as they did not receive ERA therapy. One hundred twelve patients (mean age 62.3±14.2 years, 58% female, 68% WHO FC III/IV, 88% technical inoperable) could be included in this study, with 57 patients (51%) receiving bosentan and 55 (49%) receiving macitentan (figure 1). Waiting time from baseline was not significantly longer for macitentan (0.5 years (0-6.8)). At baseline, 37 patients (65%) received bosentan monotherapy and 20 (35%) bosentan-sildenafil therapy. Fifteen patients (27%) had macitentan monotherapy, 24 (44%) macitentan-riociguat and 16 (29%) macitentan-sildenafil. Significantly more patients received bosentan monotherapy than macitentan monotherapy and no patient had bosentan-riociguat therapy (both $p=0.001$). At baseline, there were significantly more smokers in the macitentan cohort ($p=0.02$). No patient had a history of ventriculoatrial shunt or chronic osteomyelitis. Although not statistically significant, baseline NT-proBNP, right atrial pressure (RAP) and PVR were higher in patients receiving macitentan (table 1).

Table 1. Patient baseline characteristics

	All patients (n=112) (Mean ± SD)	**Bosentan (n=57)** (Mean ± SD)	**Macitentan (n=55)** (Mean ± SD)	**P-value**
Demographic characteristics, n (%)				
Age (years)	62.3 ± 14.2	62.6 ± 14.4	62.1±14.1	0.866
Female gender	65 (58.0)	32 (56.1)	33 (60.0)	0.706
Inoperable / Residual CTEPH	98 (87.5) / 14 (12.5)	50 (87.7) / 7 (12.3)	48 (87.3) / 7 (12.7)	0.943
VKA/NOAC/LMWH (%)	92/7/1	98/2/0	85/13/2	0.069
Monotherapy	52 (46.4)[#]	37 (64.9)	15 (27.3)	**0.001**
ERA + riociguat	24 (21.4)[#]	0	24 (43.6)	**0.001**
ERA + sildenafil	36 (32.1)[#]	20 (35.1)	16 (29.1)	0.548
History taking, n (%)				
Smokers (ever)	53 (48.2)	21 (38.2)	32 (58.2)	**0.024**
COPD	19 (17.0)	8 (14.0)	11 (20.0)	0.457
Hypertension	24 (21.4)	13 (22.8)	11 (20.0)	0.717
Diabetes	11 (9.8)	6 (10.5)	5 (9.1)	1.000
Hyperlipidemia	4 (3.6)	2 (3.5)	2 (3.6)	1.000
Thyroid dysfunction	8 (7.1)	4 (7.0)	4 (7.3)	0.998
Inflammatory bowel disease	3 (2.7)	2 (3.5)	1 (2.6)	0.615
Hematologic disease	29 (25.9)	13 (22.8)	16 (29.1)	0.520
Splenectomy	5 (4.5)	4 (7.0)	1 (1.8)	0.364
Cardiac device	2 (1.8)	0	2 (3.6)	0.495
Venous thrombosis	31 (27.7)	17 (29.8)	14 (25.5)	0.675
Acute pulmonary embolism	85 (75.9)	41 (71.9)	44 (80.0)	0.380
Clinical characteristics				
WHO FC I/II/III/IV (%)	1/31/64/4	2/26/68/4	0/36/60/4	0.536
NT-proBNP (pg/mL), median (IQR)	1020 (289-2145)	724 (264-1503) [1]	1409 (291-2785) [2]	0.066
6MWD (m), mean±SD	324 ± 126	324 ± 118 [3]	323 ± 134 [2]	0.955
6MWT lowest saturation (%)	83.2 ± 7.9	84.0 ± 6.4 [4]	82.6 ± 9.2 [5]	0.427
Right-sided heart catheterization				
CO (L/min)	5.1 ± 1.7	5.2 ± 1.5 [6]	5.1 ± 1.8 [7]	0.682
RAP mean (mmHg)	8.6 ± 4.5	7.9 ± 4.9 [8]	9.3 ± 3.9 [5]	0.122
PAP mean (mmHg)	42.2 ± 10.6	41.6 ± 10.2 [9]	42.9 ± 11.2 [5]	0.554
PVR (WU)	6.6 ± 3.7	6.0 ± 2.9 [4]	7.3 ± 4.4 [10]	0.087

SD: standard deviation, CTEPH: chronic thromboembolic pulmonary hypertension, COPD: chronic obstructive pulmonary disease, WHO FC: World Health Organisation functional class, NT-proBNP: N-terminal

pro brain natriuretic peptide, 6MWD: 6-minute walking distance, 6MWT: 6-minute walking test, CO: cardiac output, RAP: right arterial pressure, PAP: pulmonary arterial pressure, PVR: pulmonary vascular resistance. # Data do not add up to 100% due to rounding.
1 n=47; 2 n=52; 3 n=53; 4 n=48; 5 n=49; 6 n=50; 7 n=47; 8 n=51; 9 n=55; 10 n=46

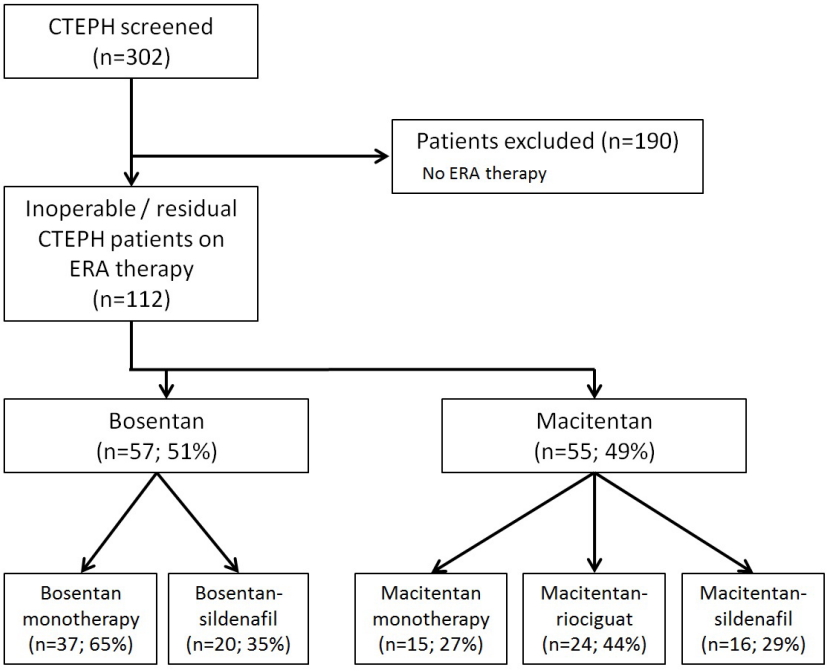

Figure 1. Flow-chart of patient selection and treatment strategies.

3.2 Survival

The two-year survival rate was 91% for bosentan and 80% for macitentan, univariate HR mortality macitentan 1.85 [0.56-6.10], p=0.31) and after IPTW adjustment HR 1.49 [0.40-5.61], p=0.55. In total 12 patients (11%) died, of which six received bosentan. Two patients on bosentan died in the first year (survival rate 96%) and four in the second year. For macitentan this were respectively three (survival rate 92%) and three patients (figure 2). Significant multivariate predictors for mortality were RAP (HR 1.13 [1.01-1.26]), cardiac output (CO) (HR 0.43 [0.24-0.79]) and 6MWT lowest saturation (HR 0.91 [0.86-0.97]), all at baseline (supplemental table 1). The type of ERA was not a predictor for survival. Patients who died used macitentan monotherapy (n=2, 17%), macitentan-riociguat combination therapy (n=4, 33%), bosentan monotherapy (n=3, 25%) and bosentan-sildenafil combination therapy (n=3, 25%). No patient using macitentan-sildenafil died (supplemental figure 1). A comparison

of bosentan versus macitentan monotherapy and bosentan-sildenafil versus macitentan-sildenafil showed no significant survival difference (p=0.2 and p=0.5, respectively).

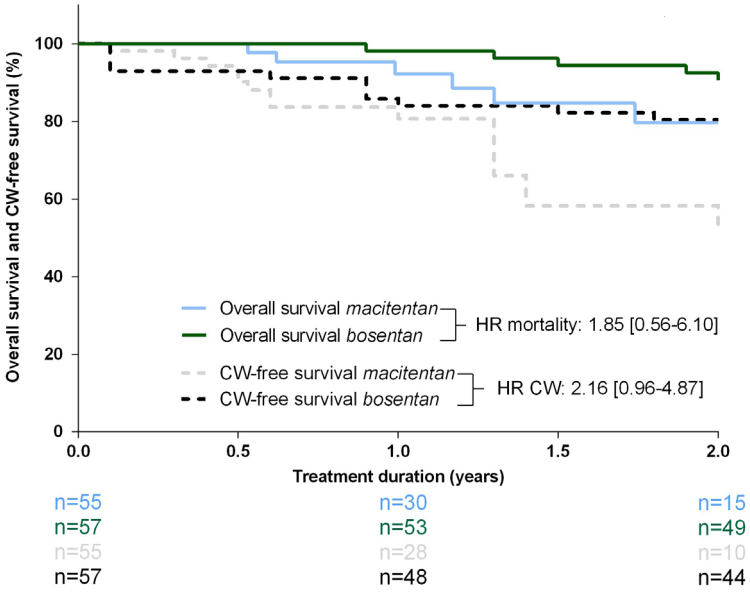

Figure 2. Kaplan-Meier survival and CW-free survival curves, number of patients at risk receiving bosentan and macitentan and univariate HR for mortality and CW.

3.3 Clinical worsening

Two-year freedom from CW was 81% for bosentan and 58% for macitentan, HR macitentan 2.16 [0.96-4.87], p=0.06. Twenty-six patients (23%) experienced CW, of whom 11 (41%) received bosentan. CW was due to hospitalisation (n=11, bosentan n=4), death (n=7, bosentan n=4), intravenous prostanoids (n=6, bosentan n=2) or worsened FC plus 6MWD (n=2, bosentan n=1). Eight bosentan patients had CW in the first year (CW-free survival 86%) and 3 in the second year. For macitentan patients this were 7 (84%) and 8 respectively (figure 2). Significant multivariate predictors for CW were RAP (HR 1.11 [1.04-1.21]) and 6MWT lowest saturation (HR 0.96 [0.92-0.99]), all at baseline. Type of ERA was not a predictor for CW (supplemental table 2).

3.4 Follow-up

The mean study treatment duration was 1.9±0.4 years for bosentan and 1.2±0.6 years for macitentan (p=0.0001). Follow-up ended in 11 (20%) patients receiving macitentan due to start of BPA treatment. Mean follow-up duration for macitentan without censoring for BPA was 1.3±0.6 years. None of these patients died or experienced clinical worsening after start of BPA.

AEs were observed in 35 patients (31%). Twenty-one patients receiving bosentan (37%) experienced an AE. Most common were increased liver enzymes (n=9, 16%), leading to discontinuation in 2 patients, and headache or dizziness (n=4, 7%). Fourteen patients receiving macitentan (26%) experienced an AE, with headache or dizziness (n=4, 7%), upper respiratory tract symptoms (n=3, 5%) and fatigue (n=3, 5%) as most common (supplemental table 3). Total AE rate did not differ between therapies (p=0.19).

WHO FC stabilised/improved compared to baseline in 48 patients (94%, p=0.001) receiving bosentan at year 1 and 46 (94%, p=0.0002) at year 2. For macitentan this were 29 (97%, p=0.001) and 12 patients (80%) respectively (supplemental figure 2). A comparison of annual change to baseline showed no statistical difference between both ERAs.

The level of NT-proBNP changed with bosentan -68 pg/mL (-403-59) at year 1 and -28 pg/mL (-432-156) at year 2, and with macitentan -293 pg/mL (-1659-91, p=0.02) and +15 pg/mL (-1130-247) respectively, but without a significant difference between therapies.

Overall mean 6MWD increased during follow-up with +21m (CI 1-42, p=0.04) at year 1 and +25m (CI 2-48, p=0.04) at year 2 for bosentan, and +57m (CI 30-85, p=0.0001) and +35m (CI 2-78, p=0.04) for macitentan respectively. Change from baseline was not significantly different between ERA type.

4. Discussion

In this study we present the first real-world two-year follow-up results of both bosentan and macitentan therapy in inoperable CTEPH and residual PH after PEA patients. We show improved clinical status compared to baseline, but without a significant difference between both drugs. This is the first study comparing outcomes of bosentan and macitentan in CTEPH till two-year follow-up.

Nowadays, PH-specific therapies for CTEPH other than riociguat are gaining more interest and the use of combination therapy increases[7,13]. In our expert centre, we often prescribe combination therapy with riociguat/sildenafil plus bosentan/macitentan. In recent years, we have prescribed more macitentan than bosentan, as comparative studies in PAH patients with congenital heart disease showed improved WHO FC, NT-proBNP and TAPSE without any AEs after switching to macitentan[15–18]. Macitentan is practical in use as it is dosed once daily, does not require monthly liver testing and has less interaction with anticoagulation therapy[15], but is also more expensive compared to an equal

defined daily dose of bosentan. Nevertheless, comparative research on clinical outcomes in CTEPH is not available.

In our cohort, survival was comparable between bosentan (91%) and macitentan (80%) at two-year follow-up. Survival was highly consistent with results reported by Hughes et al[20] in their bosentan cohort (±90% at one-year follow-up) and by Delcroix et al in their multicentre, international prospective registry (79% at two-year follow-up)[13].

CW-free survival was not significantly higher in bosentan than macitentan (81% vs 58) at two-year follow-up. The BENEFiT trial showed only 4% CW, but this was for a 16 week observation period[8]. Long-term CW-free survival results of bosentan and macitentan in CTEPH are currently unavailable.
Most AEs in our study were non-severe, except in two patients using bosentan. Their liver function deranged despite dose tapering, leading to discontinuation. Our AE rate is lower than in RCTs (bosentan 37% vs 68%, macitentan 26% vs 75%)[8,9], which might be caused by the retrospective collection of AEs. Our AE rate is comparable with previous cohort results[19]. No new safety issue was identified.

Bosentan and macitentan (significantly) improved WHO FC, NT-proBNP and 6MWD in our study, without a significant difference between both ERAs.
WHO FC improved in 15% of all patients in the BENEFiT trial, while no patient worsened in the MERIT trial[8,9]. Cohort studies showed improved WHO FC at six months (27%) and one year (24%) in patients using bosentan[19–21]. Our current results for bosentan are more profound at one-year follow-up (37%) and persist till two-year follow-up (49%), probably partially explained by our better baseline characteristics (better WHO FC and hemodynamics). Results for macitentan at one-year follow-up were highly comparable with MERIT trial results[9]. However, 20% of our patients using macitentan had worsened at two-year follow-up, but the number of patients was low.
NT-proBNP significantly decreased in the BENEFiT and MERIT trial[8,9], while there was no significant decrease in our study at two-year follow-up, probably due to our lower baseline NT-proBNP. Ulrich et al could not show significant decrease of proBNP at six-month follow-up either in their cohort study[20].
The 6MWD remained unchanged in the BENEFiT trial at 16 weeks follow-up, explained by the older age of patients and short duration of the study[8]. We show in similar aged patients improved (+25m) 6MWD till two-year follow-up. The study duration may indeed have influenced results, however, Reesink et al[22] did already show a significant improved (+33m) 6MWD at 16 weeks. The difference with the BENEFiT trial might be our real-world patients and better hemodynamics at baseline in our cohort. Less stable patients are more frequent included in cohort studies and these patients may show more improved exercise capacity with treatment. Comorbidities may also influence 6MWD, but unfortunately

these were not provided in the BENEFiT trial[8]. Two other cohort studies showed improved 6MWD at six-month (+54m) and one-year follow-up (+57m)[19,20]. Our results are probably lower due to lower baseline 6MWD values. Patients receiving macitentan had improved 6MWD at two-year follow-up in our study, comparable with short-term results (+35m vs +34m) in the MERIT trial[9]. More real-world studies are necessary to establish the long-term treatment effect of ERAs in CTEPH.

Although none of the clinical outcomes was significantly different between both ERAs, some results were less profound for macitentan therapy, partly explained by a low number of patients at risk at different time points and differences in baseline characteristics.
The low number of patients at risk for macitentan (e.g. n=15 vs n=49 at two-year follow-up) is partly explained by the significant shorter macitentan treatment duration due to shorter availability (2014) and the introduction of BPA (2016) with consequent ending of patients' follow-up for this study. Treatment duration would be (slightly) longer without censoring, which could have resulted in higher (CW-free) survival. However, censoring was necessary to separate macitentan and BPA effects, as BPA improves outcomes[14]. In addition, disease duration before start of macitentan was longer, which may have negatively influenced outcomes, although we corrected this with a time-dependent covariate.
There were significant more smokers in the macitentan group. Tobacco smoke exposure is a risk factor in PAH, elevates pulmonary arterial pressure in adults and results in PH at younger age[23–25]. Smoking may confound CTEPH and may negatively influence outcomes. Baseline NT-proBNP was higher in macitentan patients, indicating worse clinical outcomes and more disease burden during follow-up[5–8,26]. However, both smoking and NT-proBNP were not significant multivariate predictors for outcomes in our study.
Both RAP and PVR at baseline were higher for patients using macitentan, although not significantly. Previous research showed that RAP predicts survival in PAH[27–29] and CO predicts hemodynamic normalisation and in hospital mortality after PEA[30,31]. In our study, we confirm that RAP and CO are predictors for outcomes in CTEPH as well. PVR was not a multivariate predictor in our study.
Baseline 6MWT lowest saturation was a multivariate predictor for death and CW in our study. Other research showed comparable findings, as 6MWT desaturations increase mortality in PAH and correlate with pulmonary hemodynamics in CTEPH patients[32,33].

On the other hand, most bosentan patients started monotherapy, while most macitentan patients started combination therapy. When bosentan was introduced in 2003, the guideline at that time recommended starting monotherapy and, if indicated, sequential combination or triple therapy.
Nowadays, combination therapy in PAH patients is recommended, because it reduces the risk of CW and improves long-term outcomes[4,34–36] due to additive or synergistic

beneficial effects[37]. Although there is no randomized research available in inoperable CTEPH patients, combination therapy may also be beneficial in CTEPH patients. Combination therapy with macitentan versus monotherapy with bosentan may have influenced the outcomes in our study, and may overestimate the effect of macitentan alone. However, sub-analyses of both monotherapies and both combination therapies with sildenafil did not show any difference. More research is necessary to distinguish between outcomes of mono- and combination therapy.

4.1 Limitations

Our single-centre population was small and the number of outcomes was limited, which may lead to overfitting in regression analyses. However, as CTEPH data are scarce, we consider our research valuable for sharing real-world CTEPH treatment experience. There is a bias in patient selection as patients already survived time to start of ERA therapy. However, patients rarely die before therapy initiation and we corrected for waiting time with a time-dependent covariate. It is likely that the accuracy of diagnostic imaging and the experience of the CTEPH team have increased during the 16 years of patient inclusion, however, the direct effect on treatment and outcome is difficult to predict.

5. Conclusion

Inoperable CTEPH and residual PH patients using bosentan or macitentan show improved clinical outcomes up till two-year follow-up, without significant different outcomes between both therapies.

