A search for targeted therapy for PPCM

The REBIRTH trial

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Bromocriptine for the treatment of PPCM

How did the story begin?

A Cathepsin D-Cleaved 16 kDa Form of Prolactin Mediates Postpartum Cardiomyopathy

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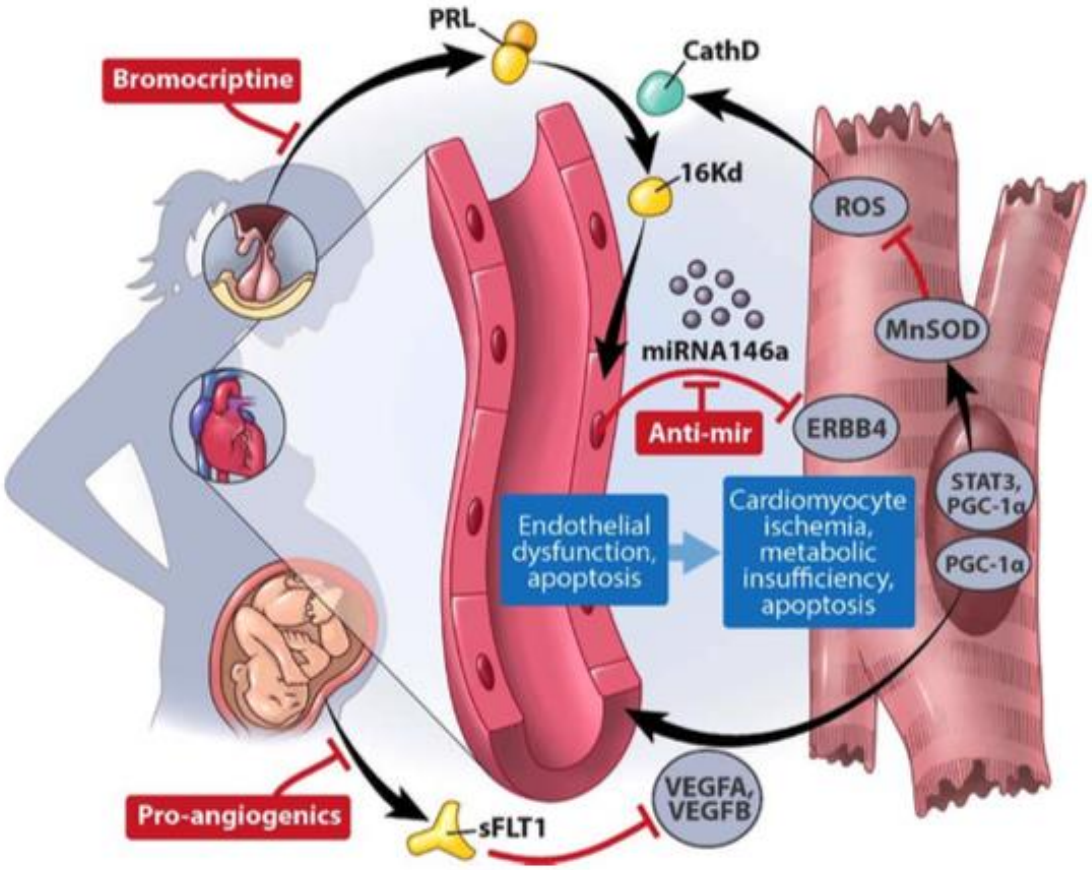
DOI 10.1016/j.cell.2006.12.036

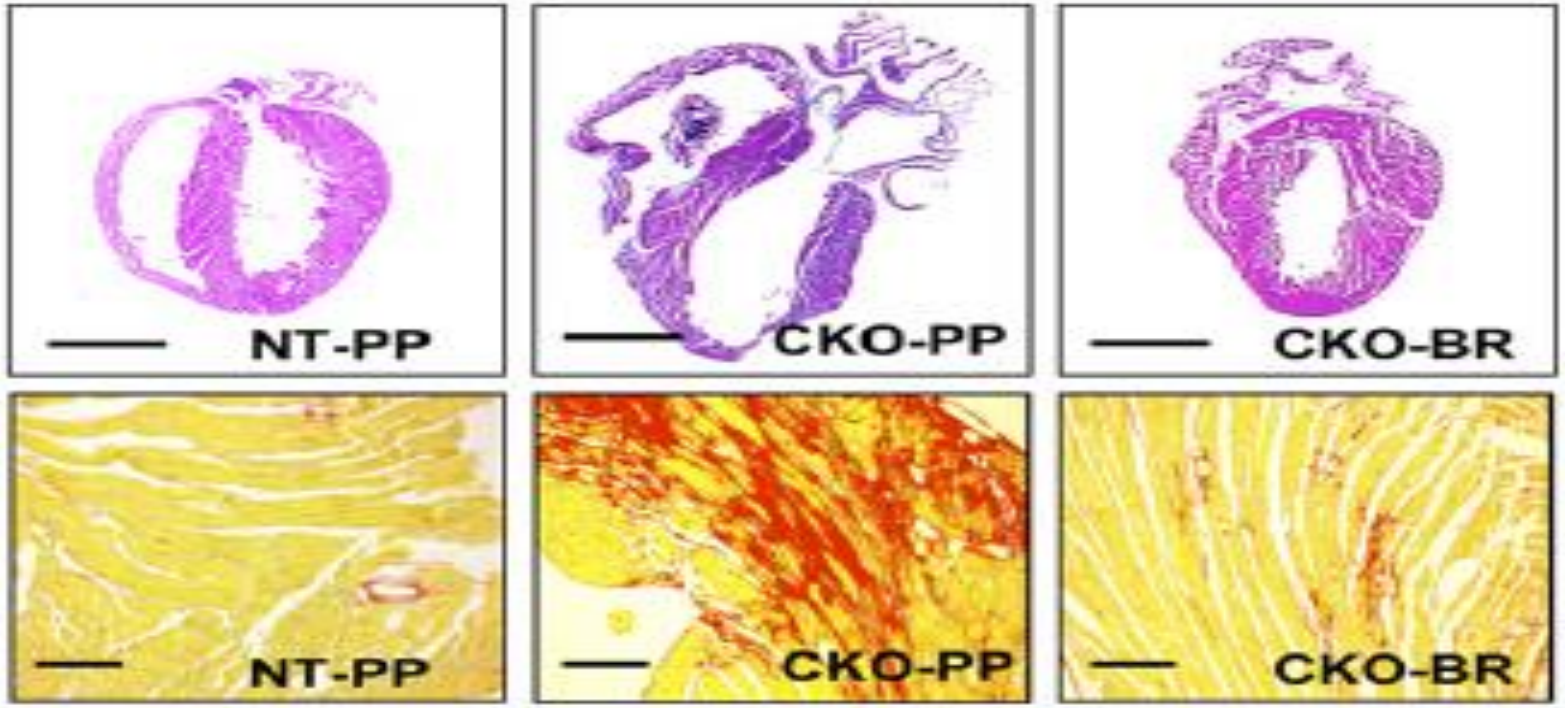
Vasculo-hormonal hypothesis of the pathophysiology of PPCM

Arany Z & Elkayam U Circulation 2016; 133:1397-1409.



