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

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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

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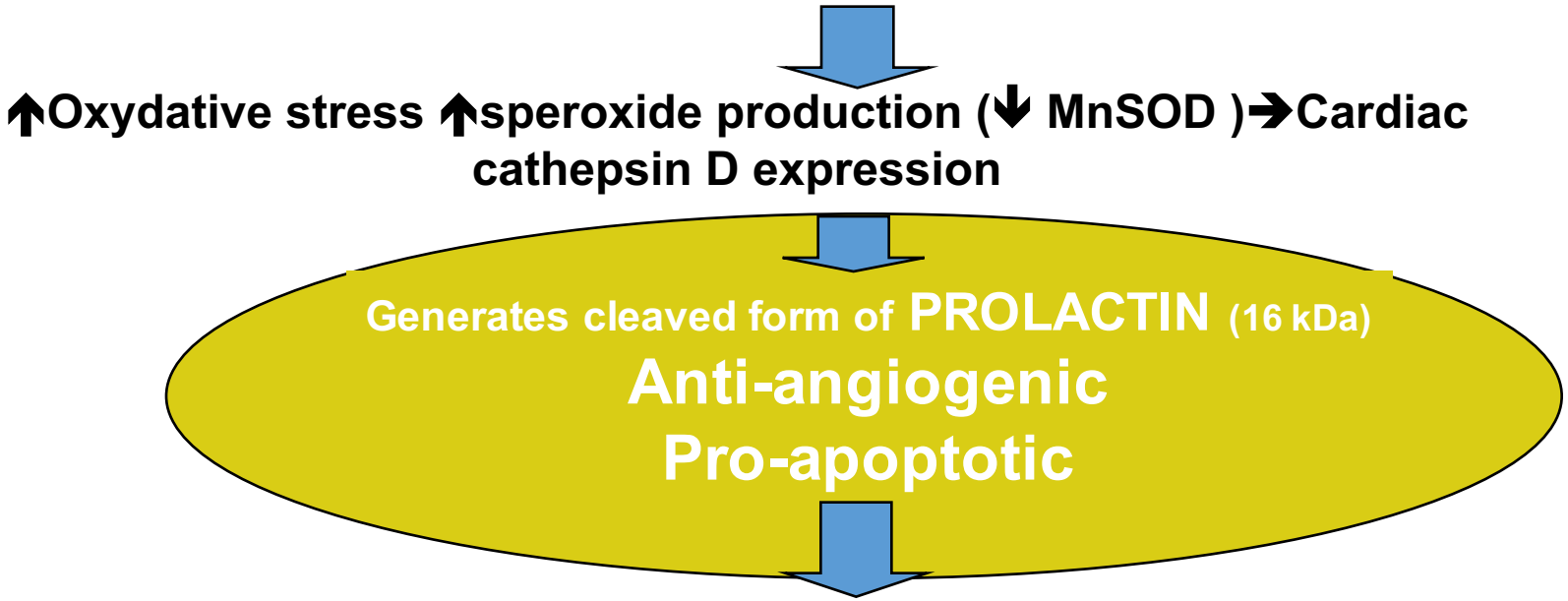
PPCM

Bromocriptine

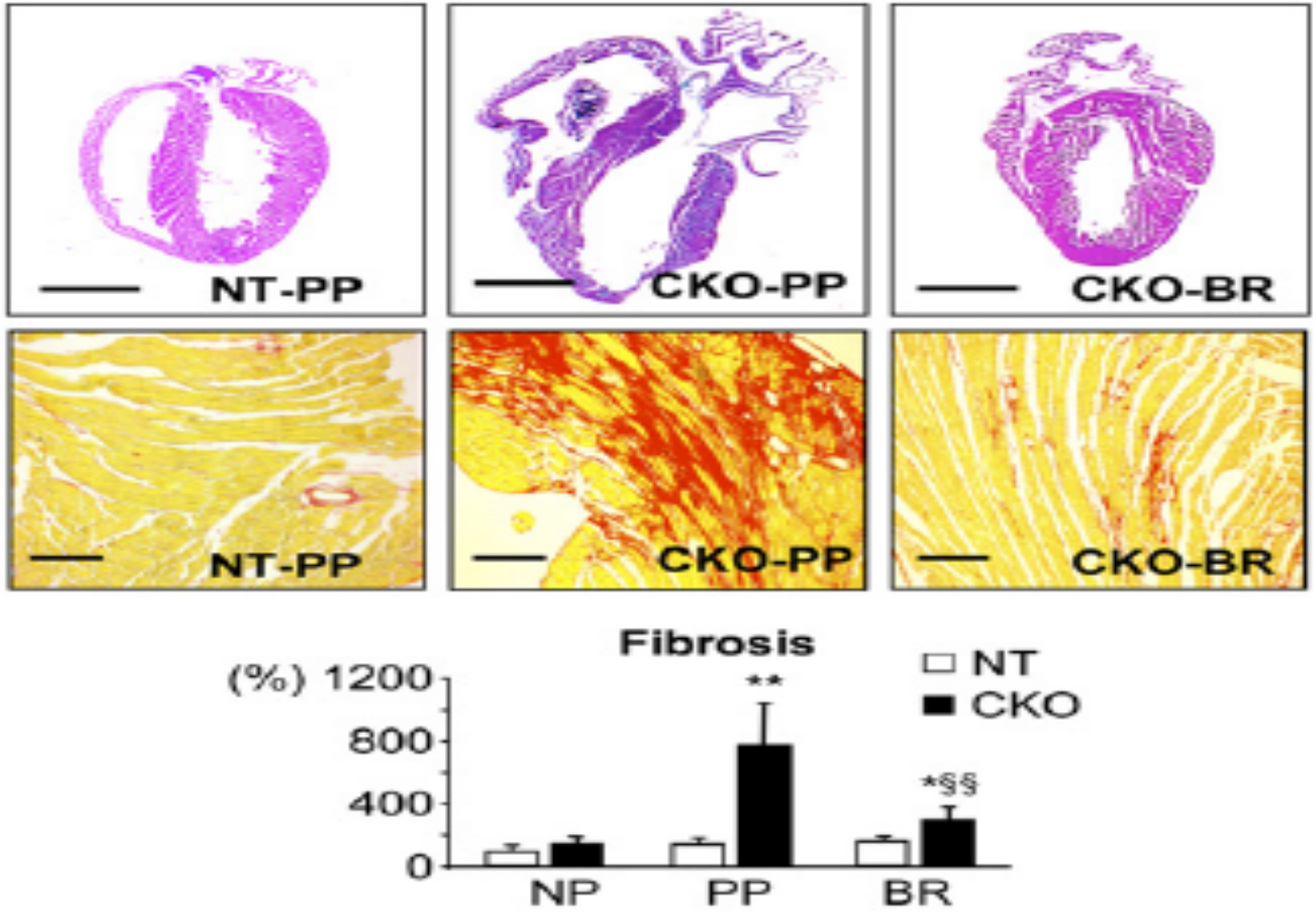
Hilfiker-Kleiner et. al.
Cell 2007;128:589

Mice with homozygous or heterozygous cardiomyocyte-specific knockout of STAT3 (transcriptional activator) develop PPCM