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Appendix

Supplemental table 1. Cox proportional hazards regression for survival

	HR (univariate)	P-value	HR (multivariate)	P-value
Age	1.02 [0.98-1.07]	0.311		
Male	3.79 [1.03-14.0]	**0.046**		NS
ERA type (macitentan)	1.85 [0.56-6.10]	0.311	0.59 [0.14-2.46]	0.468
Smokers	3.22 [0.95-10.9]	0.059		NS
WHO FC		0.936		
NT-proBNP per 1 log	6.61 [1.77-24.6]	**0.005**		NS
6MWD per 10 m	0.98 [0.94-1.03]	0.473		
6MWT lowest saturation	0.92 [0.87-0.97]	**0.003**	0.91 [0.86-0.97]	**0.004**
RAP mean	1.10 [0.99-1.22]	0.092	1.13 [1.01-1.26]	**0.030**
PAP mean	1.02 [0.97-1.08]	0.442		
PVR	1.20 [1.03-1.40]	**0.018**		NS
CO	0.45 [0.25-0.81]	**0.007**	0.43 [0.24-0.79]	**0.006**

HR: hazard ratio, NS: not significant, ERA: endothelin receptor antagonist, WHO FC: World Health Organisation functional class, 6MWD: 6-minute walking distance, 6MWT: 6-minute walking test, NT-proBNP: N-terminal pro brain natriuretic peptide, RAP: right arterial pressure, CO: cardiac output, PAP: pulmonary arterial pressure, PVR: pulmonary vascular resistance

Supplemental table 2. Cox proportional hazards regression for time to clinical worsening

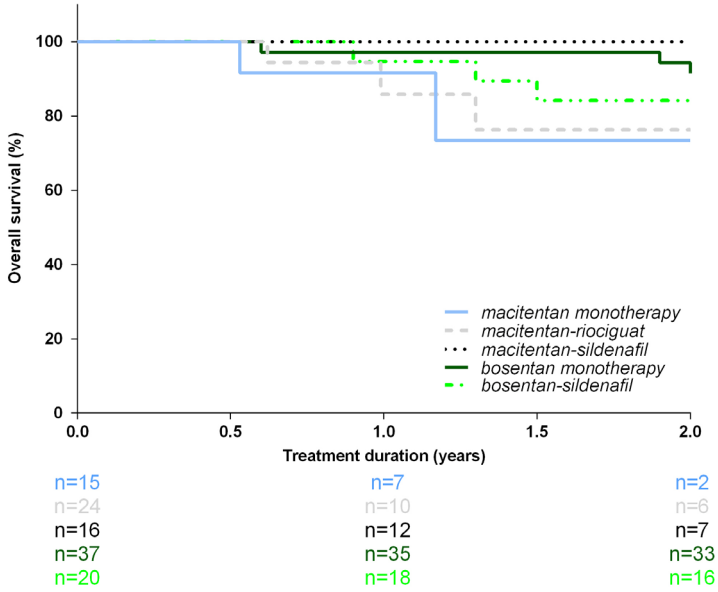
	HR (univariate)	P-value	HR (multivariate)	P-value
Age	1.02 [0.99-1.05]	0.307		
Male	1.83 [0.86-3.92]	0.117		
ERA type (macitentan)	2.16 [0.96-4.87]	0.062	1.98 [0.81-4.85]	0.134
Smokers	1.73 [0.80-3.74]	0.161		
WHO FC		0.945		
NT-proBNP per 1 log	3.51 [1.66-7.44]	**0.001**		NS
6MWD per 10 m	0.98 [0.94-1.03]	0.428		
6MWT lowest saturation	0.93 [0.88-0.98]	**0.006**	0.96 [0.92-0.99]	**0.036**
RAP mean	1.10 [1.03-1.18]	**0.009**	1.11 [1.04-1.21]	**0.004**
PAP mean	1.05 [1.02-1.09]	**0.005**		NS
PVR	1.20 [1.03-1.40]	**0.021**		NS
CO	0.59 [0.42-0.83]	**0.002**		NS

HR: hazard ratio, NS: not significant, ERA: endothelin receptor antagonist, WHO FC: World Health Organisation functional class, 6MWD: 6-minute walking distance, 6MWT: 6-minute walking test, NT-proBNP: N-terminal pro brain natriuretic peptide, RAP: right arterial pressure, PAP: pulmonary arterial pressure, PVR: pulmonary vascular resistance, CO: cardiac output

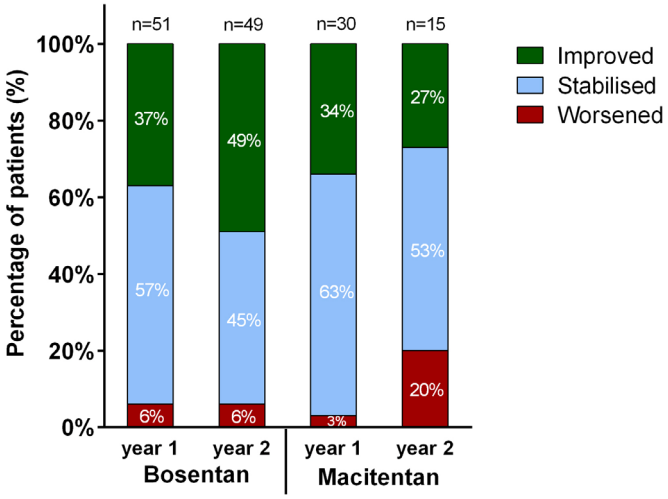
Supplemental table 3. Adverse events

Adverse events	**All patients (n=112)**	**Bosentan (n=57)**	**Macitentan (n=55)**
Adverse events, n (%)#	**35 (31.3)**	**21 (36.8)**	**14 (25.5)**
Increased liver enzymes, n (%)	9 (8.0)	9 (15.8)	0
Headache or dizziness, n (%)	8 (7.1)	4 (7.0)	4 (7.2)
Upper respiratory tract symptoms, n (%)	4 (3.6)	1 (1.8)	3 (5.5)
Fatigue, n (%)	4 (3.6)	1 (1.8)	3 (5.5)
Nausea, n (%)	4 (3.6)	3 (5.3)	1(1.8)
Peripheral edema, n (%)	4 (3.6)	2 (3.5)	2 (3.6)
Skin problems, n (%)	3 (2.7)	2 (3.5)	1 (1.8)
Joint pain, n (%)	2 (1.8)	1 (1.8)	1 (1.8)
Anemia, n (%)	1 (0.9)	1 (1.8)	0
Thrombocytopenia (%)	1 (0.9)	1 (1.8)	0
Palpitations (%)	1 (0.9)	1 (1.8)	0
Diarrhea	1 (0.9)	1 (1.8)	0
Increased creatinine, n (%)	1 (0.9)	0	1 (1.8)

Unique patients, individual patients could experience multiple adverse events.



Supplemental figure 1. Kaplan-Meier overall survival curves and number of patients at risk receiving bosentan and macitentan monotherapy and different combination therapies. The patient with triple therapy at baseline is not shown in this figure.



Supplemental figure 2. Number of patients at risk and proportion of bosentan and macitentan patients with improved/stabilised/worsened WHO FC compared to baseline.

CHAPTER 5

Does combination therapy work in chronic thromboembolic pulmonary hypertension?

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ABSTRACT

Background: The current experience with combination therapy in chronic thromboembolic pulmonary hypertension (CTEPH) is limited. We present the first survival results up to 5 years for dual combination therapy versus monotherapy in CTEPH.

Methods: All consecutive, non-operated CTEPH or residual PH after pulmonary endarterectomy patients treated with PH-specific medical therapy between January 2002 and November 2019 were included. We report and compare survival between monotherapy and (upfront or sequential) dual combination therapy until five years after medication initiation.

Results: In total, 183 patients (mean age 65±14 years, 60% female, 66% WHO FC III/IV, 86% non-operated) were included, of which 83 patients received monotherapy and 100 patients received dual combination therapy. At baseline, patients receiving combination therapy had a higher NT-proBNP (p=0.02) mean pulmonary artery pressure (p=0.0001) and pulmonary vascular resistance (p=0.02), while cardiac index was lower (p=0.03). Total follow-up duration was 3.3±1.8 years, during which 31 (17%) patients died. Estimated 1-, 3- and 5-year survival for monotherapy were 99%, 92% and 79%, respectively. For combination therapy percentages were 98%, 89% and 70%, respectively. Survival did not significantly differ between both groups (p=0.22).

Conclusion: Survival up to 5 years for patients treated with combination therapy, regardless of the combination strategy, was similar as patients with monotherapy, despite worse clinical and haemodynamic baseline characteristics.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a pulmonary vascular disease due to chronic thromboembolic obstruction. Most patients experienced an acute thromboembolic event, although a minority has no history of previous acute thromboembolism. Chronic thromboembolisms may lead to CTEPH and subsequent secondary distal vasculopathy[1]. The exact incidence of CTEPH after acute pulmonary embolism is unclear. Prospective studies report an incidence ranging from 0.4% to 6.2%[2–4].

Pulmonary endarterectomy (PEA) is the preferred treatment, as it greatly improves outcome and prognosis[5]. However, not all patients do have accessible lesions for PEA, may be inoperable due to comorbidities or decline PEA. Some may have persistent or recurrent pulmonary hypertension (PH) after PEA due to vasculopathy[6]. In these patients, both balloon pulmonary angioplasty (BPA) and PH-specific medical therapy may improve clinical outcomes[7–10]. Riociguat is currently the only registered PH-specific medical therapy for CTEPH, although other PH-specific drugs are increasingly being used[8,11].

In pulmonary arterial hypertension (PAH), the current clinical practice is to start with initial dual combination therapy to achieve a low-risk status and to reduce the risk of clinical failure[12]. Nevertheless, the current experience with early combination therapy in CTEPH is limited and is adapted from PAH treatment strategies. The aim of the current study is to provide clinical data about the usefulness of dual combination therapy in a large cohort of CTEPH patients and to identify the effect on patient-related clinical outcome in daily practice.

2. Methods

2.1 Study population and treatment strategies

All consecutive newly diagnosed CTEPH patients, either non-operated or with residual PH after PEA, treated with PH-specific medical therapy in the St. Antonius Hospital in Nieuwegein, the Netherlands between January 1, 2002 and November 1, 2019 were included. CTEPH diagnosis was established in our multidisciplinary team, consisting of cardiologists, pulmonologists, radiologists, cardiothoracic surgeons and specialised nurse practitioners. Patients received anticoagulation therapy for at least three months, had mismatched perfusion defects on lung scintigraphy and signs of chronic pulmonary embolism on multidetector CT angiography or conventional angiography. Right heart catheterisation (RHC) showed a mean pulmonary artery pressure (mean PAP) of ≥25 mmHg and a wedge pressure ≤15 mmHg.

Patients were classified as *monotherapy* if they received only one PH-specific medical therapy during the complete follow-up, although they were able to switch between different monotherapies. Patients who received dual *combination therapy* were classified as *sequential combination therapy* or *upfront combination therapy*. Upfront combination

therapy was defined as concomitant initiation of two PH-specific drugs within 3 months, sequential therapy was defined as sequential initiation of two PH-specific drugs at least 3 months apart. Patients were able to switch between different PH-specific drug groups, but follow-up ended if patients switched to triple therapy. A flowchart of subgroups and patient numbers are shown in supplemental figure 1.
From 2002 onwards, patients were initiated on monotherapy and switched to sequential combination therapy in case of insufficient improvement or clinical worsening during follow-up. In case of severely symptomatic or hemodynamic impairment at baseline, upfront combination therapy was initiated. From 2015 onwards, mainly upfront combination therapy was initiated as standard treatment for CTEPH, in accordance with PAH recommendations in the ESC/ERS guideline[12].
The local ethical commission approved the study (number W17.132).

2.2 Baseline, follow-up and outcomes

The date of multidisciplinary team discussion was classified as moment of diagnosis; date of initiation of PH-specific medical therapy was considered as baseline. Time between diagnosis and baseline was noted. Start of PH-specific medication in patients with persistent PH after PEA was set as date of PEA, while this was the date of RHC confirming PH in patients with recurrent PH after PEA.
Patient characteristics, medical history and additional tests were collected from hospital records and databases if performed within three months of diagnosis. A baseline non-invasive risk score was calculated, with WHO FC, 6-min walking distance (6MWD) and NT-proBNP, to estimate 1-year mortality [13,14]. Outpatient follow-up visits alternated between a pulmonologist and cardiologist every three months. Patients were followed for up to five years from baseline or last available information before death, start of BPA, ending of (dual) PH medical therapy or observation period (01-12-2019). Death was defined as all-cause mortality.

2.3 Statistical analyses

Statistical analyses were performed with SPSS (IBM SPSS statistics version 24). Tests were two-tailed and a p-value below 0.05 was considered statistically significant. Categorical data were presented as number and percentage. Continuous data were presented as mean and standard deviation (SD) or as median and interquartile range (IQR). Groups were compared with Chi-squared test and t-test or Mann-Whitney U test for categorical and continuous data respectively. Survival was analysed with Kaplan-Meier method and comparisons between two groups with log-rank test. Predictors for survival were assessed with Cox regression for univariate and multivariate analysis. Univariate variables with a p-value below 0.10 were included for multivariate analysis using backward stepwise elimination.

Waiting time from diagnosis to baseline was corrected with a time-dependent covariate. Additional analyses were performed to demonstrate effects of BPA and time period on the current data.

3. Results

3.1 Study population

Entire cohort

In total, 183 patients (mean age 65±14 years, 60% female, 66% WHO FC III/IV, 45/32/16/7% risk score) were included for analyses in our cohort. Most patients were non-operated (86%), while a minority had residual PH after PEA (14%). Ninety-one percent of all patients used vitamin K antagonists; the remaining nine percent used direct oral anticoagulants (DOACs). Comorbidities were frequent (systemic hypertension 29%, chronic obstructive pulmonary disease 20%). There was a history of an acute pulmonary embolism and venous thrombosis in 78% and 26% of all patients, respectively. In total, 16% of all patients did not experience any acute thromboembolic event. NT-proBNP (662 (226-2151) pg/mL) was elevated; mean 6MWD was 312±126m. RHC showed a cardiac index (CI) of 2.6±0.8 L/min/m2, with mean PAP 40.9±10.4 mmHg resulting in pulmonary vascular resistance (PVR) of 6.7±3.8 WU at baseline. Characteristics are shown in table 1.

Table 1. Patient baseline characteristics

	Entire cohort (n=183)	**Monotherapy (n=83)**	**Combination therapy (n=100)**
Demographic characteristics			
Age (years)	65±14	65±16	65±13
Female gender	60	57	62
Non-operated / residual CTEPH	86/14	82/18	90/10
VKA/DOAC	91/9	95/5	88/12
Monotherapy			
Riociguat		7	
ERA		58	
PDE5i		34	
Prostacyclin		1	
Combination therapy			
Riociguat + ERA			39
PDE5i + ERA			61
Total follow-up duration (years)	3.3±1.8	3.4±1.7	3.3±1.8

History taking			
Smokers (ever)	48	41	54
COPD	20	18	21
Systemic hypertension	29	19	36#
Diabetes	11	8	13
Hyperlipidaemia	5	2	7
Thyroid disorders	7	7	7
Inflammatory bowel disease	1	0	1
Hematologic disease	14	17	13
Malignancy	15	19	12
Splenectomy	2	1	3
Cardiac device	3	3	3
Venous thrombosis	26	33	21
Acute pulmonary embolism	78	78	78
Clinical characteristics			
WHO FC I/II/III/IV	2/32/63/3	1/38/57/4	2/27/69/2
NT-proBNP (pg/mL)	662 (226-2151)	347 (108-1273)	1341 (293-2641)#
6MWD (m)	312±126	324±135	302±118
Non-invasive risk score (0/1/2/3)	45/32/16/7	36/31/21/12	51/33/11/5#
Right-sided heart catheterization			
CO (L/min)	5.0±1.7	5.3±1.9	4.7±1.5#
CI (L/min/m^2)	2.6±0.8	2.8±0.9	2.5±0.7#
RAP mean (mmHg)	8.7±4.8	8.4±5.3	9.0±4.3
PAP mean (mmHg)	40.9±10.4	37.7±9.9	43.4±10.1#
PVR (WU)	6.7±3.8	5.9±4.0	7.3±3.5#

Data are presented as %, mean±SD, median (IQR). SD: standard deviation, IQR: interquartile range, CTEPH: chronic thromboembolic pulmonary hypertension, VKA: vitamin K antagonist, DOAC: direct oral anticoagulant, ERA: endothelin receptor antagonist, PDE5i: phosphodiesterase type 5 inhibitor, BPA: balloon pulmonary angioplasty, COPD: chronic obstructive pulmonary disease, WHO FC: World Health Organisation functional class, NT-proBNP: N-terminal pro brain natriuretic peptide, 6MWD: 6-min walking distance, CO: cardiac output, CI: Cardiac index, RAP: right arterial pressure, PAP: pulmonary arterial pressure, PVR: pulmonary vascular resistance.

# $p<0.05$ compared with monotherapy

Monotherapy

Eighty-three patients (mean age 65±16 years, 57% female, 61% WHO FC III/IV, 36/31/21/12% risk score) in our cohort used monotherapy. At baseline, six patients (7%) had riociguat, 28 (34%) phosphodiesterase type 5 inhibitors (PDE5i), 48 (58%) endothelin receptor antagonists (ERAs) and one (1%) prostacyclin. In total 7 patients (8%) switched between

monotherapies: 2 patients from PDE5i to riociguat, 3 from ERA to PDE5i, 1 from ERA to riociguat and 1 from ERA to prostacyclin. Full subgroup characteristics are shown in table 1.

Combination therapy

One hundred patients (mean age 65±13 years, 62% female, 71% WHO FC III/IV, 51/33/11/5% risk score) received combination therapy. At baseline 39 patients (39%) received riociguat/ERA, while 61 patients (61%) received PDE5i/ERA. Patients receiving combination therapy had worse baseline characteristics compared to monotherapy patients: patients were more symptomatic and had lower 6MWD, although not statistically significant. However, the percentage of patients with systemic hypertension (p=0.01), the level of NT-proBNP (p=0.02), mean PAP (p=0.0001) and PVR (p=0.02) were significantly higher, while CI and risk score were significantly lower (p=0.03 and p=0.02 respectively).

Sequential combination therapy

In our cohort, there were 58 patients (mean age 65±12 years, 55% female, 69% WHO FC III/IV, 46/42/6/6% risk score) receiving sequential combination therapy. Mean time till start of the second PH-specific drug was 1.8±1.2 years. Eighteen patients (31%) had riociguat/ERA, while 40 patients (69%) had PDE5i/ERA. Ten patients (17%) switched between groups: 5 switched from riociguat/ERA to PDE5i/ERA, 1 from riociguat/ERA to prostacyclin/ERA, 2 from PDE5i/ERA to riociguat/ERA and 2 from PDE5i/ERA to prostacyclin/ERA.

Upfront combination therapy

The 42 patients (mean age 64±13 years, 71% female, 74% WHO FC III/IV, 57/20/20/3% risk score) receiving upfront combination therapy were equally divided between riociguat/ERA and PDE5i/ERA. Four patients switched between medication groups: three switched from riociguat/ERA to PDE5i/ERA and one patient the other way around. Significant more patients received DOACs (p=0.03) compared to the sequential combination therapy group. Baseline PVR was significantly higher in the upfront combination therapy group (p=0.05) in comparison to the sequential combination therapy group. Full subgroup characteristics are shown in table 2.

Table 2. Patient baseline characteristics

	Sequential combination therapy (n=58)	**Upfront combination therapy (n=42)**	**P-value**
Demographic characteristics			
Age (years)	65±12	64±13	0.78
Female gender	55	71	0.10

Non-operated / residual CTEPH	93/7	86/14	0.31
VKA/DOAC	95/5	79/21	**0.03**
Combination therapy Riociguat + ERA PDE5i + ERA	 31 69	 50 50	0.06
Total follow-up duration (years)	4.1±1.3	2.2±1.7	**0.0001**
History taking			
Smokers (ever)	55	52	0.78
COPD	28	12	0.06
Systemic hypertension	35	39	0.64
Diabetes	9	19	0.13
Hyperlipidaemia	7	7	0.24
Thyroid disorders	7	7	0.94
Inflammatory bowel disease	0	0	1.00
Hematologic disease	16	10	0.38
Malignancy	9	15	0.52
Splenectomy	5	0	0.26
Cardiac device	2	5	0.39
Venous thrombosis	26	14	0.16
Acute pulmonary embolism	78	79	0.91
Clinical characteristics			
WHO FC I/II/III/IV	2/29/67/2	2/24/71/3	0.66
NT-proBNP (pg/mL)	1288 (280-2145)	1723 (322-3310)	0.19
6MWD (m)	300±119	306±119	0.80
Non-invasive risk score (0/1/2/3)	46/42/6/6	57/20/20/3	0.89
Right-sided heart catheterization			
CO (L/min)	5.0±1.7	4.4±1.2	0.06
CI (L/min/m^2)	2.5±0.8	2.4±0.7	0.42
RAP mean (mmHg)	8.6±4.4	9.4±4.2	0.41
PAP mean (mmHg)	43.1±10.2	43.8±10.1	0.75
PVR (WU)	6.6±2.9	8.1±4.0	**0.05**

Data are presented as %, mean±SD, median (IQR). SD: standard deviation, IQR: interquartile range, CTEPH: chronic thromboembolic pulmonary hypertension, VKA: vitamin K antagonist, DOAC: direct oral anticoagulant, ERA: endothelin receptor antagonist, PDE5i: phosphodiesterase type 5 inhibitor, BPA: balloon pulmonary angioplasty, COPD: chronic obstructive pulmonary disease, WHO FC: World Health Organisation functional class, NT-proBNP: N-terminal pro brain natriuretic peptide, 6MWD: 6-min walking distance, CO: cardiac output, CI: Cardiac index, RAP: right arterial pressure, PAP: pulmonary arterial pressure, PVR: pulmonary vascular resistance.

3.2 Outcomes

Entire cohort

Total follow-up duration was 3.3±1.8 years, during which 31 (17%) patients died. Seven patients died due to right ventricular failure, four due to sepsis and two due to malignancy, while for the remaining 18 patients the cause of death was unknown. Estimated 1-, 3- and 5-year survival were 98%, 90% and 74%, respectively. None of the patients underwent lung transplantation during the follow-up. Independent predictors at baseline of mortality in the entire cohort identified from multivariate analysis were absence of hematologic disease (HR 0.30, 95% CI 0.12-0.78), NT-proBNP (HR 3.80, 95% CI 1.68-8.60) and RAP (HR 1.15, 95% CI 1.06-1.24). Results are shown in figure 1 and supplemental table 1.

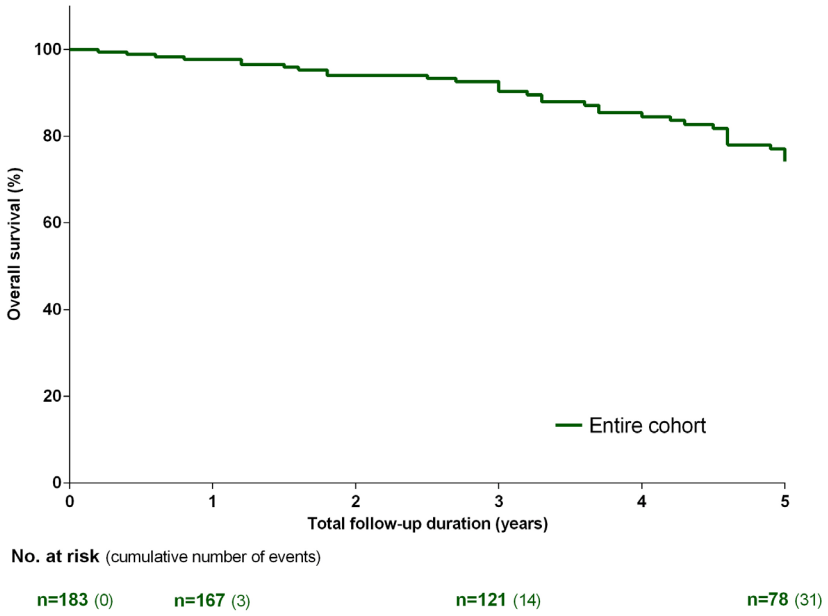

Figure 1. Kaplan-Meier estimates of survival from baseline in the entire non-operated chronic thromboembolic pulmonary hypertension (CTEPH) cohort. Number of patients at risk and cumulative number of events are shown.

