Peripartum Cardiomyopathy

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Case

- A 25 yo AA female G3,P2,Ab1.
- Had an uncomplicated C-section at 33 weeks B/O preeclampsia .
- Patient readmitted to the hospital 3 days after D/C (6 days PP) for abdominal pain and had a surgical evacuation of abdominal wall hematoma.
- D/C home in “stable condition” although HR at 115-120 bpm (attributed to anemia) and ECG demonstrated deeply inverted T-waves.

Case

- 4 days post discharged (2 weeks PP) patient was found without vital signs at home and was pronounced dead.
- Autopsy showed enlarged heart with bi ventricular dilation with normal wall thickness and normal coronaries.

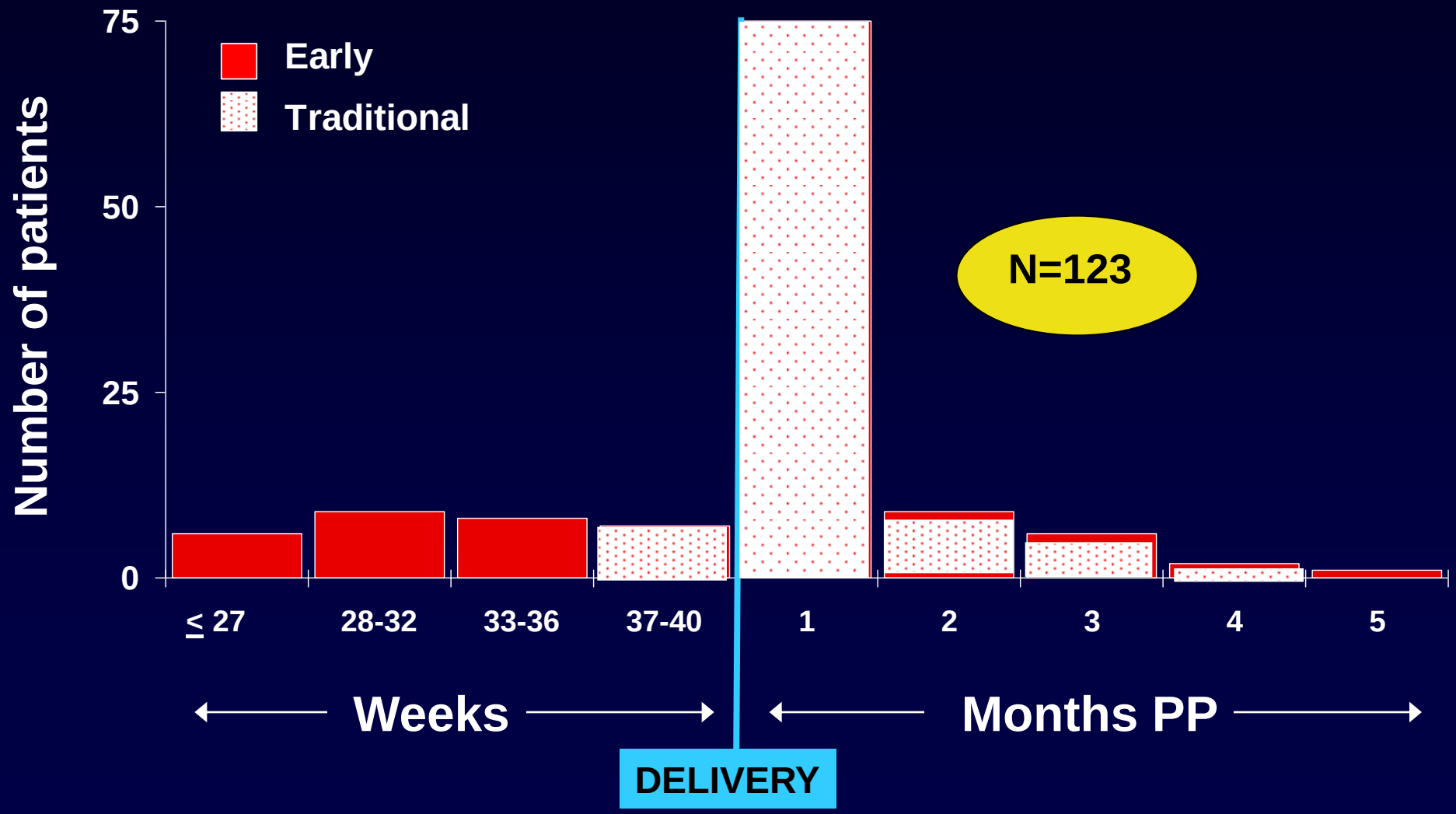
Traditional Definition

- Development of HF in the last month of pregnancy or within 5 months of delivery
- Absence of identifiable cause for HF
- Absence of recognizable heart disease prior to the last month of pregnancy
- Left ventricular systolic dysfunction demonstrated by echocardiography