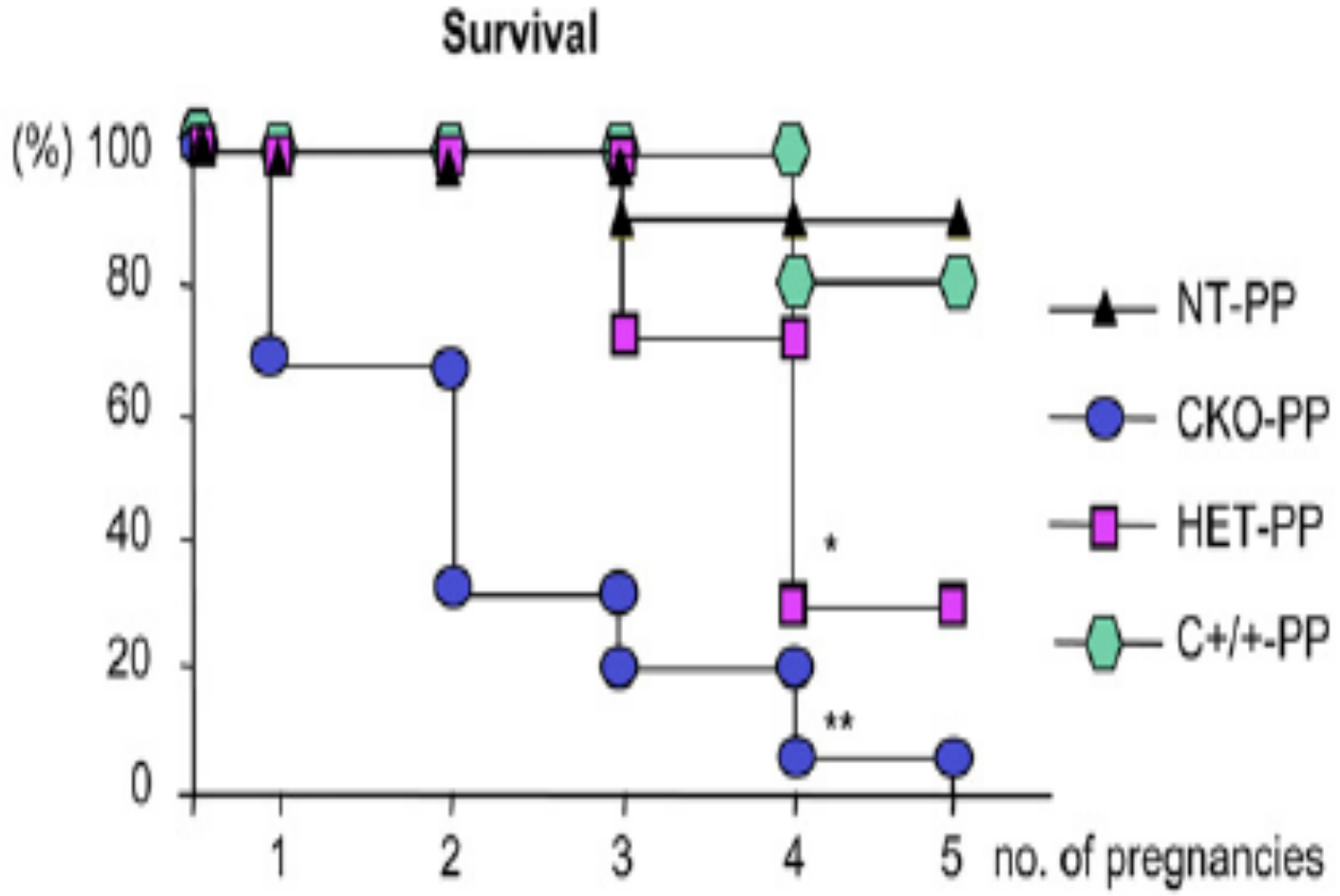
A Cathepsin D-Cleaved 16 kDa Prolactin Mediates PPCM

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



Survival in Relation to Number of Pregnancies

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], Michele R. Hacker[3], Julie S. Rhee[3], John Mitchell[4], Feroze Mahmood[4], Philip Hess[4], Caitlin Farrell[1], Nicole Koulisis[1], Eliyahu V. Khankin[5], Suzanne D. Burke[5,8], Igor Tudorache[6], Johann Bauersachs[7], Federica del Monte[1], Denise Hilfiker-Kleiner[7], S. Ananth Karumanchi[5,8] & Zoltan Arany[1]

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 peripartum cardiomyopathy

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Nature 2012;485:3

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Cardiac Angiogenic Imbalance Leads to PPCM
Patten IS et al Nature2012;485:333

- PGC-1α* - A transcriptional activator & a regulator of mitochondrial biogenesis and angiogenesis by driving the expression of angiogenic factors like VEGF.
- Pregnant rats with PGC-1α deletion develop dilated CM associated with increased sFLT-1** and insufficient up regulation of cardiac expression of VEGF blunted by sFLT-1.

- * **PGC-1α = Peroxisome proliferator-activated receptor-** γ coactivator
- ** sFLT-1 = Thyrosin Kinase an enzyme that disabales pro angiogenic proteins

Cardiac Angiogenic Imbalance Leads to PPCM

Patten IS et al Nature 2012;485:333

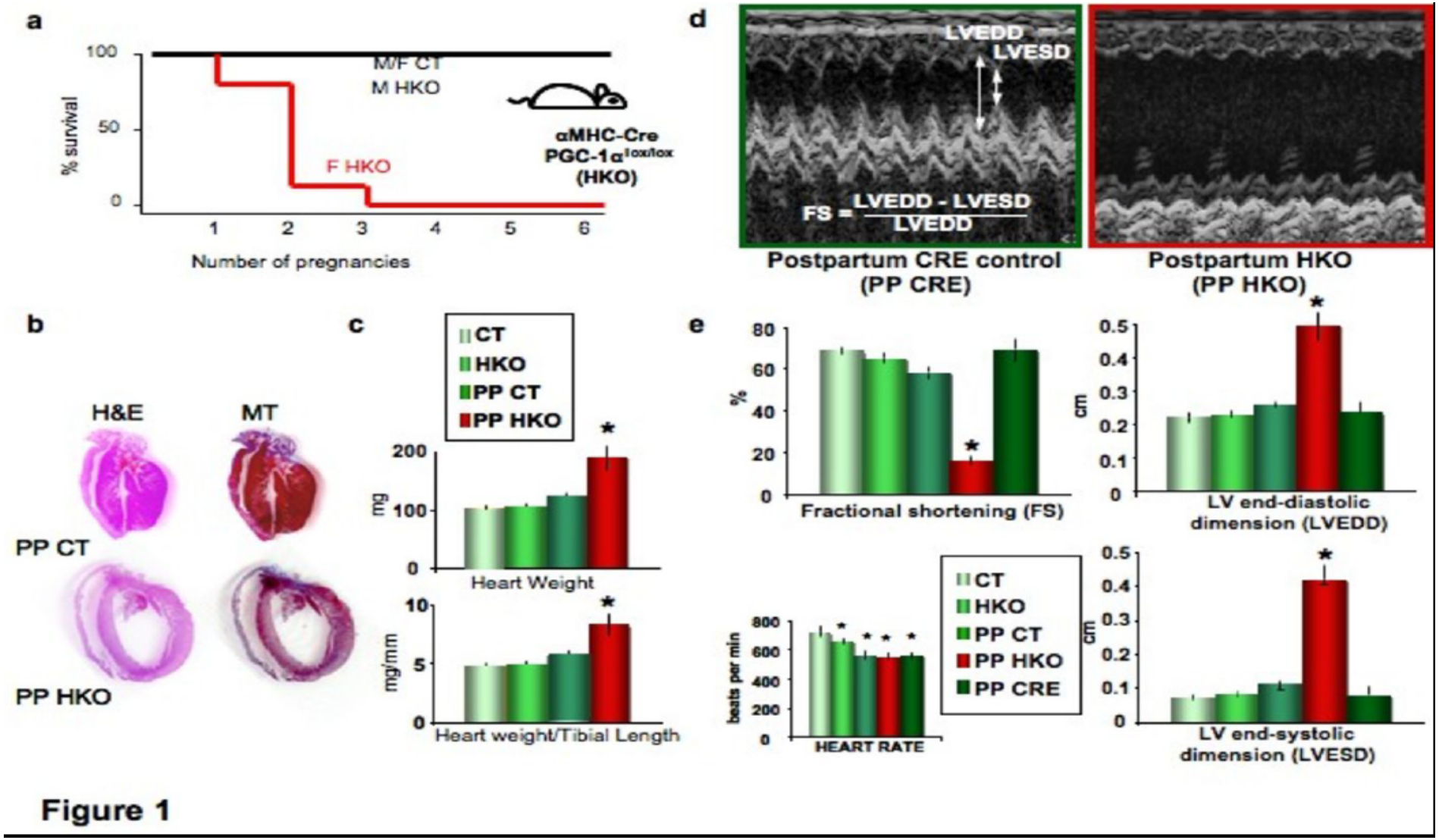
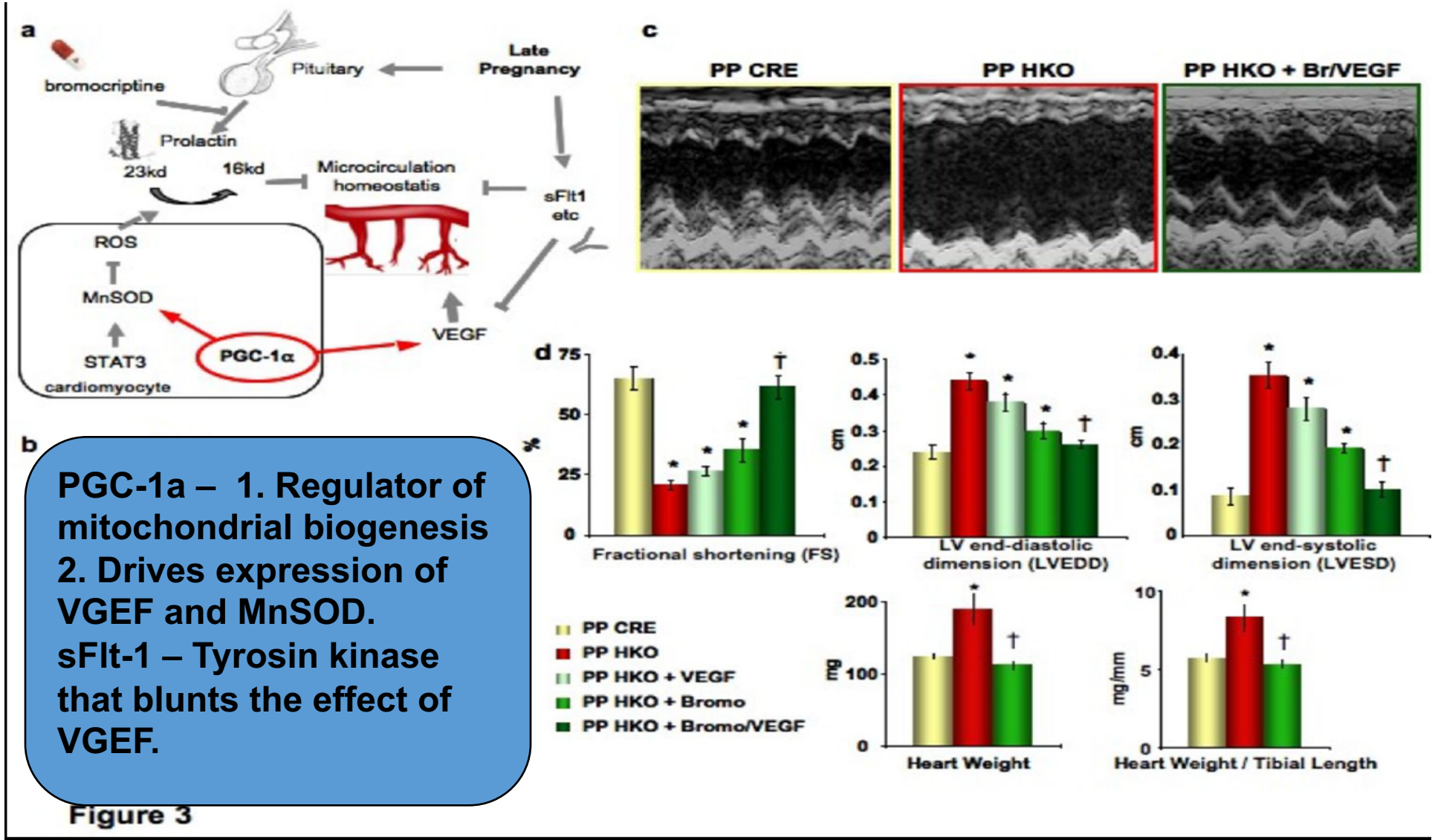