Monotherapy vs combination therapy

Patients receiving monotherapy had a mean follow-up duration of 3.4±1.7 years, while this was 3.3±1.8 years for patients receiving combination therapy. In the former group, 11 patients (13%) died, in the latter 20 patients (20%). Estimated 1-, 3- and 5-year sur-

vival for monotherapy were 99%, 92% and 79%, respectively. For combination therapy percentages were comparable, with an estimated 1-, 3- and 5-year survival of 98%, 89% and 70%. Survival did not significantly differ between both groups (p=0.22). Results are shown in figure 2.
A comparison between the different combination therapy strategies (riociguat + ERA and PDE5i + ERA) did not show any significant difference either (p=0.52).

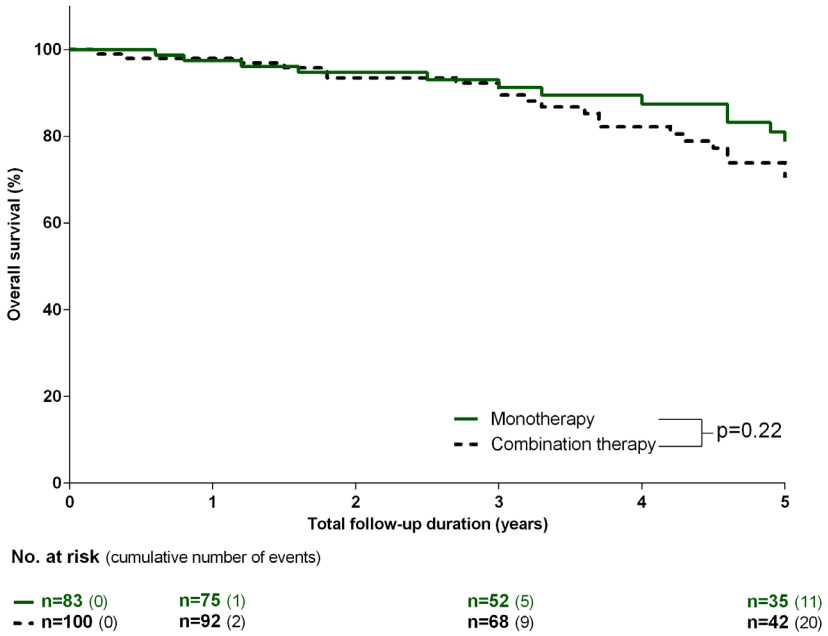

Figure 2. Kaplan-Meier estimates of survival from baseline in chronic thromboembolic pulmonary hypertension (CTEPH) monotherapy group and CTEPH combination therapy group. Number of patients at risk and cumulative number of events are shown.

Independent predictors of mortality in the monotherapy group identified from multivariate analysis were 6MWD per 10m (HR 0.87, 95% CI 0.79-0.96) and mean PAP (HR 1.08, 95% CI 1.01-1.17), all at baseline. For combination therapy this were absence of hematologic disease (HR 0.24, 95% CI 0.09-0.66) and RAP (HR 1.12, 95% CI 1.03-1.22). Results are shown in supplemental tables 2 and 3.

Sequential combination therapy vs upfront combination therapy
A comparison between combination therapy strategies, showed a significant longer follow-up for sequential combination therapy than upfront combination therapy (4.1±1.3

years vs 2.2±1.7 years, p=0.0001). Thirteen patients (22%) died in the sequential combination therapy group and seven patients (17%) in the upfront combination therapy group. Estimated 1-, 3- and 5-year survival for sequential therapy was 100%, 93% and 73%, respectively, and for upfront therapy 95%, 79% and 59%, respectively (p=0.22). Results are shown in supplemental figure 2.

3.3 Additional analyses

For this manuscript, patient follow-up was censored when BPA treatment was initiated. Outcomes and data without censoring for BPA are described hereafter.

Thirteen percent of the patients receiving monotherapy underwent BPA during follow-up, while this was 27% in the patients receiving combination therapy (p=0.02). Significantly more patients with upfront combination therapy than sequential combination therapy received BPA (p=0.002).

Total follow-up duration increased to 3.6±1.6 years, while two patients, one using monotherapy and the other using sequential combination therapy, died after start of BPA due to non-procedure related sepsis and right heart failure respectively. Estimated 1-, 3- and 5-year survival without censoring for BPA were 98%, 90% and 74%, respectively. Patients receiving monotherapy had a mean follow-up duration of 3.5±1.7 years, while this was 3.6±1.5 years for patients receiving combination therapy. Estimated 1-, 3- and 5-year survival for monotherapy were 98%, 90% and 79%, respectively. For combination therapy percentages were similar, except 71% survival at year 5. Survival did not significantly differ between both groups (p=0.31). A comparison between combination therapy strategies, showed a significant longer follow-up for sequential combination therapy than upfront combination therapy (4.3±1.1 years vs 2.7±1.6 years, p=0.0001). Estimated 1-, 3- and 5-year survival for sequential therapy was 100%, 91% and 73%, respectively, and for upfront therapy 95%, 87% and 65%, respectively (p=0.48).

The inclusion period was long and management may have changed during the time span of this study. Additional analysis to compare survival before and after 2015 (start of macitentan and riociguat use) was performed. There was no significant difference in survival for mono- and combination therapy (p=0.18) or monotherapy alone (p=0.93) before and after 2015.

4. Discussion

The current study is the first to investigate the effect of dual combination therapy versus monotherapy in patients with non-operated CTEPH or residual PH after PEA on survival up to 5 years.

Despite worse clinical and haemodynamic characteristics at baseline in the combination therapy group, survival was similar compared to patients receiving monotherapy, regardless of the combination therapy strategy used.

The pathophysiology of CTEPH is currently not completely known. It is assumed that CTEPH is usually a consequence of prior acute pulmonary embolism[1]. Seventy-eight percent of all patients in our cohort had a history of an acute pulmonary embolism, similar as reported in an international CTEPH registry[15]. Common risk factors for CTEPH, such as thyroid disorders, malignancy, splenectomy and hematologic disorders, were present in our cohort. Patients also frequently had cardiovascular comorbidities. The prevalence of risk factors was comparable with results from the CTEPH registry[15].

Operable CTEPH patients treated with PEA have the best prognosis, with an estimated 1-, 3- and 5-year survival of >90%, >84% and >80%, respectively[5,16]. However, not all patients are operable. In addition, operated patients may reveal residual PH after PEA, what leads to a decreased prognosis especially when pulmonary hemodynamics after PEA are severely impaired[16]. These two groups do probably suffer from vasculopathy[1]. This vasculopathy in CTEPH shows similarities in pathological features with PAH, what makes it likely that PAH therapy may also be useful in CTEPH[8].

A large, prospective European registry showed an estimated 1- and 3-year survival of 88% and 70% in non-operated patients[17]. In this registry, 61% of the patients received PH-specific medical therapy at any time, with 18% receiving dual combination therapy with sildenafil and ERA[17]. In our cohort of medically treated patients, we report higher survival percentages: an estimated 1-, 3- and 5-year survival of 98%, 90% and 74%, respectively. A comparison of our baseline characteristics with the European registry showed less symptomatic patients and a slightly lower mean PAP and PVR in our cohort[17], this might partly explain the difference in survival as the pulmonary hemodynamics are predictors for mortality[18]. It is also likely that the different percentage of patients receiving PH-medical (combination) therapy is very important, probably explaining the survival difference between both cohorts.

Historically, most CTEPH patients receive monotherapy[19]. In our study, 45% of patients received monotherapy, predominantly ERA or PDE5i. Most of these patients (75%) were diagnosed before the introduction of riociguat/macitentan/combination therapy, and received bosentan or sildenafil as monotherapy. Statistical analysis did not show a significant survival difference between the two time periods (before and after 01/01/2015). Long-term survival data of patients treated with monotherapy in randomised controlled trials is scarce: the CHEST-2 study reported a survival of 97% at 1-year follow-up, comparable with our percentage[20]. Cohort studies showed a 1-year survival of 96% with bosentan and 100% survival with sildenafil monotherapy[21,22]. A large cohort study in the UK, with 72% of technically-operable-not-operated patients and 86% of nonsurgical-disease-distribution patients treated with PH-specific therapy of whom most received PDE5i, showed a 5-year survival of 55% and 60% respectively[18]. CTEPH registries in Spain and

Switzerland showed similar results[23,24]. However, our estimated 5-year survival of 79% is higher; all of our patients received PH-specific medical therapy, were less symptomatic and had better baseline hemodynamics, probably explaining the difference[18].

The concept of combination therapy is more established in PAH compared with CTEPH. To achieve a low-risk status and to improve outcomes, the initial use of combination therapy in PAH is advised[13,14,25–27]. Studies directly assessing this concept in CTEPH are limited. A review of the available literature shows the use of background PAH-therapy combined with macitentan in 61% of all patients in the MERIT-1 trial, although these patients did predominantly receive PDE5i and follow-up duration was limited[28]. Cohort studies using combination therapy showed a reduction in PVR with sildenafil and inhaled prostacyclin[29,30]. A case report described improved hemodynamics, WHO FC and 6MWD in one CTEPH patient receiving riociguat and treprostinil[31]. Currently, most of our patients are initiated on combination therapy and more than half of the patients in the current study received combination therapy. At baseline, these patients had worse clinical characteristics, risk score and hemodynamics compared to patients treated with monotherapy. Despite this, survival was similar between both groups, indicating the importance and potential of combination therapy in CTEPH.

Combination therapy can be given upfront or sequential. For PAH treatment, upfront combination therapy is preferred over sequential combination therapy[12,27]. Nevertheless, both combination therapy strategies were never compared directly, but only with monotherapy.
We show in our CTEPH cohort a comparable survival between upfront and sequential combination therapy, despite higher baseline PVR in the upfront combination therapy group. More (randomised) research is necessary to compare both strategies.

4.1 Limitations

We described outcomes of different therapy strategies in a single-centre CTEPH population. In The Netherlands we are able to initiate PAH therapy in CTEPH patients. However, this may not always be possible in other countries. The number of events in the monotherapy group was low, what may lead to overfitting in the regression analyses. The period of patient inclusion was long and the preferred treatment (strategy) has changed over time. However, analyses did not show a significant difference between survival outcomes before and after 2015. Although all patients were discussed in the multidisciplinary team, bias for treatment strategy may be present. The group receiving combination therapy is heterogeneous, with a significant higher baseline PVR in the upfront combination therapy group. Nevertheless, PVR was not a predictor for mortality. It may be interesting for future research to differentiate therapy strategies results in a standardised population

with risk stratification.

5. Conclusion

Survival up to five years for patients treated with dual combination therapy, regardless of the combination strategy, was similar as compared with patients receiving monotherapy, despite worse clinical and haemodynamic characteristics at baseline.

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Appendix

Supplemental table 1. Cox regression survival analysis for the entire cohort

Covariate		Univariate analysis		Multivariate analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age	Per year	1.04 (1.01-1.07)	**0.018**		
Sex	Ref: female	0.68 (0.34-1.37)	0.281		
Systemic hypertension	Ref: absent	1.65 (0.68-4.01)	0.273		
Diabetes	Ref: absent	0.76 (0.27-3.17)	0.604		
COPD	Ref: absent	0.67 (0.29-1.56)	0.356		
Hematologic disease	Ref: absent	0.35 (0.16-0.76)	**0.008**	0.30 (0.12-0.78)	**0.013**
Malignancy	Ref: absent	0.90 (0.32-2.59)	0.851		
Therapy type	Ref: monotherapy (vs combination)	0.64 (0.31-1.34)	0.241		
WHO FC	FC I/II vs III/IV	1.28 (0.59-2.78)	0.530		
NT-proBNP	Per log	3.95 (1.99-7.84)	**0.001**	3.80 (1.68-8.60)	**0.001**
6MWD	Per 10m	0.95 (0.91-0.98)	**0.004**		
RAP mean	Per mmHg	1.12 (1.05-1.20)	**0.001**	1.15 (1.06-1.24)	**0.001**
PAP mean	Per mmHg	1.04 (1.01-1.07)	**0.028**		
CI	Per L/min/m^2	0.74 (0.46-1.21)	0.232		
PVR	Per WU	1.08 (0.98-1.19)	0.126		

Univariate variables with a p-value below 0.10 were included for multivariate analysis. HR: Hazard ratio, ref: reference parameter, COPD: chronic obstructive pulmonary disease, WHO FC: World Health Organisation functional class, NT-proBNP: N-terminal pro brain natriuretic peptide, 6MWD: 6-min walking distance, RAP: right arterial pressure, PAP: pulmonary arterial pressure, CI: Cardiac index, PVR: pulmonary vascular resistance.

Supplemental table 2. Cox regression survival analysis for monotherapy

Covariate		Univariate analysis		Multivariate analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age	Per year	1.07 (1.01-1.13)	**0.034**		
Sex	Ref: female	0.63 (0.19-2.08)	0.450		
Systemic hypertension	Ref: absent	2.39 (0.31-18.7)	0.407		
Diabetes	Ref: absent	0.30 (0.08-1.13)	0.074		
COPD	Ref: absent	0.23 (0.06-0.80)	**0.022**		
Hematologic disease	Ref: absent	0.47 (0.13-1.79)	0.269		

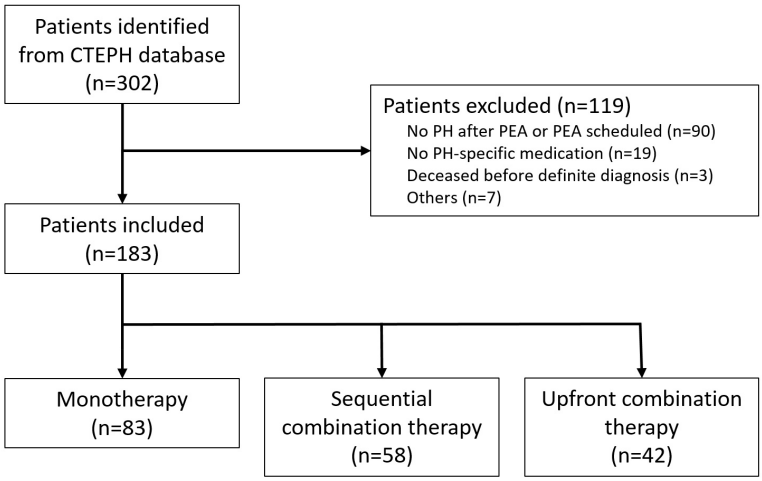
Malignancy	Ref: absent	0.53 (0.14-2.01)	0.352		
WHO FC	FC I/II vs III/IV	1.37 (0.40-4.70)	0.613		
NT-proBNP	Per log	17.9 (3.44-92.9)	**0.001**		
6MWD	Per 10m	0.90 (0.84-0.97)	**0.005**	0.87 (0.79-0.96)	**0.004**
RAP mean	Per mmHg	1.12 (1.00-1.26)	**0.048**		
PAP mean	Per mmHg	1.05 (1.00-1.12)	0.073	1.08 (1.01-1.17)	**0.043**
CI	Per L/min/m^2	0.71 (0.33-1.56)	0.397		
PVR	Per WU	1.06 (0.90-1.24)	0.494		

Univariate variables with a p-value below 0.10 were included for multivariate analysis. HR: Hazard ratio, ref: reference parameter, COPD: chronic obstructive pulmonary disease, WHO FC: World Health Organisation functional class, NT-proBNP: N-terminal pro brain natriuretic peptide, 6MWD: 6-min walking distance, RAP: right arterial pressure, PAP: pulmonary arterial pressure, CI: Cardiac index, PVR: pulmonary vascular resistance.

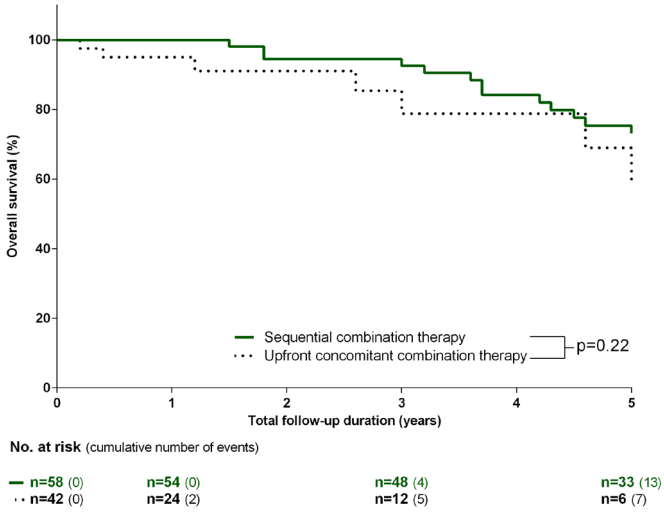
Supplemental table 3. Cox regression survival analysis for combination therapy

Covariate		Univariate analysis		Multivariate analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age	Per year	1.02 (0.99-1.07)	0.228		
Sex	Ref: female	0.67 (0.28-1.62)	0.374		
Systemic hypertension	Ref: absent	1.68 (0.61-4.63)	0.313		
Diabetes	Ref: absent	2.12 (0.28-15.9)	0.464		
COPD	Ref: absent	1.40 (0.41-4.79)	0.588		
Hematologic disease	Ref: absent	0.27 (0.10-0.71)	**0.008**	0.24 (0.09-0.66)	**0.005**
Malignancy	Ref: absent	1.61 (0.21-12.1)	0.646		
Combination therapy type	Ref: upfront	1.79 (0.70-4.57)	0.221		
WHO FC	FC I/II vs III/IV	1.07 (0.39-2.94)	0.901		
NT-proBNP	Per log	2.44 (1.05-5.71)	**0.039**		
6MWD	Per 10m	0.98 (0.93-1.02)	0.282		
RAP mean	Per mmHg	1.11 (1.02-1.20)	**0.012**	1.12 (1.03-1.22)	**0.010**
PAP mean	Per mmHg	1.02 (0.98-1.06)	0.309		
CI	Per L/min/m2	0.83 (0.43-1.60)	0.579		
PVR	Per WU	1.07 (0.94-1.23)	0.296		

Univariate variables with a p-value below 0.10 were included for multivariate analysis.. HR: Hazard ratio, ref: reference parameter, COPD: chronic obstructive pulmonary disease, WHO FC: World Health Organisation functional class, NT-proBNP: N-terminal pro brain natriuretic peptide, 6MWD: 6-min walking distance, RAP: right arterial pressure, PAP: pulmonary arterial pressure, CI: Cardiac index, PVR: pulmonary vascular resistance.



Supplemental figure 1. Patient cohort flowchart with subgroup classification. CTEPH: chronic thromboembolic pulmonary hypertension, PEA: pulmonary endarterectomy, PH: pulmonary hypertension.



Supplemental figure 2. Kaplan-Meier estimates of survival from baseline in chronic thromboembolic pulmonary hypertension (CTEPH) sequential combination therapy group and CTEPH upfront combination therapy group. Number of patients at risk and cumulative number of events are shown.

PART II

Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension

CHAPTER 6

Safety and efficacy of balloon pulmonary angioplasty in chronic thromboembolic pulmonary hypertension in the Netherlands

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ABSTRACT

Background: Balloon pulmonary angioplasty (BPA) is an emerging treatment in patients with chronic thromboembolic pulmonary hypertension (CTEPH) and chronic thromboembolic disease (CTED). We describe the first safety and efficacy results of BPA in the Netherlands.

Methods: We selected all consecutive patients with inoperable CTEPH and CTED accepted for BPA treatment and who had a six-month follow-up in the St. Antonius Hospital in Nieuwegein and Amsterdam UMC. Functional class (FC), NT-proBNP, 6-minute walking test distance (6MWD) and right heart catheterisation were performed at baseline and six months after last BPA. Complications for each BPA procedure were noted.

Results: One hundred seventy-two BPA procedures were performed in 38 patients (61% female, mean age 65±15 years). Significant improvements six months after BPA treatment were observed for: functional class (63% FC I/II to 90% FC I/II, p=0.014), mean pulmonary artery pressure (-8.9 mmHg, p=0.0001), pulmonary vascular resistance (-2.8 WU, p=0.0001), right atrial pressure (-2.0 mmHg, p=0.006), stroke volume index (+5.7 mL/m2, p=0.009) and 6MWD (+48m, p=0.007). Non-severe complications occurred in 20 (12%) procedures.

Conclusion: BPA performed in a CTEPH expert centre is an effective and safe treatment in patients with inoperable CTEPH.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a pulmonary artery disease caused by chronic thromboembolisms, leading to pulmonary hypertension (PH) despite the use of anticoagulation. The pulmonary vascular resistance (PVR) increases due to vascular occlusions and a consequential distal arteriopathy, eventually resulting in right ventricular failure and death if left untreated[1].

When CTEPH patients are technically operable, i.e. in central or segmental disease, pulmonary endarterectomy (PEA) is the treatment of choice[2,3]. Patients who are considered inoperable, based on a distal localisation of chronic thromboembolisms or due to comorbidities resulting in a nonacceptable risk-benefit, are currently treated with PH-specific medication[3,4]. However, recent studies reported that balloon pulmonary angioplasty (BPA) might be of value in carefully selected patients[5]. Treatment with BPA aims to restore blood flow in the pulmonary arteries by opening (partially) obstructed vessels leading to improved pulmonary hemodynamics[5]. In addition, patients with symptomatic chronic thromboembolic disease (CTED) without PH, may also benefit from BPA[6].

We evaluated the safety and efficacy of BPA treatment in inoperable CTEPH and CTED patients and present the first results of the two specialised CTEPH centres in the Netherlands.

