

Bromocriptine for the treatment of peripartum cardiomyopathy: a multicentre randomized study

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Aims

An anti-angiogenic cleaved prolactin fragment is considered causal for peripartum cardiomyopathy (PPCM). Experimental and first clinical observations suggested beneficial effects of the prolactin release inhibitor bromocriptine in PPCM.

Methods and results

In this multicentre trial, 63 PPCM patients with left ventricular ejection fraction (LVEF) $\leq 35\%$ were randomly assigned to short-term (1W: bromocriptine, 2.5 mg, 7 days) or long-term bromocriptine treatment (8W: 5 mg for 2 weeks followed by 2.5 mg for 6 weeks) in addition to standard heart failure therapy. Primary end point was LVEF change (delta) from baseline to 6 months assessed by magnetic resonance imaging. Bromocriptine was well tolerated. Left ventricular ejection fraction increased from $28 \pm 10\%$ to $49 \pm 12\%$ with a delta-LVEF of $+21 \pm 11\%$ in the 1W-group, and from $27 \pm 10\%$ to $51 \pm 10\%$ with a delta-LVEF of $+24 \pm 11\%$ in the 8W-group (delta-LVEF: $P = 0.381$). Full-recovery (LVEF $\geq 50\%$) was present in 52% of the 1W- and in 68% of the 8W-group with no differences in secondary end points between both groups (hospitalizations for heart failure: 1W: 9.7% vs. 8W: 6.5%, $P = 0.651$). The risk within the 8W-group to fail full-recovery after 6 months tended to be lower. No patient in the study needed heart transplantation, LV assist device or died.

Conclusion

Bromocriptine treatment was associated with high rate of full LV-recovery and low morbidity and mortality in PPCM patients compared with other PPCM cohorts not treated with bromocriptine. No significant differences were observed between 1W and 8W treatment suggesting that 1-week addition of bromocriptine to standard heart failure treatment is already beneficial with a trend for better full-recovery in the 8W group.

Clinical trial registration:

ClinicalTrials.gov, study number: NCT00998556.

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Keywords

Peripartum cardiomyopathy • Bromocriptine • Prolactin • heart failure

Introduction

Peripartum cardiomyopathy (PPCM) is increasingly recognized as a major cause of pregnancy related heart failure with high morbidity and mortality.^{1–4} The reported incidence of PPCM is regionally different ranging between 1 per 100 in Nigeria, 1 in 299 in Haiti to 1 in 1149–3189 live births in the USA.^{1,5–7} To date no evidence-based disease specific therapy is available for PPCM. Recommended treatment for PPCM is similar to that of heart failure from other aetiologies based on registry data and expert opinion.^{2,4,8–10} Although the aetiology of PPCM is still under investigation, in recent years a number of contributory mechanisms have been recognized to initiate and propagate the disease.^{1–4} Hereby, high levels of the nursing hormone prolactin and the production of a cleaved 16kDa N-terminal fragment of prolactin have emerged as potential key factors in the pathophysiology of PPCM. Experimental studies suggest that 16kDa prolactin induces profound endothelial damage and subsequent cardiomyocyte dysfunction and full-length prolactin promotes inflammation in PPCM while inhibition of prolactin release by the dopamine-D2-receptor agonist bromocriptine prevents onset of PPCM.^{11–14} Bromocriptine has been used for many years to stop lactation in postpartum women. In addition, prolactin-independent cytoprotective effects of bromocriptine were also shown in various organs including the heart.^{14,15} The strong improvement of cardiac function in previous reports including a clinical pilot study and register-based data demonstrating that prolonged treatment of PPCM patients with bromocriptine is feasible and may improve left ventricular (LV) recovery and clinical outcome^{12,16,17} lend support to the hypothesis that prolonged bromocriptine treatment beyond the cumulative dose to stop lactation might be needed to achieve maximum clinical benefits. We therefore designed this randomized multicentre trial to compare the effects of prolonged bromocriptine treatment vs. short-term treatment sufficient to stop lactation in addition to guideline-based heart failure therapy^{9,10} on LV function and clinical outcomes in patients with PPCM.¹⁸

Methods

The study design has been reported previously.¹⁸

Detailed information on the study protocol and methods are provided in the Supplementary material online.