Demakis et al 1971, Hibbard et al 1999, NIH Workshop Recommendations and Review 1997, Pearson et al, JAMA 2000; 283:1183

PPCM – Time of Diagnosis

Elkayam et al. Circulation 2005;111:2050



Peripartum Cardiomyopathy Updated Definition

ESC Working Group. Eur J Heart Failure 2010;12:767

- **PPCM is an idiopathic cardiomyopathy presenting with HF secondary to LV systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of HF is found.**
- **It is a diagnosis of exclusion.**

PPCM – Population birth Prevalence and 7 Year Mortality

Harper MA Obstet Gynecol 2012;120:1031

Table 1. Distribution of Cases, Birth Prevalence, and Case-Fatality by Race, Ethnicity, and Age

Race and Ethnicity	Distribution of All Cases	Cases Per Live Birth	Prevalence, Cases Per 10,000 Live Births (95% CI)	No. of Deaths (Fatality Rate Per 100 Cases)
Total	85 (100)	1/2,772	3.61 (2.88–4.46)	14 (16.5)
Race and ethnicity				
White non-Hispanic	33 (38.9)	1/4,266	2.34 (1.61–3.29)	2 (6.1)
Black non-Hispanic	50 (58.9)	1/1,087	9.20 (6.83–12.12)	12 (24.0)
Hispanic	1 (1.1)	1/31,140	0.32 (0–1.79)*	0
Asian or Pacific Islander	1 (1.1)	1/5,954	1.68 (0.04–9.35)*	0
Age (y)				
Younger than 18	2 (2.3)	1/4,763	2.10 (0.25–7.58)*	0
18—24	23 (27.1)	1/3,563	2.81 (1.78–4.21)	4 (17.4)
25—29	16 (18.8)	1/3,904	2.56 (1.46–4.16)	4 (25.0)
30—34	17 (20.0)	1/3,188	3.14 (1.82–5.02)	1 (5.9)
35—39	23 (27.1)	1/997	10.03 (6.36–15.04)	4 (17.4)
Older than 39	4 (4.7)	1/1,134	8.82 (2.40–22.56)	1 (25.0)

CI, confidence interval. Data are n (%) unless otherwise specified.
* These estimates are unstable because of small numbers.

235,599 live births in North Carolina between 2002-2003, Incidence 1:2772

PPCM – Population birth Prevalence and 7 Year Mortality

Harper MA Obstet Gynecol 2012;120:1031

Pregnancy-Related Complications	All (N=79)*	Survivors (n=71)	Decedents (n=8)†
Chronic hypertension	10 (12.7)	9 (12.7)	1 (12.5)
Gestational hypertension	18 (22.8)	15 (21.1)	3 (37.5)
Preeclampsia	11 (13.9)	9 (12.7)	2 (25.0)
HELLP syndrome	1 (1.3)	1 (1.4)	0
Eclampsia	1 (1.3)	1 (1.4)	0
Preeclampsia superimposed on chronic hypertension	10 (12.7)	8 (11.3)	2 (25.0)
Gestational diabetes	7 (8.9)	7 (9.9)	0
Pregestational diabetes	5 (6.3)	5 (7.0)	0
Multifetal gestation	7 (8.9)	5 (7.0)	2 (25.0)
Ejection fraction at time of diagnosis	0.28 (0.08-0.50)‡	0.30 (0.08-0.50)§	0.18 (0.10-0.20)‖

29%

Multifetal gestation 9%

Peripartum Cardiomyopathy

Associated conditions in the US

- Maternal age > 30 yrs.
- Black.
- Twin pregnancies.
- History of HTN / Preeclampsia.
- Multiparity.

Preeclampsia and PPCM

An e-mail from a patient

“My OB was concerned with my high BP and swelling but his only thought was preeclampsia. He did tests to rule it out but didn't rule out issues with my heart or asked me if I had difficulty breathing while laying down”.