Figure 1

Cardiac Angiogenic Imbalance Leads to PPCM

Patten IS et al, Nature 2012;485:333

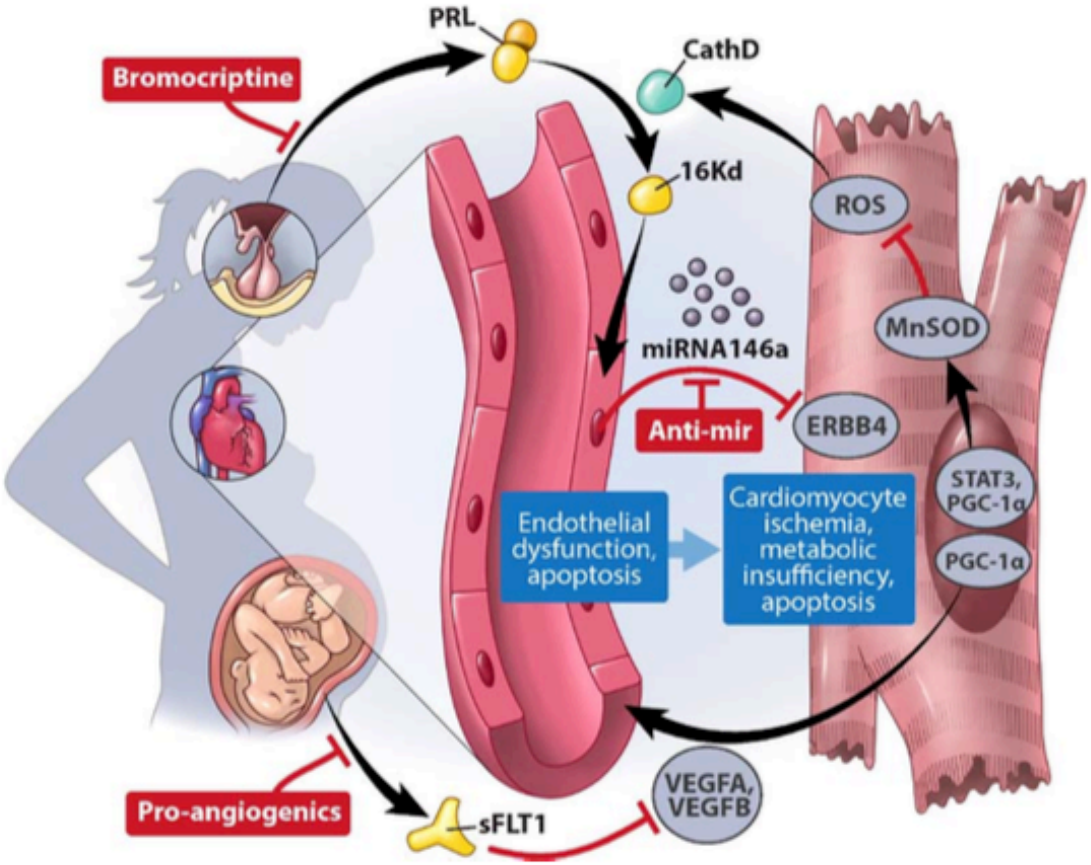


PGC-1a – 1. Regulator of mitochondrial biogenesis 2. Drives expression of VGEF and MnSOD. sFlt-1 – Tyrosin kinase that blunts the effect of VGEF.

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.
- Prolactine 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 forthe treatment of women with PPCM : are we there yet?

Bromocriptine in PPCM: Argument against #1

-Very limited clinical information.

-Results are not relevant to patients in Europe and the US/Canada.

Effect of Bromocriptine for 3 month post delivery

Hilfiker-kleiner D et al Cell 2007;128:589

Cardiac dimensions and function in patients with subsequent pregnancies with (n=6) or without (n=6) BR treatment

	Peripartum UT group	Peripartum BR group	Postpartum UT group	Postpartum BR group
LVEDD (cm)	6.2±0.6	5.5±0.5	6.7±1.2	5.3±0.5**
LVESD (cm)	4.8±5	4.2±0.7	5.9±0.3	3.8±0.5**
EF (%)	45±7	40±14	23±3	52±6**
NYHA	1.4±0.5	1.8±0.9	2.3±0.6	1±0*

Effect of Bromocriptine for 3 month post delivery

Hilfiker-kleiner D et al Cell 2007;128:589

Cardiac dimensions and function in patients with subsequent pregnancies with (n=6) or without (n=6) BR treatment

	Peripartum		Postpartum	Postpartum BR group
LVEDD (cm)				5.3±0.5**
LVESD (cm)	4.8±5		5.9±0.3	3.8±0.5**
EF (%)	45±7	40±14	23±3	52±6**
NYHA	1.4±0.5	1.8±0.9	2.3±0.6	1±0*

Mortality
With BR 0/6
Without BR 3/6

Subsequent pregnancy in women with Hx of PPCM and persistent LVD before pregnancy

TABLE 3 Patients With Persistent Left Ventricular Dysfunction Before Subsequent Pregnancy

First Author (Ref. #)	Year	No. of Pregnancies	Deterioration of LV Function	Symptoms of Heart Failure	Persistently Decreased LVEF at Follow-Up	Death
Elkayam (10)	2001	12	4 (33)	6 (50)	5 (42)	3 (25)
Avila (12)	2002	9	NA	4 (44)	2 (22)	1 (11)
Sliwa (13)	2004	4	4 (100)	4 (100)	2 (50)	2 (50)
Chapa (14)	2005	4	0 (0)	0 (0)	4 (100)	0 (0)
Fett (15)	2006	16	8 (50)	8 (53)	7 (44)	1 (6)
Habli (16)	2008	10	9 (53)	NA	5 (29)	1 (6)
Hilfiker-Kleiner (18)	2007	12	5 (42)	NA	6 (50)	3 (25)
Fett (19)*	2010	26	10 (46)	NA	5 (80)	1 (0.4)*
Total		93	40/84 (48)	22/45 (49)	36/93 (39)	11/67 (16)

Values are n (%). *Most patients identified by an Internet support group of living patients with a history of peripartum cardiomyopathy; mortality rate was thereforenot available.

Abbreviations as in Table 2.