Results

Screening, inclusion criteria, and randomization of study patients

From June 2010 until September 2015, 140 patients at 12 centres were screened for eligibility. Of these patients, 63 were included in the study while 77 patients did not fulfil the criteria for randomization. Reasons for exclusion were LVEF > 35%, other reasons for heart failure, time since delivery more than 6 months, social reasons,

not agreed to participate in the study, drug abuse, noncompliance and other reasons. All patients included in the study were postpartum. Accordingly, 32 patients were randomly assigned to receive 2.5 mg bromocriptine for 1 week (1W group) and 31 to receive 5 mg bromocriptine for 2 weeks followed by 2.5 mg for 6 weeks (8W group). In the 1W group, three patients withdrew consent after randomization, one was lost to follow-up, one did not undergo valid randomization. An additional patient of the 1W group was not treated according to the protocol but received higher dose of bromocriptine (up to 10 mg) and relevantly longer so that the clinical event committee (CEC) decided to exclude her from all between-groups comparisons of efficacy end points. Therefore, 31 patients per group comprised the efficacy analysis set of patients. In total, 26 patients from the 1W group and 31 from the 8W group completed the study with follow-up data of 6 months after diagnosis (Figure 1). Of these patients, 23 patients from the 1W and 28 patients from the 8W group met the imaging quality standards evaluated by the CEC in order to be taken into consideration for the primary end point (trial profile is shown in Figure 1).

Baseline characteristics of study patients

The characteristics of all randomized patients at baseline (Visit 1) are shown in Table 1. More details about the baseline characteristics are

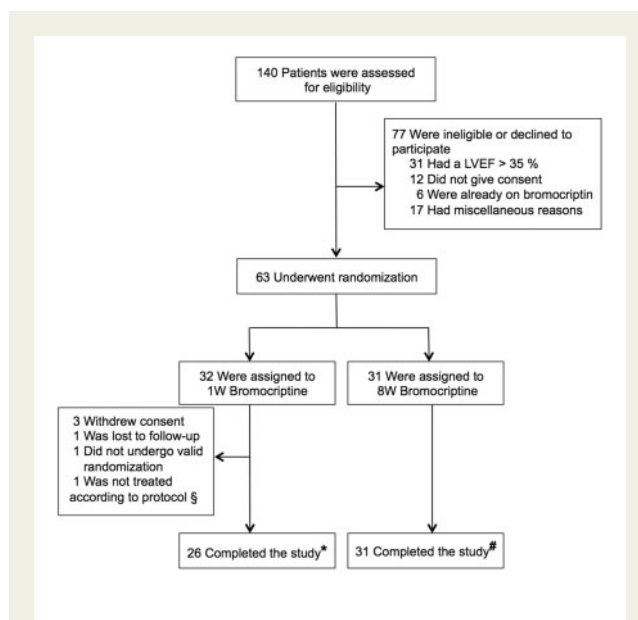


Figure 1 Randomization, treatment, and follow-up of the patients. Left ventricular ejection fraction (LVEF), §patient was excluded from all between-groups comparisons for efficacy; *23 with adequate imaging quality for primary end point. # 28 with adequate imaging quality for primary end point. §One patient was not treated according to protocol and excluded from efficacy analyses.

Table 1 Baseline characteristics of all randomized patients

Characteristic	1W bromocriptine (N = 32)	8W bromocriptine (N = 31)
Age—year	33.8 ± 5.8	34.0 ± 4.5
Median gravida (range)	1.5 (1–7)	2 (1–5)
Median parity (range)	1.5 (1–7)	2 (1–6)
Race or ethnic group—number (%) ^a		
Caucasian	32 (100)	30 (97)
Black	0 (0)	1 (3)
Systolic blood pressure—mmHg	117 ± 18	111 ± 17
Heart rate—beats per minute	90 ± 16	84 ± 12
Body mass index ^b	28.3 ± 6.8	29.0 ± 7.9
Serum creatinine—mg/dL	0.8 ± 0.2	0.9 ± 0.2
Clinical features of heart failure		
Left ventricular ejection fraction—(%)	28 ± 10	27 ± 9
Right ventricular ejection fraction—(%) ^c	48 ± 12	42 ± 13
Median NT-proBNP—pg/mL	2164 (1290–3066)	2437 (1423–4158)
NYHA functional class—number (%) ^d		
I	0 (0)	1 (3.2)
II	4 (12.5)	4 (12.9)
III	10 (31.3)	9 (29.0)
IV	18 (56.3)	17 (54.8)
Medical history—number (%)		
Hypertension	7 (21.9)	11 (35.5)
Diabetes	2 (6.3)	1 (3.2)
Smoker or former smoker	16 (50)	15 (48)
Pregnancy related conditions—number (%)		
Preeclampsia	5 (15.6)	8 (25.8)
Gestational diabetes	3 (9.4)	2 (6.5)
Treatment at randomization—number (%)		
ACE inhibitor	30 (93.8)	27 (87.1)
Angiotensin receptor blocker	3 (9.4)	3 (9.7)
Mineralcorticoid antagonist	27 (84.6)	25 (80.6)
Beta-blocker	29 (90.6)	31 (100)
Diuretic	28 (88.5)	28 (90.3)

