Lung (2019) 197:753–760
https://doi.org/10.1007/s00408-019-00274-9

PULMONARY HYPERTENSION

Bosentan or Macitentan Therapy in Chronic Thromboembolic Pulmonary Hypertension?

M. C. J. van Thor[1,2] · L. ten Klooster[2] · R. J. Snijder[2] · J. C. Kelder[3] · J. J. Mager[2] · M. C. Post[1]

Received: 28 June 2019 / Accepted: 19 September 2019 / Published online: 3 October 2019

Abstract

Objective 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, 2-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-min walking test (6MWT) until 2 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 2-year follow-up.

Conclusion CTEPH patients receiving bosentan or macitentan have improved clinical outcomes till 2-year follow-up, without significant differences in outcomes between both therapies.

Keywords Chronic thromboembolic pulmonary hypertension · Bosentan · Macitentan · Survival · Clinical worsening

Abbreviations

6MWD	6-Minute walking distance
6MWT	6-Minute walking test
BPA	Balloon pulmonary angioplasty
CO	Cardiac output
COPD	Chronic obstructive lung disease
CT	Computed tomography
CTEPH	Chronic thromboembolic pulmonary hypertension
CW	Clinical worsening
e.g.	Exempli gratia
ERA(s)	Endothelin receptor antagonist(s)
FC	Functional class
HR	Hazards regression
i.e.	Id est
IPTW	Inverse probability of treatment weighting
mPAP	Mean pulmonary arterial pressure
NT-proBNP	*N*-Terminal pro-brain natriuretic peptide
PAH	Pulmonary arterial hypertension
PEA	Pulmonary endarterectomy
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
RAP	Right atrial pressure
SD	Standard deviation

Electronic supplementary material The online version of this article (doi:https://doi.org/10.1007/s00408-019-00274-9) contains supplementary material, which is available to authorized users.

✉ M. C. Post
m.post@antoniusziekenhuis.nl

[1] Department of Cardiology, St. Antonius Hospital, Nieuwegein, The Netherlands

[2] Department of Pulmonology, St. Antonius Hospital, Nieuwegein, The Netherlands

[3] Department of Epidemiology, St. Antonius Hospital, Nieuwegein, The Netherlands

TAPSE Tricuspid annular plane systolic excursion
WHO World Health Organisation

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 Organisation 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-min 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 2 years after treatment initiation and compare bosentan and macitentan therapy results.

Methods

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, 13], in our CTEPH multidisciplinary team, including cardiologists, pulmonologists, radiologist, cardiothoracic surgeons and nurse practitioners.

PH was defined as mean pulmonary artery pressure (mPAP) $\geq$ 25 mmHg and wedge pressure $\leq$ 15 mmHg at right heart catheterisation (RHC). CTEPH was diagnosed 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 at least 3 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 $\geq$ 25 mmHg immediately post-PEA by Swan-Ganz measurement and persistent elevated on RHC 6 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 [14]. 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 [15], even if clinically stable. Patient follow-up was censored from the first BPA onwards, to differentiate between ERA and BPA effect.

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 3 months of diagnosis. Outpatient follow-up visits alternated between a pulmonologist and cardiologist every 3 months.

Outcomes

Patients were followed from baseline till 2 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 1- and 2-year follow-up dates.

Statistical Analyses

Statistical analyses were performed with SPSS software (IBM SPSS statistics version 24). Tests were two-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 χ^2 and Fisher exact tests. Differences 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).

Results

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 (Fig. 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).