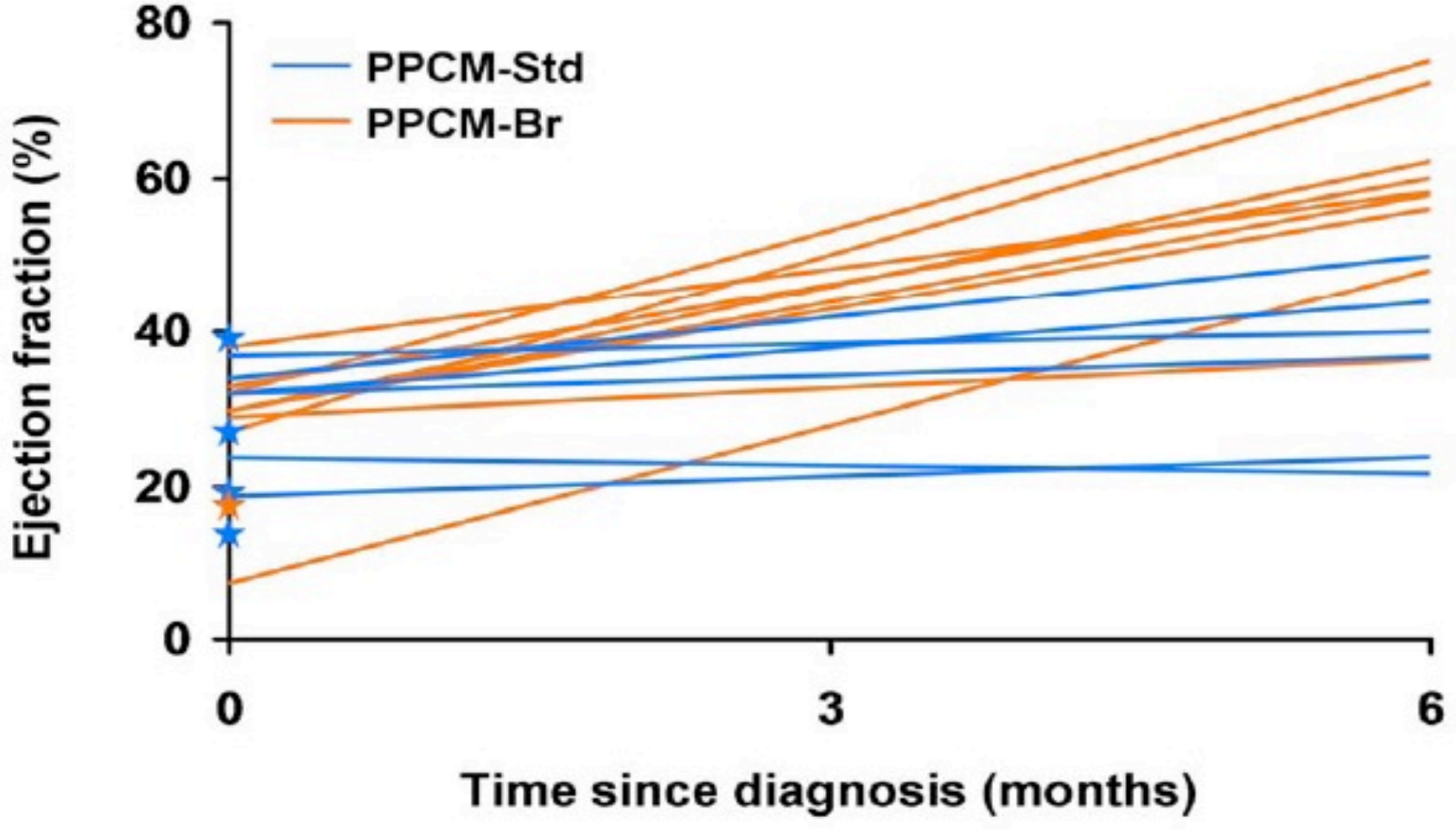
Effect of Bromocriptine for 3 month post delivery

Hilfiker-kleiner D et al Cell 2007;128:589

- Very small number of patients.
- No information on timing of therapy.
- Very high mortality in patients on standard therapy.
- Not relevant to my patients or yours.

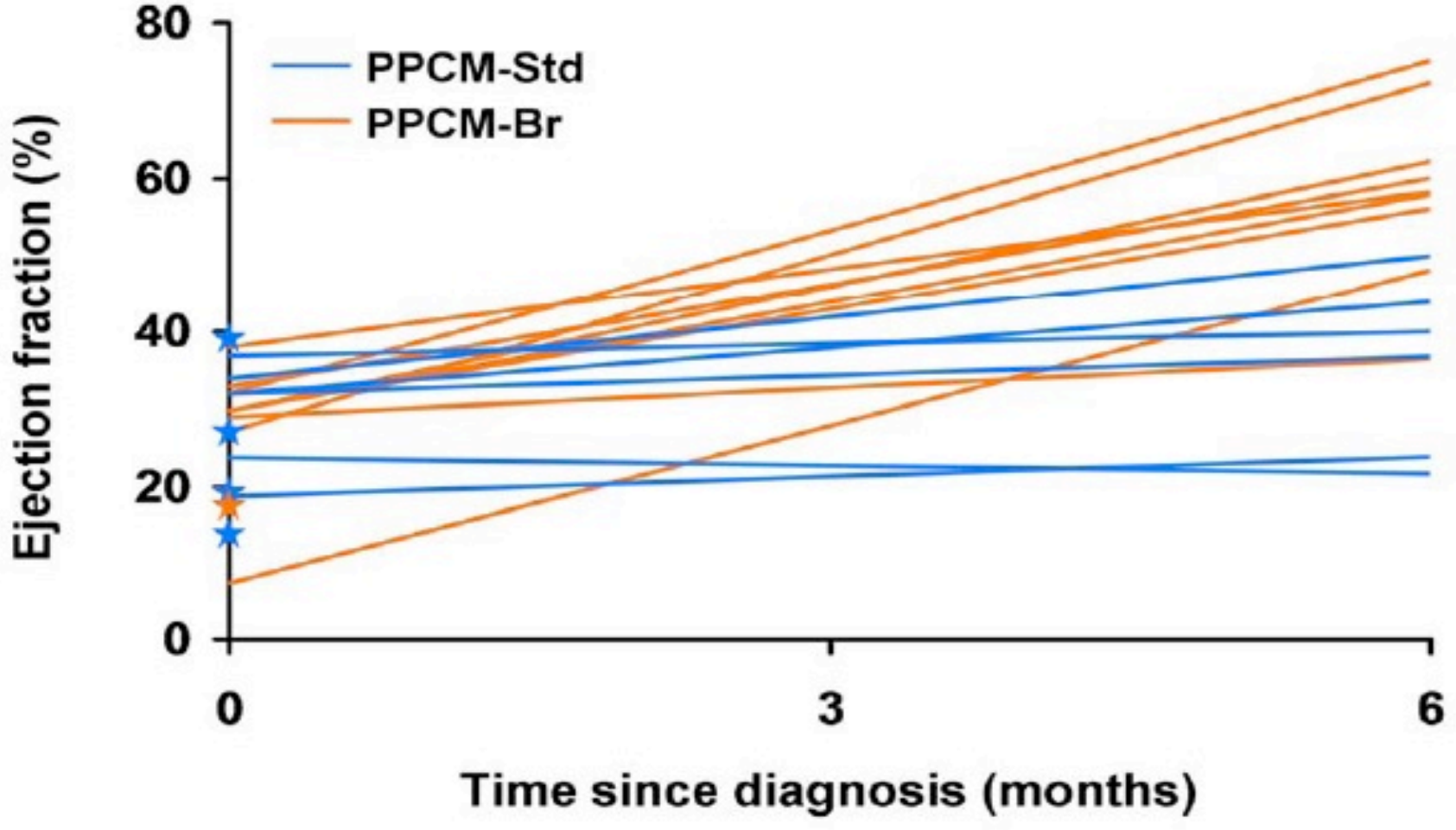
Bromocriptine in The Treatment of PPCM: Proof of concept