2. Methods

2.1 Study population

CTEPH diagnosis was established and operability was assessed in multidisciplinary CTEPH teams according to the current guideline[4]. The teams consist of (interventional) cardiologists, pulmonologists, (interventional) radiologists, cardiac thoracic surgeons and specialised nurse practitioners. PH was defined as a mean pulmonary artery pressure (mPAP) of ≥25 mmHg and a pulmonary artery wedge pressure (PAWP) ≤15 mmHg on right-sided heart catheterisation (RHC). The diagnosis of CTEPH was established with mismatched perfusion defects on lung scan in the presence of specific diagnostic signs for CTEPH on multidetector CT angiography or conventional pulmonary angiography, after anticoagulation for a minimum of three months. Symptomatic patients with perfusion defects, but with a mPAP <25 mmHg, were classified as CTED.

PH-specific medical therapy was initiated in case of symptomatic, inoperable CTEPH. Patients remained on the same therapy during BPA procedures, unless a change in therapy was clinically necessary.

All patients were discussed in the CTEPH team. Inoperable CTEPH/CTED patients or patients reluctant to undergo surgery were accepted for BPA treatment if they had accessible thromboembolic lesions and did not have severe contraindications (i.e.

right-sided valvular endocarditis, a right-sided mechanical heart valve or a thrombus or myxoma in the right atrium). Patients with relative contraindications (i.e. patients with an estimated creatinine clearance <30 mL/min/1.73m2, hypersensitivity to contrast media, coagulopathy or pregnancy) were individually reviewed. Patients accepted for BPA treatment, were enrolled in a standardised BPA (follow-up) protocol, including BPA treatment and a follow-up evaluation six months after the last BPA. All patients accepted for BPA in the St. Antonius Hospital in Nieuwegein between 01-2016 and 10-2018, and in the Amsterdam UMC between 06-2015 and 02-2019, were included in this study. Data from all patients who completed their six-month follow-up before end of the study period were used for statistical analyses.

2.2 BPA procedure and right-sided heart catheterisation St. Antonius Hospital

Oral anticoagulation was maintained throughout all interventions with an international normalized ratio (INR) between 2.5 and 3.5. Patients on direct oral anticoagulants (DOACs) were actively switched to vitamin K antagonists to minimize the risk of procedure related thromboembolisms. RHC was performed with a Swan-Ganz 7F catheter, at baseline and six months after the last BPA procedure. BPA procedures were performed using femoral access with a 6F to 9F sheath and a 6F guide wire and catheter (Terumo Corporation, Tokyo, Japan). Activated clotting time was kept between 200 and 300 seconds by administration of intravenously heparin (2500-5000 IE). The 0.014-inch guide wire was directed into the affected pulmonary artery branches, which were visualised with jopromide (ULTRAVIST). After identification of the affected vessels and correct positioning of the guide wire, dilatation with semi-compliant balloons (Emerge 2.5-4.0 / 15-20 mm or Maverick XL 5.0 / 15-20mm, Boston Scientific, Marlborough, MA and Tazuna RX 3.0 /20 mm, Terumo Corporation, Tokyo, Japan) was performed. During each procedure, up to four vessels were treated or the procedure ended when more than 500 mL contrast or more than 60 minutes procedure time were used. Time to the next BPA procedure varied between four to six weeks. Vital signs and signs of potential complications were monitored at the coronary care unit after each procedure. Figure 1 shows images and results of BPA in an inoperable CTEPH patient.

2.3 BPA procedure and right-sided heart catheterisation Amsterdam UMC

Vitamin K antagonists were stopped at least two weeks prior to the procedure and were switched to DOACs. Patients stopped antiplatelet medication at least one week before the procedure. Depending on the renal clearance, anticoagulation was stopped 24-48 hours prior to BPA. The procedure took place if the INR was ≤1.5 on the day of procedure. RHC was performed with a Swan-Ganz 8F catheter during the diagnostic pulmonary angiogram, and six months after the last BPA procedure. BPA procedures were performed using femoral access with a 6F Destination sheath (Terumo) and a

6F guiding catheter (Cordis Corporation, Miami Lakes, FL USA and Medtronic Inc, Medtronic Parkway, Minneapolis, MN USA). Activated clotting time was kept between 250 and 350 seconds by administration of intravenously heparin (starting with 5000 IE). A 0.014-inch guide wire was directed into the affected pulmonary artery branches, which were visualised with jodixanol (Visipaque 320). Dilatation was performed with semi-compliant balloons (Emerge 2.0-3.0 / 20 mm, Maverick XL 5.0 / 15 mm, Boston Scientific, Marlborough, MA USA and TREK 3.5-4.0 /20 mm, Abbott Vascular, Santa Clara, CA USA). The procedure ended if a maximum of ten segments in one lung were treated or more than 200 mL contrast was used. Time to the next BPA procedure varied between four to six weeks. Patients were monitored for potential complications at the coronary care unit or pulmonary ward.

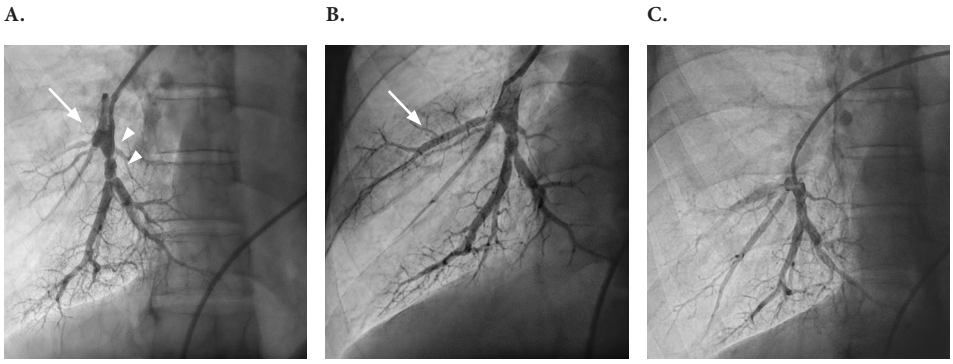

Figure 1. Three images of the right lower and middle pulmonary artery lobe on pulmonary angiography in the same CTEPH patient
A: Pre-BPA, with significant lesions in the middle lobe (total occlusion, white arrow) and lower lobe (webs, white arrow heads).
B: Result after the first BPA procedure, with opening of the total occlusion in the middle lobe.
C: Result after the second BPA procedure, with dilatation of web lesions in the lower lobe.

2.4 Baseline and follow-up

We defined baseline as the date of CTEPH diagnosis in our multidisciplinary CTEPH teams. Additional research with imaging tests, RHC, World Health Organization Functional Class (WHO FC), N-terminal pro brain natriuretic peptide (NT-proBNP) and 6-minute walking test distance (6MWD) were performed at baseline and six months after the last BPA. Complications for each BPA procedure were noted.

2.5 Statistical analyses

Statistical analyses were performed with SPSS software (IBM SPSS statistics version 24). Tests were 2-tailed and with a p-value <0.05 considered statistically significant. Continuous data were presented as mean ± standard deviation (SD) or as median with interquartile range (IQR), and categorical data as number and percentage. Differences between baseline and six-month follow-up after BPA were assessed with the Wilcoxon signed-rank test and (exact) McNemar test. The study was approved by the local ethical commissions in the St. Antonius Hospital (number W17.132) and Amsterdam UMC (number 2017.400).

3. Results

3.1 Study population

We included 55 CTEPH/CTED patients accepted for BPA in this study, of which 38 had completed their treatment and six-month follow-up before end of the study period. Seventeen patients were excluded from statistical analyses because these patients did not reach their six-month follow-up yet (n=4), died before the six-month follow-up evaluation (n=4) or were still undergoing BPA procedures at the end of the study period (n=9). The four patients in the Amsterdam UMC who died before their six-month follow-up, died due to metastatic cancer (n=2; diagnosed after final BPA), a hip fracture (n=1) and right ventricular failure (n=1) (figure 2).

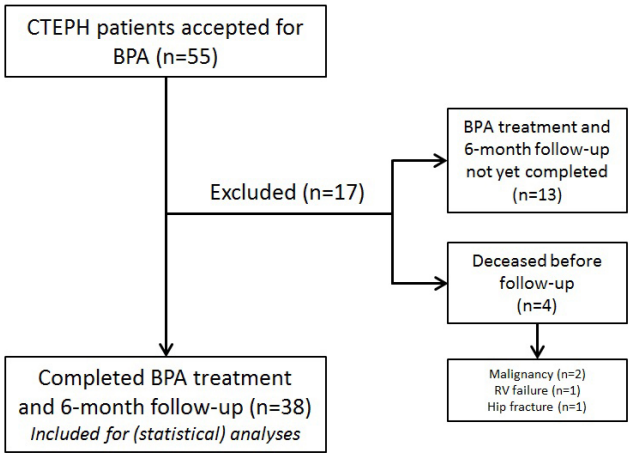

Figure 2. Flowchart with patient in- and exclusion.

Thirty-eight patients (St. Antonius Hospital n=15, Amsterdam UMC n=23) were included for analyses in this study. The mean age was 65.0±14.6 years, 61% was female and 63% of the patients were in WHO FC II (table 1). Twenty-six (69%) patients had technical inoperable disease (inaccessible for PEA), 7 (18%) patients had operable disease but with comorbidities resulting in a nonacceptable risk-benefit for PEA and 5 (13%) patients were operable but had declined PEA. None of the included patients had BPA after PEA. One female patient (40 years old, WHO FC III, mPAP 22 mmHg and PVR 1.6 WU) suffered from severely symptomatic CTED. There were no patients with a history of chronic osteomyelitis, inflammatory bowel disease, ventriculoatrial shunt or cardiac device; furthermore most patients (87%) did have a history of a prior thromboembolic event and four (11%) patients had a coagulation disorder (polycythemia vera n=3, factor V Leiden n=1). Two (5%) patients had concomitant coronary artery disease.

Table 1. Patient baseline characteristics pre- and post-BPA

	Pre-BPA (n=38)	**Post-BPA (n=38)**	**P-value**
Demographic characteristics			
Age (years)	65.0 ± 14.6		
Female gender, n (%)	23 (61)		
Length (cm)	173.6 ± 9.2		
Weight (kg)	83.6 ± 17.8		
BMI (kg/m^2)	27.9 ± 6.2		
BSA (m^2)	2.0 ± 0.2		
Medical history, n (%)			
Smokers (ever)	11 (29)		
COPD	6 (16)		
Hypertension	11 (29)		
Diabetes	3 (8)		
Coronary artery disease	2 (5)		
Thyroid dysfunction	3 (8)		
Coagulation disorder	4 (11)		
Venous thromboembolism	33 (87)		
Pharmacologic therapy, n (%)			
VKA / NOAC	15 (39) / 23 (61)		
Loop diuretics	14 (37)		
No PH medication	7 (18)	5 (13)	0.500
sGC stimulator	8 (21)	10 (26)	0.500

PDE5-i	3 (9)	4 (11)	1.000
ERA	5 (13)	8 (21)	0.250
sGC stimulator + ERA	7 (18)	6 (16)	1.000
PDE5-i + ERA	8 (21)	5 (13)	0.250
Clinical characteristics			
WHO FC I/II/III/IV (%)	0/63/34/3	39/50/11/0	**0.014**
NT-proBNP (pg/mL), median (IQR), n=36	195 (96-1811.5)	154 (71-387)	0.078
Log NT-proBNP (pg/mL), n=36	2.5 ± 0.8	2.2 ± 0.6	**0.008**
6MWD (m), n=31	374 ± 124	422 ± 125	**0.007**
Right-sided heart catheterization			
Heart rate (bpm), n=31	72.3 ± 11.6	71.6 ± 11.8	0.630
CO (L/min), n=36	5.7 ± 2.3	6.0 ± 1.6	0.510
CI (L/min/m^2), n=36	2.9 ± 1.1	3.0 ± 0.8	0.479
SVi (ml/m^2), n=31	37.5 ± 10.9	43.2 ± 10.2	**0.009**
Mean RAP (mmHg), n=33	8.9 ± 3.5	6.9 ± 3.0	**0.006**
Systolic PAP (mmHg)	63.6 ± 19.8	50.6 ± 15.0	**0.0001**
Diastolic PAP (mmHg)	24.1 ± 6.1	18.4 ± 4.2	**0.0001**
Mean PAP (mmHg)	39.5 ± 11.6	30.6 ± 8.2	**0.0001**
PAWP (mmHg)	11.5 ± 2.7	12.1 ± 3.6	0.340
PVR (WU), n=36	6.1 ± 4.7	3.3 ± 2.0	**0.0001**

Data are presented as mean ± standard deviation or median (interquartile range). BPA: Balloon pulmonary angioplasty, SD: standard deviation, BMI: body mass index, BSA: body surface area, COPD: chronic obstructive pulmonary disease, VKA: vitamin K antagonist, NOAC: novel oral anticoagulants, PH: pulmonary hypertension, sGC stimulator: soluble guanylyl cyclase stimulator, PDE5-i: phosphodiesterase type 5 inhibitor, ERA: endothelin receptor antagonist, WHO FC: World Health Organisation functional class, NT-proBNP: N-terminal pro brain natriuretic peptide, IQR: interquartile range, 6MWD: 6-minute walking distance, CO: cardiac output, CI: cardiac index, SVi: stroke volume index, RAP: right arterial pressure, PAP: pulmonary arterial pressure, PAWP: pulmonary artery wedge pressure, PVR: pulmonary vascular resistance.

3.2 BPA procedure and complications

In total, 172 BPA sessions were performed (mean 4.5±1.3 BPA sessions per patient). The total hospital stay was between 1.5 and 2.1 days per BPA session. Twenty (12%) complications were recorded (table 2). Complications included mild haemoptysis (n=14), temporary conduction or rhythm disturbances (n=3), pulmonary vascular dissection (n=2) and pulmonary vascular perforation (n=1). There were no patients with vascular access complications in our cohort. Overall complication rates were similar between the two hospitals (St. Antonius Hospital 10% and Amsterdam UMC 12%). Mild haemoptysis was observed in, respectively, 4% and 10% of all procedures in St. Antonius hospital and Amsterdam

UMC (difference not statistically significant), while temporary conduction or rhythm disturbances were only observed in the St. Antonius Hospital.
Multiple patients experienced haemoptysis during one BPA session only, although one patient experienced haemoptysis during 3 different BPA sessions, without angiographic vessel rupture, perforation or dissection. Haemoptysis not ending spontaneously was treated in two patients with intravascular pulmonary balloon occlusion of the vessel for 1-15 minutes and infusion of protamine. The two cases of pulmonary vascular dissection and the pulmonary vascular perforation, all in subsegmental pulmonary arteries, were treated successfully in a similar way. In one patient, continuous positive airway pressure (CPAP) was deemed clinically necessary after BPA. None of the complications resulted in a longer hospital stay, death or need for intubation.

Table 2. BPA related complications

	Total BPA procedures (n=172)
Overall complications	**20 (12)**
Mild haemoptysis	14 (8)
Temporary conduction / rhythm disturbances	3 (2)
Pulmonary vascular dissection	2 (1)
Pulmonary vascular perforation	1 (1)

3.3 Follow-up results

The six-month follow-up after BPA was available in 38 patients and showed, compared to baseline, an improvement in WHO FC (63% FC I/II to 90% FC I/II, p=0.014), with 58% of the patients improving at least one FC (figure 3), and increased 6MWD (+48 meters, p=0.007). The median NT-proBNP decreased not significantly, although the log NT-proBNP decreased significantly (-0.3 log pg/mL, p=0.008).
The systolic PAP (-13.0 mmHg (p=0.0001)), diastolic PAP (-5.6 mmHg (p=0.0001)) and mPAP (-8.9 mmHg (p=0.0001)) significantly decreased, without a significant change in cardiac output and PAWP. This resulted in significant improvement in PVR of -2.8 Woods Units (p=0.0001). Stroke volume index (SVi) and right atrial pressure (RAP) significantly improved (+5.7 ml/m2 , p=0.009 and -2.0 mmHg, p=0.006, respectively) (figure 4).
At baseline, 23 (61%) patients were using DOACs and 14 (37%) patients received concomitant loop diuretic therapy. At six-months follow-up, 87% of the patients were on PH-specific therapy and 7 patients (18%) had a change in their PH-specific therapy compared to baseline. Two patients started PH-specific therapy (riociguat n=1 and bosentan n=1), while five patients switched from combination therapy at baseline to monotherapy during follow-up due to

clinical or hemodynamic improvement (table 1).
The patient with CTED showed better values of 6MWD (+30m) and mPAP (-6.0 mmHg), but without improvement in WHO FC (FC III).

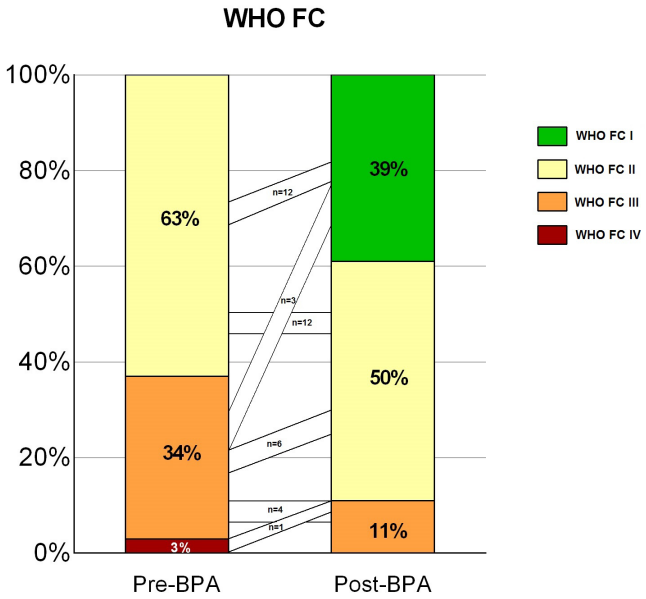

Figure 3. Pre-BPA and six months post-BPA change and results for WHO functional class.

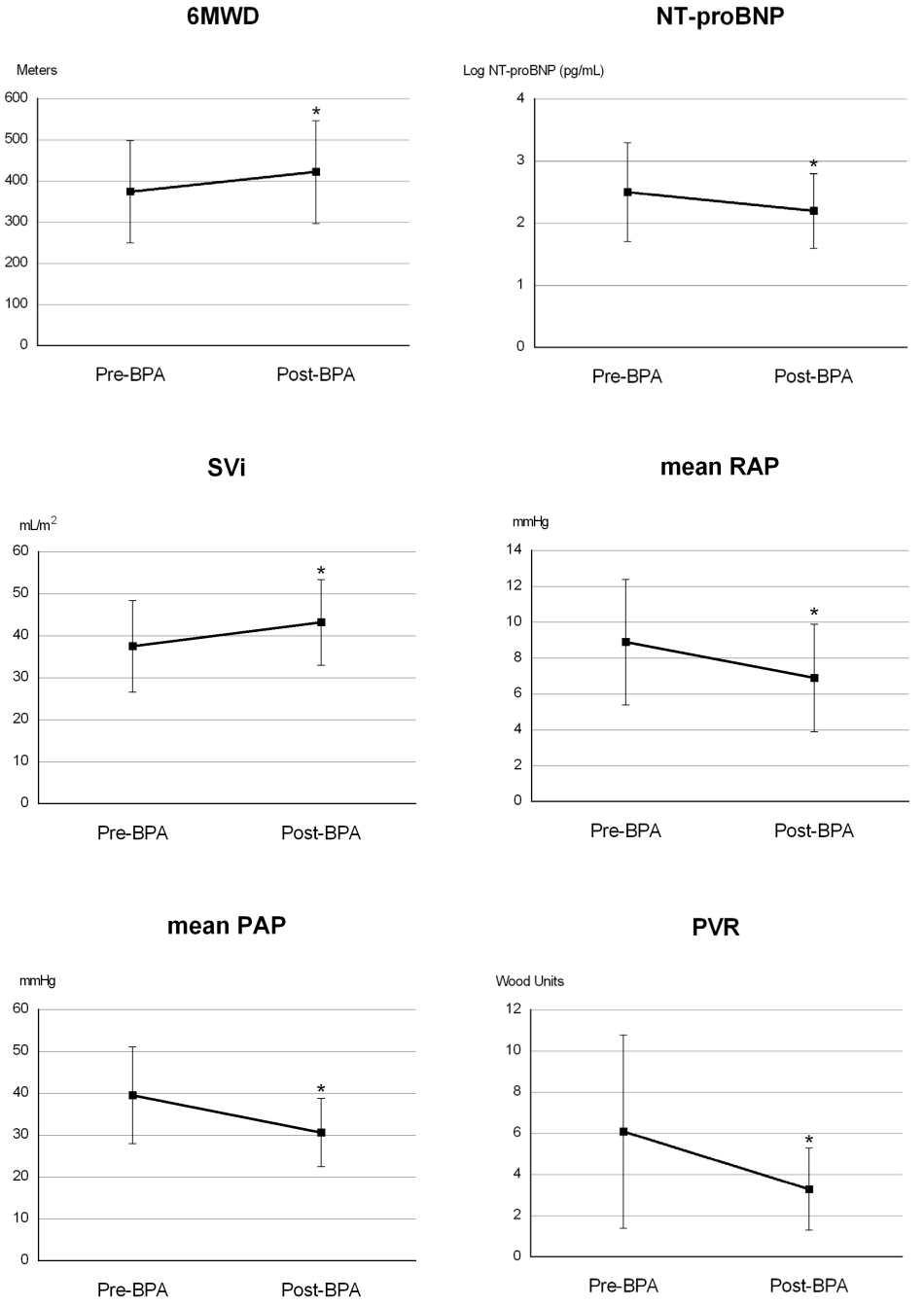

Figure 4. Pre-BPA and six months post-BPA results for 6MWD, log NT-proBNP, SVi , mRAP, mPAP and PVR. * indicates $p<0.05$

4. Discussion

Historically, the first BPA was performed in 1988 in Leiden, the Netherlands[7]. Results of the first series of patients who underwent BPA were reported in 2001, but due to a high percentage of severe complications, BPA was not used for years[8]. After several years, however, the technique was reintroduced in Japan. Since then, BPA has gained more interest and is now being used in many countries around the world[5]. The St. Antonius Hospital, Nieuwegein/Utrecht and the Amsterdam UMC, Amsterdam, are the two CTEPH centres in the Netherlands where BPA procedures are performed. In this study we present the safety and efficacy of BPA treatment in inoperable CTEPH patients. The main findings of the study are: 1) BPA is a safe and effective treatment in patients with inoperable CTEPH, 2) BPA significantly improves symptoms, exercise capacity and pulmonary hemodynamics. This is the largest cohort of patients evaluated in the Netherlands.