A Cathepsin D-Cleaved 16 kDa Prolactin Mediates PPCM

Hilfiker-kliner d et al Cell 2007;128:589



Cardiac angiogenic imbalance leads to peripartum cardiomyopathy

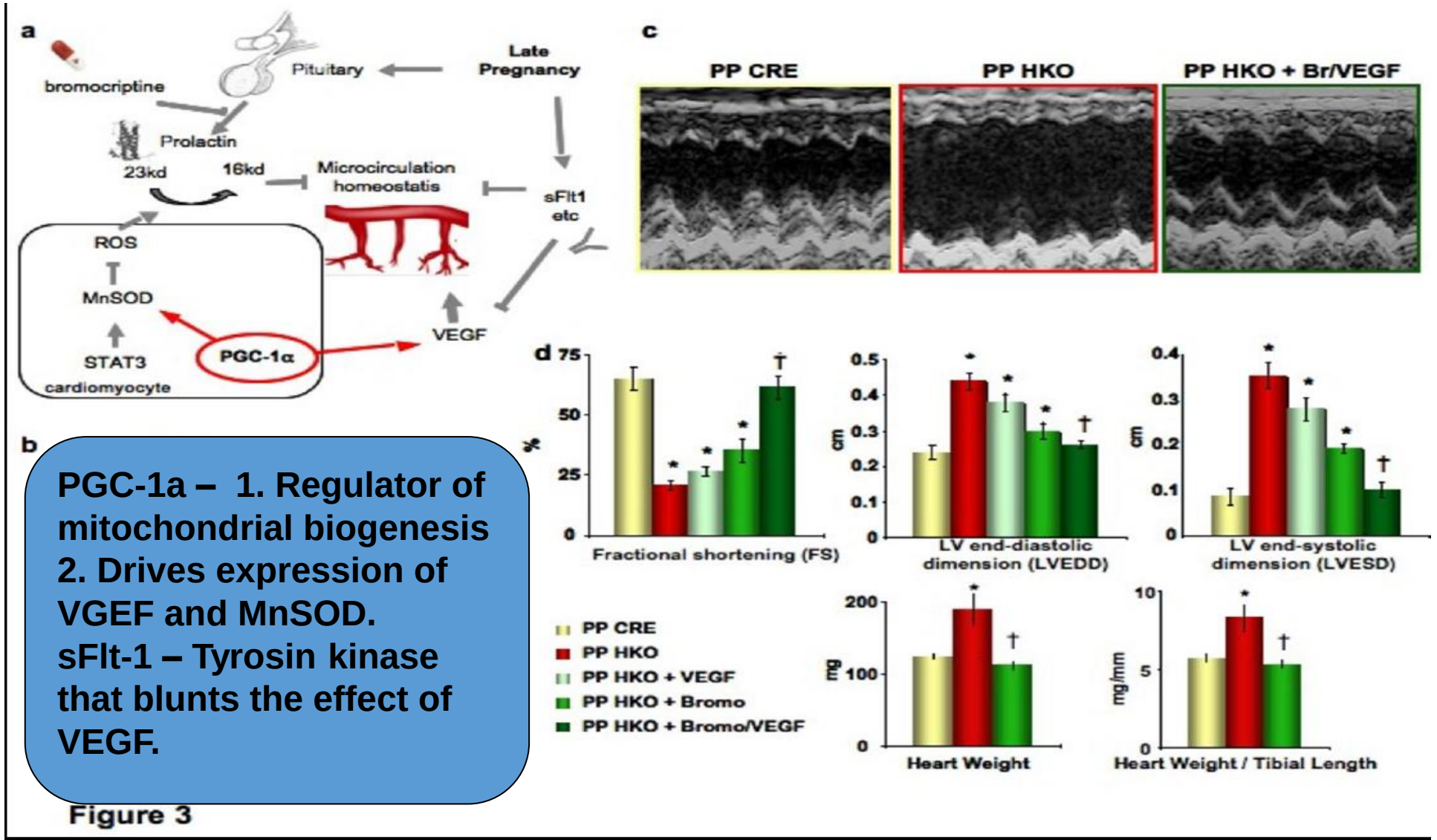
Ian S. Patten[1,2]*, Sarosh Rana[3]*, Sajid Shahul[4], Glenn C. Rowe[1], Cholsoon Jang[1], Laura Liu[1], Miche
John Mitchell[4], Feroze Mahmood[4], Philip Hess[4], Caitlin Farrell[1], Nicole Koulisis[1], Eliyahu V. Khanl
Igor Tudorache[6], Johann Bauersachs[7], Federica del Monte[1], Denise Hilfiker-Kleiner[7], S. Ananth K

Nature 2012;485:333

Peripartum cardiomyopathy (PPCM) is an often fatal disease that affects pregnant women who are near delivery, and it occurs more frequently in women with pre-eclampsia and/or multiple gestation. The aetiology of PPCM, and why it is associated with pre-eclampsia, remain unknown. Here we show that PPCM is associated with a systemic angiogenic imbalance, accentuated by pre-eclampsia. Mice that lack cardiac PGC-1α, a powerful regulator of angiogenesis, develop profound PPCM. Importantly, the PPCM is entirely rescued by pro-angiogenic therapies. In humans, the placenta in late gestation secretes VEGF inhibitors like soluble FLT1 (sFLT1), and this is accentuated by multiple gestation and pre-eclampsia. This anti-angiogenic environment is accompanied by subclinical cardiac dysfunction, the extent of which correlates with circulating levels of sFLT1. Exogenous sFLT1 alone caused diastolic dysfunction in wild-type mice, and profound systolic dysfunction in mice lacking cardiac PGC-1α. Finally, plasma samples from women with PPCM contained abnormally high levels of sFLT1. These data indicate that PPCM is mainly a vascular disease, caused by excess anti-angiogenic signalling in the peripartum period. The data also explain how late pregnancy poses a threat to cardiac homeostasis, and why pre-eclampsia and multiple gestation are important risk factors for the development of PPCM.

Cardiac Angiogenic Imbalance Leads to PPCM

Patten IS et al, Nature 2012;485:333

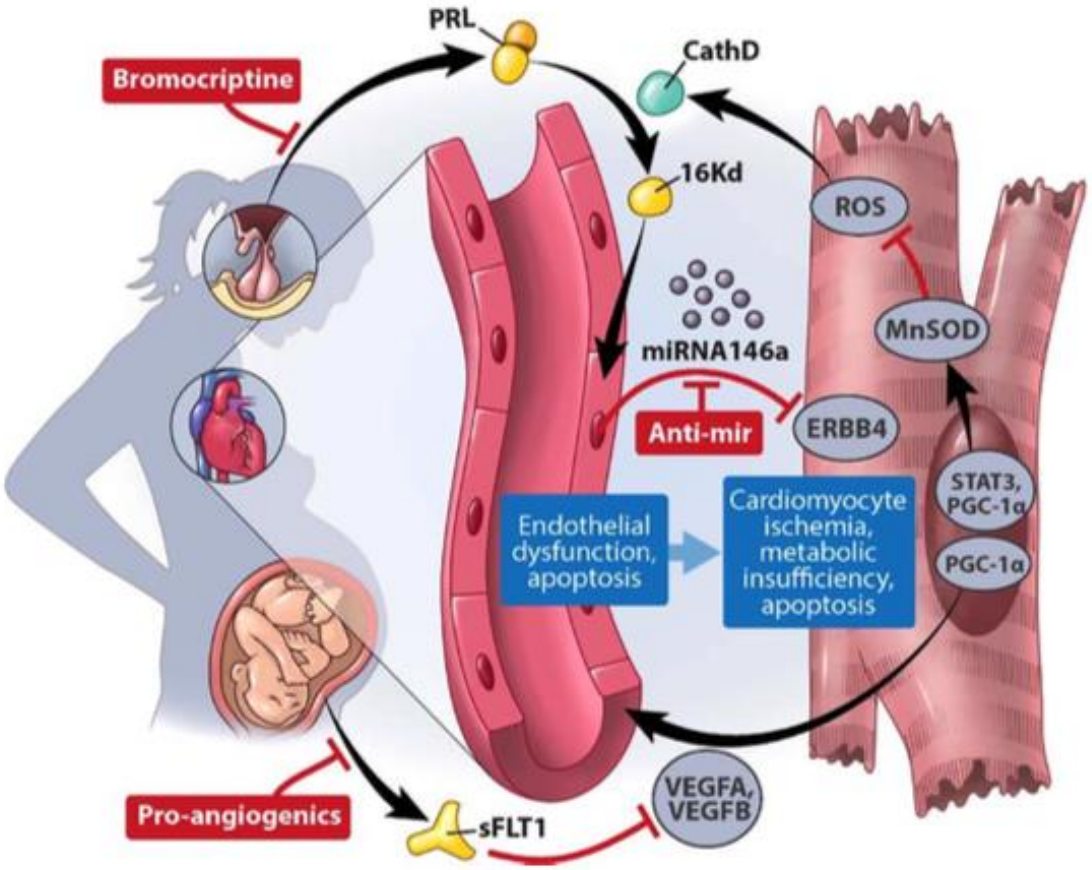


PGC-1a – 1. Regulator of mitochondrial biogenesis 2. Drives expression of VGEF and MnSOD.
sFlt-1 – Tyrosin kinase that blunts the effect of VEGF.

Figure 3

Vasculo-hormonal hypothesis of the pathophysiology of PPCM

Arany Z & Elkayam U Circulation 2016; 133:1397-1409.



Bromocriptine in mice induced PACM

- 2 elegant studies demonstrating the development of PACM similar to human PPCM.
- Prolactin 16 kDa seems to play a major role in causing myocardial dysfunction due to apoptosis, cell damage, endothelial dysfunction and decreased capillary density.
- Bromocriptine either prevented the development of CM or partially recovered cardiac function.

Use of Bromocriptine for Treatment of PPCM : Are We There Yet?