Sliwa K et al Circulation 2010;121:1465

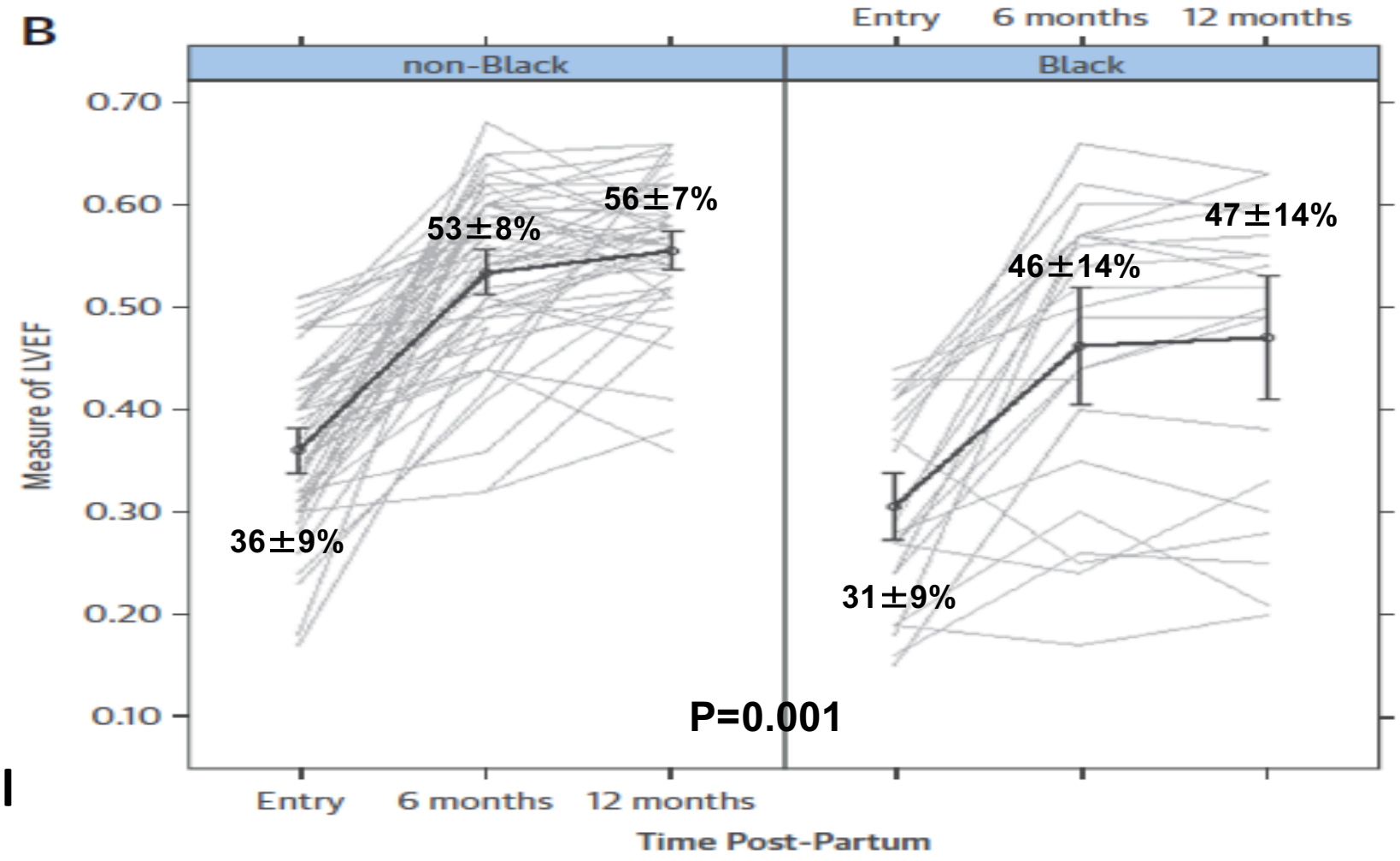


Bromocriptine in The Treatment of PPCM: a pilot study

Sliwa K et al Circulation 2010;121:1465



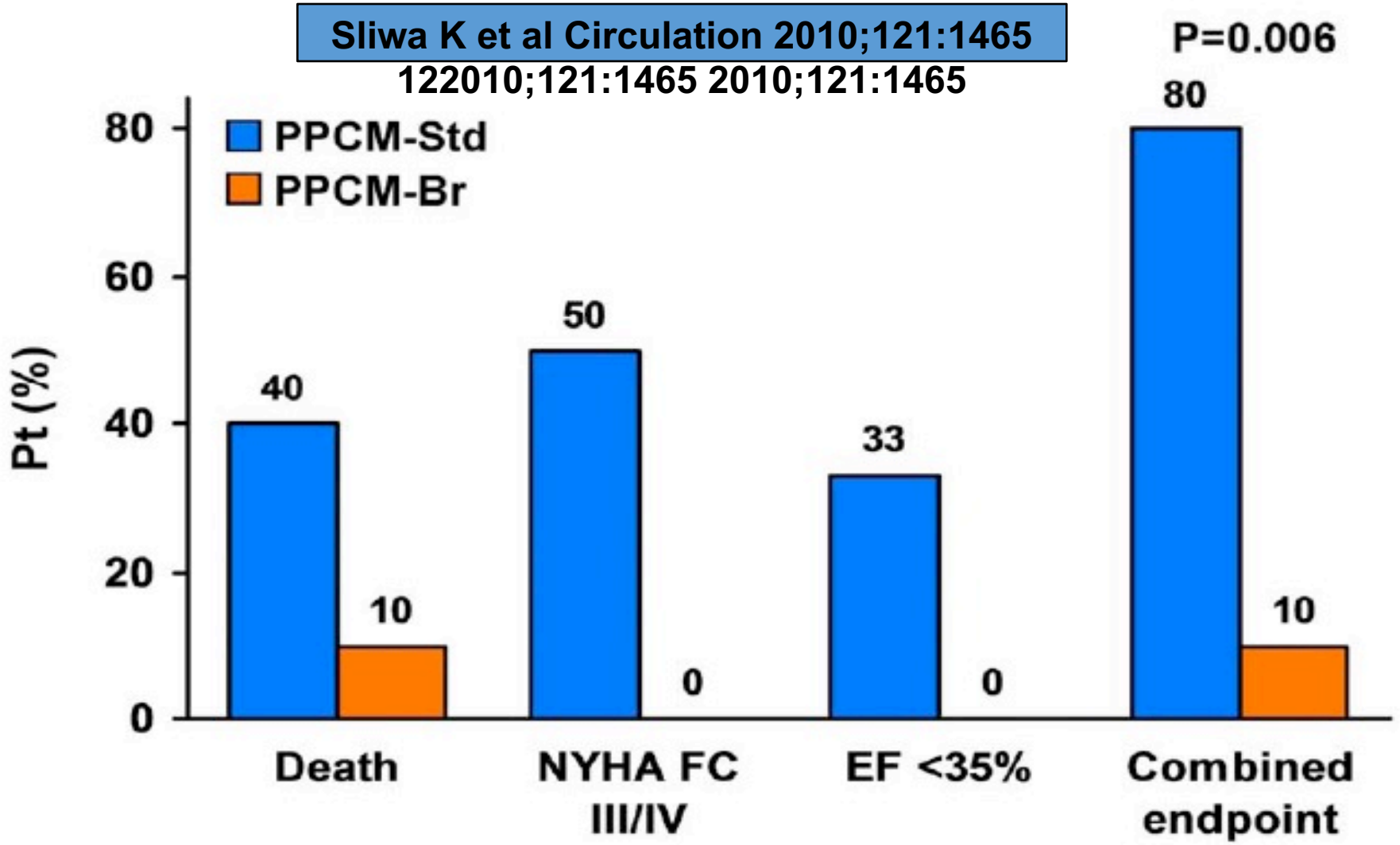
Racial Differences in Baseline and F/U LVEF The IPAC Study