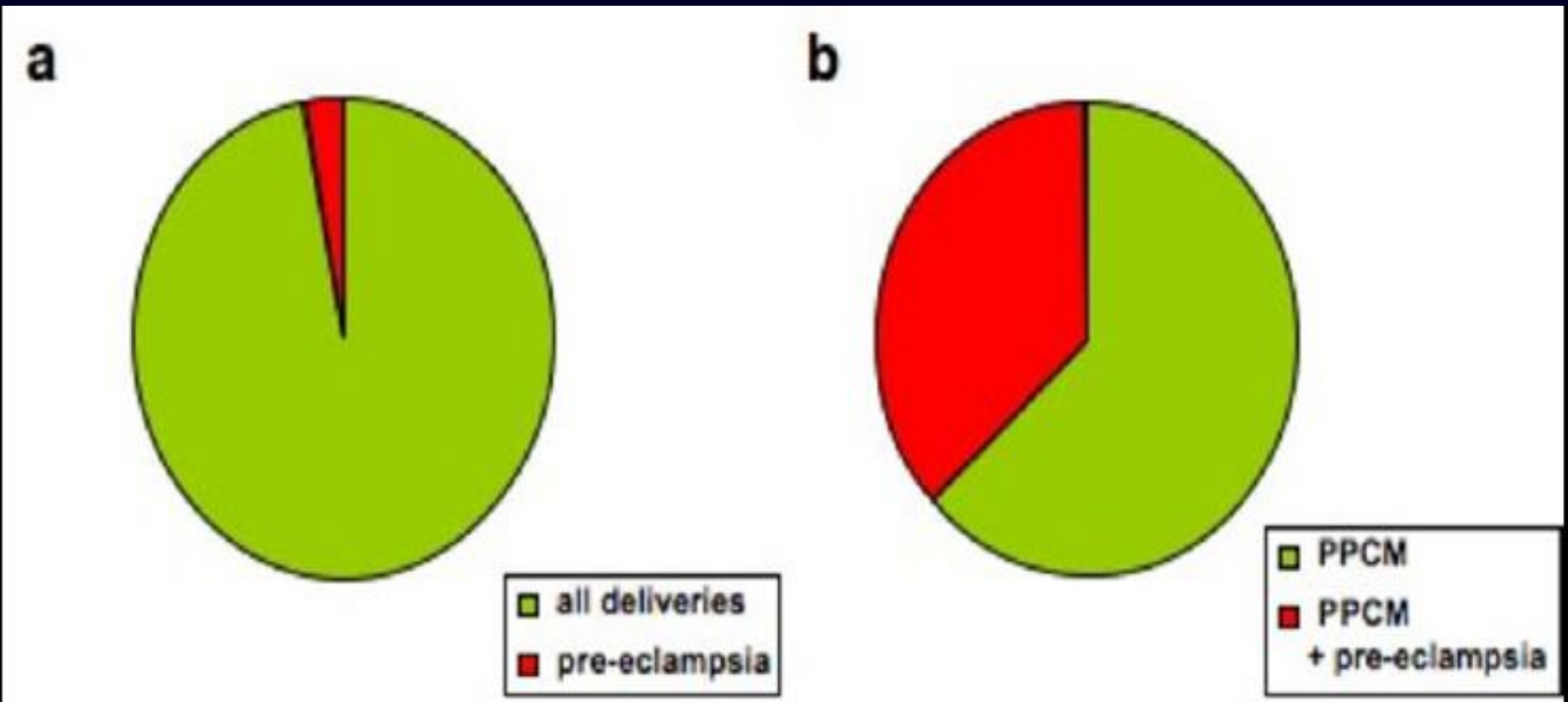
Preeclampsia and PPCM

An e-mail from a patient

"When a patient is experiencing high BP and edema PPCM needs to come to their minds just as preeclampsia does. The doctors need to be more educated so they can educate their patients on signs and symptoms of PPCM".

Cardiac Angiogenic Imbalance Leads to PPCM

Patten IS et al, Nature 2012



Sup Figure 8

Harvard teaching hospitals last 9 years

PPCM or Preeclampsia?

Left Ventricular Structure and Function in Preeclampsia

Variable	Preeclampsia	Normotensive pregnant	Normotensive non pregnant
Number	40	35	10
LA Dimension (mm)	36±3	35±3	31±2
LVED Volume (ml)	115±17	103±12	103±20
LVES Volume (ml)	39±10	33 ±8	30 ±10
LVEF(%)	66 ±6	68 ±5	71 ±5

Borghi C et al Am J Obstet Gynecol 2000;183:140-7

PPCM or Preeclampsia?