TRENDS IN CARDIOVASCULAR MEDICINE 25 (2015) 505–507

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ScienceDirect

www.elsevier.com/locate/tcm

Editorial Commentary

"Of mice and (wo)men": The need to confirm results of animal experimentations with solid clinical data

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[a]*Heart Institute, Kaplan Medical Center, Rehovot, affiliated to the Hebrew University, Jerusalem, Israel*
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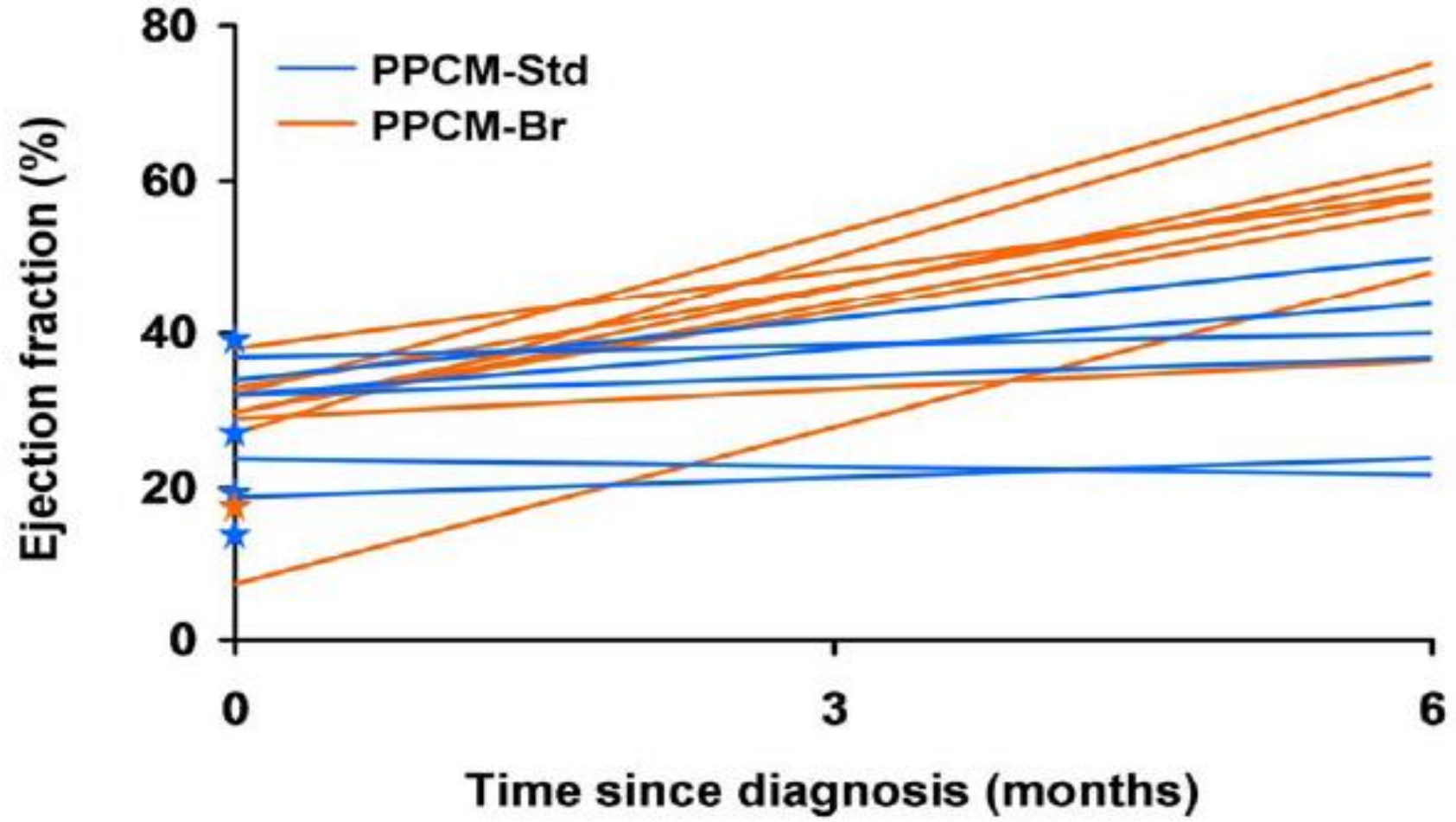
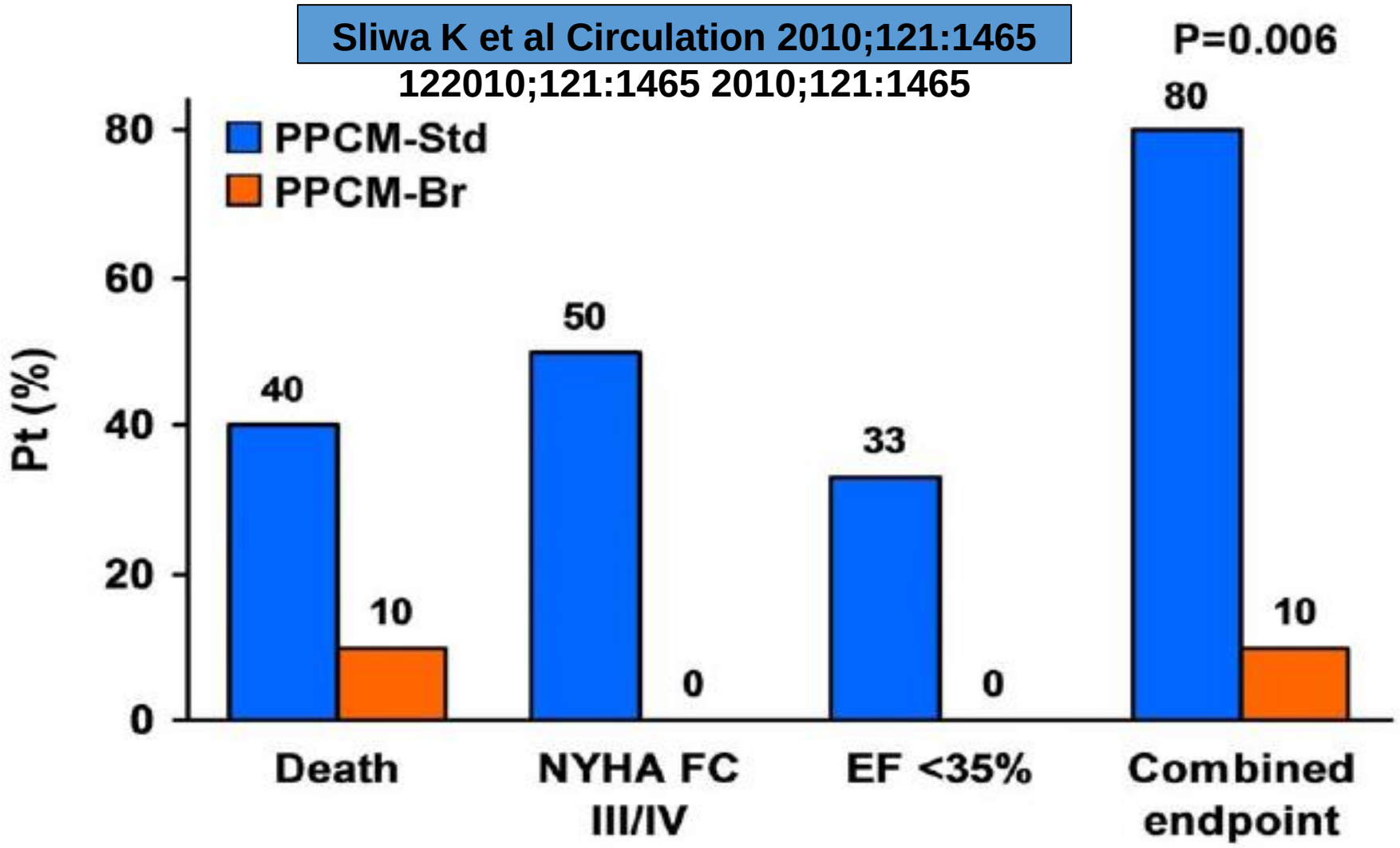
Bromocriptine in The Treatment of PPCM: Proof of concept