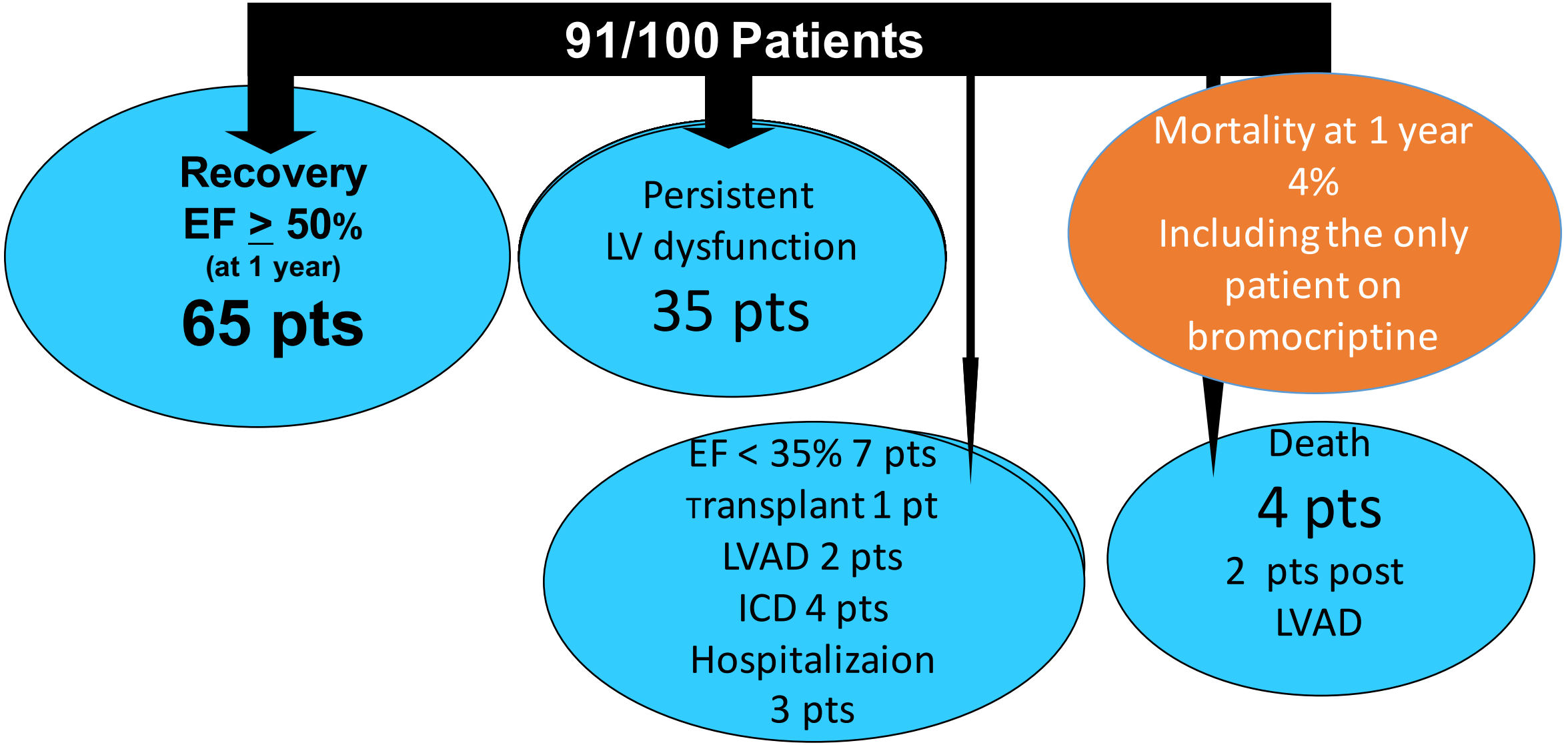
McNamara D, Elkayam U et al JACC 2015

Complete recovery: all patients 72%
White 77% , black 59%

Bromocriptine in The Treatment of PPCM



IPAC Study
One Year Outcome of PPCM in the US



Bromocriptine in The Treatment of PPCM - A Proof of Concept?

Elkayam U, Goland S, Circulation 2010;121:1463

- Very small study.
- A proof of concept? No, a pilot study.
- Very high mortality rate in controls.
- No LV recovery in majority of the controls.
- Data is not applicable to non-African patients.
- Completely irrelevant to patients in US and Europe.

Bromocriptine in PPCM: Argument against #2

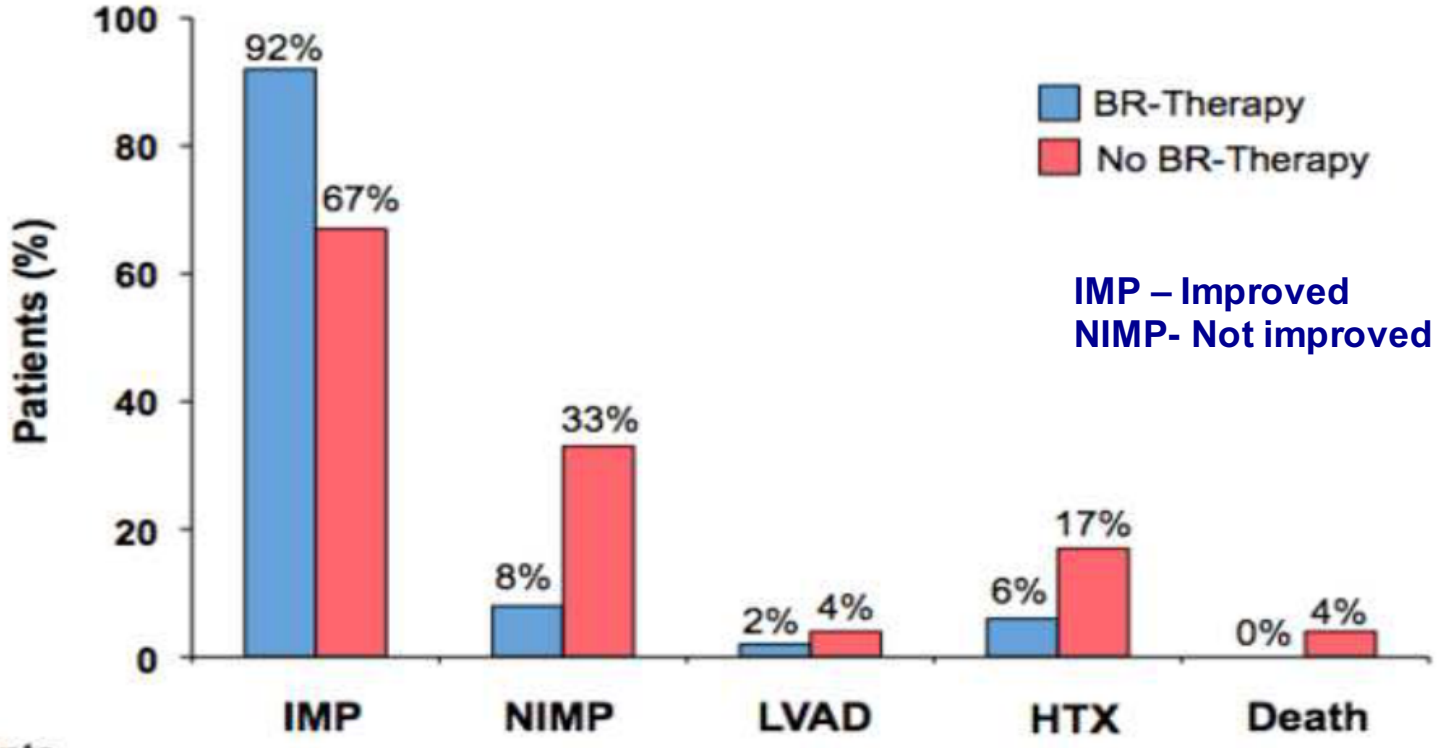
The majority of women with PPCM, including AAs, recover on conventional therapy without bromocriptine

German cohort of patients with PPCM

Haghikia a et al 2012

Figure 3

N=77 patients



No. of Patients	IMP	NIMP	LVAD	HTX	Death
BR-Therapy, n=50	46	4	1	3	0
No BR-Therapy, n=24	16	8	1	4	2

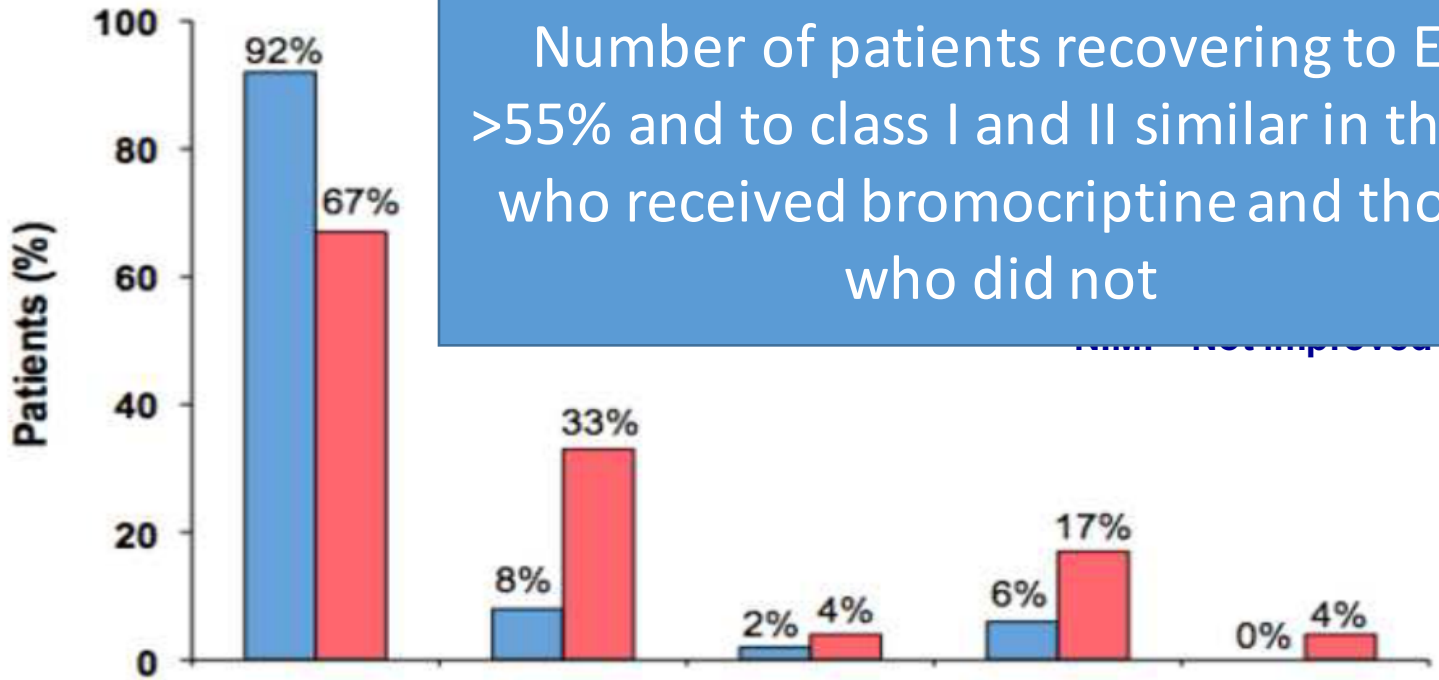
German cohort of patients with PPCM

Haghikia a et al 2012

Figure 3

N=77 patients

Number of patients recovering to EF >55% and to class I and II similar in those who received bromocriptine and those who did not