- Preeclampsia presenting with heart failure – Think PPCM.
- Order an echocardiogram to assess LV function and BNP.

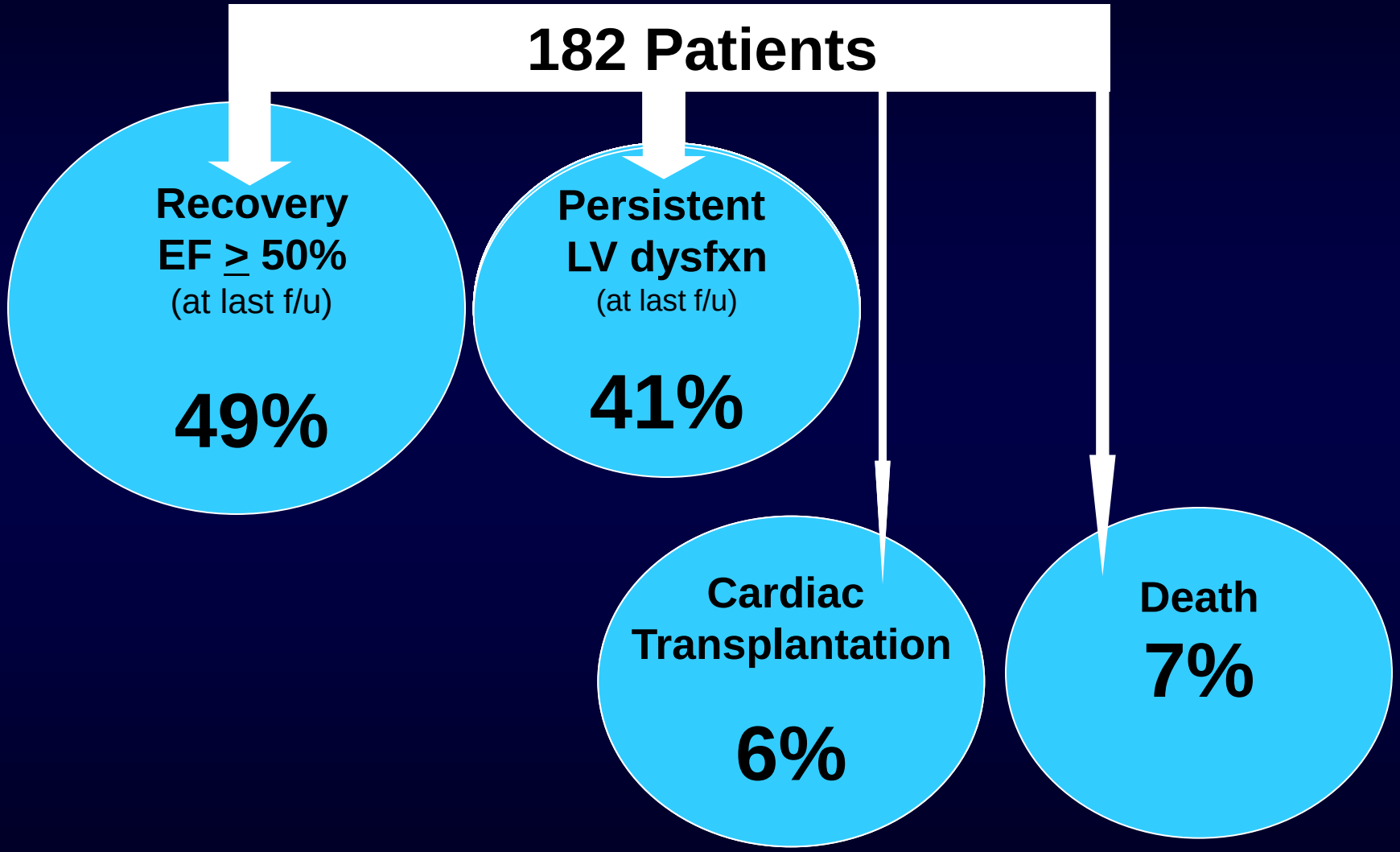
Delayed diagnosis is common
(Goland, Elkayam, J cardiac Failure 2009)

- ≥ 1 week delay in diagnosis after onset of symptoms reported in 60% of 182 cases.
- Complications preceded the diagnosis of PPCM in 50% of pts.
- 32% of surviving patients without cardiac transplantation, had residual brain damage.

periartum Cardiomyopathy
Clinical Presentation

- CHF signs and symptoms.
- Arrhythmias
  (with or without CHF).
- Thromboembolism.