Sliwa K et al Circulation 2010;121:1465



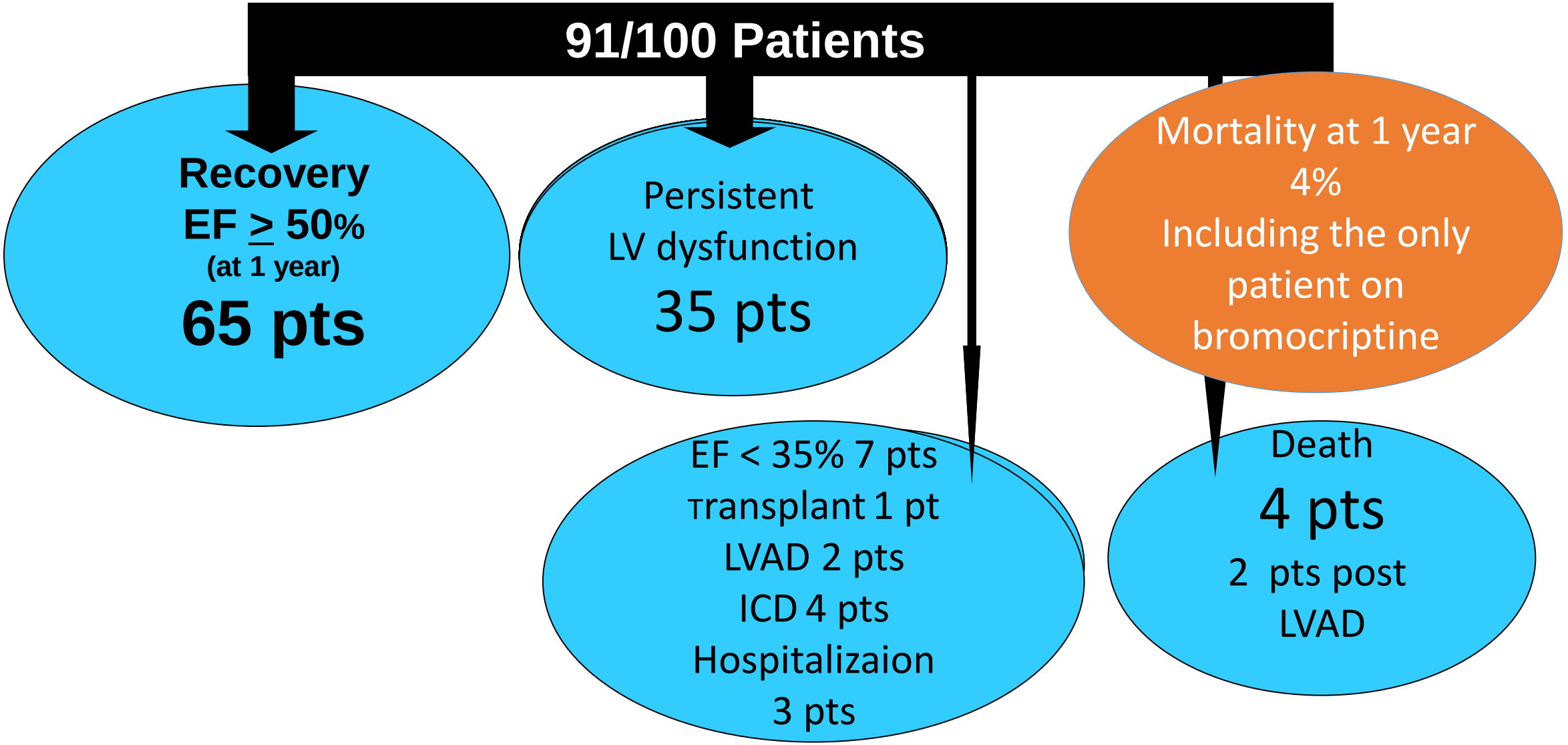
Bromocriptine in The Treatment of PPCM



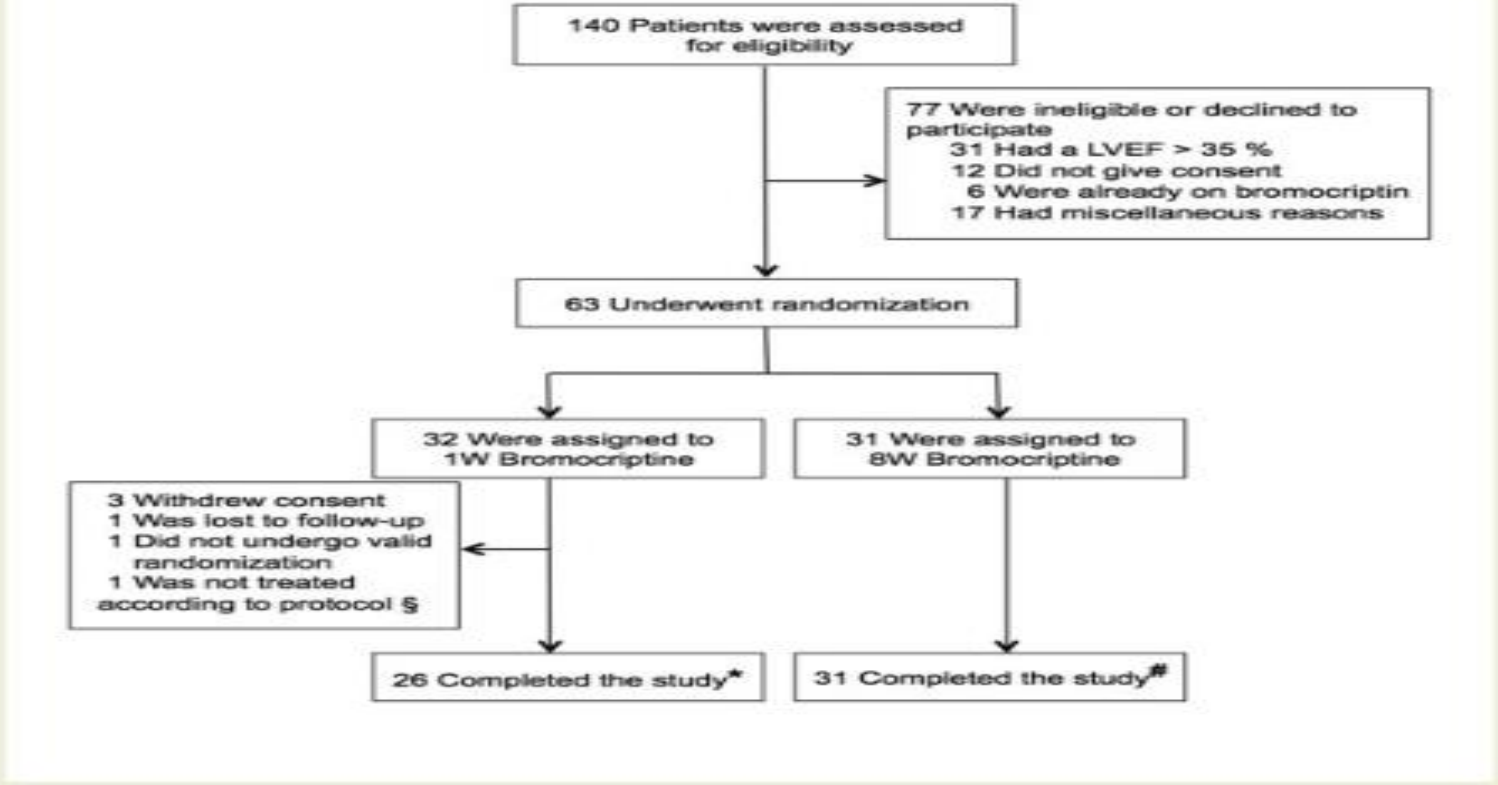
Bromocriptine in Management of PPCM
A Randomized Study on 96 Women in Burkina Faso
Yameogo NV et al J Cardiol Clin Res 2017

Parameters	STHF+BR N=48	STHF N=48	P value
BL LVEDD (mm)	59±3	58±4	0.6
BL LVEF	37±7%	37±5%	0.12
6 months LVEDD (mm)	53±2	55±2	0.002
6 months LVEF	50±2%	41±6%	0.001
12 months LVEDD (mm)	52±2	54±3	0.001
12 months LVEF	54±4%	46±6%	0.001
6 months mortality	17%	29%	0.0001

IPAC Study
One Year Outcome of PPCM in the US



A randomized, Controlled Multicenter Clinical Trial to Evaluate the Effect of Bromocriptine on LV Function in PPCM



23 and 28 patients with adequate imaging quality

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.

Change in LVEF

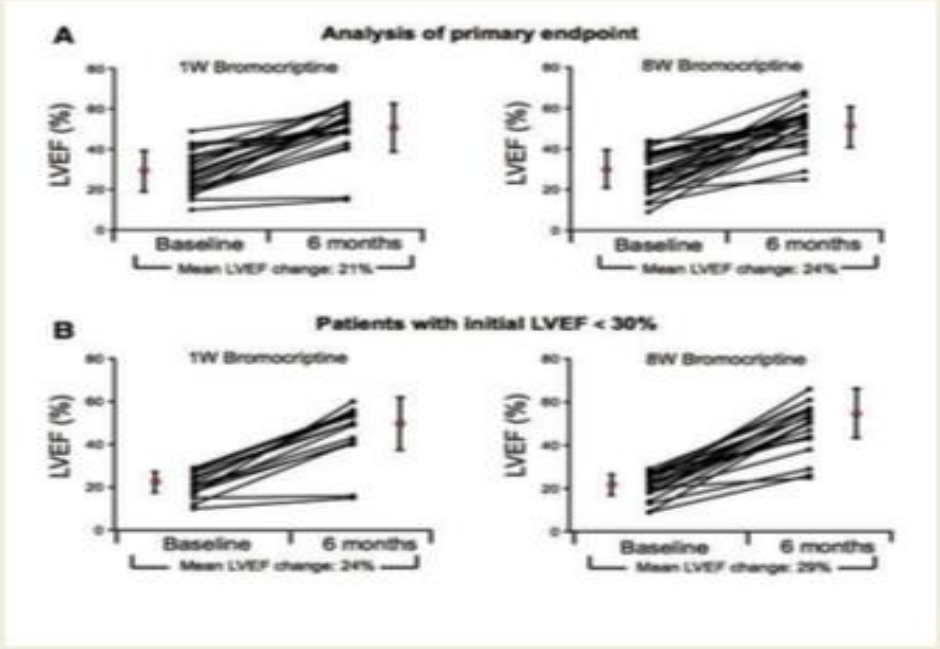


Figure 2 Analyses of global left ventricular ejection fraction (LVEF) change from baseline to 6 months follow-up determined by CMR. (*A*) Individual courses of LVEF change from baseline to 6-months follow-up in the 1W group ($n = 23$) and 8W group ($n = 28$) with a between-groups difference at 6-months 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 1 W 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 ($P = 0.22$).