Plus-minus values are means ± SD. There were no significant differences between the two groups. Data were missing for the following characteristics: N-terminal pro-B-type natriuretic peptide for 1 patient in the 1W group and 1 in the 8W group, respectively, body-mass index, for 1 patient in the 1W group. Percentages may not total 100 because of rounding. To convert the values for creatinine to micromoles per litre, multiply by 88.4.

IQR, interquartile range; NYHA, New York Heart Association.

^aRace or ethnic group was reported by the investigators.

^bThe body mass index is the weight in kilograms divided by the square of the height in meters.

^cThe data for right ventricular ejection fraction were available for $n = 44$ patients (1W: $n = 20$; 8W: $n = 24$).

^dThe data for NYHA class reflect the status of patients at the time of randomization.

provided in the Supplementary material online, *Appendix Tables S1–S8*. The groups were balanced with respect to baseline characteristics (age, gravida, parity, race, body mass index, haemodynamics, cardiac function New York Heart Association class), cardiovascular and pregnancy-related risk factors. Data for right ventricular ejection fraction (RVEF) as assessed by CMR were available for 44 patients. Baseline RVEF did not differ significantly between 1W ($48 \pm 12\%$, $n = 20$) and 8W ($42 \pm 13\%$, $n = 24$; 1W vs. 8W: $P = 0.20$). The prevalence of impaired RV function (RVEF < 40%) did not differ significantly between both groups (20% in 1W vs. 42% in 8W, $P = 0.19$) although patients in the 8W group tended to have more often impaired RV function at baseline. No patient was diagnosed with PPCM in a

previous pregnancy or was diagnosed during pregnancy. Diagnosis was made 1.6 ± 1.6 months after delivery and average time between first symptoms and diagnosis was 0.8 ± 1.2 months with no difference between groups. All patients were randomized postpartum. Randomization was done no more than 7 days after first diagnosis of PPCM. One patient was of African race, all other were of Caucasian race. Notably, use of guideline-based heart failure therapy including ACE inhibition or angiotensin receptor blocker (ARB), beta-blockade and mineralocorticoid receptor antagonist (MRA)^{9,10} during the study was high and did not differ between both groups (*Table 1*). No patient in the 1W group resumed lactation after bromocriptine treatment.

Change in left ventricular function as primary end point

The LVEF increased from a mean of $28 \pm 10\%$ at baseline to $49 \pm 12\%$ at 6 months in the 1W group ($n = 23$), and from $27 \pm 10\%$ to $51 \pm 10\%$ in the 8W group ($n = 28$) with a between-groups difference at 6-months follow-up of 2.0 [95% confidence limit: -4.2; 8.2]% in favour of the 8W groups. Individual courses are presented in Figure 2A. Delta LVEF was slightly higher in the 8W group ($+24 \pm 11\%$) compared with the 1W group ($+21 \pm 11\%$) but this was not statistically significant ($P = 0.381$) with 2.5 [95% confidence limit: -3.2; 8.3]%. In order to analyse effects of the two treatment concepts in more critically ill patients, a subgroup analysis was performed including only patients in whom baseline LVEF was $<30\%$. As shown in Figure 2B, the LVEF increased from a mean of $21 \pm 6\%$ at baseline to $45 \pm 14\%$ at 6 months in the 1W group ($n = 14$), and from $21 \pm 6\%$ to $50 \pm 11\%$ in the 8W group ($n = 18$) again showing a slightly higher delta LVEF in the 8W subgroup ($+29 \pm 10\%$) as compared with delta LVEF of the 1W subgroup ($+24 \pm 11\%$) which was not statistically significant (8W vs. 1W: $P = 0.222$). Between-groups differences at 6-months follow-up of LVEF change of 4.3 [95% confidence limit: -4.6; 13.2]% and for LVEF change of 4.7 [95% confidence limit: -2.9; 12.4]% in favour of the 8W groups were observed.