Complications occurred in 12% of all procedures, but without any severe consequences. Our complication rate was comparable to the complication rate reported in France – the largest single-centre BPA experience outside Japan – (initial period 16%), and Germany (9%)[9,10]. However, it was slightly lower compared to results from large Japanese cohorts[5]. Our baseline pulmonary hemodynamics were slightly better compared with the other studies, as hemodynamics at baseline are predictors for outcome after BPA[5], this might partly explain the difference in complication rate.

Three episodes of temporary conduction and rhythm disturbances were observed after BPA, which resolved spontaneously; so clinical importance was low. It is possible that these abnormalities were already present before BPA and were seen coincidentally. However, electrocardiograms at admission did not show these abnormalities. Conduction or rhythm disturbances have been described as complications of RHC procedures[11], but other BPA studies do not often report these. Nevertheless they can become clinical important when they do not resolve spontaneously.

On the other hand, haemoptysis is often reported as a consequence of pulmonary artery injury and can be treated with balloon sealing by prolonged, low-pressure dilatation, slow infusion of protamine, embolization or stenting[5]. Although we did not see severe pulmonary artery injury in the patients with haemoptysis during angiographic evaluation, except for one pulmonary vascular perforation, it is likely that the haemoptysis was caused by small pulmonary vascular injuries. It is striking that one patient experienced haemoptysis during 3 different BPA procedures, but this patient had severe impaired pulmonary hemodynamics (mPAP 50 mmHg and PVR 12 WU), which may explain the increased risk and occurrence of complications. The usual treatments with balloon occlusion of the vessel, protamine infusion and CPAP were also effective in our patients.

The significant improvement in functional class (63% to 90% FC I/II) and exercise capacity (6MWD +48m) was comparable with results (35% to 79% FC I/II, 6MWD +45m) reported in the French study[9] and were slightly better than results (15% to 73% FC I/II, 6MWD +33m) reported in the German study[10], although there patients had more symptomatic and severe disease at baseline. Our results were comparable with the Japanese cohorts[5]. In accordance to other studies, the log NT-pro BNP decreased significantly after BPA[12].

The baseline pulmonary hemodynamics in our patients were slightly better and the decrease in mPAP after BPA treatment (-9 mmHg) was slightly lower compared to the French study (-12 mmHg), although the change in PVR was similar (both -3 WU)[9]. This lower decrease in mPAP is probably related to the already better haemodynamic baseline values, as this may indicate less severe (treatable) CTEPH disease in the presence of a normal cardiac output. A Japanese multicentre registry showed a more pronounced decrease in post-procedural mPAP (43 to 22 mmHg)[13]. However, the Japanese have more experience and perform BPA in different CTEPH patients[14].

In terms of clinical and hemodynamic improvement, results of BPA are lower than previous PEA results (6MWD +97m, mPAP -20 mmHg and PVR -7 WU), emphasising the importance of PEA as first choice in operable patients.

The SVi predicts outcomes in pulmonary arterial hypertension. Furthermore, SVi increased during treatment with PH-specific treatment in CTEPH (31 to 43 mL/m2)[15–17]. We report an increase in SVi (38 to 43 mL/m2) after BPA as an addition to PH-specific medical therapy, as well.

We performed BPA in one symptomatic CTED patient. Benefit from BPA treatment in CTED was shown previously, with improved functional class, exercise capacity and pulmonary hemodynamics[6]. Several parameters improved after BPA in our CTED patient, unfortunately without improvement in functional class. This might be explained by the fact that this patient had other severe comorbidities. More research about the effectiveness of BPA in CTED is necessary.

Healthcare costs are becoming increasingly important these days, with the total costs of five BPA procedures in the St. Antonius Hospital currently slightly cheaper than 1 year riociguat treatment.

4.1 Limitations

There was a different anticoagulation strategy in our two CTEPH centres. There are currently no guidelines/protocols about anticoagulation therapy during BPA, and so our hospitals made their own local protocols, based on their clinical practice. However, there needs to be a balance between bleeding complications and re-thrombosis in both strategies.

There were two (5%) patients in whom PH-specific therapy was initiated after baseline assessment. As PH-specific medical therapy also improves clinical outcomes (6MWD +3-51m) and hemodynamics (mPAP -5 mmHg, PVR -2 WU)[18–22], our results may slightly overestimate the effect of BPA alone. However, there were also five patients in whom dual PH-specific therapy could be downgraded to monotherapy. Trials about PH-specific medical therapy versus BPA in CTEPH are currently ongoing.
As we are specialised, referral hospitals for BPA treatment in CTEPH, there may be a bias in patients (not) referred for BPA (e.g. severely symptomatic or hemodynamically compromised patients not referred or patients incompletely evaluated for BPA and therefore not referred).

5. Conclusion

Balloon pulmonary angioplasty in inoperable CTEPH has a low complication rate and results in a significant improvement in symptoms, exercise capacity and pulmonary hemodynamics, when performed in a CTEPH expert centre.

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CHAPTER 7

Assessment of change of perfusion on ventilation / perfusion scan after balloon pulmonary angioplasty in chronic thromboembolic pulmonary hypertension

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ABSTRACT

Background: Balloon pulmonary angioplasty (BPA) is frequently used in patients with chronic thromboembolic pulmonary hypertension (CTEPH) and chronic thromboembolic disease (CTED). Nevertheless, research about change in non-invasive pulmonary perfusion imaging after BPA is scarce. In this study, change of perfusion on ventilation/perfusion (V/Q) scan after BPA was assessed with gestalt interpretation and a pulmonary vascular obstruction (PVO) index. We evaluated inter-observer variability and compared change in perfusion with clinical outcome after BPA.

Methods: A consecutive series of CTEPH/CTED patients who completed BPA treatment and six-month follow-up were included in this retrospective study. In all patients, planar V/Q scans were obtained before and six months after BPA. Results of change in perfusion using gestalt interpretation, based on the experience of the observer, as well as change in semi-quantitative calculation of the PVO, with obligatory use of the lung segment reference chart, were compared with clinical outcome. Inter-observer variability was assessed for both methods.

Results: Twenty CTEPH/CTED patients (mean age 60±16 years, 70% female) underwent 86 BPA procedures. Gestalt interpretation showed improved perfusion in 65% of all patients and PVO decreased significantly compared to baseline (43±14% to 34±15%, p=0.0001). Assessment of change in lung perfusion was only reliable if a PVO was calculated (intra class correlation ≥0.84). However, change in perfusion did not correlate with clinical outcome.

Conclusion: CTEPH/CTED patients after BPA had significantly improved perfusion on V/Q scan. Semi-quantitative calculation of PVO with obligatory use of the lung segment reference chart was highly reliable in this population, although not correlated with clinical outcome.

1. Introduction

Chronic thromboembolic obstruction of the pulmonary arteries may lead, despite anticoagulation, to chronic thromboembolic pulmonary hypertension (CTEPH) or chronic thromboembolic disease (CTED). If left untreated, macrovascular obstruction can cause microvascular disease, with a subsequent increase of pulmonary vascular resistance (PVR). This may lead to hemodynamic impairment with right ventricular failure and death[1].

Pulmonary endarterectomy (PEA) is the recommended treatment for operable, symptomatic CTEPH. Inoperable patients should be treated with PH-specific therapy and/or balloon pulmonary angioplasty (BPA)[2–7]. BPA, an endovascular technique to recover pulmonary artery perfusion, aims to improve clinical outcome and pulmonary hemodynamics in CTEPH and CTED patients[5,6,8].

Ventilation/perfusion (V/Q) scan is the cornerstone for CTEPH diagnosis and can also be used to calculate the percentage of pulmonary vascular obstruction (PVO)[9]. However, research establishing the effect of BPA on pulmonary perfusion imaging is scarce. Planar V/Q scan in routine use is mainly judged using gestalt interpretation, an integration of different sets of criteria and the physician's own experience[10]. The aim of the study was to investigate the change of perfusion on V/Q scan after BPA treatment and to assess the inter-observer variability of gestalt interpretation versus a semi-quantitative PVO calculation with obligatory use of the lung segment reference chart in this specific patient population (fig. 1)[11]. Change of perfusion on V/Q scan using gestalt interpretation and PVO calculation was compared with clinical outcome after BPA.

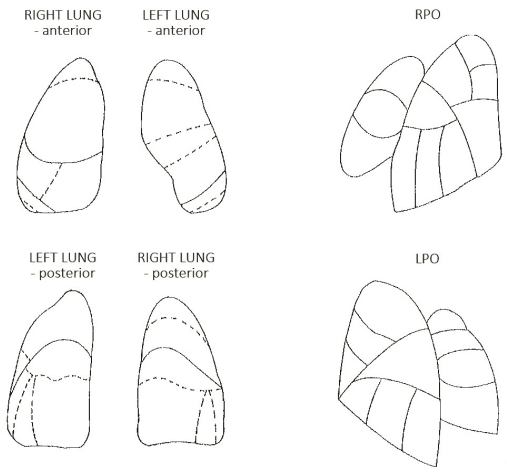

Figure 1. Lung segment chart. RPO: right posterior oblique, LPO: left posterior oblique

2. Material and methods

2.1 Study population

According to the guideline[3], CTEPH/CTED diagnosis and operability were assessed in our multidisciplinary CTEPH team. The team consisted of (interventional) cardiologists, pulmonologists, (interventional) radiologists, cardiothoracic surgeons and specialised nurse practitioners.

Mismatched perfusion defects on V/Q scan and specific thromboembolic signs on multi-detector CT angiography or conventional pulmonary angiography were, in the presence of PH after a minimum of three months anticoagulation treatment, used to diagnose CTEPH. Pre-capillary PH was defined as mean pulmonary artery pressure (mPAP) of ≥25 mmHg and wedge pressure ≤15 mmHg on right-sided heart catheterisation (RHC). Patients with symptomatic chronic thromboembolism but without PH were classified as CTED. Symptomatic CTEPH patients received PH-specific therapy according to the guideline and local practice patterns, including the use of pulmonary artery hypertension (PAH) medical therapy. Medical therapy remained unchanged during BPA, unless a change was clinically necessary.

Patients with distal thromboembolic lesions or a nonacceptable risk-benefit ratio (e.g. severe lung or renal disease) were considered unfit for PEA. The latter and patients reluctant to undergo PEA, were accepted for BPA if they had accessible thromboembolic lesions and did not have contraindications for BPA (i.e. right-sided valvular endocarditis, a right-sided mechanical heart valve or a thrombus or myxoma in the right atrium).

All patients who completed BPA and standardised six-month follow-up in our hospital between 01-2016 and 03-2019, were retrospectively included in this study. Baseline was defined as date of CTEPH diagnosis.

Symptoms, measured with World Health Organization Functional Class (WHO FC), N-terminal pro brain natriuretic peptide (NT-proBNP), 6-min walking test distance (6MWD), V/Q scan and RHC were performed at baseline and six months after last BPA. The study has been approved by the local ethical commission (number W17.132).

2.2 BPA procedure

As described earlier[12], oral anticoagulation was maintained throughout interventions. Patients received direct oral anticoagulants or vitamin K antagonists with a target international normalized ratio between 2.5 and 3.5. RHC was performed with a Swan-Ganz 7 French catheter, at baseline and six months after the last BPA procedure. BPA procedures were performed through femoral access with a 6-9 French sheath and standard coronary intervention guidewires and balloons. Intravenous heparin (2500-10000 IE) was administered with a target activated clotting time between 200s and 300s. Affected pulmonary artery branches were visualised with jopromide (ULTRAVIST). All accessible lesions were

treated with semi-compliant balloons. During each procedure, up to eight vessels were treated or the procedure ended when more than 250 mL contrast was used. Time to the next BPA procedure was four weeks. BPA treatment finished if all accessible lesions were treated.

2.3 Ventilation/perfusion scan

Planar V/Q scans, performed at baseline and six months after last BPA, were obtained in all patients after administration of Technetium-99m labelled macroaggregated albumin (Technescan LyoMAA) intravenously. Additional to lung perfusion scintigraphy, in order to exclude consolidative or obstructive matched or reversed mismatched defects, subsequent ventilation scans were obtained with the patient breathing room air through a mouthpiece to which a constant supply of Krypton-81m gas was added. Images were performed in anterior, posterior, right posterior oblique and left posterior oblique views. Two experienced nuclear medicine physicians independently reviewed all V/Q scans blinded to clinical results, using gestalt interpretation[10], based on the physician's experience. Perfusion was graded as decreased / unchanged / improved and improvement was divided in <25%, 25-75% and ≥75%. After a minimum period of six months, the same observers randomly reviewed the V/Q scans again with obligatory use of the lung segment reference chart (fig. 1)[11] and calculated a PVO index[13]. The PVO index consists of a perfusion score for each lung lobe multiplied by a pre-specified weight (left upper lobe 0.13, left lower lobe 0.20, lingula 0.12, right upper lobe 0.18, right lower lobe 0.25 and middle lobe 0.12), based on lung lobe blood flow distribution in supine position[13]. Lung lobe perfusion score was estimated using a semi-quantitative score (0, 0.25, 0.50, 0.75 and 1), with 0 scored as 'no perfusion' and 1 as 'normal perfusion'. PVO (%) was calculated as (1 – sum of lobar scores) multiplied by 100[11,13]. In case of vascular steal in a lung segment, i.e. a new perfusion defect in a normally perfused lung segment at baseline without thrombi on angiography, the baseline value was used[14]. Results of PVO difference between baseline and six months after BPA were compared with clinical outcome. Inter-observer variability was assessed for both V/Q scan measurements.

2.4 Statistical analyses

All statistical analyses were performed with SPSS (IBM SPSS statistics version 26), were two-tailed and were considered statistically significant if the p-value was <0.05. Categorical data were presented as number and percentage. Continuous data were presented as mean ± standard deviation (SD) or as median with interquartile range (IQR). Differences between baseline and six-month follow-up after BPA were assessed with the Wilcoxon signed-rank test, (exact) McNemar test and student t-test. Correlation was assessed with the Pearson's correlation coefficient. Reproducibility was analysed with Cohen's weighted kappa coefficient (with 95% confidence interval) for gestalt interpretation and Bland-Altman analysis with intra-class correlation coefficient (ICC) for PVO measurement.

3. Results

3.1 Study population

Twenty patients (70% female) completed BPA treatment and six-month follow-up and could be included for analyses. The mean age was 60.1±16.3 years, 70% were in WHO FC III/IV and the mPAP was 35.4±9.6mmHg (table 1 and 2). Two patients (10%) were classified as CTED. All patients had a history of venous thromboembolism, of which two (10%) had a coagulation disorder (polycythemia vera and factor V Leiden). Comorbidities were common (hypertension 40% and chronic obstructive pulmonary disease 30%). Total disease duration was 3.9 years (2.2-6.5 years). Sixteen patients (80%) received PH-specific medical therapy: monotherapy in six patients (30%) and combination therapy in ten patients (50%).

Table 1. Baseline characteristics

	Baseline (n=20)
Demographic characteristics, n (%)	
Age (years), mean±SD	60.1±16.3
Female	14 (70)
Medical history, n (%)	
Deep venous thrombosis	2 (10)
Acute pulmonary embolism	19 (95)
Smoker (ever)	10 (50)
COPD	6 (30)
Thyroid dysfunction	2 (10)
Coagulation disorder	2 (10)
Hypertension	8 (40)
Treatment, n (%)	
Total disease duration (years), median (IQR)	3.9 (2.2-6.5)
VKA / NOAC	18 (90) / 2 (10)
PH-specific therapy	
None	4 (20)
Monotherapy	6 (30)
Combination therapy	10 (50)
PH-specific monotherapy	
Riociguat	2 (33)
Tadalafil	2 (33)
Macitentan	1 (17)
Bosentan	1 (17)
PH-specific combination therapy	
Riociguat + ERA	4 (40)
PDE5i + ERA	6 (60)

COPD: chronic obstructive pulmonary disease, VKA: Vitamin K antagonists, NOAC: novel oral anticoagulant, PH: pulmonary hypertension, ERA: endothelin receptor antagonist, PDE5i: phosphodiesterase-5 inhibitor, SD: standard deviation, IQR: interquartile range.

3.2 BPA procedures and clinical outcome

In total, 86 BPA sessions were performed (mean 4.3±1.2 BPA sessions per patient). Compared to baseline, significant improvement was seen for WHO FC (FC III/IV 70% to 30%, p=0.04), NT-proBNP (184 pg/mL (93-2188 pg/ml) to 110 pg/ml (69-229 pg/ml), p=0.04) and 6MWD (368m (209-444m) to 438m (325-480m), p=0.001). The pulmonary hemodynamics improved significantly after BPA: mPAP (35.4±9.6 mmHg to 29.9±10.0 mmHg, p=0.0001) and pulmonary vascular resistance (PVR) (3.9 WU (2.2-6.5 WU) to 2.2 WU (1.6-3.7 WU), p=0.005). These data are summarised in table 2.

Table 2. Characteristics pre- and post-BPA

n=20	Pre-BPA	Post-BPA	P-value
Clinical and hemodynamic characteristics, mean±SD			
WHO FC, n (%)			**0.04**
I	0	4 (20)	
II	6 (30)	10 (50)	
III	13 (65)	6 (30)	
IV	1 (5)	0	
NT-proBNP (pg/mL), median (IQR)[1]	184 (93-2188)	110 (69-229)	**0.04**
6MWD (m), median (IQR)	368 (209-444)	438 (325-480)	**0.001**
CO (L/min)	6.1±2.4	6.3±1.7	0.94
RAP (mmHg)[2]	8.7±3.7	8.3±3.4	0.20
mPAP (mmHg)	35.4±9.6	29.9 ±10.0	**0.0001**
PVR (WU), median (IQR)	3.9 (2.2-6.5)	2.2 (1.6-3.7)	**0.005**
Ventilation/perfusion scan, n (%)			
PVO, mean±SD	43±14	34±15	**0.0001**

BPA: Balloon pulmonary angioplasty, WHO FC: World Health Organisation functional class, NT-proBNP: N-terminal pro brain natriuretic peptide, 6MWD: 6-minute walking distance, CO: cardiac output, RAP: right arterial pressure, mPAP: mean pulmonary arterial pressure, PVR: pulmonary vascular resistance, PVO: pulmonary vascular obstruction. SD: standard deviation, IQR: interquartile range.
[1] n=19; [2] n=18.

3.3. Ventilation/perfusion scan

Time between baseline and six-month follow-up V/Q scans was 2.5 (2.0-3.0) years. Using gestalt interpretation of the V/Q scans, the independent observers agreed that in 13 out of 20 patients (65%) the perfusion had improved after BPA, although most improvement was

less than 25%. In three patients (15%) both observers found the lung perfusion unchanged (table 3).
Using semi-quantitative PVO calculation with obligatory use of the lung segment reference chart, PVO decreased in 17 patients (85%) and remained unchanged in 2 patients (10%). Overall, PVO significantly decreased from 43±14% at baseline to 34±15% at six-month follow-up (p=0.0001, table 2 and fig. 2).
Both gestalt interpretation and PVO calculation did not correlate with clinical outcome (table 4).

Table 3. Inter-observer agreement for gestalt interpretation

n=20		**Observer 1**		
		Worsened	Unchanged	Improved
Observer 2	Worsened	0	0	1 (5%)
	Unchanged	0	3 (15%)	2 (10%)
	Improved	1 (5%)	0	13 (65%)

n=13 (improved patients)		**Observer 1**		
		Improved <25%	Improved 25-75%	Improved >75%
Observer 2	Improved <25%	8 (62%)	2 (15%)	0
	Improved 25-75%	1 (8%)	1 (8%)	0
	Improved >75%	0	1 (8%)	0

Data do not add up to 100% due to rounding

Table 4. Correlations for gestalt and PVO interpretation.

	Gestalt	**P-value**	**PVO**	**P-value**
WHO FC	r(20) = 0.04	0.86	r(20) = 0.29	0.22
Log NT-proBNP	r(17) = 0.12	0.64	r(17) = 0.19	0.46
NT-proBNP	r(17) = 0.14	0.60	r(17) = 0.23	0.38
6MWD	r(19) = -0.21	0.40	r(19) = 0.41	0.08
mPAP	r(20) = 0.11	0.65	r(20) = 0.01	0.98
PVR	r(20) = 0.01	0.99	r(20) = 0.11	0.65

WHO FC: World Health Organisation functional class, NT-proBNP: N-terminal pro brain natriuretic peptide, 6MWD: 6-minute walking distance, mPAP: mean pulmonary arterial pressure, PVR: pulmonary vascular resistance, PVO: pulmonary vascular obstruction.