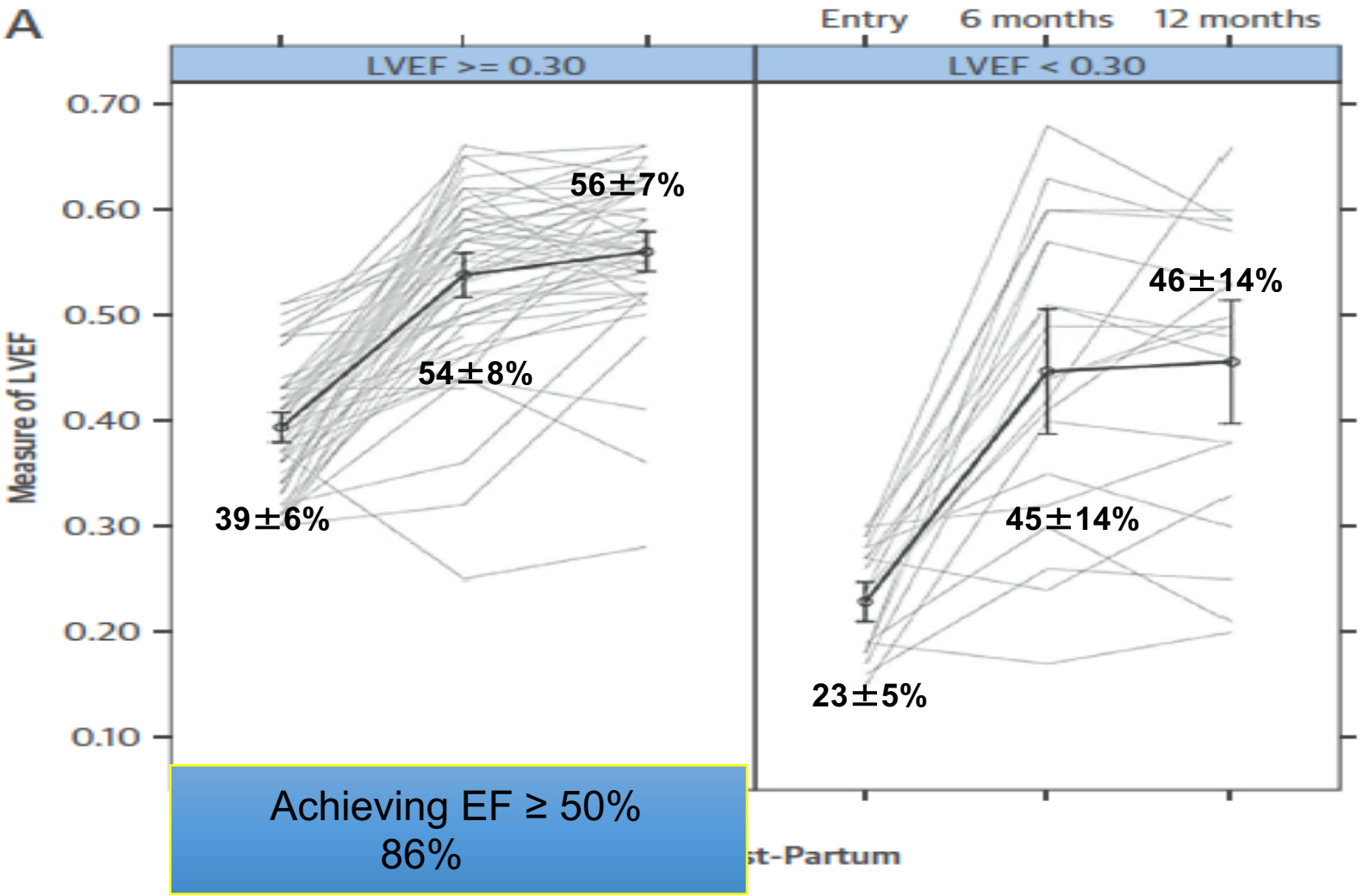
No. of Patients	IMP	NIMP	LVAD	HTX	Death
BR-Therapy, n=50	46	4	1	3	0
No BR-Therapy, n=24	16	8	1	4	2

German cohort of patients with PPCM

Haghikia a et al 2012

- These findings suggest that patients treated with standard therapy plus bromocriptine may have a higher chance for recovery.

Effect Of Baseline LVEF on Recovery



Achieving EF ≥ 50%
86%

German cohort of patients with PPCM

Why am I not impressed?

- Open registry.
- Small number of patients (Only 12 patients in the NR group).
- NR significantly sicker.

German cohort of patients with PPCM

Haghikia a et al 2012

Parameter	Improved (N=65)	Not improved (N=12)	P value
LVEF	28 + 9 %	17+5%	<0.0001
LVEDD	59+7 mm	70+8 mm	0.002
NYHA IV	42%	85%	
Heart Rate	94+27 bpm	104+19 bpm	0.16
Hypertension	49%	7%	0.009
Bromocriptine	72%	35%	0.013
Beta blockers	95%	50%	0.0001
ACEi/ARB	93%	71%	0.04
MRA	65%	57%	NS

German cohort of patients with PPCM

Why am I not impressed?

- Rate of LV recovery very similar to that found in the IPAC Study where Bromocriptine was not used
- 72% of all IPAC patients and 77% of whites improved to >50% v. 47% of german patients improved to >55% (same in BR and non BR)

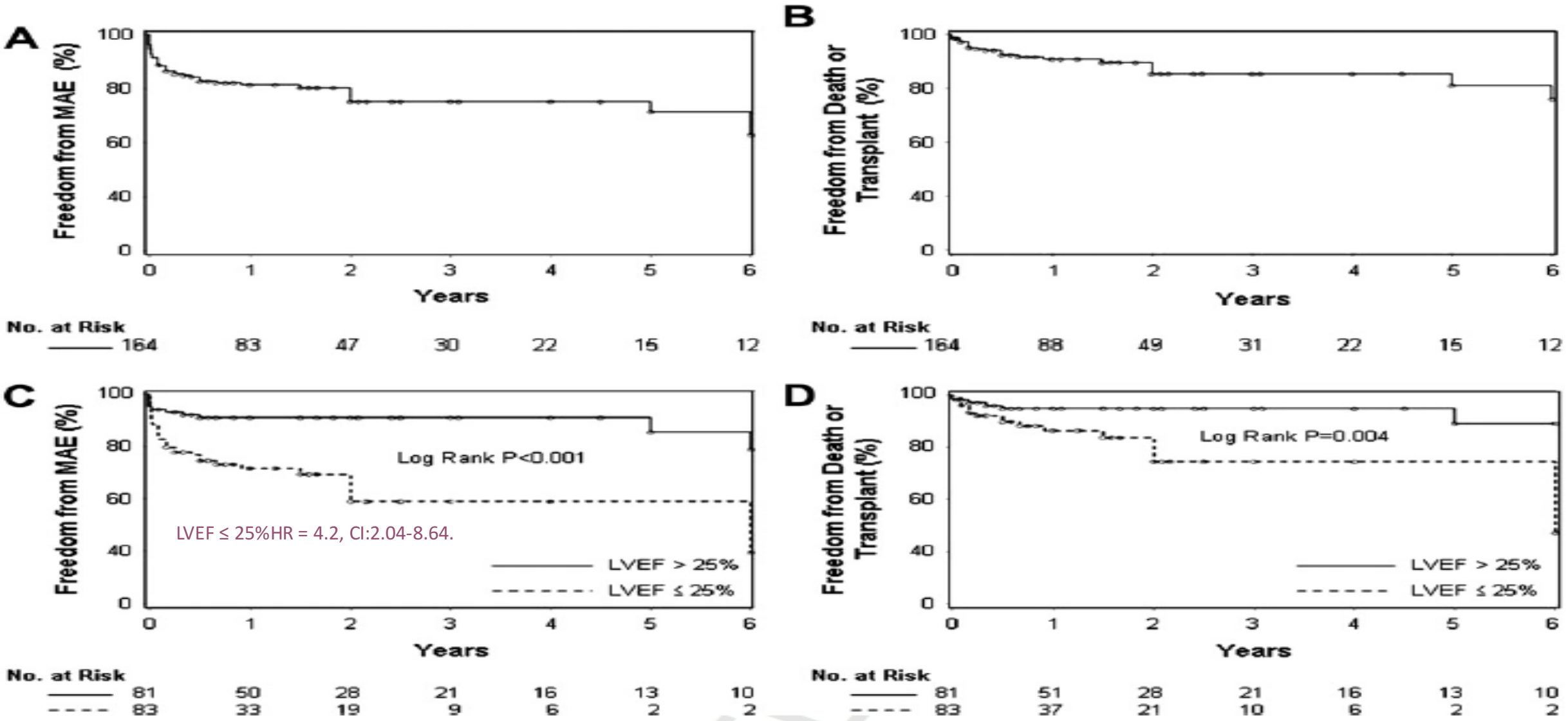
German cohort of patients with PPCM

Why am I not impressed?