Recovery rate of left ventricular function in peripartum cardiomyopathy patients after 6-months follow-up

After 6 months follow-up 52% of the 1W-patients ($n = 32$) showed full functional LV recovery (LVEF $\geq 50\%$), 21% partial recovery (LVEF between 35% and $<50\%$) and 28% no recovery (LVEF $<35\%$), prematurely terminated the trial or had missing LVEF data. In the 8W arm ($n = 31$), the respective rates were 68% for full functional recovery, 25% for partial recovery, and 7% for no recovery. Full recovery rates showed a descriptive benefit for the 8W group (68% compared with 52% in 1W group).

Fisher exact test (two-sided) resulted in $P = 0.283$ and revealed an OR = 0.508 [confidence limit: 0.173, 1.490] showing that—although not significant—the risk within the 8W group to fail ‘full recovery’ after 6 months is reduced.

Change in left ventricular function over time as assessed by echocardiography

We also analysed LVEF determined by echocardiography, which was performed immediately after patients’ inclusion (Visit 1) with sequential performance at 2 weeks (Visit 2), 1 month (Visit 3), 3 months (Visit 4) and 6 months (Visit 5) after randomization (Figure 3B). Echocardiographic recordings meeting the quality standards of the core lab were available from 45 patients displaying a mean baseline LVEF of $23 \pm 7\%$. There was no difference in baseline LVEF measured by echocardiography between the 1W ($23 \pm 7\%$, $n = 21$) and the 8W ($23 \pm 8\%$, $n = 24$) group. After the 6 months follow-up, the absolute improvement (delta LVEF) in the 1W group was $+25 \pm 12\%$ and $+27 \pm 11\%$ in the 8W group, which was not statistically significant ($P = 0.581$).

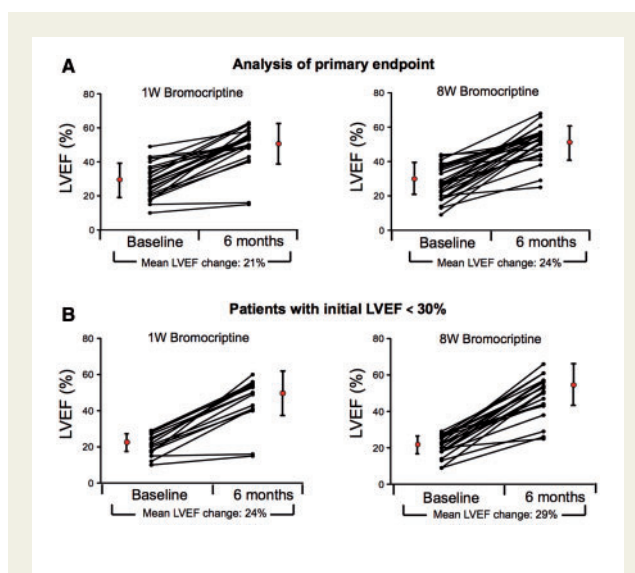


Figure 2 Analyses of global left ventricular ejection fraction (LVEF) change from baseline to 6 months follow-up determined by CMR. (A) Individual courses of LVEF change from baseline to 6-months follow-up in the 1W group ($n = 23$) and 8W group ($n = 28$) with a between-groups difference at 6-months follow-up of 2.0% in favour of the 8W groups ($P = 0.38$). (B) Individual courses of LVEF change from baseline to 6-months follow-up for the subgroup of patients with LVEF $<30\%$ at study entry in the 1W group ($n = 14$) and the 8W group ($n = 18$) with between-groups differences at 6-months follow-up of 4.3% and for LVEF change of 4.7% in favour of the 8W groups ($P = 0.22$).

Secondary end points of study outcome

Secondary end points were hospitalization for heart failure, cardiac transplantation, and death of patient during trial, or combinations of these conditions (Table 2). Among the patients of the 1W group 3 of 31 (=9.7%) and among the patients of the 8W group 2 of 31 (=6.5%) were hospitalized for heart failure until the end of study (Table 2). Only one patient was listed for transplantation during the trial but was removed from the waiting list at follow-up due to improvement of the clinical condition and cardiac function. None of the patients received a left ventricular assist device (LVAD) or a heart transplantation, and no patient died. Altogether, the secondary end points of clinical events did not significantly differ between treatment groups ($P = 0.651$).