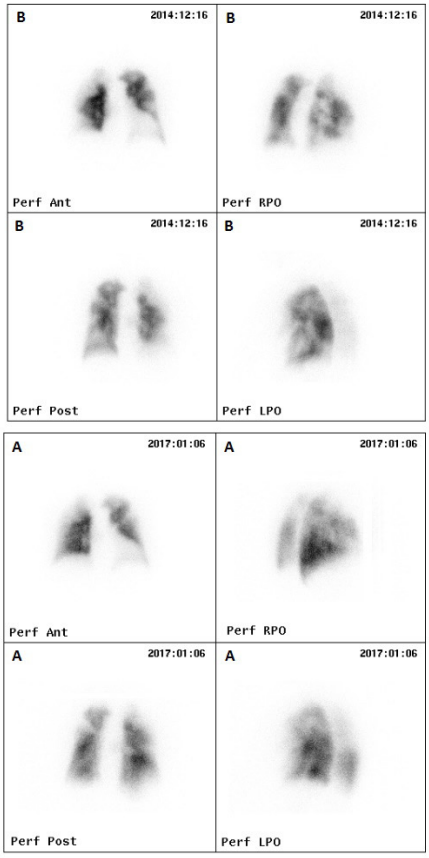

Figure 2. Perfusion images before (B) and after (A) BPA. Perf: perfusion; Ant: anterior; RPO: right posterior oblique; post: posterior; LPO: left posterior oblique.
Pulmonary vascular obstruction (PVO) index was 61% before and 32% after BPA.
PVO calculation before BPA: 1–(left superior lobe (0.13 x 0.75) + left inferior lobe (0.20 x 0.50) + lingula (0.12 x 0.25) + right superior lobe (0.18 x 0.25) + right inferior lobe (0.25 x 0.25) + right middle lobe (0.12 x 0.50)).
PVO calculation after BPA: 1–(left superior lobe (0.13 x 0.75) + left inferior lobe (0.20 x 0.75) + lingula (0.12 x 0.25) + right superior lobe (0.18 x 0.50) + right inferior lobe (0.25 x 1.0) + right middle lobe (0.12 x 0.50)).

3.4 Reproducibility

Inter-observer agreement for gestalt interpretation was moderate reliable with κ coefficient 0.50 (confidence interval 0.11-0.89, p=0.006). ICC for baseline PVO was 0.95 and for six-month follow-up 0.96, both indicating excellent reliability. ICC for PVO difference was 0.84, which indicates good reliability.

4. Discussion

The first BPA was already performed in 1988. Initially severe complications occurred, but years later the technique was refined and reintroduced in Japan[5,15,16]. Nowadays, the

use of BPA for CTEPH is increasing and so are data about BPA efficacy and safety. In the current study, we assessed the effect of BPA on perfusion imaging in relation to clinical outcome in CTEPH/CTED patients. In addition, reliability was assessed for V/Q gestalt interpretation versus semi-quantitative PVO calculation with obligatory use of the lung segment reference chart. We found perfusion improvement on V/Q scan after BPA with PVO calculation as most reliable method. Nevertheless, there was no association between the improvement in perfusion and clinical parameters six months after last BPA.

BPA aims to reduce right ventricular afterload and prevent right ventricular failure[5]. Patients in our cohort showed significant clinical improvement, comparable with our previously reported results[12]. However, in the current study the pulmonary hemodynamics were mild as also patients with CTED were included. Nevertheless, BPA seems effective in CTED patients as well[8]. A comparison with French, German and Japanese studies shows similar clinical outcomes[5,17,18], except for a lower improvement in pulmonary hemodynamics in our cohort, partly explained by the aforementioned reason and the small study size.

V/Q scan is the first-line imaging modality to diagnose CTEPH[3]. It typically shows mismatched perfusion defects and has a high diagnostic accuracy[3,19]. In our study, a decrease in PVO after BPA was found in 85% of all patients, although the improvement was never above 75% compared to baseline. Furthermore, there was no correlation with change in the other measured clinical outcome parameters. V/Q scan interpretation using semi-quantitative PVO calculation with obligatory use of the lung segment reference chart showed much higher reproducibility than gestalt interpretation; good to excellence reliability in PVO versus moderate reliability in gestalt, respectively. This was not a surprise, as it was already known since 1992 that obligatory use of the lung segment reference chart in the interpretation of V/Q scan for diagnosing pulmonary embolism shows better inter-observer variability compared to gestalt interpretation[11]. Despite this knowledge, routine use of gestalt interpretation of the lung V/Q scan in the diagnostic workup of chronic pulmonary embolism or after invasive treatment is common practise in many centres. The interpretation of lung perfusion on the V/Q scan is complicated by the 'vascular steal phenomenon', first described in PEA patients as hyperperfusion at endarterectomised segments and new hypoperfused areas in non-endarterectomised segments[20]. This 'vascular steal phenomenon' is due to a redistribution of pulmonary arterial resistance after opening of obstructed vessels[14]. Re-examination at mid-term follow up (at least 6 months after PEA) showed a normalisation of the hypoperfused areas and a more homogenous perfusion[20]. Nuclear physicians should be aware of this phenomenon in such a patient population as this may occur in patients after BPA as well.

CT pulmonary angiography after PEA showed a decrease in affected pulmonary arteries (51%±21% to 20±15%, p<0.001)[21]. It is known that hypoperfusion, visualised with lung perfusion magnetic resonance imaging, significantly decreased after PEA (29±9% to 21±5%, p<0.001)[21]. Nevertheless, both differences could not be correlated with improvement in hemodynamics and did not differ between patients with or without residual PH after surgery. This is probably explained by microvascular pathology in addition to macrovascular thromboembolic disease. This theory may also apply to our current BPA research, as we show significant but limited macrovascular improvement on V/Q scans, while clinical parameters showed a more prominent improvement. In addition, due to the more subsegmental disease localisation in patients who underwent BPA, (visual) improvement is probably less than after PEA, as the latter is used for larger, segmental lesions. Therefore, we might be unable to show a correlation between perfusion improvement and clinical outcome.

Another study comparing lung perfusion blood volume and lung perfusion single-photo emission CT with catheter pulmonary angiography did show residual perfusion defects in up to 22% of all treated vessels[22].

Predominantly webs and incomplete obstructions are excellent targets for BPA, while complete obstructions are more difficult to treat and result in higher complication rates. In contrast, V/Q scan is more sensitive for complete obstructions as perfusion will be blocked completely, while webs or partial obstructions may be missed due to sustained vessel perfusion. Consequently, it may also be likely that planar V/Q scan is unable to visualise macrovascular improvements after BPA treatment and underestimates the perfusion improvement.

4.1 Limitations

We present results from a single-centre study with a low number of patients included, which might be reason not finding a correlation between the improvement in lung perfusion and clinical outcome. In our study, a planar V/Q scan is used and has disadvantages in comparison to lung perfusion single photon emission computed tomography (SPECT) because of the two-dimensional versus three-dimensional interpretation, respectively[23]. Nevertheless, also for SPECT it remains unsure if correlation with clinical parameters may be established in the follow up of BPA in CTEPH/CTED patients. Patients received treatment according to the current guideline and most patients were treated with both PH-specific medical therapy and BPA[3]. Therefore, change in clinical outcome may also partly be due to the use of PH-specific medical therapy[4]. In addition, the lack of correlation between improved perfusion and clinical outcomes could also reflect heterogeneity imparted by medical therapy. Due to the aforementioned limitations, we are unable to draw a firm conclusion about the role of V/Q scans after BPA. Further and larger research is necessary to establish the role of routine (perfusion) imaging after BPA.

5. Conclusion

Lung perfusion on V/Q scan significantly improved after BPA in CTEPH/CTED patients. The use of a PVO index with obligatory use of the lung segment reference chart was highly reliably in these patients. However, change in perfusion was not correlated with change in clinical outcome.

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PART III

Quality of life in patients with chronic thromboembolic pulmonary hypertension

CHAPTER 8

The longitudinal use of EmPHasis-10 and CAMPHOR questionnaire health-related quality of life scores in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension

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ABSTRACT

Background: Health-related quality of life (HRQoL) is impaired in patients with pulmonary hypertension (PH). The EmPHasis-10 and CAMPHOR questionnaires are developed to evaluate HRQoL specifically in patients with PH. Data on the longitudinal use of both questionnaires are still limited. We evaluated the longitudinal value of both questionnaires and established minimal clinically important differences (MCID).

Methods: Sixty-one treatment naïve pulmonary arterial hypertension or chronic thromboembolic patients were prospectively included. Patients were treated according to the current ESC/ERS guidelines. We compared EmPHasis-10 and CAMPHOR scores between baseline, 6 and 12 months of follow-up and evaluated the correlation between these scores and a 5-scale symptom severity score, 5-scale overall health score, NYHA-classification, six minute walk test distance (6MWD), NT-proBNP and echocardiographic parameters.

Results: After one year of treatment a significant reduction in EmPHasis-10 score and CAMPHOR QoL and symptoms domain score was observed. Moderate to good correlations were observed between the questionnaires and the overall-health and symptom severity score and 6MWD. No relevant correlations were seen between the questionnaires and NT-pro-BNP and echocardiographic parameters. EmPHasis-10 scores showed strong correlations with all CAMPHOR domains. The MCID for the EmPHasis-10 questionnaire was -8. The MCIDs for the CAMPHOR domains were: activity -3, symptoms -4, QoL -3.

Conclusion: The EmPHasis-10 and CAMPHOR questionnaires are valid tools for the longitudinal measurement of HRQoL in patients with PH. The much shorter EmPHasis-10 correlates well with the CAMPHOR domain scores and with the clinical endpoints and it may be easier to use in daily practice.

1. Introduction

Pulmonary hypertension (PH) is a progressive disease of the pulmonary vasculature characterized by increased pulmonary vascular resistance and elevated pulmonary arterial pressures[1]. This may eventually lead to right ventricular failure and ultimately death. PH is a heterogeneous condition, and it is divided into five categories by the WHO-classification based on etiology and pathophysiology. Group 1 refers to pulmonary arterial hypertension (PAH), characterized by arteriolar remodeling leading to PH. Group 2 and 3 are respectively caused by left heart disease and lung disease or hypoxia. Group 4 is caused by chronic arterial obstruction with often (distal) arteriopathy, and the etiology of group 5 PH is unclear or multifactorial[2]. Only for group 1 and 4, PH-specific (medical) treatments are currently available. Patients with chronic thromboembolic pulmonary hypertension (CTEPH) are also being evaluated for treatment by means of pulmonary endarterectomy (PEA) or balloon pulmonary angioplasty (BPA) when indicated[3].

It is known that health-related quality of life (HRQoL) is impaired in patients with PH and that HRQoL might be an important prognostic factor in PH[4–8]. General HRQoL measures employed in PAH populations have proved to be of limited value. Their outcome might be inconsistent in patients with PH and they might be unable to detect relevant change in HRQoL[4,9]. Therefore PH-specific HRQoL measurements have been developed like the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR)[10]. The CAMPHOR is comprised of three domains that assess symptoms, activity and QoL. It has been translated into several languages including Dutch[11–15]. This is a valid and reliable instrument for assessment of HRQoL in PAH and CTEPH patients. It provides a valid tool for a single point measurement in cross-sectional studies. Recent studies investigated the longitudinal effect of the CAMPHOR questionnaire in idiopathic PAH (IPAH) and CTEPH patients separately and showed that scores were responsive to treatment[16,17]. Another shorter HRQoL questionnaire for PH, the EmPHasis-10, has also been developed[18]. The EmPHasis-10 questionnaire has also been translated and validated in multiple languages[19,20]. Since the EmPHasis-10 score consists of only 10 questions, it might be easier applicable in daily clinical practice than the CAMPHOR questionnaire[18]. Both the EmPHasis-10 and CAMPHOR questionnaire are shown to be of prognostic value[16,21–23]. The aim of this study is to investigate the longitudinal validity and responsiveness of the CAMPHOR and EmPHasis-10 questionnaires and to establish the minimal clinically important differences (MCID) for both questionnaires.

2. Methods

2.1 Study population

In this prospective study, all consecutive incident PH patients who were diagnosed with

PAH (WHO 1) or CTEPH (WHO 4) in the PH expertise centers Erasmus MC in Rotterdam and St. Antonius Hospital in Nieuwegein were eligible for the study. Patients who were not able to read or write in Dutch or who were unable to understand the questionnaires were excluded from this study. All patients were diagnosed according to the ERS/ESC guidelines[3]. At baseline, all patients were treatment naïve. They were subsequently treated according to the current ESC/ERS guidelines, including initiation of PH-specific medical therapy and treatment with BPA or PEA in CTEPH patients[3]. The medical ethical committee approved the study protocol and all patients gave written informed consent (MEC-2016-683). This study was performed according to the principles outlined in the Declaration of Helsinki.

2.2 Baseline, follow-up and outcomes

All patients were examined by a pulmonary physician and cardiologist and underwent an inpatient PH screening visit, during which the following tests were performed: 6-minute walking test, 12-lead ECG, transthoracic echocardiography (TTE), venous blood sampling, lung perfusion scintigraphy, chest computed tomography scan and a right heart catheterization.

Demographic data, 6-minute walk test distance (6MWD), NT-pro-BNP levels and TTE parameters were retrieved for this study. The following TTE parameters were used in this study: cardiac output, left ventricular ejection fraction, left ventricular end diastolic diameter, tricuspid annular plane systolic excursion, right ventricular fractional area change, right atrial area, peak tricuspid regurgitation velocity, right ventricular end diastolic diameter, presence of pericardial effusion and the estimated right atrial pressure. Imaging analysis of two-dimensional TTE was performed according to the Recommendations for Cardiac Chamber Quantification in Adults by the American Society of Echocardiography and the European Association of Cardiovascular Imaging [24]. The right atrial pressure was estimated by evaluation of the inferior vena cava (IVC). An IVC diameter <2.1cm that collapses >50% with a sniff corresponds with a normal right atrial pressure quantified as 3 mmHg. If the IVC diameter is >2.1 cm and collapses <50% with a sniff, this corresponds to a high right atrial pressure of 15 mmHg. If the IVC does not fit this paradigm, the intermediate value of 8 mmHg was used[24].

To assess HRQoL and the severity of functional limitations the New York Heart Association (NYHA) classification, a 5-scale symptom severity score and a 5-scale overall health score were used as anchor points. The symptom severity score allowed patients to score their symptoms on a 5 point scale : no -, mild -, moderate-, moderate-severe or severe symptoms. The overall health score allowed patients to score their overall health perception as: very good, good, fair, poor or very poor[25–27]. In addition to the health related quality of life questionnaires, all patients completed in a symptom severity score and an overall health

score during each follow-up visit. Patients were reevaluated at the outpatient clinic at 6 and 12 months after inclusion. NYHA functional class, 6MWD, NT-pro-BNP level and treatment were assessed at both follow-up moments, while TTE was repeated at 12 months after inclusion. The French registry non-invasive model was used to calculate a risk score based on the number of low-risk criteria fulfilled: NYHA-classification I or II, 6MWD > 440m and NT-pro-BNP <300mg/L or < 35.7 pmol/L[28,29].

2.3 Health-related quality of life questionnaires

The CAMPHOR and EmPHasis-10 questionnaires were taken at baseline, 6 and 12 months after inclusion. The symptoms and QoL domains of the CAMPHOR are scored from 0-25 each. The activity domain scores of the CAMPHOR range from 0-30. Higher scores indicate a worse QoL. Missing questions were imputed according to the CAMPHOR Guidelines for Users[30]. The EmPHasis-10 questionnaire consists of 10 questions, each scored from 0-5. The score is inversely correlated with QoL (the higher the score, the worse the QoL). EmPHasis-10 questionnaires with missing questions were excluded from analysis. Correlations were evaluated between the questionnaire scores QoL and clinical parameters: 5-scale overall health score, 5-scale symptom severity score, NYHA-classification, non-invasive risk score, 6MWD, NT-proBNP and TTE parameters.

2.4 Statistical analysis

Statistical analysis was performed using SPSS v25 (IBM, Chicago). Normality was assessed using histograms and the Shapiro-Wilk test. Continuous and ordinal variables were presented as mean ± standard deviation if normally distributed or as median (interquartile range) if non-normally distributed. Categorical variables were presented as counts (percentage). Questionnaire scores were considered to be ordinal variables. Continuous data between subgroups were compared using an unpaired t-test or a Wilcoxon signed-rank test for normally and non-normally distributed data respectively. Categorical data were compared using a chi-square test. The difference between visits was evaluated using a paired t-test (normally distributed data) or Wilcoxon signed-rank test (non-normally distributed data). A p-value of <0.05 was considered statistically significant.

Correlation coefficients (categorical parameters) were calculated to evaluate the correlation between the outcome of the questionnaires and the clinical anchor points. Pearson correlation coefficients were used for normally distributed continuous data and Spearman correlation coefficients were used for categorical data and non-normally distributed continuous data. Similarly, correlations of the mean differences were calculated. Correlation coefficients between 0-0.2 were considered as very weak, 0.2-0.39 as weak, 0.4-0.59 as moderate, 0.6-0.79 as strong and 0.80-1.0 as very strong[31].

The MCIDs were calculated by the mean MCID of the anchor and distributional based

MCID. Anchor based MCIDs were calculated using the general HRQoL measures: 5-point overall health score, 5-point symptom severity scale and the NYHA-classification. An improvement of one step on these scales was considered as a clinically relevant difference. The mean change in questionnaire score of patients improving one step on the overall health score, symptom severity score or NYHA-classification was calculated. The anchor based MCID represents the mean of these scores[32,33]. Another way to determine the MCID is by using the distribution of the data. The distributional MCID was calculated by the 0.5SD method where half the baseline standard deviation represents the MCID[33,34].

3. Results

3.1 Study population

A total number of 62 consecutive newly diagnosed patients were screened for inclusion between December 2016 and December 2019. One patient was excluded because she didn't complete the questionnaires at baseline. In total, 61 patients were included. Thirty-one patients were diagnosed with PAH and 30 patients with CTEPH. The mean age was 63.5 years (± 15.6), 59.0% of the patients was female (table 1). At baseline there were no statistically significant differences between the two WHO groups (table 1-2). Marital and working status are shown in supplementary table 1. Since there were no significant differences between demographic data and the clinical parameters of the PAH and CTEPH patients at baseline, we combined both groups for further analyses. Subgroup analysis of the evolution of the quality of life questionnaires is available in supplementary table 2. The median EmPHasis-10 score was 21, and median CAMPHOR domain scores were: activity 8, QoL 8, symptoms 8.

Table 1. Patient demographic and quality of life data

	Whole cohort (n= 61)	**PAH (n= 31)**	**CTEPH (n= 30)**	**P-value**
Age (years)	63.5 (±15.6)	62.3 (±16.4)	64.8 (±14.9)	0.603
Sex (female)	36 (59.0%)	21 (67.7%)	15 (50.0%)	0.159
Quality of life				
Symptom severity score				0.217
No symptoms	2 (3.4%)	2 (6.4%)	0 (-)	
Mild	9 (15.3%)	7 (22.6%)	2 (7.1%)	
Moderate	23 (39.0%)	9 (29.0%)	14 (50.0%)	
Moderate severe	23 (39.0%)	12 (38.7%)	11 (39.3%)	
Severe	2 (3.4%)	1 (3.2%)	1 (3.6%)	

Overall health score				0.182
Very good	1 (1.7%)	0 (-)	1 (3.6%)	
Good	7 (11.9%)	6 (19.4%)	1 (3.6%)	
Fair	33 (55.9%)	15 (48.4%)	18 (64.3%)	
Poor	17 (28.8%)	10 (32.3%)	7 (25.0%)	
Very poor	1 (1.7%)	0 (-)	1 (3.6%)	
NYHA-classification				0.070
I	0 (-)	0 (-)	0 (-)	
II	19 (31.7%)	6 (19.4%)	13 (44.8%)	
III	36 (60.0%)	21 (67.7%)	15 (51.7%)	
IV	5 (8.3%)	4 (12.9%)	1 (3.4%)	
CAMPHOR activity	8 (5-14)	9 (5-14)	8 (5-14)	0.828
CAMPHOR QoL	8 (4-13)	7 (4-12)	9 (4-14)	0.578
CAMPHOR symptoms	8 (6-13)	9 (6-13)	9 (6-16)	0.514
EmPHasis-10	21 (16-33)	20 (15-33)	24 (18-36)	0.223

CTEPH: Chronic thromboembolic pulmonary hypertension; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; QoL: quality of life

Table 2. Baseline clinical and echocardiographic parameters

	Whole cohort (n= 61)	**PAH (n= 31)**	**CTEPH (n= 30)**	**P-value**
Clinical outcome measures				
6MWD (m)	346 (248-434)	346 (267-403)	347 (241-452)	0.967
NT-pro-BNP (pmol/L)	62 (30-270)	62 (31-311)	62 (28.75-244.0)	0.891
Non-invasive risk score*				
0	25 (45.5%)	15 (57.7%)	10 (34.5%)	
1	15 (27.3%)	5 (19.2%)	10 (34.5%)	0.128
2	11 (20.0%)	5 (19.2%)	6 (20.7%)	
3	4 (7.3%)	1 (3.8%)	3 (10.3%)	
Echocardiography				
CO (L/min)	5.1 (4.0-5.9)	5.2 (4.2-6.0)	5.1 (3.7-5.6)	0.850
LVEF (%)	56.8 (± 6.9)	56.9 (± 7.1)	57.4 (± 6.4)	0.812
LVEDD (cm)	4.3 (± 0.8)	4.2 (± 0.8)	4.5 (± 0.6)	0.131
RA area (mm^2)	19.8 (17.0-23.6)	19.8 (17.3-26.4)	19.8 (15.8-22.9)	0.262
RVEDD (cm)	4.6 (± 0.9)	4.6 (± 0.8)	4.8 (± 1.0)	0.648
Peak TRV (m/sec)	4.0 (± 0.6)	3.9 (± 0.6)	3.6 (± 0.8)	0.174
TAPSE (cm)	2.0 (1.6-2.3)	1.9 (1.4-1.9)	2.0 (1.8-2.5)	0.131
RVFAC (%)	32.8 (25.9-40.0)	35.0 (29.1-41.6)	32.0 (23.1-36.7)	0.227
Estimated RA pressure (mmHg)				
3	32 (62.7%)	17 (58.6%)	15 (68.2%)	0.671
8	12 (23.5%)	7 (24.1%)	5 (22.7%)	
15	7 (13.7%)	2 (17.2%)	2 (9.1%)	

Abbreviations: 6MWD: 6 minute walking distance; CO: Cardiac output; LVEDD: Left ventricular end diastolic diameter; LVEF: Left ventricular ejection fraction; RA: right atrial; RVEDD: Right ventricular end diastolic diameter; RVFAC: Right ventricular fractional area change; TAPSE: Tricuspid annular plane systolic excursion; TRV: Tricuspid regurgitation velocity
* Number of low-risk criteria: NYHA-classification I or II, 6MWD > 440m and NT-pro-BNP <300mg/L or < 35.7 pmol/L

3.2 Outcomes and health-related quality of life questionnaires

During follow-up two patients died, one because of heart failure due to PH and one because of a traumatic subdural hematoma. Two patients were lost to follow-up; one patient because he regarded completing the questionnaires too time consuming and the other patient continued PH treatment and follow-up in another PH center. One year after inclusion, 5 patients (8.2%) were treated with mono, 44 patients (72.1%) with dual and 9 (14.8%) patients with triple PAH-specific combination therapy. Three patients with CTEPH who underwent a PEA or BPA were not started on PH-specific medication. Three CTEPH patients underwent a PEA and six patients started BPA. Table 3 shows the evolution of QoL following treatment. After 1-year follow-up, there was a significant improvement of the general QoL scores: symptom severity, overall health and NYHA classification. EmPHasis-10 scores decreased significantly after treatment initiation. The QoL and symptoms domains scores of the CAMPHOR questionnaire decreased significantly. No significant improvement was seen in the activity domain (p=0.500). The 6MWD significantly increased whereas NT-pro-BNP significantly decreased (table 4). The non-invasive risk score improved significantly (table 4). All TTE parameters showed a positive trend, a significant improvement was seen in left ventricular end diastolic diameter, right ventricular fractional area change, peak tricuspid regurgitation velocity and tricuspid annular plane systolic excursion (table 4). Fifty-five patients (90.2%) completed all the questionnaires during follow-up. Analysis of the 6-month follow-up showed still limited effect of treatment. Hence, we reported the baseline and one year follow-up here.