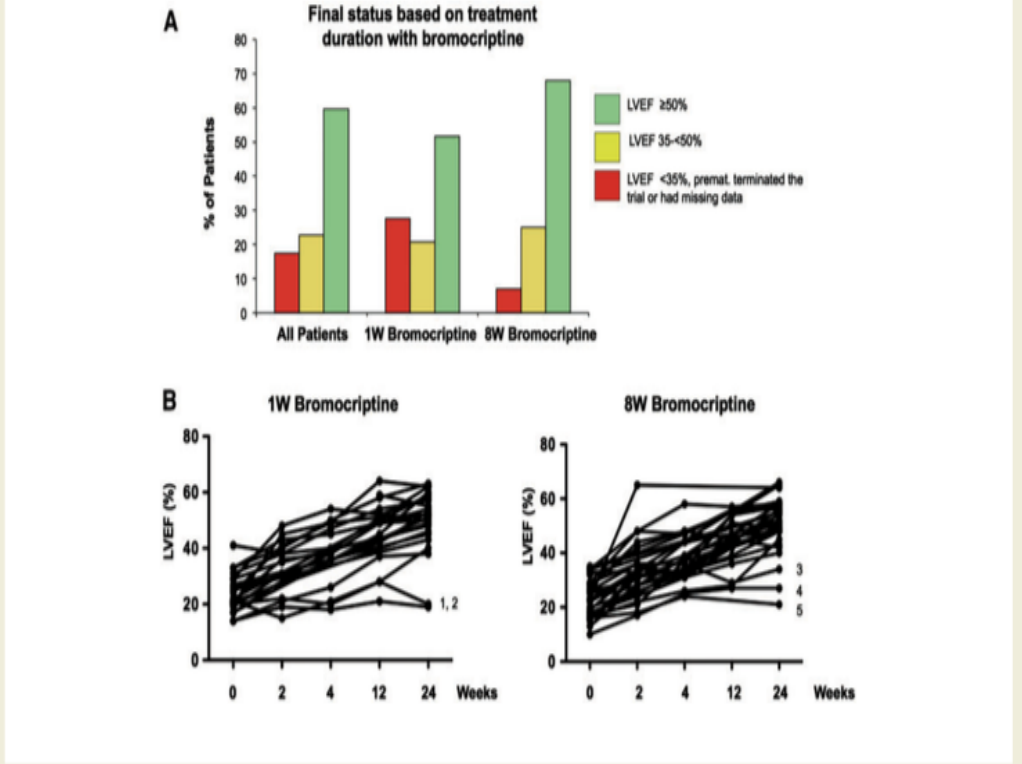
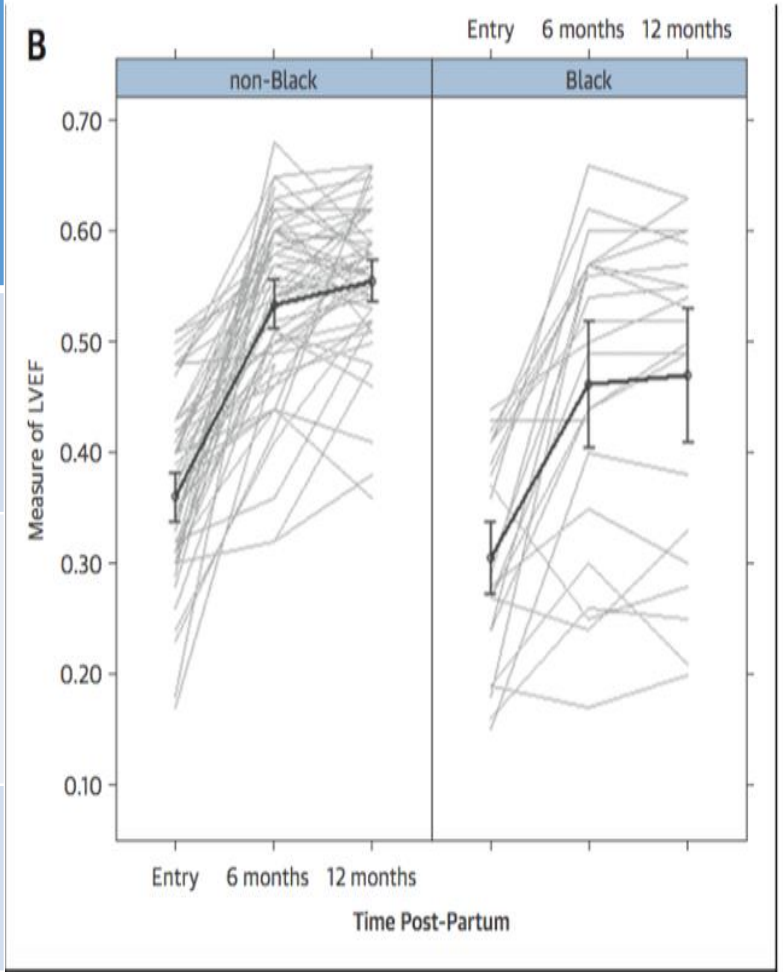


Figure 3 Outcome of patients at 6-months follow-up. (*A*) Left ventricular ejection fraction (LVEF) at 6-months follow-up according to predefined categories in all patients of the present study (treated 1W, $n = 32$ or 8W, $n = 31$ with bromocriptine, baseline LVEF <35%). Red columns illustrate the percentage 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 ≥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 IPAC with the randomized trial of bromocriptine and a German PPCM registry with 67% of women(64/96) treated with bromocriptine

Parameters	Bromocrip Trial[1] (<30%) (n=37)	Bromocrip registry[2] (≤45%) (n=96)	IPAC subset[3] (<30%) (n=30)	IPAC registry[3] (≤45%) (n=92)
Full recovery	62%	47% (LVEF>55%)	37%	52% (LVEF>55%)
Severe heart failure (LVEF<0.35	3%	5%	18.5%	7%
Death/Tx/LVAD	0%	10%	18.5%	7%



[1]Hilfiker-Kleiner, EHJ 2017; [2]Haghikia, Basic Res Cardiol, 2013; [3]McNamara, JACC, 2015;

NIH funded REBIRTH trial

Randomized **E**valuation of
Bromocriptine **I**n Myocardial
Recovery **TH**erapy **(REBIRTH)**

for Peripartum Cardiomyopathy

Peripartum Cardiomyopathy Network (PCN)

REBIRTH – Evaluation of bromocriptine and breast feeding on recovery of cardiac function

- REBIRTH will randomize 200 women at 50 centers across North America to either 8 weeks of bromocriptine therapy or a placebo
- The study will determine if bromocriptine therapy improves myocardial recovery and overall event free survival for women with PPCM
- Women who want to breastfeed, cannot get bromocriptine and can not enter REBIRTH, so a cohort of up to 50 women excluded from REBIRTH due to a desire to breastfeed will be followed

REBIRTH – Evaluation of bromocriptine and breast feeding on recovery of cardiac function

- Enroll 200 women at 50 centers:
  - ✓ newly diagnose with PPCM
  - ✓ within 5 months postpartum
  - ✓ LVEF <=0.35

- Randomize to bromocriptine (2.5 mg twice daily for 2 weeks then once daily for 6 weeks) or placebo

- Primary endpoint LVEF at 6 months post randomization. Secondary endpoints LVEF at 12 months post and event free survival for up to 3 years