Safety of study treatment

A total of six serious adverse events (SAEs) in four patients were reported, and all SAEs occurred in patients of the 1W group (Table 3). Therefore, no dose relationship can be concluded from the results. For three of the SAEs, causality was considered possible with respect to treatment with bromocriptine. In all three cases, SAE occurred after termination of bromocriptine therapy. These SAEs included two venous embolisms and one peripheral artery occlusion. A complete list of all adverse events (AEs) and adverse reactions is provided in the Supplementary material online, Appendix Tables S12–S14.

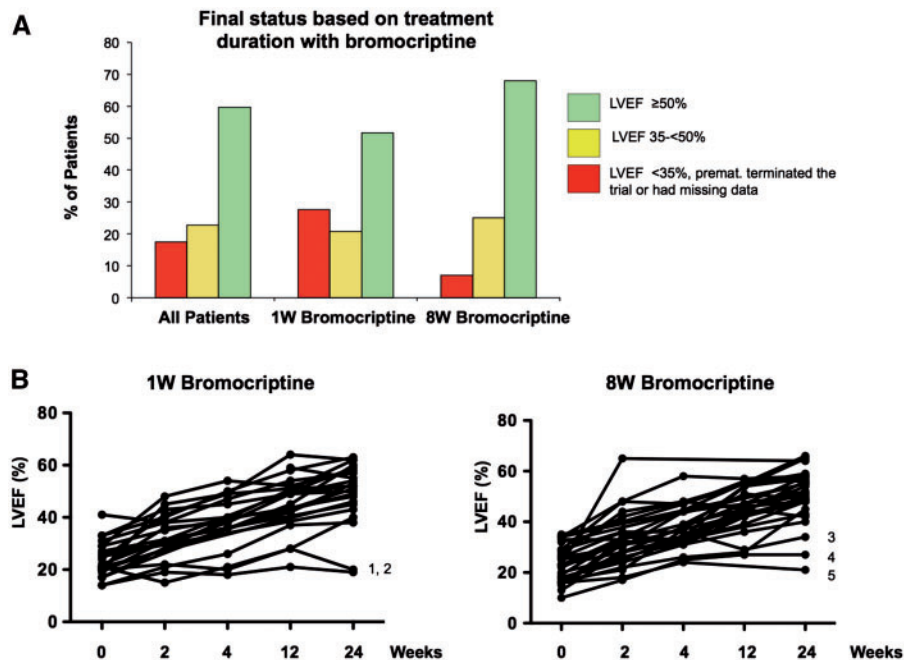


Figure 3 Outcome of patients at 6-months follow-up. (A) Left ventricular ejection fraction (LVEF) at 6-months follow-up according to predefined categories in all patients of the present study (treated 1W, $n = 32$ or 8W, $n = 31$ with bromocriptine, baseline LVEF <35%). Red columns illustrate the percentage of patients with no recovery (event or final LVEF <35%, prematurely terminated the trial or had missing LVEF data), yellow columns illustrate the percentage of patients with partial recovery (final LVEF 35% to <50%) and green columns depict percentage of women with complete recovery (final LVEF $\geq 50\%$). (B) Step-wise change in LVEF measured by echocardiography during follow-up period in the 1 W ($n = 21$) and the 8W group ($n = 24$). The number 1–5 marks time course of the five patients who did not recover LVEF >35% after 6-months. However, after ≥ 12 months Number 1 displayed a LVEF = 62%, 2 a LVEF = 47%, 3 and 4 a LVEF = 50%, and 5 a LVEF = 15%.