Table 3. Quality of life measurements at baseline and after 1-year follow-up

	Baseline	**1 year**	**P-value**
Quality of life			
Symptom severity score			**0.016**
No symptoms	2 (3.4%)	4 (7.1%)	
Mild	9 (15.3%)	7 (12.5%)	
Moderate	23 (39.0%)	31 (55.4%)	
Moderate severe	23 (39.0%)	13 (25.0%)	
Severe	2 (3.4%)	0	

Overall health score			0.197
Very good	1 (1.7%)	1 (1.8%)	
Good	7 (11.9%)	6 (10.7%)	
Fair	33 (55.9%)	40 (71.4%)	
Poor	17 (28.8%)	9 (16.1%)	
Very poor	1 (1.7%)	0	
NYHA class			**0.001**
I	0	6 (12.5%)	
II	19 (31.7%)	20 (41.7%)	
III	36 (60.0%)	22 (45.1%)	
IV	5 (8.3%)	0	
CAMPHOR activity	8 (5-14)	8 (4-12)	0.500
CAMPHOR QoL	8 (4-13)	6 (3-12)	**0.040**
CAMPHOR symptoms	8 (6-13)	6 (3-11)	**0.002**
EmPHasis-10	21 (16-33)	20 (12-31)	**0.044**

Table 4. Clinical outcome parameters at baseline and after 1-year follow-up

	Baseline	**1 year**	**P-value**
Clinical outcome parameters			
6MWD (m)	346 (248-434)	386 (328-503)	**<0.001**
NT-proBNP (pmol/L)	62 (30-270)	36 (16-68)	**<0.001**
Non-invasive risk score*			**<0.001**
0	25 (45.5%)	11 (25.6%)	
1	15 (27.3%)	11 (25.6%)	
2	11 (20.0%)	21.3 (30.2%)	
3	4 (7.3%)	8 (18.6%)	
Echocardiography			
CO (L/min)	5.1 (4.0-5.9)	5.3 (4.4-6.7)	0.421
LVEF (%)	56.8 (± 6.9)	55.6 (± 5.8)	0.354
LVEDD (cm)	4.3 (± 0.8)	4.7 (± 0.7)	**0.006**
RA area (mm^2)	19.8 (17-23.6)	18.3 (15.2-24.2)	0.167
RVEDD (cm)	4.6 (± 0.8)	4.4 (± 0.9)	0.930
Peak TRV (m/sec)	4.0 (± 0.6)	3.5 (± 0.6)	**0.004**
TAPSE (cm)	2.0 (1.6-2.3)	2.1 (1.8-2.5)	**0.012**
RVFAC (%)	32.8 (25.9-40.0)	41.4 (37.0-45.3)	**0.011**
Estimated RA pressure (mmHg)			0.168
3	32 (62.7%)	28 (77.8%)	
8	12 (23.5%)	7 (19.4%)	
15	7 (13.7%)	1 (2.8%)	

Abbreviations: 6MWD: 6 minute walking distance; CO: Cardiac output; LVEDD: Left ventricular end diastolic diameter; LVEF: Left ventricular ejection fraction; RA: right atrial; RVEDD: Right ventricular end diastolic

diameter; RVFAC: Right ventricular fractional area change; TAPSE: Tricuspid annular plane systolic excursion; TRV: Tricuspid regurgitation velocity

* Number of low-risk criteria: NYHA-classification I or II, 6MWD > 440m and NT-pro-BNP <300mg/L or < 35.7 pmol/L

We evaluated the correlations between the CAMPHOR and EmPHasis-10 questionnaires and our clinical anchor points (table 5). The EmPHasis-10 questionnaire as well as the CAMPHOR domains showed moderate to good correlations with the overall health score during the complete follow-up. They also showed moderate to good correlations with the symptom severity score. The baseline activity domain and the QoL domain at 6 months follow-up showed weak correlations with the symptom severity score. At baseline, the activity and symptom domain showed weak correlations with the NYHA classification. During follow-up weak-to-moderate correlations were seen between the questionnaires and the NYHA classification and non-invasive risk score. Moderate to strong correlations were seen between the 6MWD and the questionnaires at baseline and during follow-up. Only the QoL domain showed no correlation with the 6MWD at 6 months follow-up. NT-proBNP levels correlated poorly with the CAMPHOR domains at baseline and showed no correlation with the EmPHasis-10 score at baseline nor with the CAMPHOR and EmPHasis-10 questionnaires during follow-up. There were weak correlations between TTE data at baseline and the QoL domain and TAPSE, between the symptoms domain and LVEF and RVFAC and between the EmPHasis-10 and LVEF. No other significant correlations were seen between the questionnaires and echocardiographic data (supplementary table 3).

The outcomes of the EmPHasis-10 questionnaire showed strong correlations with the domains of the CAMPHOR questionnaire at baseline (Activity: r=0.631; QoL r=0.707, Symptoms r=0.832; all p<0.001), 6 months (Activity: r=0.614; QoL r=0.637, Symptoms r=0.755; all p<0.001) and 1 year of follow-up (Activity: r=0.715; QoL r=0.772, Symptoms r=0.784; all p<0.001).
The change in EmPHasis-10 score after one year of follow-up showed a good correlation with the change in the total CAMPHOR score (r=0.686, p<0.001). With the separate CAMPHOR domains the change in 1 year in EmPHasis-10 score showed moderate correlations: Activity r=0.512, p<0.001; Quality of life r=0.512, p<0.001; Symptoms r=0500, p<0.001 (supplementary table 4).

Anchor based MCIDs represent the mean change in CAMPHOR or EmPHasis-10 scores of patients who improved one step on a 5-scale symptom severity score, 5-scale overall health score or NYHA-classification. MCIDs for the CAMPHOR domains were: Activity: -3 points, QoL: -2 points, Symptoms -3 points. The anchor based MCID of the EmPHasis-10 questionnaire was -9. Distributional-based MCIDs of the CAMPHOR domains using the 0.5SD method were Activity: -3, Quality of life -3, Symptoms -4. The distributional MCID

of the EmPHasis-10 was -6. We estimated the final MCID by taking the mean of the anchor and distributional based MCIDs, these were for the CAMPHOR domains: Activity -3, Quality of Life -3, Symptoms -4. The mean MCID for the EmPHasis-10 was -8 (table 6). In our population, the CAMPHOR MCIDs were reached in 18 patients (32.1%) for the activity domain, 19 patients (34.5%) for the QoL domain and 18 patients (32.7%) for the symptoms domain. Seven patients (12.7%) reached the MCID of all CAMPHOR domains. The EmPHasis-10 MCID was reached by 17 patients (30.9%).

Table 5. Correlation coefficients between questionnaire scores and clinical anchor-points

	Overal Health score	**Symptom Severity Score**	**NYHA classification**	**6MWT**	**NT-proB-NP**	**Non-invasive risk score**
Baseline						
EmPHasis-10	**0.553***	**0.683***	0.198	**-0.530***	0.191	**-0.341***
CAMPHOR						
Activity	**0.458***	**0.381***	**0.275***	**-0.679***	**0.301***	**-0.397***
QoL	**0.511***	**0.485***	0.251	**-0.410***	**0.258***	**-0.251***
Symptoms	**0.516***	**0.642***	**0.308***	**-0.591***	**0.342***	**-0.355***
6 month follow-up						
EmPHasis-10	**0.650***	**0.547***	**0.310***	**-0.406***	0.080	-0.159
CAMPHOR						
Activity	**0.597***	**0.671***	**0.536***	**-0.589***	0.163	**-0.328***
QoL	**0.477***	**0.341***	**0.300***	-0.204	0.023	-0.011
Symptoms	**0.594***	**0.559***	**0.493***	**-0.554***	0.058	**-0.326***
12 month follow-up						
EmPHasis-10	**0.711***	**0.715***	**0.366***	**-0.539***	0.217	**-0.286***
CAMPHOR						
Activity	**0.663***	**0.631***	**0.496***	**-0.730***	0.182	**-0.515***
QoL	**0.572***	**0.564***	**0.308***	**-0.469***	0.060	**-0.349***
Symptoms	**0.677***	**0.697***	**0.404***	**-0.488***	0.227	**-0.359***

*p-value < 0.01

Table 6. MCID determination of the CAMPHOR and EmPHasis-10 questionnaires

	CAMPHOR activity	CAMPHOR symptoms	CAMPHOR QoL	EmPHasis-10
Anchor based MCID				
Overall health score	-2.5	-4.6	-3.0	-11
Symptom severity score	-3.0	-3.3	-1.5	-8.0
NYHA-classification	-4.0	-2.0	-2.0	-8.5
Mean anchor based MCID	**-3.2**	**-3.3**	**-2.2**	**-9.2**
Distributional based MCID				
0.5SD	-3.1	-4.1	-3.0	-5.8
Overall mean	-3.2	-3.7	-2.6	-7.5

MCID: minimal clinically important difference; NYHA: New York Heart Association; QoL: SD: standard deviation

4. Discussion

This study demonstrates good-to-moderate correlations at baseline and during every point in follow-up between the EmPHasis-10 score, all three CAMPHOR domain scores and the anchor points: overall health and symptom severity score and the 6MWD. To our knowledge, this is the first study that prospectively evaluates two PH-specific HRQoL measures in the same patient cohort and evaluated the correlation of these questionnaires with a broad spectrum of QoL, clinical and echocardiographic parameters. We observed good correlations between the EmPHasis-10 score and all domains of the CAMPHOR questionnaire. We calculated MCIDs for the EmPHasis-10 score and the CAMPHOR domains in PAH and CTEPH.

Similar to previous studies, QoL measures improved after initiation of treatment in patients with PAH and CTEPH[16,17]. However, in our population we did not observe improvement in the CAMPHOR activity domain despite significant and clinically important improvement in the 6MWD. In previous work from our research group, we did not see significant improvement of the CAMPHOR activity domain either after a 10-week outpatient pulmonary rehabilitation program, while both other domains of the CAMPHOR showed significant improvement[35]. This could be due to lack of (discriminative) power in this domain specifically. Another recent publication found a small improvement in the activity domain in patients with idiopathic PAH after treatment initiation[17]. However this improvement was also borderline significant compared to the other CAMPHOR domains. The patients in our study were older compared to the patients in the study mentioned previously. Inactivity due to the COVID-19 pandemic could also have played a role.

Lewis et al. demonstrated a moderate correlation (r= -0.55) between the EmPHasis-10 score and the 6MWD at baseline[22]. This is in line with our observations at baseline. Furthermore, we demonstrated similar correlations with the 6MWD during follow-up and with general HRQoL measures. This suggests that the EmPHasis-10 is a suitable tool to measure PH-specific HRQoL during follow-up. Moderate to good correlations were also demonstrated between the CAMPHOR domains and the 6MWD and general HRQoL measurements. These are similar to correlations found in the literature[16,17]. We evaluated possible correlations between PH-specific HRQoL measures and echocardiographic data. However, we did not find any important correlations between these echocardiographic data and the questionnaire outcomes. Nor did we find any correlation between NT-pro-BNP and the results of the questionnaires. Previous work of our group also showed no correlations between the CAMPHOR domains and NT-pro-BNP in the validation study of the CAMPHOR questionnaire for the Netherlands[15]. Short-term improvement in QoL might depend relatively more on the function of the pulmonary vasculature than on cardiac function alone in an early disease stage. It is feasible that cardiac factors may become more important on the longer term, because structural cardiac improvement and adaptation may take longer. It is possible that these correlations might become more pronounced in the long term follow-up, but more research is needed to investigate this subject. Additionally, correlations might be weak because of a lack of power regarding echocardiographic data.

Good correlations were demonstrated between the EmPHasis-10 questionnaire and the CAMPHOR domains. Moderate-to-good correlations were observed between the change in EmPHasis-10 score and the change in the domain scores of the CAMPHOR. The EmPHasis-10 is easily accessible and less time consuming to complete than the CAMPHOR. It can easily be completed at home or in the waiting room of the outpatient clinic. The EmPHasis-10 is also easy to interpret by the medical staff in clinical practice and might therefore be more suitable to use in routine clinical care than the CAMPHOR questionnaire. The CAMPHOR might be more useful to evaluate specific domains of QoL and for research purposes.

The MCID represents the minimal change which patients perceive as an improvement. We established a MCID of -8 for the EmPHasis-10 questionnaire. One previous study by Borgese et al. proposed a MCID for the EmPHasis-10 score of -6 in patients with PAH[36]. These calculations were based on distributional estimates of the MCID. Our distributional MCID calculated by the 0.5SD method is also equal to -6. Our MCID is based on both distributional and clinical anchor based calculations. Anchor based MCID calculations, especially when based on multiple well-correlated anchor points, provide more insight in the patient perceived change in health[33]. Therefore, the use of both anchor and dis-

tributional methods might provide a better estimation of the true change perceived as an improvement by patients. Our MCID estimates for the CAMPHOR domains are similar to those previously cited in a study investigating CTEPH by Newnham et al. and in study concerning IPAH by Bunclark et al.[16,17]. Only 13 percent of our patients achieved the MCID of all three CAMPHOR domains. The median age in our patient population is relatively high and HRQoL might also be limited due to higher age and comorbidities. Bunclark et al. demonstrated a similar improvement in patients with idiopathic PAH[17]. A recent study of Newnham et al. showed that the median increase in QoL exceeded the MCID in CTEPH patients undergoing PEA[16]. In our study, unfortunately, there was a delay for patients undergoing PEA and BPA sessions because of the COVID-19 pandemic. Approximately one third of our patients achieved the MCID of at least one CAMPHOR domain or the EmPHasis-10 score, which is similar to a previous study investigating idiopathic PAH patients[17].

4.1 Limitations

A limitation of our study was that our follow-up was partly disrupted by the COVID-19 pandemic. Due to governmental and hospital policies, not strictly necessary real-world patient-doctor contact was limited for some time. Regular clinical follow-up visits were in some cases replaced by telephone or digital consults. Therefore, unfortunately not all patients underwent a TTE during the follow-up. These earlier mentioned restrictions in the provision of regular care also caused a delay in the invasive treatment of patients with CTEPH, either by PEA or BPA. It might therefore be possible that the optimal treatment effect for certain CTEPH patients was not reached yet.

5. Conclusion

In this study we found a significant improvement of PH-specific HRQoL measures in patients with PAH and CTEPH in response to treatment. Both the EmPHasis-10 and the CAMPHOR questionnaire showed moderate to good correlations with general QoL scales and 6MWD, both at baseline and during follow-up. Based on this study, both questionnaires are suitable for longitudinal follow-up to evaluate HRQoL in PAH and CTEPH patients. We also found acceptable MCIDs for both questionnaires.

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Appendix

Supplementary table 1. Marital and working status

	Whole cohort	PAH	CTEPH	P-value
Marital status				0.645
Maried/living together	40 (65.6%)	20 (64.5%)	20 (66.7%)	
Widow(er)	10 (16.4%)	4 (12.9%)	6 (20.0%)	
Divorced	1 (1.6%)	1 (3.2%)	0 (-)	
Single	9 (14.8%)	5 (16.1%)	4 (13.3%)	
Relation, not living together	1 (1.6%)	1 (3.2%)	0 (-)	
Working status				0.214
Fulltime	6 (10.0%)	4 (12.9%)	2 (6.9%)	
Part-time	2 (3.3%)	1 (3.2%)	1 (3.4%)	
Homemaker	5 (8.3%)	1 (3.2%)	4 (13.8%)	
Retired	32 (53.3%)	18 (58.1%)	14 (48.3%)	
Long term sick leave	6 (10.0%)	2 (6.5%)	4 (13.8%)	
Unemployed	3 (5.0%)	0 (-)	3 (10.3%)	
Student	2 (3.3%)	2 (6.5%)	0 (-)	
Other	4 (6.7%)	3 (9.7%)	1 (3.4%)	

Supplementary table 2. Subgroup analysis of the Health related quality of life questionnaires at baseline and after 1 year

	PAH			CTEPH		
	Baseline	**1-year**	**p-value**	**Visit 1**	**Visit 3**	**p-value**
Questionnaire						
CAMPHOR Activity	8 (5-14)	8 (5-11)	0.491	8 (5-14)	8 (4-15)	0.837
CAMPHOR QoL	7 (4-12)	6 (4-11)	0.387	9 (4-14)	5 (1-13)	**0.034**
CAMPHOR symptoms	8 (6-13)	6 (3-9)	**0.020**	9 (6-16)	9 (12-34)	**0.035**
EmPHasis-10	20 (15-33)	18 (12-27)	0.165	26 (18-36)	22 (12-34)	0.102
Outcome						
6MWT (m)	328 (136)	370 (149)	**0.006**	359 (241-452)	440 (285-527)	**0.041**
NT-pro-BNP (pmol/L)	62 (280)	41 (46)	**0.001**	62 (29-244)	36 (13-63)	**0.004**
Non-invasive risk score*			**0.006**			**0.017**
0	15 (57.7%)	8 (29.6%)		10 (34.5%)	3 (18.8%)	
1	5 (19.2%)	7 (25.9%)		10 (34.5%)	4 (25.0%)	
2	5 (19.2%)	8 (25.8%)		6 (20.7%)	5 (31.3%)	
3	1 (3.8%)	4 (14.8%)		3 (10.3%)	4 (25.0%)	

* Number of low-risk criteria: NYHA-classification I or II, 6MWD > 440m and NT-pro-BNP <300mg/L or < 35.7 pmol/L

Supplementary table 3. Correlation coefficients between questionnaire outcome and echocardiographic data

	CO	LVEDD	LVEF	pTRV	RA area	RVFAC	RVEDD	TAPSE
Baseline								
EmPHasis-10	-0.185	-0.04	-0.307*	-0.174	-0.185	-0.293	-0.049	-0.269
CAMPHOR Activity	-0.117	0.012	-0.157	-0.072	-0.108	-0.137	-0.057	-0.213
CAMPHOR QoL	-0.216	-0.120	-0.238	-0.263	-0.053	-0.276	0.021	-0.329*
CAMPHOR symptoms	-0.127	0.004	-0.337*	0.107	-0.043	-0.317*	-0.068	-0.197
1 year follow-up								
EmPHasis-10	-0.009	-0.030	-0.28	-0.159	-0.067	0.283	0.051	0.06
CAMPHOR activity	-0.138	0.125	-0.347	-0.216	-0.151	0.252	-0.023	0.033
CAMPHOR QoL	-0.100	0.236	-0.377	-0.172	0.002	0.245	0.186	0.012
CAMPHOR symptoms	-0.021	0.054	-0.174	-0.133	0.057	0.28	0.155	-0.132

Abbreviations: CO = Cardiac Output; LVEDD = Left ventricular end diastolic diameter; LVEF = Left ventricular ejaction fraction; pTRV = peak tricuspid regurgitation velocity; RA-area = Right atrial area; RVEDD = Right ventricular end diastolic dimension; TAPSE = Tricuspid annular plain systolic excursion. *p-value < 0.05

Supplementary table 4. Correlation coefficients between the change in questionnaire score

	Corresponding change in CAMPHOR domain		
	Activity	QoL	Symptoms
Change in EmPHasis-10 score			
Baseline – 6m follow-up	0.347*	0.480*	0.619*
6m follow-up – 12m follow-up	0.427*	0.450*	0.665*
Baseline – 12m follow-up	0.512*	0.521*	0.500*

*p-value < 0.01

PART IV

Summary and general discussion

CHAPTER 9

Summary

SUMMARY

This thesis focuses on clinical outcomes of CTEPH patients treated with PH-specific medical therapy or balloon pulmonary angioplasty (BPA). It provides long-term results of medically treated patients, the first results of BPA treatment in the Netherlands and assesses quality of life (QoL) in CTEPH patients.

Part I of this thesis describes the use of PH-specific medical therapy for CTEPH patients. PH-specific medical therapy lowers pulmonary vascular tone and causes vasodilatation, resulting in a decreased pulmonary vascular resistance and improved clinical outcome. There are currently mainly short-term results of PH-specific medical therapy in CTEPH patients available, while long-term outcomes are unknown.