Breath feeding and PPCM

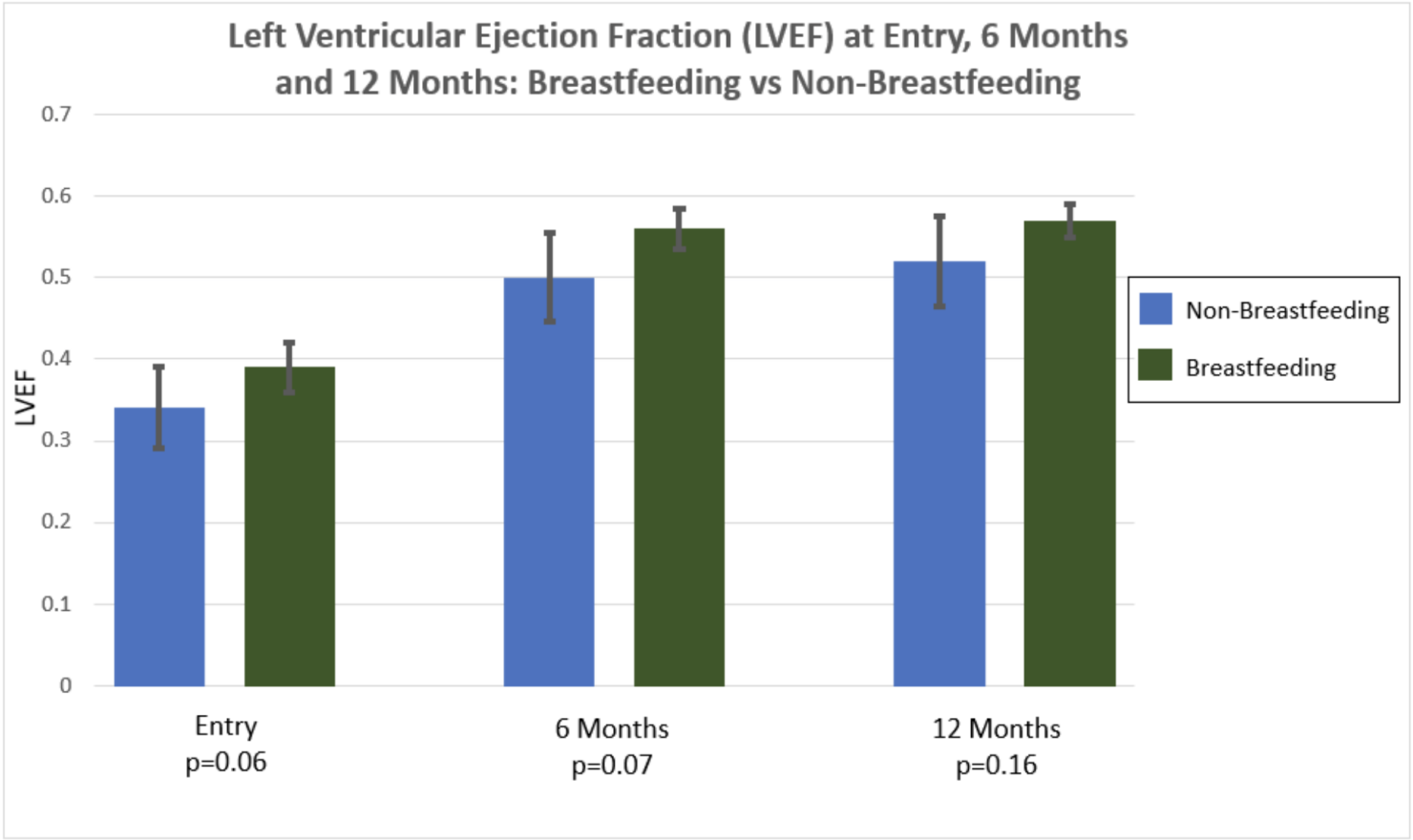
- The potential therapeutic impact of prolactin suppression with bromocriptine has led some to recommend against breast feeding for women with PPCM
- A ban on breastfeeding would have a significant impact on neonatal survival in developing countries where PPCM is more prevalent

Impact of breathfeeding on child survival:UNICEF

"Optimal breastfeeding of infants under two years of age has the greatest potential impact on child survival of all preventive interventions, **with the potential to prevent over 800,000 deaths** (13 per cent of all deaths) in children under five in the developing world"

(Lancet, 2013)

LVEF at BL & at 6 months and 12 months F/U Breast feeding vs non breast feeding



Koczo, Marino, et al
JACC-BTS, 2019

Breath feeding cohort

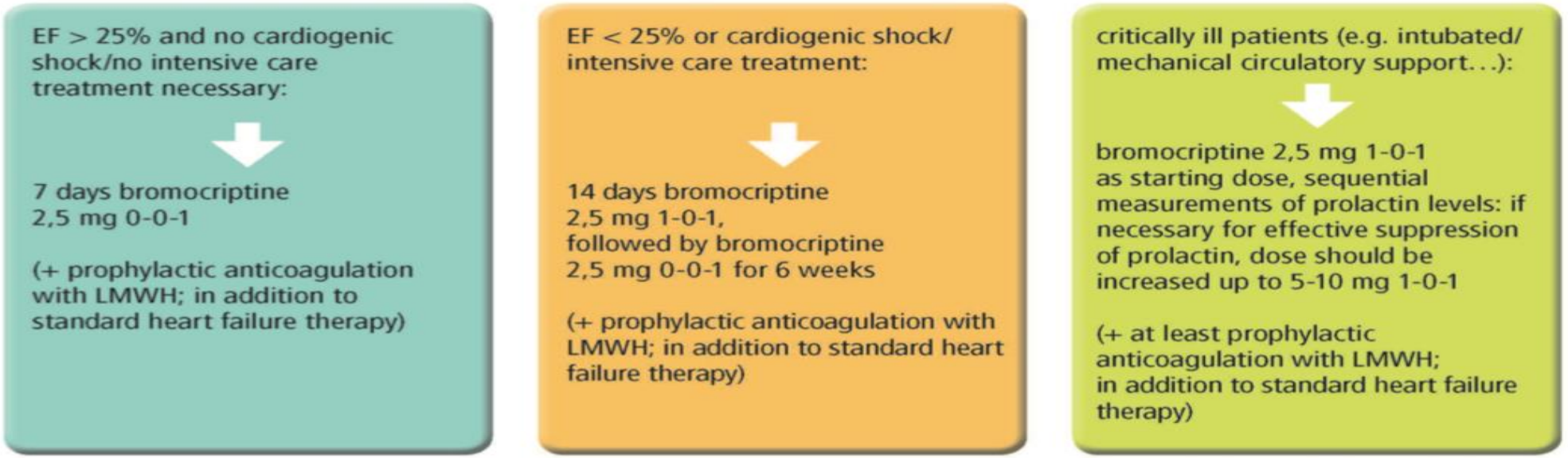
- A cohort of 50 women, excluded from the trial due to breastfeeding will be enrolled in an observational cohort
- Same entry criteria as the randomized trial
- Important analysis of impact of breastfeeding on myocardial recovery in compensated women with PPCM
- If bromocriptine treatment group is the “low prolactin group”, breast feeding cohort is the “high prolactin” group

Summary

- PPCM remains a major cause of maternal morbidity and mortality
- Results with bromocriptine appears promising but a well controlled study in a diverse cohort is required
- The impact of breastfeeding on outcomes in PPCM remains controversial
- REBIRTH will address the impact of both bromocriptine and breastfeeding on outcomes in PPCM

Current treatment scheme at Hannover Medical School in patients with acute PPCM.

Suppl Figure 1



Outcome of subsequent pregnancies in 36 patients with a history of PPCM

Clinical Presentation and Outcome

Hilfiker-Kleiner D et al Eur J Heart Failure March 27 2017

Paramter	LVEF < 50% (N=16)	LVEF ≥ 50% (N=18)	P-Value
Age at index (Years ± SD)	27±7	29±5	0.50
Age at PPP (Years ± SD)	30±7	31±5	0.59
African origin	75%	44%	0.09
LVEF at diagnosis of index pregnancy	31±7%	32±8%	0.68
LVEF prior to SSP	42±6%	58±5%	<0.0001
LVEF after delivery	43±11%	51±13	0.022
LVEF at follow up	43±15%	50±13%	0.24
Full recovery	31%	56%	0.28
Death	25%	0%	0.04

Outcome of subsequent pregnancies in 36 patients with a history of PPCM

Comparison of cardiac and clinical parameters on STHF therapy vs. SHFT+BR

Parameters	BR-group N=21	STHF-group N=9	P- value
LVEF at index PPCM	32±8%	31±7%	0.07
LVEF prior to SSP	51±9%	48±11%	0.35
LVEF ≥ 50% prior to SSP	57%	33%	0.43
LVEF after delivery	51±9%	38±16%	0.07
LVEF at follow up	51±11%	35±14	0.02
Full recovery after ssp	62%	11%	0.017

Hilfiker Kleinr D et al Eur J Heart Failure March 27, 2017

Outcome of subsequent pregnancies in 36 patients with a history of PPCM

Comparison of cardiac and clinical parameters on STHF therapy vs. SHFT+BR

Parameters	BR-group N=21	STHF-group N=9	P- value
LVEF at index PPCM	32±8%	31±7%	
LVEF prior to SSP	51±9%	48±11%	
LVEF ≥ 50% prior to SSP	57%	33%	
LVEF after delivery	51±9%	38±16%	
LVEF at follow up	51±11%	35±14	
Full recovery after ssp	62%	11%	

We observed sig. better cardiac function at follow-up on STHF+BR compared to STHF alone.

Our data suggest that progression of HF and fatal outcome of SSP may be attenuated or prevented if a STHF+BR therapy is initiated immediately after SSP delivery.

Hilfiker Kleinr D et al Eur J Heart Failure March 27, 2017

- we observed significantly better cardiac function at follow-up in patients obtaining STHF+BR compared to patients obtaining STHF alone.
- Moreover, no patient in the STHF+BR group died, while 2 patients in STHF group died during follow up suggesting that this treatment may indeed prevent relapse of PPCM and has beneficial effects when started as early as possible after delivery.
- Our data suggest that progression of HF and fatal outcome of SSP may be attenuated or prevented if a STHF+BR therapy is initiated immediately after SSP delivery.

Bromocriptine in PPCM
Two ways to interpret

- The Findings support a potential benefit of BR in addition to standard therapy.
- Low dose is sufficient in most cases.
- Additional advantage of BR is ablactation which enables optimal HF treatment.

- The study failed to meet it primary end point of demonstrating a superior effect of a full dose BR vs. control on recovery of EF .
- A possible effect of low dose is an hypothesis that needs to be tested against standard HF therapy alone.
- Most HF medications including Enalapril, captopril, beta-blockers and spironolactone are compatible with breast feeding.