Comparison of outcome with IPAC study

As a limitation of our study, we do not have a placebo control group because it was considered unethical given the results of previous registry data and pilot studies^{12,16,17} and the risk for mastitis for stopping lactation without medical support. We therefore compared a subgroup of our collective characterized by a baseline LVEF <30% (echocardiography) with a subgroup of PPCM patients with a baseline LVEF <30% (echocardiography) from the Investigation in Pregnancy Associate Cardiomyopathy (IPAC) collective, which has been analysed over the same time period and obtaining comparable standard therapy for heart failure but no bromocriptine.¹⁹ In the IPAC subgroup ($n = 27$ patients), 37% remained in severe heart failure after a follow-up period of 6–12 months. In addition, the rate of transplantation and/or use of LVAD was 19%, and the mortality rate was 15% (Table 4). In the present study, 37 patients ($n = 18$ in the 1W and $n = 19$ in the 8W group) displayed a baseline LVEF <30% with at least 6-months follow-up. No patient in the 1W or the 8W group died, needed heart transplantation or a LVAD (Table 4). In the 1W group two and in the 8W group three patients did not recover LVEF above 35% after 6 months. Follow-up analyses after ≥ 12 months were available for these five patients showing that three patients displayed complete recovery (LVEF $\geq 50\%$), and one patient showed substantial recovery with an LVEF of 47% and only one patient in the

8W group remained in severe heart failure (Table 4). However, this patient showed poor adherence to standard heart failure medication during follow-up.

Discussion

Our study is the first prospective, randomized, and multicentre trial at adequate size to test short- vs. long-term inhibition of prolactin by bromocriptine as a causal therapy for PPCM. It demonstrates that inhibition of prolactin release with long-term or short-term bromocriptine in addition to standard therapy for heart failure in patients with severe forms of PPCM is associated with a high recovery rate and very low rate of adverse outcome. In fact no patient died or needed a heart transplantation or a LVAD and full recovery rate was higher than in any ever published PPCM collective.^{3,6,16,20–26} In addition, our study population tolerated bromocriptine well suggesting that both, short- and long-term application appear to be safe since attention was paid to ensure sufficient anticoagulant therapy during treatment. The study did not detect a significant benefit for prolonged inhibition of prolactin release with bromocriptine in addition to standard therapy for heart failure in increasing LVEF or reducing hospitalization for heart failure compared with short-term

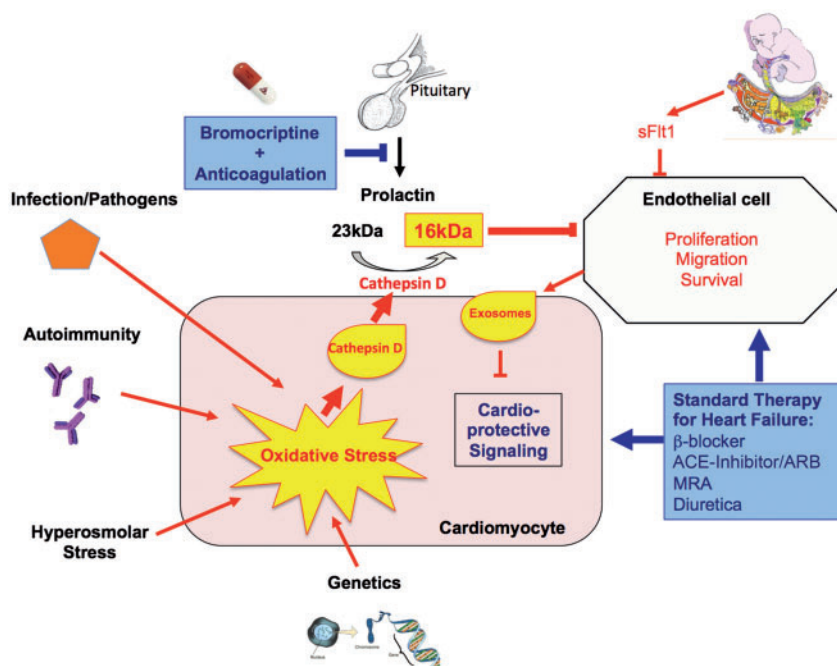


Figure 4 Disease specific therapy with bromocriptine. Scheme depicting inducers of increased oxidative stress in the peripartum maternal heart that mediate the generation of antiangiogenic 16kDa prolactin from the nursing hormone prolactin which drives PPCM as well as the hypothetical mechanisms how the prolactin release blocker bromocriptine together with standard heart failure medication interferes with it.

Table 2 Effect of treatment on secondary end points

End point	1W bromocriptine (N = 31) ^a	8W bromocriptine (N = 31)	P-value
Hospitalization for heart failure	3 (9.7)	2 (6.5)	0.651
Cardiac transplantation	0 (0)	0 (0)	n.a.
Death of patient during trial period	0 (0)	0 (0)	n.a.
Combination of hospitalization for heart failure, cardiac transplantation or death	3 (9.7)	2 (6.5)	0.651

Data are numbers of events (%).