Survival

The 2-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 6 received bosentan. Two patients on bosentan died in the first year (survival rate 96%) and 4 in the second year. For macitentan this were respectively 3 (survival rate 92%) and 3 patients (Fig. 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 (Table A.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 (Figure B.1). A comparison of bosentan versus

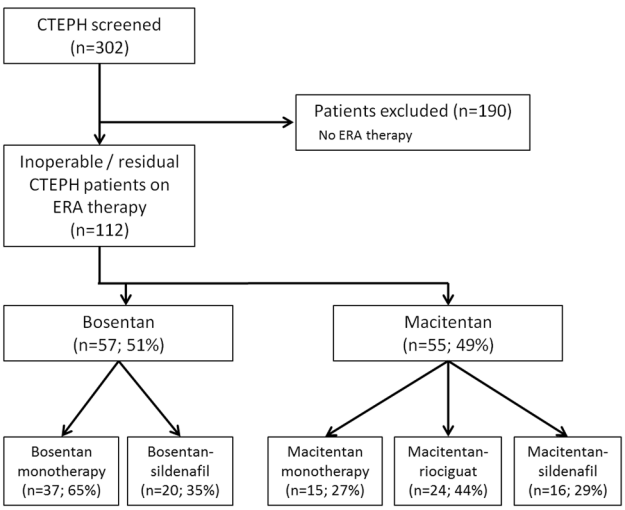

Fig. 1 Flow-chart of patient selection and treatment strategies

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)[a]	37 (64.9)	15 (27.3)	0.001
ERA + riociguat	24 (21.4)[a]	0	24 (43.6)	0.001
ERA + sildenafil	36 (32.1)[a]	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
Hyperlipidemia	4 (3.6)	2 (3.5)	2 (3.6)	1
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) [b]	1409 (291–2785) [c]	0.066
6MWD (m), mean ± SD	324 ± 126	324 ± 118 [d]	323 ± 134 [c]	0.955
6MWT lowest saturation (%)	83.2 ± 7.9	84.0 ± 6.4 [e]	82.6 ± 9.2 [f]	0.427
Right-sided heart catheterization				
CO (L/min)	5.1 ± 1.7	5.2 ± 1.5 [g]	5.1 ± 1.8 [h]	0.682
RAP mean (mmHg)	8.6 ± 4.5	7.9 ± 4.9 [i]	9.3 ± 3.9 [d]	0.122
PAP mean (mmHg)	42.2 ± 10.6	41.6 ± 10.2 [j]	42.9 ± 11.2 [d]	0.554
PVR (WU)	6.6 ± 3.7	6.0 ± 2.9 [e]	7.3 ± 4.4 [k]	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

[a]Data do not add up to 100% due to rounding

[b]$n=47$

[c]$n=52$

[d]$n=53$

[e]$n=48$

[f]$n=49$

[g]$n=50$

[h]$n=47$

[i]$n=51$

[j]$n=55$

[k]$n=46$

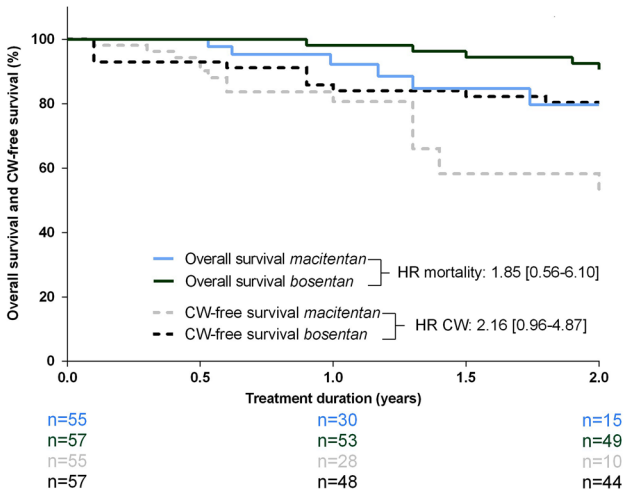

Fig. 2 Kaplan–Meier survival and CW-free survival curves, number of patients at risk receiving bosentan and macitentan and univariate HR for mortality and CW

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

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 (Fig. 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 (Table A.2).

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 (Table A.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 (Figure B.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 to 59) at year 1 and −28 pg/mL (−432 to 156) at year 2, and with macitentan -293 pg/mL (−1659 to 91, $p=0.02$) and +15 pg/mL (−1130 to 247), respectively, but without a significant difference between therapies.

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

Discussion

In this study, we present the first real-world 2-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 2-year follow-up.