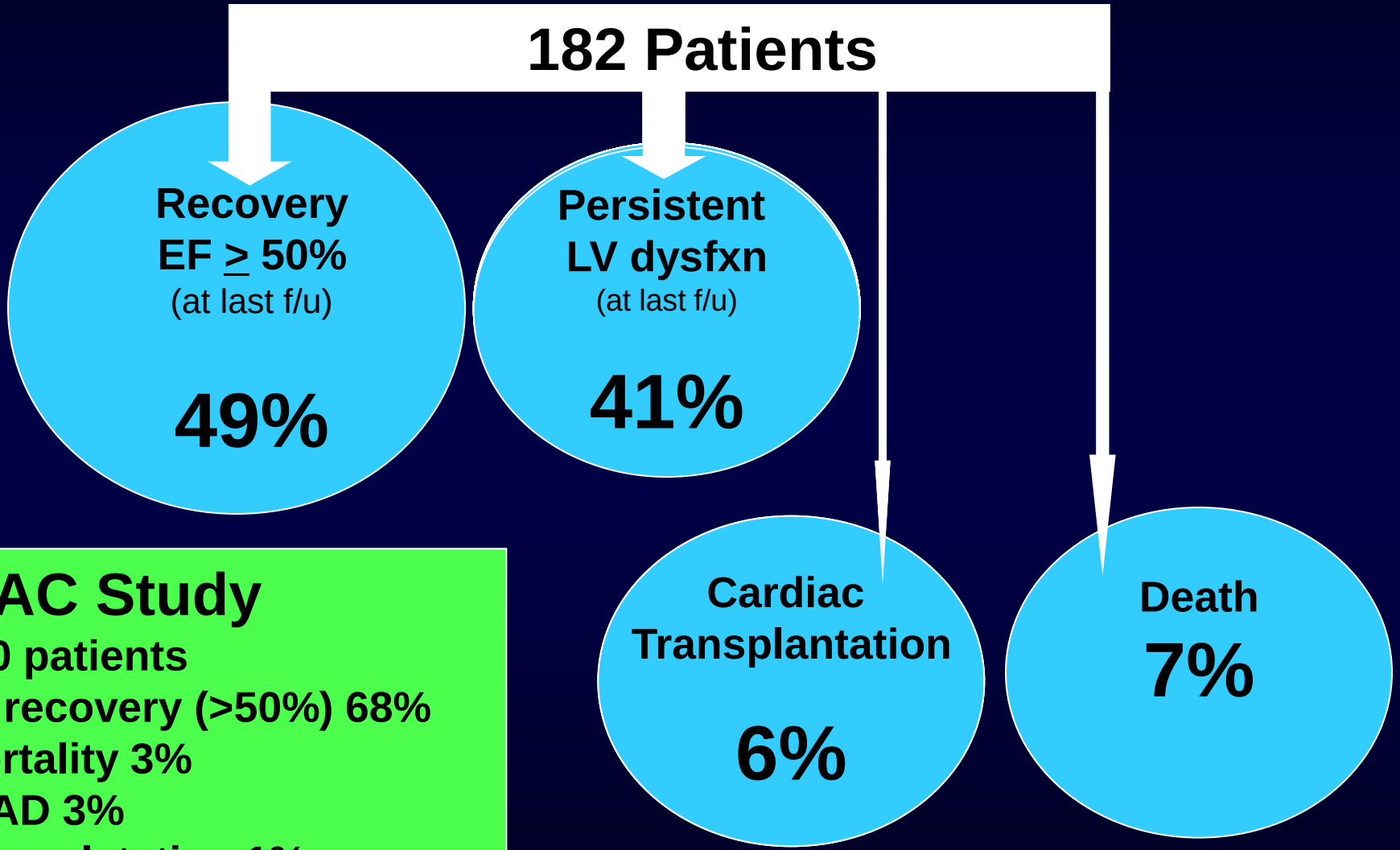
Outcome of PPCM in the US



Goland et al. J cardiac Fail 2009;15:645

Outcome of PPCM in the US

Goland, Elkayam et al J Cardiac Failure 2009;15:645



IPAC Study

100 patients
LV recovery (>50%) 68%
Mortality 3%
LVAD 3%
Transplatation 1%

Baseline LVEF a strong predictor of LV Recovery in PPCM