In **chapter 2** the long-term outcome of CTEPH patients using riociguat is assessed. Riociguat is a soluble guanylate cyclase stimulator and is currently the only approved medical CTEPH treatment. After a follow-up of three years, 94% of all patients using riociguat was still alive and 78% of all patients did not experience clinical worsening (all-cause mortality, hospital admission or lower 6-minute walking distance (6MWD) plus lower functional class). In addition, patients using riociguat experienced significant improved functional class, exercise tolerance (measured with 6MWD) and lower NT-proBNP compared to measurements before the start of PH-specific medical therapy.

In **chapter 3** long-term results of CTEPH patients using macitentan are described. CTEPH patients using macitentan were divided in two groups: one group with technical inoperable disease and another group with clinical inoperable disease. Patients in the first group had distal lesions unsuitable for PEA, while patients in the latter group were inoperable due to comorbidities or were reluctant to undergo PEA. Survival rates two years after the start of treatment with macitentan were 86% and 100% for the technical and clinical inoperable CTEPH patients respectively. Both groups had significant improved 6MWD, while 30% of all patients experienced non-severe adverse events.

In **chapter 4** the outcomes between CTEPH patients using macitentan and bosentan are compared.
Macitentan is a relatively new PH-specific medical therapy and may have sustained receptor binding properties and an enhanced tissue distribution compared to bosentan. In our cohort, survival and improvements in functional class, NT-proBNP and 6MWD of patients using macitentan were similar compared to patients using bosentan. Significant baseline predictors of survival were right atrial pressure, cardiac output and lowest saturation during 6MWD.

In **chapter 5** outcomes of CTEPH patients using PH-specific medical monotherapy are compared with CTEPH patients using PH-specific medical combination therapy.
While there is no research available comparing monotherapy versus combination therapy in CTEPH patients, it is recommended in pulmonary arterial hypertension (PAH) patients to start with combination therapy to improve outcome. In our study, patients starting combination therapy had more severe disease at baseline (higher NT-proBNP and worse hemodynamics), but survival up to five years after start of therapy was similar in both groups.

Part II of this thesis focusses on results of BPA treatment in CTEPH patients. BPA is a relatively new, endovascular treatment of occluded and obstructed pulmonary arteries not treatable with PEA. The aim of BPA is to open these occluded or obstructed pulmonary arteries, resulting in improved pulmonary hemodynamics, as well as improved symptoms and exercise tolerance.

In **chapter 6** the first results of BPA in the Netherlands are reported.
Our study includes data of 38 CTEPH patients who underwent 172 BPA procedures. There was a significant improvement of functional class, 6MWD and pulmonary hemodynamics. Non-severe complications occurred in 12% of all procedures, but none of the patients died or needed mechanical ventilation.

In **chapter 7** results of change in ventilation/perfusion (V/Q) scan after BPA treatment are presented.
A V/Q scan was performed in 20 CTEPH patients at baseline and 6 months after completion of BPA treatment. Both visual assessment and a semi-quantitative calculated pulmonary vascular obstruction index showed perfusion improvement. Nevertheless, the improvement of perfusion was small and did not correlate with clinical outcome.

Part III of this thesis addresses QoL in CTEPH patients. There is currently only limited research available about QoL in CTEPH patients, showing QoL after PEA. Research assessing QoL in other PH patients shows a high disease burden, anxiety and depression.

In **chapter 8** we reported longitudinal follow-up results of the use of the EmPHasis-10 and CAMPHOR questionnaires in CTEPH and PAH patients.
We showed a significant reduction in scores of both the EmPHasis-10 and CAMPHOR (quality of life and symptoms) domains after one year of treatment. In addition, the EmPHasis-10 score showed a good correlation with the scores of all CAMPHOR domains. Although both questionnaires are valid tools for longitudinal QoL measurements in these patients, the much shorter EmPHasis-10 may be easier to use in daily practise.

CHAPTER 10

General discussion

GENERAL DISCUSSION

PH-specific medical therapy for chronic thromboembolic pulmonary hypertension

The use of riociguat in patients with chronic thromboembolic pulmonary hypertension (CTEPH) showed promising short-term results. It improved exercise capacity and pulmonary vascular resistance (PVR) and was therefore approved as PH-specific medical therapy for CTEPH[1–3]. Nevertheless, long-term outcomes of CTEPH patients using riociguat in a daily clinical practice are scarce.

In our manuscript we confirmed the safety and effectivity of riociguat at long-term follow-up. Survival was 100% and 80% at two- and four-year follow-up respectively, while this was 89% and 63% respectively for clinical worsening (CW) free survival. These results were in agreement with the CHEST studies, but were better than reported in a multicentre, non-randomized observational study[1,2,4]. Definitions of CW, however, were different between studies and so were treatment strategies. We defined CW as death, need of rescue prostanoid treatment, PH hospitalisation or a decreased 6-min walking test combined with worsened functional class. Furthermore, we frequently used background pulmonary artery hypertension (PAH) therapy and balloon pulmonary angioplasty (BPA) to optimize treatment of our patients. It is therefore important to define and use uniform definitions of outcomes to improve generalisability and to be able to compare results of future studies.

The concept of using PAH therapy as background therapy in CTEPH is interesting, as CTEPH and PAH are two different disease entities with different aetiologies and outcomes. However, due to similarities in molecular mechanisms of vasculopathy in both diseases, the use of PAH therapy is also justified in CTEPH patients[5,6]. This is particularly useful in CTEPH patients if treatment with riociguat is not feasible (e.g. due to adverse events) or if treatment goals are not achieved with riociguat monotherapy.

Both bosentan and macitentan, endothelin receptor antagonists (ERAs) approved for PAH treatment, have been used in CTEPH patients before in the BENEFiT and MERIT-1 trials respectively. Both medicine improved PVR, while only macitentan improved exercise capacity[7,8].

We evaluated the use of macitentan in our CTEPH population and found that it was safe and did improve exercise capacity till two-year follow-up. For this study, patients using macitentan were categorised as clinical inoperable (i.e. comorbidities or were reluctant to undergo pulmonary endarterectomy (PEA)) and technical inoperable (i.e. distal disease not suitable for PEA). Survival in the first group was 100%, while for the latter it was 86%. A comparison of both groups with other cohort studies showed better survival in our patients, probably explained by differences in baseline characteristics and the frequent use of PH-specific

medical therapy in our cohort[9][10]. Nevertheless, it is interesting that patients with proximal disease, but who were reluctant to undergo PEA, also benefit of PH-specific medical therapy.

We also compared outcomes between CTEPH patients using macitentan and bosentan, and showed that (CW-free) survival and improvement of symptoms and exercise tolerance were similar for both drugs. However, these two drugs differ in feasibility and price: while macitentan is more practical in use (dosed once daily, no need for liver function tests and less interaction with anticoagulants), it is also more expensive. Therefore ERA selection should be tailored and based on the specific patient characteristics.

The concept and efficacy of combining PH-specific medical therapies was established in PAH[3,11]. Historically, most CTEPH patients received PH-specific monotherapy, but after introduction of riociguat and macitentan the number of patients receiving combination therapy increased.

In our cohorts, combination therapy is used in up to 55% of all patients and this even increases to almost 90% if only patients who started treatment after 2014 (introduction of riociguat, macitentan and use of combination strategy in the Netherlands) are selected. We therefore published a large study investigating outcomes of CTEPH patients with PH-specific combination therapy compared to monotherapy. While patients receiving PH-specific combination therapy in our cohort had more severe CTEPH disease at baseline, outcomes were similar as patients using PH-specific monotherapy. Although the use of combination therapy is not possible in every country around the world, our initial results are promising and advocate more use and research of combination therapy in CTEPH patients (with severe disease).
In conclusion, the optimal PH-specific medical therapy for CTEPH patients is still not determined.

As CTEPH is a rare disease with a low number of patients in the Netherlands, participation in international, randomised PH-specific medical trials may provide opportunities to improve CTEPH outcomes. We showed that the use of PH-specific combination therapy in severely symptomatic CTEPH patients may be promising, which emphasizes that the immediate initiation of concomitant PH-specific combination therapy deserves attention in future trials. In addition, investigation of the role of PH-specific medical therapy in clinical versus technical inoperable patients may add opportunities to improve CTEPH treatment.

Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension
Balloon pulmonary angioplasty (BPA) for CTEPH patients was already introduced in 1988[12]. The concept was interesting and surprisingly simple: open obstructed pulmonary

vessels endovascular to improve pulmonary flow and improve outcome. However, the initial complication rate was high because technique, materials and experience were not as refined as they are nowadays. We now show that BPA is safe and does improve outcome in CTEPH patients after its introduction in the Netherlands in 2015.

PEA remains the gold standard for operable CTEPH patients as it results in the best symptomatic and prognostic improvement[13]. Nevertheless, PEA is also an invasive procedure requiring sternotomy with the patient undergoing deep hypothermic circulatory arrest. Although mortality is low in specialised CTEPH centres, some operated patients require intensive postoperative care and rehabilitation[14]. In contrast, BPA is a less invasive (endovascular) treatment which takes up to 2 hours per session with patients staying only one night in the hospital for observation.

Nevertheless, a direct comparison of results of both treatments is not fair as different patients are selected and baseline characteristics differ. Both treatments improve CTEPH outcome and may show a synergetic effect if combined. For example, patients with persistent or recurrent PH after PEA are currently already treated with BPA. In addition, some centres use BPA in operable patients with severe CTEPH to improve the pulmonary hemodynamics and reduce the chance of complications before patients undergoing PEA. Further refinement and combining of these techniques seems promising.

To understand BPA physiology we assessed change in perfusion after BPA with a ventilation/perfusion (V/Q) scan. The perfusion, assessed visually and with a semi-quantitative method, improved after BPA treatment. However, the perfusion change was small and could not be correlated with change in haemodynamic and clinical outcome. The explanation is probably that BPA is excellent for opening (partially) obstructed vessels and dilating webs and bands. However, as these lesions do not completely block pulmonary flow, partially sustained perfusion may be observed at baseline and the subsequent change after BPA may be small. So a V/Q scan may not be the optimal imaging method to visualise non-occlusive lesions and perfusion improvement after BPA. Research with other imaging modalities is necessary.

In conclusion, BPA is an emerging and effective treatment for CTEPH patients in the Netherlands.

The optimal interventional CTEPH treatment should be based on patient characteristics and should not be restricted to one treatment modality only. Future research into the combination of BPA with PH-specific medical therapy would be interesting, as it seems that both therapies have different and synergistic targets in the pulmonary vasculature. In addition, a review of periprocedural BPA anticoagulation strategy may improve safety and effectivity, as there are currently different strategies, namely with interrupted and uninterrupted periprocedural anticoagulation.

Quality of life in chronic thromboembolic pulmonary hypertension

There are several factors, such as anxiety, depression, physical impairment and a high disease burden, that impair the health-related quality of life (HRQoL) in PH patients[15,16]. QoL has been evaluated in PH and CTEPH patient with generic QoL questionnaires, but nowadays also several PH-specific questionnaires have been developed.

One of these PH-specific questionnaires is the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), which is also able to predict clinical deterioration in PH patients[17]. However, there is currently only one large retrospective study that assessed QoL with the CAMPHOR in CTEPH patients. This study showed improved CAMPHOR scores after PEA compared to not operated CTEPH patients[18]. Although the CAMPHOR is a valid PH-specific questionnaire, it has the disadvantage that it consists of 55 questions. For most patients it is time consuming to complete all questions and some questions may be forgotten or misunderstood.

We therefore performed a prospective cohort study in CTEPH and PAH patients and assessed change in QoL with the CAMPHOR and the EmPHasis-10 questionnaire. The EmPhasis-10 is another and much shorter PH-specific questionnaire. We showed longitudinal QoL improvement in our CTEPH patients, who received PEA, BPA or PH-specific medical treatment, and showed that this improvement also correlated with improved overall-health, symptom severity and exercise capacity. In addition, the EmPhasis-10 score showed good correlation with all of the CAMPHOR domains.

The EmPHasis-10 questionnaire seems useful in CTEPH patients, although further (and larger) research may be needed to correlate the questionnaire with more clinical outcome parameters.

The standardised use of PH-specific questionnaires in future CTEPH research should be encouraged to obtain more information about the well-being of CTEPH patients.

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PART V

Appendix

NEDERLANDSE SAMENVATTING

Hoofdstuk 1 (introductie)
Chronische trombo-embolische pulmonale hypertensie (CTEPH) is een zeldzame aandoeningen van de pulmonaalvaten, welke met name ontstaat als acute longembolieën onvoldoende verdwijnen ondanks behandeling met antistolling. Deze longembolieën resulteren in een obstructie van de grote pulmonaalvaten. Daarnaast verandert ook in de kleinere, distale pulmonaalvaten de bloedflow en wordt de vaatwand geactiveerd. Hierdoor ontstaat een verhoogde vaatweerstand en stijgt de druk in de longen. Uiteindelijk kunnen deze veranderingen leiden tot hartfalen, met de daarbij behorende morbiditeit en mortaliteit.

Het is momenteel nog niet volledig duidelijk waarom sommige patiënten met acute longembolieën uiteindelijk CTEPH ontwikkelen. Wel zijn er diverse risicofactoren, die van invloed zijn op ontstekingsprocessen, het stollingssysteem of de fibrinolyse, die kunnen bijdragen aan het ontstaan van CTEPH.

Bij een verdenking op CTEPH wordt er eerst een echocardiogram gemaakt. Indien daarbij afwijkingen worden gezien die passen bij PH, volgt er een ventilatie/perfusie-scan. Als deze scan aanwijzingen toont voor chronische longembolieën na drie maanden antistolling gebruik, en er bij rechter hartkatheterisatie ook pre-capillaire PH (gemiddelde pulmonaal druk ≥25 mmHg en wedge druk ≤15 mmHg) aanwezig is, is de diagnose CTEPH te stellen. Idealiter is er een multidisciplinair CTEPH team dat de diagnose stelt en tevens beoordeelt hoe een patiënt het beste behandeld kan worden.
Een operatie middels pulmonalis endarterectomie (PEA) geeft de beste prognose en verbetering van klinische uitkomsten. Er zijn echter ook patiënten die niet geopereerd wensen te worden, die niet geopereerd kunnen worden (door comorbiditeiten of technisch niet mogelijk) en waarbij er ondanks een PEA nog steeds sprake is van PH. Deze patiënten komen in aanmerking voor PH-specifieke medicatie en, indien mogelijk, ook voor behandeling middels ballon pulmonalis angioplastiek (BPA).

Deel I van dit proefschrift is gericht op de medicamenteuze therapie van CTEPH patiënten.
Het gebruik van PH-specifieke medicatie heeft als doel om de kleine longvaten van CTEPH patiënten te verwijden waardoor de vaatweerstand afneemt. Dit resulteert in een verbetering van klinische uitkomsten zoals inspanningscapaciteit en hemodynamiek op korte termijn. Hoewel momenteel alleen het medicijn riociguat geregistreerd is voor de behandeling van CTEPH, is het in Nederland ook toegestaan om PH-specifieke medicatie voor pulmonale arteriële hypertensie (PAH) te gebruiken voor CTEPH patiënten. Literatuur over de langetermijneffecten van PH-specifieke medicatie bij CTEPH patiënten in de dagelijkse praktijk is echter beperkt.

In **hoofdstuk 2** worden de lange termijn uitkomsten beschreven van CTEPH patiënten die riociguat gebruiken. Na een follow-up van drie jaar is 94% van de patiënten in leven en daarnaast heeft 78% van de patiënten geen verergering van de ziekte of een ziekenhuisopname nodig gehad. CTEPH patiënten die riociguat gebruiken hebben na 3 jaar behandeling een significante verbetering van klachten, inspanningsmogelijkheden en van de NT-proBNP waarde.

In **hoofdstuk 3** worden uitkomsten beschreven van CTEPH patiënten die macitentan gebruiken. Er wordt een onderscheid gemaakt tussen patiënten die technisch inoperabel zijn (chronische embolieën niet bereikbaar voor PEA) en die klinisch inoperabel zijn (comorbiditeiten of persoonlijke voorkeur). Twee jaar na start van macitentan heeft de eerste groep patiënten een overlevingspercentage van 86% en de tweede groep van 100%. In beide groepen is er sprake van een significante verbetering van de inspanningstolerantie. In 30% van de patiënten worden niet-ernstige bijwerkingen geobjectiveerd.

In **hoofdstuk 4** worden de uitkomsten van CTEPH patiënten die macitentan gebruiken vergeleken met patiënten die bosentan gebruiken. De middelen hebben een vergelijkbaar effect op overleving en verbetering van symptomen, NT-proBNP en inspanningsmogelijkheden. Op baseline zijn de rechter atrium druk, cardiac output en laagste saturatie tijdens de 6-minuten wandeltest voorspellers voor overlijden.

In **hoofdstuk 5** worden klinische uitkomsten vergeleken tussen CTEPH patiënten die PH-specifieke monotherapie gebruiken en patiënten die PH-specifieke combinatietherapie gebruiken. Patiënten die combinatietherapie kregen hadden slechtere uitgangswaarden op het moment van starten van de medicatie (hoger NT-proBNP en slechtere hemodynamiek), maar overleving na 1, 3 en 5 jaar behandeling is gelijk aan de groep met monotherapie.

Deel II van dit proefschrift is gericht op de BPA behandeling van CTEPH patiënten. BPA is een relatief nieuwe, endovasculaire behandeling die toegepast kan worden bij vernauwingen in de middelgrote pulmonaalvaten. Deze letsels zijn meestal niet (volledig) te bereiken met een PEA. Het doel is de vernauwde of afgesloten pulmonaalvaten weer doorgankelijk te maken, waardoor de pulmonale hemodynamiek, klachten en inspanningsmogelijkheden verbeteren. Niet-ernstige complicaties zoals milde haemoptoë, tijdelijke geleidingsstoornissen en vasculaire complicaties treden relatief frequent op tijdens procedures.

In **hoofdstuk 6** worden de eerste Nederlandse BPA resultaten beschreven van 38 patiënten die samen 172 BPA's hebben ondergaan. Na behandeling is er een significante verbetering zichtbaar van klachten, inspanningsmogelijkheden en de pulmonale hemodynamiek. Niet-ernstige complicaties ontstaan bij 12% van de procedures.

In **hoofdstuk 7** wordt gekeken naar verandering van perfusie op ventilatie/perfusie-scans van 20 CTEPH patiënten die een volledige BPA behandeling hebben ondergaan. Zowel visueel als met een semi-kwantitatieve pulmonale vasculaire obstructie index wordt er een verbetering gezien in perfusie. Deze perfusieverbetering is echter klein en correleert niet met de sterke klinische verbetering die deze patiënten laten zien.

Deel III van dit proefschrift is gericht op de kwaliteit van leven van patiënten met CTEPH.

CTEPH patiënten ervaren veel klachten en hebben een verminderde inspanningstolerantie. Van PH patiënten is bekend dat de kwaliteit van leven laag is en dat zij vaak angst of depressies ervaren. CTEPH patiënten die een PEA hebben ondergaan, bemerken een verbetering in kwaliteit van leven. De invloed van PH-specifieke medicatie en BPA op kwaliteit van leven is slechts beperkt onderzocht.

In **hoofdstuk 8** wordt het effect van behandeling op kwaliteit van leven in CTEPH en PAH patiënten gemeten door middel van de EmPHasis-10 en CAMPHOR vragenlijsten. Na 1 jaar behandeling is er een significante reductie van zowel de EmPHasis-10 als de CAMPHOR scores, wijzend op een significante verbeterde kwaliteit van leven. Daarnaast correleert de EmPHasis-10 score goed met de score van alle CAMPHOR domeinen.

Beide vragenlijsten zijn valide voor een longitudinale meting van kwaliteit van leven in PAH en CTEPH patiënten, maar de veel kortere EmPHasis-10 is wellicht praktischer in de dagelijkse praktijk.

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CURRICULUM VITAE

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Mitch Christian Johan van Thor was born on January 21th 1992 in Maastricht, the Netherlands. He attended high school at the Bonnefanten College in Maastricht and graduated in 2010. Mitch continued his studies at the Faculty of Health, Medicine and Life Sciences at Maastricht University, where he studied Biomedical Sciences for one year (2010). The following year Mitch could follow his dreams, as he was enrolled in the Medicine studies program at Maastricht University.

During his medical education Mitch was able to expand his knowledge and network by participating in international internships at the 'Università degli Studi di Ferrara' in Italy (2013) and the 'University of Pretoria' in South-Africa (2015). He also took place in several University committees and aimed to improve medical education for both medical students and residents of Maastricht.

During the fourth year of his medical studies, Mitch got interested in the cardiovascular system. He therefore decided to spend both his elective and final clinical rotation at the department of cardiology at the Maastricht University Medical Center. As part of his Master's thesis, Mitch moved to Utrecht to conduct research in 'speckle tracking echocardiography in cardiac sarcoidosis' at the department of cardiology at the St. Antonius Hospital in Nieuwegein. He graduated from University and obtained the degree of 'Master of Science in Medicine' with distinction in 2017.

Later that year Mitch started working on his PhD in 'chronic thromboembolic pulmonary hypertension' at the St. Antonius Hospital, under supervision of prof. dr. M.C. Post, dr. J.J. Mager and drs. R.J. Snijder. During this trajectory he was also an active board member of 'de PromovendiClub', a committee at the local hospital providing training and support for fellow researchers. In order to gain more clinical experience, he combined his PhD with working as a medical doctor in the pulmonary and cardiology department for three years.

In January 2021 he started his residency in cardiology, working under supervision of dr. M.C.E.F. Wijffels, in the St. Antonius Hospital. As part of his specialization in cardiology, he is currently working at the department of internal medicine under supervision of dr. P.C. de Jong.