^aOne patient of the 1W group who was not treated according to the protocol but received higher dose of bromocriptine (up to 10 mg) for a relevantly longer time was excluded from the endpoint analysis.

bromocriptine application sufficient to stop lactation in patients with PPCM. However, we observed a trend for more patients reaching full recovery after 6 months in the 8W group suggesting a small benefit of prolonged bromocriptine treatment.

Despite advances in understanding the pathomechanisms of PPCM, clinical trials testing disease-specific therapeutics beyond standard therapy for heart failure in this condition are scarce.^{2,4,8–10} The nursing hormone prolactin and specifically its cleaved 16kDa form is considered to play a key role in the pathophysiology of PPCM (Figure 4).^{12,13,16,17} However, unlike the placebo controlled study by Sliwa et al.¹⁷ the present study was not designed to compare bromocriptine therapy with placebo but to compare two different dose

regimes of bromocriptine in severely diseased PPCM patients: A short-term regime that is sufficient to suppress lactation and a long-term regime that may exert additional cardioprotective effects.

The primary end point of our study, the global improvement in LVEF at 6 months, was not significantly different among the short-term and long-term bromocriptine groups, although the long-term treatment descriptively showed a higher rate of predefined full LV recovery. It is important to note, that the overall outcome among all patients enrolled in this study was better than the outcome of any prospective study on PPCM reported so far: Only 7% of all patients remaining in the study with complete data sets were still in severe LV dysfunction (EF <35%) at 6-months follow-up and only 3% remained

Table 3 Incidence of serious adverse events during the study by system organ class

System organ class	1W bromocriptine (N = 32) ^a	Relation to bromocriptine	8W bromocriptine (N = 31)	P-value
Cardiac disorders				
Coronary artery occlusion ^b	1 (3.2)	Not related	0(0)	1.000
Musculoskeletal disorders				
Chest pain	1 (3.2)	Unlikely related	0(0)	1.000
Respiratory disorders				
Dyspnoea	1 (3.2)	Unlikely related	0(0)	1.000
Vascular disorders				
Venous Embolism	2 (6.4)	Possibly related	0(0)	0.491
Peripheral artery occlusion	1 (3.2)	Possibly related	0(0)	1.000

Data are numbers of events (%).

^aThe one patient of the 1W group who was not treated according to the protocol but received higher dose of bromocriptine (up to 10 mg) for a relevantly longer time was included in the safety analyses.

^bOcclusion was due to air embolism as a complication during coronary angiography.

Table 4 Effect of treatment on outcome in peripartum cardiomyopathy patients with left ventricular ejection fraction <30% in the bromocriptine study (treated either with 1W or 8W bromocriptine) compared with the IPAC study without bromocriptine treatment¹⁹

Follow-up characteristics	1W bromocriptine baseline LVEF <30% (n = 18)	8W bromocriptine baseline LVEF <30% (n = 19)	1W and 8W bromocriptine baseline LVEF <30% (n = 37)	IPAC study placebo baseline LVEF <30% (n = 27)
LVEF <35%	0% (0/18)	5% (1/19)	3% (1/37)	37%
LVEF 35–49%	22% (6/18)	37% (7/19)	35% (13/37)	26%
Full recovery, LVEF ≥50	67% (12/18)	58% (11/19)	62% (23/37)	37%
LVAD and HTX	0% (0/18)	0% (0/19)	0% (0/37)	19% (5/27)
Death	0% (0/18)	0% (0/19)	0% (0/37)	15% (4/27)

LVEF was analysed by echocardiography in the core labs of both studies. Follow-up in the IPAC study was 12 months, follow-up in our study was at 6–36 months. LVEF, left ventricular ejection fraction; LVAD, left ventricular assist device; HTX, heart transplantation.