Nowadays, PH-specific therapies for CTEPH other than riociguat are gaining more interest and the use of combination therapy increases [7, 14]. 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 [16–19]. Macitentan is practical in use as it is dosed once daily, does not require monthly liver testing and has less interaction with anticoagulation therapy [16], 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 2-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. [14] in their multicentre, international prospective registry (79% at 2-year follow-up).

CW-free survival was not significantly higher in bosentan than macitentan (81% vs 58) at 2-year follow-up. The BENEFiT trial [8] showed only 4% CW, but this was for a 16-week observation period. 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 2 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 [20]. 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 [8], while no patient worsened in the MERIT trial [9]. Cohort studies showed improved WHO FC at 6 months (27%) and one year (24%) in patients using bosentan [20–22]. Our current results for bosentan are more profound at 1-year follow-up (37%) and persist till 2-year follow-up (49%), probably partially explained by our better baseline characteristics (better WHO FC and hemodynamics). Results for macitentan at 1-year follow-up were highly comparable with MERIT trial results [9]. However, 20% of our patients using macitentan had worsened at 2-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 2-year follow-up, probably due to our lower baseline NT-proBNP. Ulrich et al. could not show significant decrease of proBNP at 6-month follow-up either in their cohort study [21].

The 6MWD remained unchanged in the BENEFiT trial at 16-week follow-up, explained by the older age of patients and short duration of the study [8]. We show in similar aged patients improved (+25 m) 6MWD till 2-year follow-up. The study duration may indeed have influenced results, however, Reesink et al. [23] did already show a significant improved (+33 m) 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 6-month (+ 54 m) and 1-year follow-up (+ 57 m) [20, 21]. Our results are probably lower due to lower baseline 6MWD values. Patients receiving macitentan had improved 6MWD at 2-year follow-up in our study, comparable with short-term results (+35 m vs + 34 m) 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 2-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 [15]. 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 [24–26]. 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, 27]. 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 [28–30] and CO predicts hemodynamic normalisation and in hospital mortality after PEA [31, 32]. 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 [33, 34].

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 [13].

Nowadays, combination therapy in PAH patients is recommended, because it reduces the risk of CW and improves long-term outcomes [4, 35–37] due to additive or synergistic beneficial effects [38]. Although there is no randomised 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.

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.

Conclusion

Inoperable CTEPH and residual PH patients using bosentan or macitentan show improved clinical outcomes up till 2-year follow-up, without significant different outcomes between both therapies.

Acknowledgements MvT, HK and MP had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. MvT, LtK, RS, HK, JM and MP contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. All authors approve the final version to be submitted.

Compliance with Ethical Standards

Conflict of interest M. van Thor, J. Mager and M. Post report grants from Actelion Pharmaceuticals. R. Snijder reports grants from Pfizer and Actelion Pharmaceuticals. L ten Klooster and J. Kelder have nothing to disclose.

