

Bromocriptine for the treatment of peripartum cardiomyopathy: welcome on BOARD

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This editorial refers to ‘Bromocriptine for the treatment of peripartum cardiomyopathy: a multicentre randomized study’, by D. Hilfiker-Kleiner, doi: 10.1093/eurheartj/ehx355.

Peripartum cardiomyopathy (PPCM), according to the actual definition proposed by the Study Group on PPCM of the Heart Failure Association of the European Society of Cardiology (ESC), is an idiopathic cardiomyopathy frequently presenting with left ventricular (LV) systolic dysfunction (LV ejection fraction <45%) towards the end of pregnancy or in the months following delivery in the absence of other causes.¹ The most common clinical presentation consists of acute heart failure (AHF) occurring in the first weeks after delivery.

The worldwide burden of PPCM is estimated based on single-centre case series from Haiti, South Africa, and the USA showing incidences ranging from ~1:3000 to 1:100 pregnancies. Women of African origin display a significantly higher risk of developing PPCM.² The clinical outcome of women with PPCM seems to vary across the world, probably because of differences in ethnic and social factors and access to AHF treatment, but also due to heterogeneity in the inclusion criteria in the studies. Accordingly, reported mortality rates may vary from <5% up to 50%. Moreover, despite the fact that several publications reported rapid recovery of LV function (within 6 months after diagnosis) in the majority of patients,³ other studies reported delayed LV recovery in a significant proportion of patients.⁴ Notably, Afro-American women showed lower rates of recovery and worse prognosis compared with Caucasians.⁴ New insights into the epidemiology and outcome of PPCM from the EURObservational Research Programme of the ESC may, however, suggest comparable outcome between European and non-European regions.⁵

The management of women presenting with AHF due to PPCM remains very challenging. The initial treatment depends on the time point of onset and the ability to have a diagnosis. Women presenting with PPCM during pregnancy require joint cardiac and obstetric care, because therapeutic interventions need always to consider the health of both the mother and the foetus. Women presenting after delivery

can generally be treated according to the ESC Guidelines for heart failure.⁶ Very recently, the Study Group on PPCM of the Heart Failure Association of the ESC published a practical guidance paper on the management of acute PPCM patients.⁷

The treatment of post-partal AHF due to PPCM consist—similarly to other forms of AHF—of (i) decongestive treatment via vasorelaxing agents, diuretics, and non-invasive ventilation to improve symptoms and reduce organ dysfunction; (ii) neuro-humoral inhibition via oral heart failure therapies (e.g. beta-blockers, ACE inhibitors, and mineralocorticoid receptor antagonists) to improve LV recovery and outcome; and (iii) in selected patients, device therapy to reduce symptoms and improve outcome. Ideally, a specific pathophysiology-directed therapy should complete the treatment: for that purpose, knowledge of mechanisms involved in disease onset is required.

The paper by Hilfiker-Kleiner *et al.* in this issue of the journal confirmed that PPCM should be treated with bromocriptine as specific aetiological therapy for PPCM.⁸ In recent years, multiple mechanisms, in addition to general cardiovascular risk and pregnancy-related factors, have been described as having a role in the aetiology of PPCM, albeit that the exact pathophysiology remains poorly understood.⁹ A ‘double-hit’ model of angiogenic imbalance in the heart during the peripartal period has been proposed, combining systemic antiangiogenic signals during late pregnancy and host susceptibility through insufficient local proangiogenic defences in the heart.^{1,10–12} Evidence of dysregulated plasma levels of pro- and antiangiogenic factors supports early diagnosis of PPCM.¹² Angiogenic imbalance can further be triggered by oxidative stress activating cathepsin D, a protease responsible for the cleavage of the nursing hormone prolactin into the angiostatic and proapoptotic 16 kDa subfragment.¹³ In a previous mouse model, suppression of prolactin production prevented the onset of PPCM.¹³

Bromocriptine, a substance used for many years to stop lactation in post-partum women by suppressing prolactin production, was evaluated as adjunctive treatment of PPCM in a proof-of-concept clinical study.¹⁴ Hence, in an open-label study, 20 women with severe acute PPCM were randomized to receive either standard heart fail-