in heart failure thereafter. Moreover, none of the patients experienced a major adverse event including death, cardiac transplantation or LVAD implantation. It has to be noted that all patients were randomized no longer than 7 days after first diagnosis in a severe disease state (LVEF ≤35%), thereby no selection for more stable patients was ensured. In a comparable group of patients in Germany, we previously reported a 15% treatment failure in a German registry with prospective data of 96 PPCM patients despite standard heart failure drug therapy.^{1,16} Importantly, in the German registry the percentage of patients with persistent severe LV dysfunction was significantly higher among those patients who did not receive bromocriptine. The rate of maternal major adverse events among all patients in the German registry was 10% with a mortality rate of 2%. Interestingly, in the recent prospective North American IPAC study including PPCM patients with LVEF <45% a comparable event rate of 7% and a mortality rate of about 4% were reported.¹⁹ In the IPAC study a subgroup of severely diseased patients with an LVEF <30% was analysed of whom 37% reached an LVEF ≥50% (full recovery) and an equal number, 37% experienced a major event (transplantation/LVAD: 19% or death: 15%) or a final LVEF <35%.¹⁹ We

identified a similar subgroup in our study that presented with a baseline LVEF <30%, that however displayed a substantially better outcome (62% full recovery and 0% LVAD, HTX or death, only 3% with persistently LVEF <35%). Although this indirect comparison has to be interpreted with caution given some differences in the population characteristics, in particular the proportion of patients with African origin (2% in our study vs. 27% in the IPAC study) for whom prognosis might be worse,²¹ it seems to further support the view that there is a benefit of bromocriptine treatment. In fact, also in non-African countries, i.e. for example in Turkey, mortality rates for PPCM between 25 and 30% were reported.²⁰ In view of these studies, a treatment concept that combines short-term low dose bromocriptine with standard heart failure therapy, as evaluated in the present study, appears to be associated with a better outcome, although a number of factors have to be taken into account which may have an impact on patient outcome, such as different ethnicities with potentially different genetic dispositions and different medical care opportunities.

An important reason for the beneficial effect of bromocriptine treatment may also be the associated ab lactation which enables early

optimal heart failure treatment with beta-blockade, ACE inhibition, MRA, and ivabradine.^{2,8,27} No controlled studies have ever analysed the potential adverse effects of heart failure medication transferred to the infant in the breast milk, whereas normal growth percentiles and no adverse outcome were observed for the infants of PPCM patients in South Africa who terminated breastfeeding.¹⁷ Thus, terminating breastfeeding with bromocriptine appears to be safe for the child and may enable implementation of early intensive heart failure therapy at high dosages associated with faster recovery of the mother enabling her to better care for her newborn.

Some concerns have been raised about a potential risk for cerebral and cardiovascular complications in patients treated with high doses of bromocriptine.^{28,29} However, our observation that no adverse event associated with bromocriptine occurred during bromocriptine treatment in both groups suggests that bromocriptine (together with anticoagulant therapy) is safe and potentially effective in PPCM patients although the optimal dosage and duration of therapy to achieve maximal cardioprotective effects still remains a matter of investigation. Future studies should also explore whether extended prophylactic anticoagulation beyond the period of bromocriptine treatment is required in these patients with a considerable risk of thromboembolism.

Recent nation-wide observations and population-based studies estimated a rise in incidence of PPCM worldwide,^{5–7} emphasizing that future research should focus on investigating preventive strategies. Moreover, modern echocardiography and cardiac magnetic resonance imaging have broadened the phenotypic profile of PPCM showing for example, that in about one-third of PPCM patients the right ventricle is affected by the disease with lower likelihood to recover despite optimal therapy.³⁰ The phenotypic heterogeneity of this disease with variable outcome may reflect additional contributing factors such as genetic or (auto-)immune mechanisms^{31,32} that may determine the course of disease and the clinical outcome. Thus, the challenge of future research will be to elaborate specific therapeutic concepts for patients who are likely to be refractory to current treatment options. Since improvement of LV function was similar between the two bromocriptine regimens, an outcome study testing the concept appears worthwhile. Currently, our own experience suggests that critically ill patients (baseline LVEF <25%, cardiogenic shock) may profit from a prolonged treatment with a higher initial dosage of bromocriptine (see Supplementary material online, Figure S1), a feature that is also supported by the trend for faster full-recovery in the 8W group. This hypothesis needs to be scrutinized in a prospective randomized outcome trial.

In conclusion, the findings of our study further support a potential benefit of bromocriptine in addition to standard heart failure therapy and best supportive care in PPCM patients (Figure 4). It appears that a short low dose bromocriptine therapy aiming to stop lactation is sufficient in most forms of PPCM. However, the limited numbers of patients available in single countries warrant large international prospective registries, i.e. PPCM EORP registry [ESC EURObservational Research Programme (<http://www.eorp.org>)], to get further insights into the efficiency of treatment strategies.

Manufacturer of the study drug

AbZ-Pharma GmbH

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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