- Percent of patients showing full recovery similar in those who did and did not receive bromocriptine,
- The benefits from bromocriptine in patients at high risk of not recovering (Low EF, large LVEDP) still uncertain.

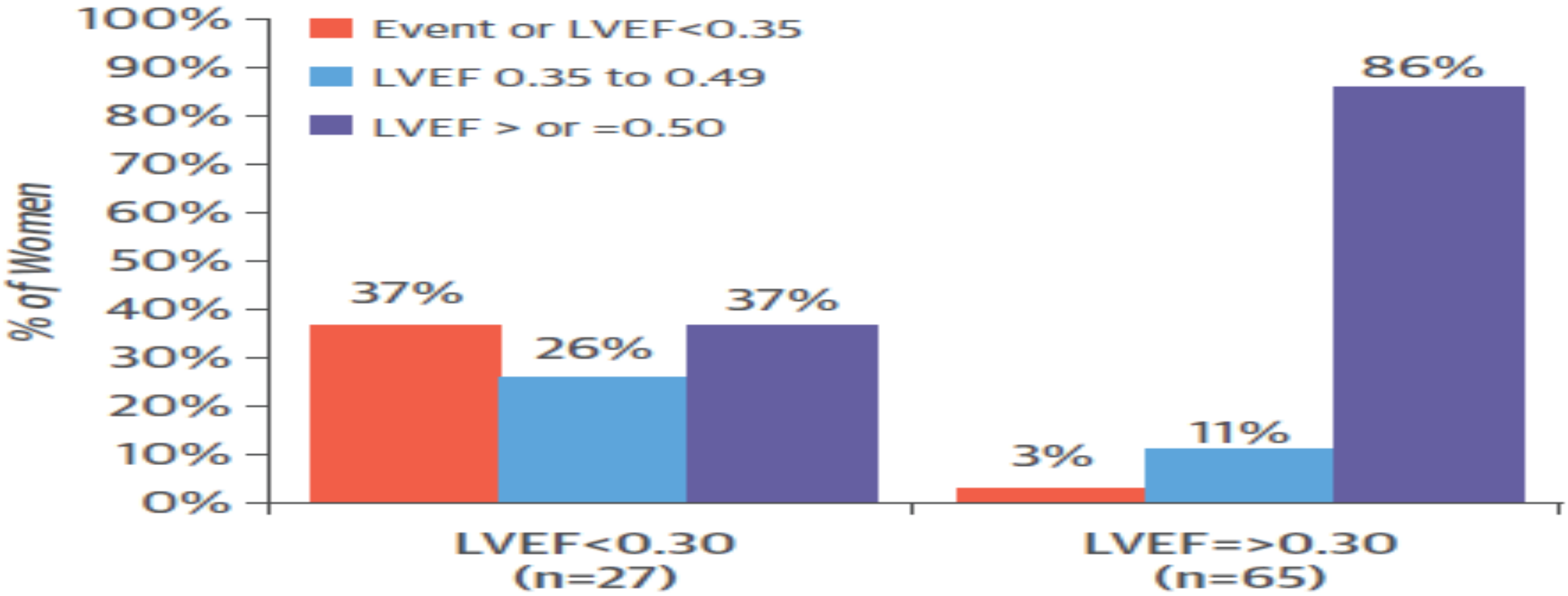
Relations Between LVEF and Major Complications

Goland, Elkayam. J Cardiac Failure 2009



Final Status Based On Initial LVEF

FIGURE 4 **Final Status Based on the Initial LVEF**



ELSEVIER

The European Journal of Heart Failure 4 (2002) 305–309

The European Journal of Heart Failure

www.elsevier.com/locate/heafai

The addition of pentoxifylline to conventional therapy improves outcome in patients with peripartum cardiomyopathy

Karen Sliwa*, Daniel Skudicky, Geoffrey Candy, Anette Bergemann, Mark Hopley, Pinhas Sareli

Department of Cardiology, Baragwanath Hospital, University of the Witwatersrand, PO Bertsham 2013, Johannesburg, South Africa

Received 29 June 2001; received in revised form 3 August 2001; accepted 23 October 2001

30 women with PPCM received 400 mg tid of pentoxifylline plus standard care vs. 29 women on standard care alone.
Combine end point: death, failure to improve EF > 10%, Class III-IV.
Results 52% on standard care vs. 27% on PF P=0.03.

ELSEVIER

The European Journal of Heart Failure 4 (2002) 305–309

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Bromocriptine in PPCM: Argument against #3

Bromocriptine prevents breast feeding

Breast feeding

On the basis of the postulated negative effect of prolactin sub fragment, breast feeding is not advised in women with PPCM

Sliwa K et al 2010,

ESC working group on PPCM

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 US$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.

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

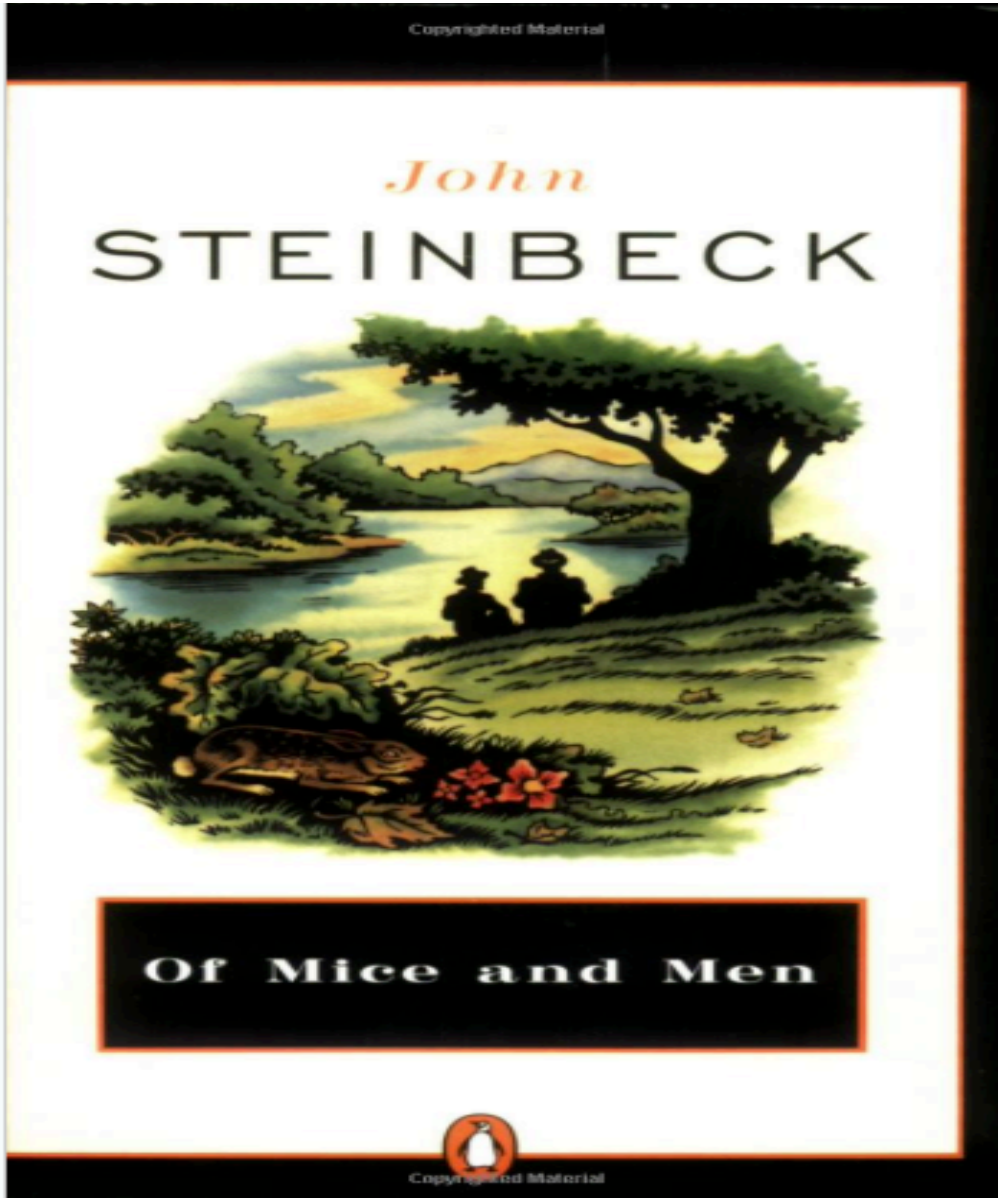
Why is it not ready for routine use?

- 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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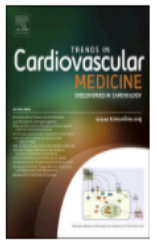

Editorial Commentary

"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