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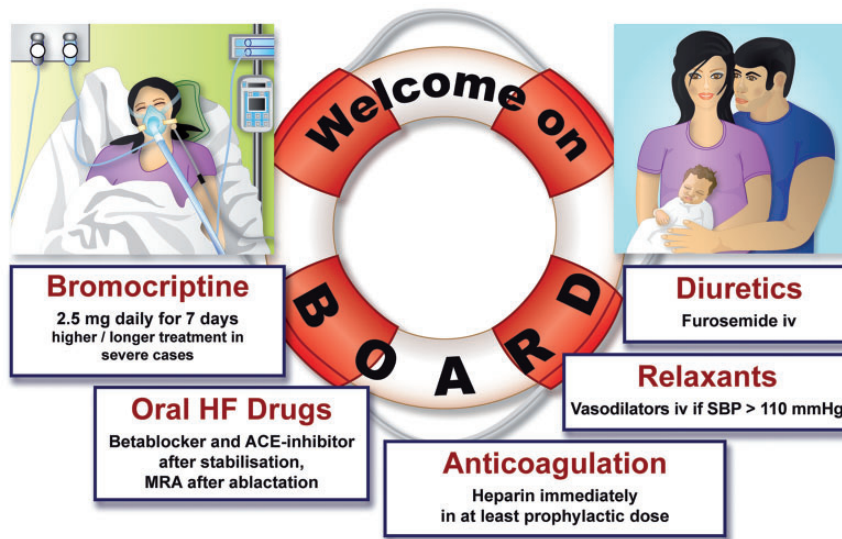


Figure 1 The BOARD therapies for acute peripartum cardiomyopathy (PPCM). The treatment of PPCM, should consists of Bromocriptine, Oral heart failure therapies, Anticoagulation, vasoRelaxing agents, and Diuretics. Non-invasive ventilation should be added in patients with pulmonary congestion.

ure treatment alone or standard treatment plus bromocriptine for 8 weeks (2.5 mg twice daily for 2 weeks followed by 2.5 mg daily for 6 weeks). At 6 months, the recovery of LV ejection fraction was greater in the bromocriptine group compared with the standard group (from 27% to 58% vs. from 27% to 36%, respectively, $P = 0.012$). Whether prolonged treatment with bromocriptine beyond the cumulative dose to stop lactation might be needed to achieve maximal clinical benefits was unknown to date. The present randomized study by Hilfiker-Kleiner *et al.*, by comparing two different dose regimes of bromocriptine (2.5 mg daily for 1 week vs. 5 mg daily for 2 weeks followed by 2.5 mg daily for 6 weeks) in severe PPCM patients, addressed this question. The particular design of this study, lacking a placebo arm, did not test—in a larger cohort compared with the previous proof-of-concept study—the benefit of added bromocriptine to standard oral heart failure therapy. However, women included in this study displayed a high LV recovery rate at 6 months, confirming a beneficial association between the use of bromocriptine in acute PPCM and clinical outcome. The improvement in LV ejection fraction was similar in the short-term (one week) and long-term (8 weeks) bromocriptine groups, albeit that a trend, not statistically significant, for more patients reaching full recovery at 6 months was found in the long-term group. Based on these data, the optimal bromocriptine regimen has still to be determined, and further studies are needed. As suggested by Hilfiker-Kleiner *et al.*, bromocriptine-induced ablation may have another benefit that is to allow the introduction of oral heart failure therapies without harming the newborn. Indeed, several drug classes are contraindicated during lactation because of safety concerns (e.g. mineralocorticoid-receptor antagonists and sacubitril/valsartan).

Bromocriptine treatment should always be accompanied by anticoagulation, with heparin at least at prophylactic dose, to reduce the

thrombo-embolic risk. Indeed, bromocriptine was suspected to be associated with thrombotic events.¹⁵ Despite low rates of adverse events associated with bromocriptine therapies in the study of Hilfiker-Kleiner *et al.*, 2 out of 63 patients developed thrombo-embolic events, exclusively in the 1-week treatment group, after bromocriptine was stopped. This could be related to a rebound effect because prolactin was not blocked for a sufficient time. This rate is surprisingly much lower than the 6.8% of thrombo-embolic events recently published.⁵ Thrombo-embolic events in young mothers, especially arterial emboli, are often dramatic and can lead to stroke or arm/leg amputation or death. Future studies should aim to suppress all thrombo-embolic events whether related to PPCM, bromocriptine, or both. Studies should assess whether a longer period of anticoagulation and/or starting at therapeutic dose may suppress those events.

Taken together, we urge international societies of cardiology to update recommendations on management of PPCM. A recent survey from the Heart Failure Association of the ESC showed that clinical parameters of PPCM were similar between ESC and non-ESC countries, while treatment management was heterogeneous.⁵ We propose to regroup all essential and concomitant therapies under the BOARD label: Bromocriptine, Oral heart failure therapies, Anticoagulants, vasoRelaxing agents, and Diuretics. In the study of Hilfiker-Kleiner *et al.*, the BOARD treatment regimen was successfully tested in Germany, mostly in Caucasian patients. Whether the BOARD regimen may also be beneficial in patients from other continents is unknown and should be tested in future studies.

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