SciMedCentral

Journal of Cardiology & Clinical Research

Research Article

Bromocriptine in Management of Peripartum Cardiomyopathy: A Randomized Study on 96 Women in Burkina Faso

Nobila Valentin Yaméogo[1,2]*, Larissa Justine Kagambèga[1], Arthur Seghda[1], Amalia Owona[1], Olivia Kaboré[1], Elisée Kaboré[1], Georges Rc Millogo[1,2], KJonas Kologo[1], BJean Yves Toguyéni[1], André K Samadoulougou[1,2], Jean L Ankoandé[3], and Patrice Zabsonré[1,2]

[1]Department of Cardiology, Yalgado OuédraogoUniversity Hospital of Ouagadougou, Africa

*Corresponding author

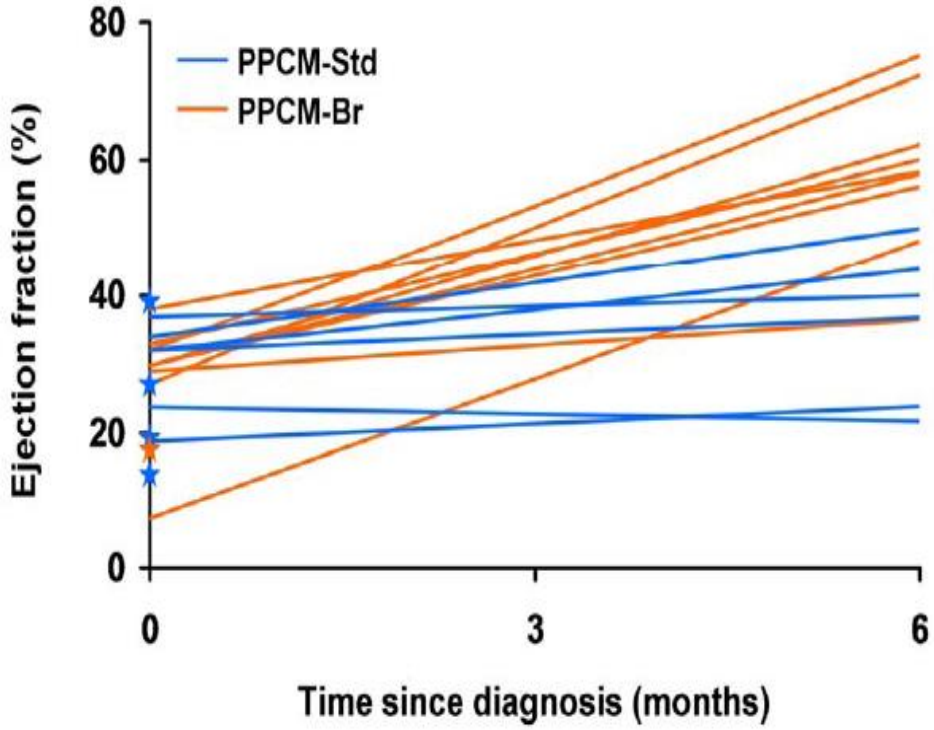
96 women with PPCM, mean age 29±3
Randomized to STHF therapy limited to diuretics and Captopril and to STHF therapy + Bromocriptine 2.5 mg bid for 4 weeks

Bromocriptine in Management of PPCM
A Randomized Study on 96 Women in Burkina Faso
Yameogo NV et al J Cardiol Clin Res 2017

Parameters	STHF+BR N=48	STHF N=48	P value
BL LVEDD (mm)	59±3	58±4	0.6
BL LVEF	37±7%	37±5%	0.12
6 months LVEDD (mm)	53±2	55±2	0.002
6 months LVEF	50±2%	41±6%	0.001
12 months LVEDD (mm)	52±2	54±3	0.001
12 months LVEF	54±4%	46±6%	0.001
6 months mortality	17%	29%	0.0001

Breast Feeding

- No adverse outcome were observed for the infants of PPCM patients in south Africa who terminated breast feeding.
- Sliwa K et al Circulation 2010



The Safety of Termination of Breast Feeding

- Normal growth percentiles and no adverse outcome were observed for the infants of PPCM patients in South Africa who terminated breast feeding.
- Hilfiker-Kleiner Eur Heart Journal based on 10 patients receiving BR in a pilot study in South Africa (Sliwa K , Circulation 2010)

Benefits of breast feeding

Infant

- Nutrition source
- Immunoprotection
- Reduced risk of infant death
- Reduced risk of obesity
- Reduced risk of diabetes
- Improved cognitive development and intelligence

Mother

- Reduced risk of:
- Breast cancer
- Ovarian cancer
- Diabetes
- Hypertension

Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect

- In low-income countries, most infants are still breastfed at 1 year.
- Meta-analyses indicate protection against child infections and malocclusion, increases in intelligence, and probable reductions in overweight and diabetes.
- For women, breastfeeding gave protection against breast cancer, improved birth spacing, and might also protect against ovarian cancer and type 2 diabetes.

The Lancet 2016

Breastfeeding: achieving the new normal

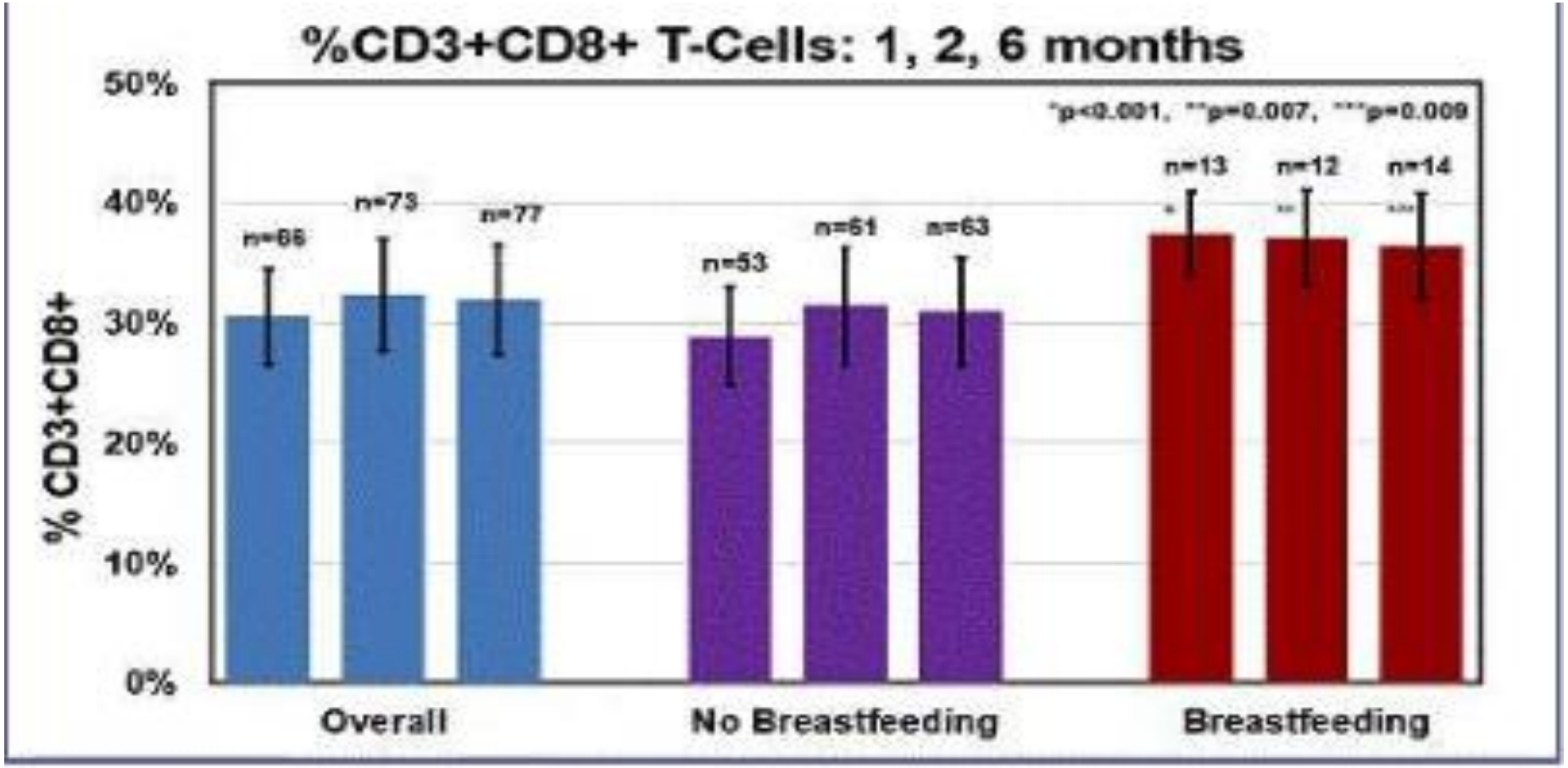
The Lancet, Vol 387 January 30, 2016

- Breastmilk makes the world healthier, smarter, and more equal.
- The deaths of 823,000 children and 20,000 mothers each year could be averted through universal breastfeeding, along with economic savings of $300 billion.