References

1. Simonneau G, Torbicki A, Dorfmüller P, Kim N (2017) The pathophysiology of chronic thromboembolic pulmonary hypertension. Eur Respir Rev 26:160112. https://doi.org/10.1183/16000617.0112-2016
2. Jenkins D, Madani M, Fadel E, D'Armini AM, Mayer E (2017) Pulmonary endarterectomy in the management of chronic thromboembolic pulmonary hypertension. Eur Respir Rev 26:160111. https://doi.org/10.1183/16000617.0111-2016
3. Galiè N, Humbert M, Vachiery JL, ESC Scientific Document Group et al (2016) 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the european society of cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 37:67–119. https://doi.org/10.1093/eurheartj/ehv317
4. Ghofrani HA, D'Armini AM, Grimminger F, CHEST-1 Study Group et al (2013) Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med 369:319–329. https://doi.org/10.1056/NEJMoa1209657
5. Simonneau G, D'Armini AM, Ghofrani HA et al (2015) Riociguat for the treatment of chronic thromboembolic pulmonary hypertension: a long-term extension study (CHEST-2). Eur Respir J 45:1293–1302. https://doi.org/10.1183/09031936.00087114
6. van Thor MCJ, Ten Klooster L, Snijder RJ, Post MC, Mager JJ (2019) Long-term clinical value and outcome of riociguat in chronic thromboembolic pulmonary hypertension. Int J Cardiol Heart Vasc 22:163–168. https://doi.org/10.1016/j.ijcha.2019.02.004
7. Kim NH, Delcroix M, Jais X et al (2019) Chronic thromboembolic pulmonary hypertension. Eur Respir J. 53(1):1801915. https://doi.org/10.1183/13993003.01915-2018
8. Jaïs X, D'Armini AM, Jansa P et al (2008) Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension: BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension), a randomized, placebo-controlled trial. J Am Coll Cardiol 52:2127–2134. https://doi.org/10.1016/j.jacc.2008.08.059
9. Ghofrani HA, Simonneau G, D'Armini AM, MERIT study investigators et al (2017) Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1): results from the multicentre, phase 2, randomised, double-blind, placebo-controlled study. Lancet Respir Med 5:785–794. https://doi.org/10.1016/S2213-2600(17)30305-3
10. Iglarz M, Bossu A, Wanner D et al (2014) Comparison of pharmacological activity of macitentan and bosentan in preclinical models of systemic and pulmonary hypertension. Life Sci 118:333–339. https://doi.org/10.1016/j.lfs.2014.02.018
11. Khadka A, Singh Brashier DB, Tejus A, Sharma AK (2015) Macitentan: An important addition to the treatment of pulmonary arterial hypertension. J Pharmacol Pharmacother 6:53–57. https://doi.org/10.4103/0976-500X.149151
12. Boss C, Bolli MH, Gatfield J (2016) From bosentan (Tracleer®) to macitentan (Opsumit®): the medicinal chemistry perspective. Bioorg Med Chem Lett 26:3381–3394. https://doi.org/10.1016/j.bmcl.2016.06.014
13. Rich S, Rubin LJ, Abenhail L et al (1998) Executive summary from the world symposium on primary pulmonary hypertension (Evian, France, September 6–10, 1998). The World Health Organization publication via the Internet. https://www.who.int/ncd/cvd/pph.html
14. Delcroix M, Staehler G, Gall H (2018) Risk assessment in medically treated chronic thromboembolic pulmonary hypertension patients. Eur Respir J 52:1800248
15. Lang I, Meyer BC, Ogo T et al (2017) Balloon pulmonary angioplasty in chronic thromboembolic pulmonary hypertension. Eur Respir Rev 26:160119. https://doi.org/10.1183/16000617.0119-2016
16. Aypar E, Alehan D, Karagöz T, Aykan HH, Ertugrul İ (2018) Clinical efficacy and safety of switch from bosentan to macitentan in children and young adults with pulmonary arterial hypertension. Cardiol Young 28:542–547. https://doi.org/10.1017/S1047951117002542
17. Safdar Z, Thakur A, Frost A (2017) Tolerability of switch to macitentan from bosentan in pulmonary arterial hypertension. South

Med J 110:223–228. https://doi.org/10.14423/SMJ.0000000000000607
18. Blok IM, van Riel ACMJ, van Dijk APJ, Mulder BJM, Bouma BJ (2017) From bosentan to macitentan for pulmonary arterial hypertension and adult congenital heart disease: further improvement?. Int J Cardiol 227:51–52. https://doi.org/10.1016/j.ijcard.2016.11.211
19. Delcroix M, Lang I, Pepke-Zaba J et al (2016) Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. Circulation 133:859–871
20. Hughes RJ, Jais X, Bonderman D et al (2006) The efficacy of bosentan in inoperable chronic thromboembolic pulmonary hypertension: a 1-year follow-up study. Eur Respir J 28(1):138–143
21. Ulrich S, Speich R, Domenighetti G et al (2007) Bosentan therapy for chronic thromboembolic pulmonary hypertension. A national open label study assessing the effect of Bosentan on haemodynamics, exercise capacity, quality of life, safety and tolerability in patients with chronic thromboembolic pulmonary hypertension (BOCTEPH-Study). Swiss Med Wkly 137(41–42):573–580
22. Vassallo FG, Kodric M, Scarduelli C et al (2009) Bosentan for patients with chronic thromboembolic pulmonary hypertension. Eur J Intern Med 20(1):24–29
23. Reesink HJ, Surie S, Kloek JJ et al (2010) Bosentan as a bridge to pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. J Thorac Cardiovasc Surg 139(1):85–91
24. Schiess R, Senn O, Fischler M et al (2010) Tobacco smoke: a risk factor for pulmonary arterial hypertension? A case-control study. Chest 138:1086–1092. https://doi.org/10.1378/chest.09-2962
25. Guglin M, Kolli S, Chen R (2012) Determinants of pulmonary hypertension in young adults. Int J Clin Pract Suppl 177:13–19. https://doi.org/10.1111/ijcp.12008
26. Keusch S, Hildenbrand FF, Bollmann T et al (2014) Tobacco smoke exposure in pulmonary arterial and thromboembolic pulmonary hypertension. Respiration 88:38–45. https://doi.org/10.1159/000359972
27. Suntharalingam J, Goldsmith K, Toshner M et al (2007) Role of NT-proBNP and 6MWD in chronic thromboembolic pulmonary hypertension. Respir Med 101:2254–2262
28. Raymond RJ, Hinderliter AL, Willis PW et al (2002) Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. J Am Coll Cardiol 39:1214–1219
29. Benza RL, Gomberg-Maitland M, Miller DP et al (2012) The REVEAL Registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. Chest 141:354–362. https://doi.org/10.1378/chest.11-0676
30. Fares WH, Bellumkonda L, Tonelli AR et al (2016) Right atrial pressure/pulmonary artery wedge pressure ratio: a more specific predictor of survival in pulmonary arterial hypertension. J Heart Lung Transplant 35:760–767. https://doi.org/10.1016/j.healun.2015.12.028
31. Tromeur C, Jaïs X, Mercier O et al (2018) Factors predicting outcome after pulmonary endarterectomy. PLoS ONE 13:e0198198. https://doi.org/10.1371/journal.pone.0198198
32. Nierlich P, Hold A, Ristl R (2016) Outcome after surgical treatment of chronic thromboembolic pulmonary hypertension: dealing with different patient subsets. A single-centre experience. Eur J Cardiothorac Surg 50:898–906
33. Paciocco G, Martinez FJ, Bossone E, Pielsticker E, Gillespie B, Rubenfire M (2001) Oxygen desaturation on the six-minute walk test and mortality in untreated primary pulmonary hypertension. Eur Respir J 17:647–652
34. Inagaki T, Terada J, Yahaba M et al (2018) Heart rate and oxygen saturation change patterns during 6-min walk test in subjects with chronic thromboembolic pulmonary hypertension. Respir Care 63:573–583. https://doi.org/10.4187/respcare.05788
35. Lajoie AC, Lauzière G, Lega JC et al (2016) Combination therapy versus monotherapy for pulmonary arterial hypertension: a meta-analysis. Lancet Respir Med 4:291–305. https://doi.org/10.1016/S2213-2600(16)00027-8
36. Fox BD, Shtraichman O, Langleben D, Shimony A, Kramer MR (2016) Combination therapy for pulmonary arterial hypertension: a systematic review and meta-analysis. Can J Cardiol 32:1520–1530. https://doi.org/10.1016/j.cjca.2016.03.004
37. Ghofrani HA, Humbert M (2014) The role of combination therapy in managing pulmonary arterial hypertension. Eur Respir Rev 23:469–475. https://doi.org/10.1183/09059180.00007314
38. Lajoie AC, Bonnet S, Provencher S (2017) Combination therapy in pulmonary arterial hypertension: recent accomplishments and future challenges. Pulm Circ 7:312–325. https://doi.org/10.1177/2045893217710639