Breast feeding and PPCM

- No negative effect on recovery of LV function in the IPAC study.
- Higher degree of recovery of LV function in women who breast fed (Safirstein 2011).
- Most HF medications categorized as compatible with breast feeding by AAP.

Cellular Immune Activation and Breastfeeding



Baseline EF non breast feeding (NBF) 39% vs 34% for BF p0.06
12 months 57% vs. 52%, p=0.10

Bromocriptine in PPCM

- Available studies and observations provide a signal for a potential beneficial effect of bromocriptine on the outcome of women with PPCM.
- Beneficial effect was reported in African patients where Phenotypic presentation is very different compared to American or European patients.
- Full dose BR failed to show a benefit compared to control group on low dose BR.

Bromocriptine in PPCM

- Comparison between studies with IPAC as an end points, not valid.
- Conclusion that even low dose BR is effective is tempting but is only hypothesis generating .
- The decision to use Br in women with PPCM should also take into consideration potential complications of and the effect of breast feeding.

Bromocriptine in PPCM

- More information in a large study will be require to further evaluate safety and efficacy.

- Patients should be well informed on the potential efficacy but also on the limited information, potential side effect and the value of breast feeding.
- Investigators and funding institutions should design and support a large international study in order to establish the safety and efficacy in the treatment of ppcm.

Pathophysiology and epidemiology of PPCM

Hilfiker-Kleiner D and Sliwa K. Nat. Rev Cardiol 2014;11:364

- The combination of bromocriptine and standard therapy for HF must be tested in large, multicenter, randomized, controlled trials.
- We are currently performing such a trial in Germany, where we aim to randomly allocate 60 patients with PPCM to standard therapy for HF with or without the addition of bromocriptine.

Why is the German Bromocriptine Study not likely to provide the information?

- Control women receive bromocriptine.
- Open-label study.
- Too small (a total number of 60 patients minus anticipated dropout of 6 patients = 54 patients)
- Anticipated recovery (spontaneous and due to standard drug therapy) ~ 60%.
- Number of transplant free surviving patients without recovery independent of bromocriptine ~ 22.

Haghikia A et al. Rationale and design of a randomized, controlled multicenter clinical trial to evaluate the effect of bromocriptine on LV function in women with PPCM. Clin Res Cardiol 2015;104:911

Bromocriptine in PPCM: Argument against #4

Safety

FDA Withdrawal of Bromocriptine for Lactation Suppression

- The indication of lactation suppression has been withdrawn in the US and discouraged in other countries because it increases the risk of maternal stroke, seizures, cardiovascular disorders, death and possibly psychosis.

Severe adverse effects of bromocriptine in lactation inhibition: a pharmacovigilance survey

Bernard N et al Int J Obstet Gynecol March 2015

Table 4. Serious ischaemic disorders reported in the current French pharmacovigilance survey and from the literature

	Number *n* (%)	Fatal cases	Cardiovascular facto *n* (%)	Misuse* *n* (%)
All ischaemic disorders	92	8 (8.7)	47 (51.1)	27 (57.4)
Myocardial infarction[14–25]	26	5 (19.2)	15 (57.7)	4 (36.4)
Hemorrhagic stroke[26–30]	12	1 (8.3)	7 (58.3)	1 (100.0)
Ischemic stroke[31–33]	22	2 (9.1)	11 (50.0)	12 (66.7)
Postpartum cerebral angiopathy[34–43]	22	0	9 (40.9)	7 (70.0)
Other strokes	5	0	3 (60.0)	2 (40.0)
Peripheral ischaemic disorders[25,44,45]	5	0	2 (40.0)	1 (50.0)

*In cases from the literature, misuse exclusively consisted of a combination with another vasoconstrictor ergot drug; other misuses were not described. Consequently, the rate of misuse was only calculated from cases in the survey.

1994-2010

Bromocriptine for the treatment of PPCM

Why is it not ready for routine use?

- Very little clinical data.
- Available data not relevant to my patients or yours.

Use of bromocriptine for the treatment of PPCM: are we there yet?

NO

Bromocriptine for the treatment of PPCM

Why is it not ready for routine use?

- The majority of women with PPCM recover on conventional HF therapy without bromocriptine.
- Bromocriptine prevents breast feeding.
- Safety concerns including MI and Stroke.

Bromocriptine for the treatment of PPCM

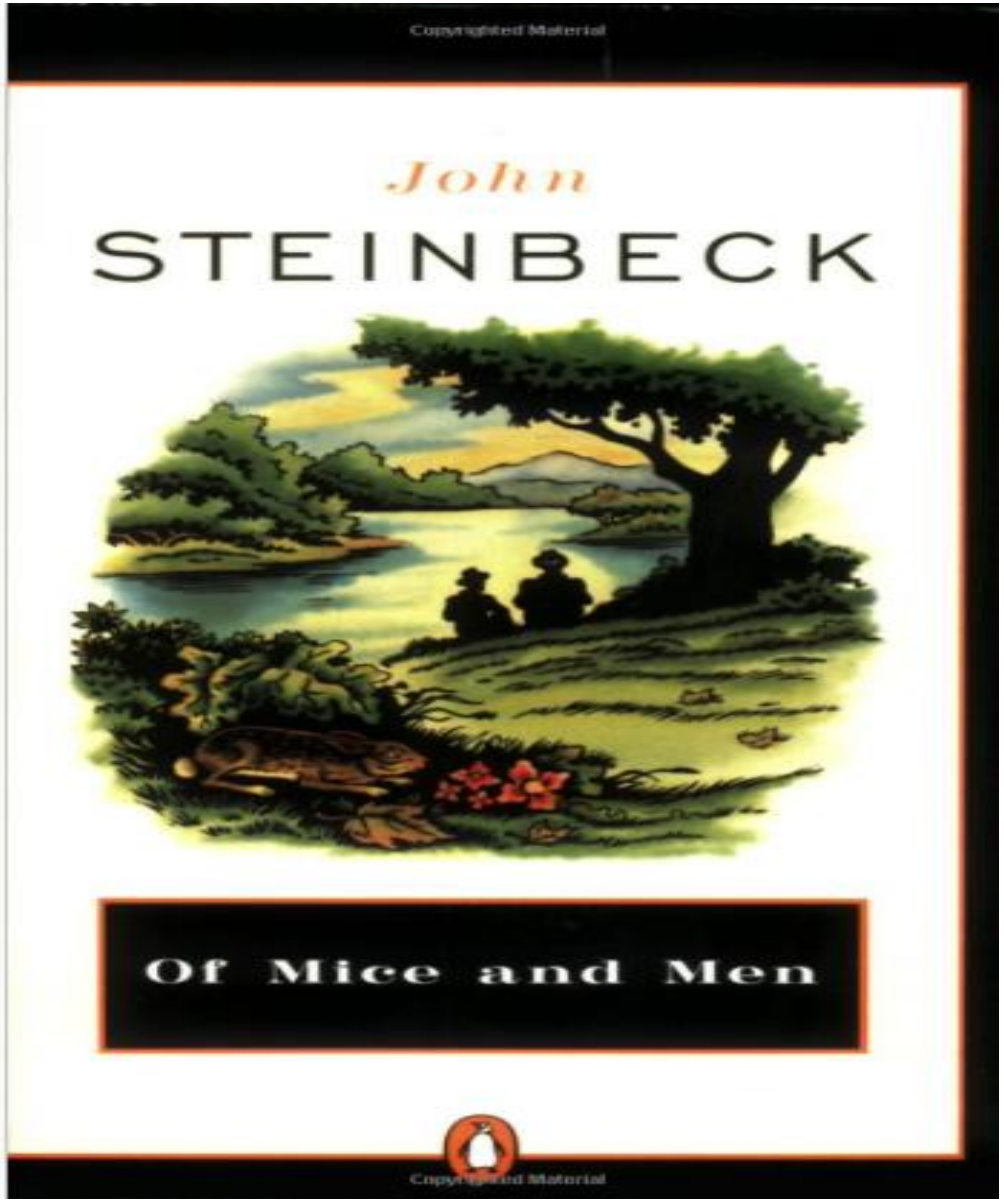
Why is it not ready for routine use?

- Do you really have a good enough evidence to justify not allowing a women to breast feed her baby ?.
- And what do you say to a patient who develops a complication. (It works in rats?)
- Adaption of bromocriptine therapy will reduce the chance to ever have an appropriate and large enough study of the safety and efficacy of the drug in the treatment of PPCM.

John

STEINBECK

Of Mice and Men



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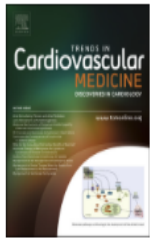

Editorial Commentary

"Of mice and (wo)men": The need to confirm results of animal experimentations with solid clinical data

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Of Mice and (Wo)men

Goland S, Elakayam U. Trends in CV MED 2015;25:507

A strong plea should be made for an international, multicenter, large-scaled study to establish safety and efficacy of bromocriptine as a part of standard management of PPCM.

Use of bromocriptine for the treatment of PPCM: are we there yet?

Thank You