Goland S, Modi K, Safirstein J, Elkayam U JCF 2011 2011;17:426-30

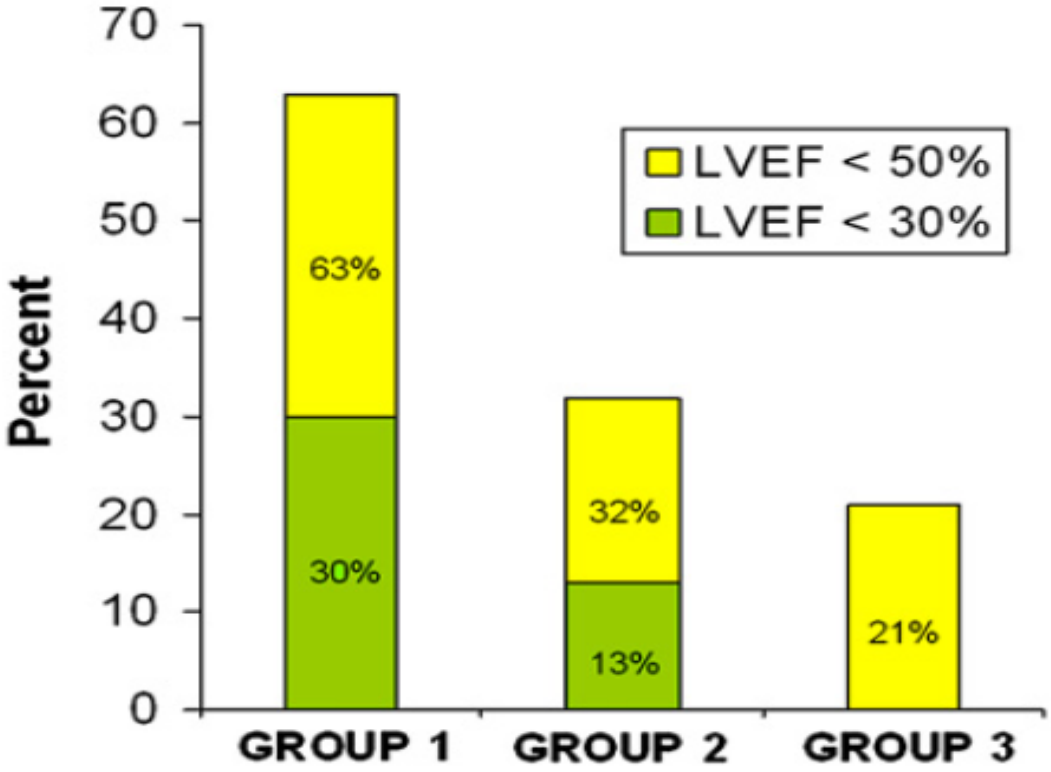


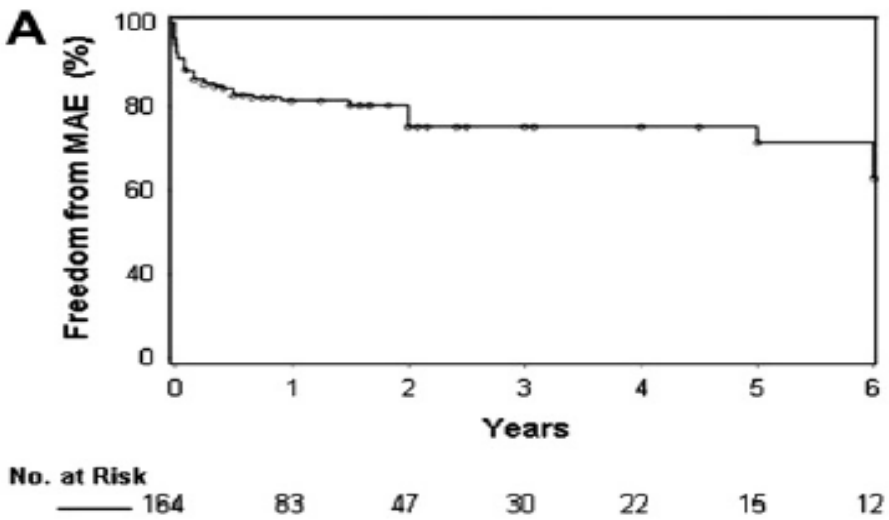
Fig. 2. Failure to achieve left ventricular ejection fraction (LVEF) of 50% and 30% at ≥6 month in different groups according to baseline LVEF: group I: 10%—19%; group II: 20%—29%; and group III: 30%—45%.

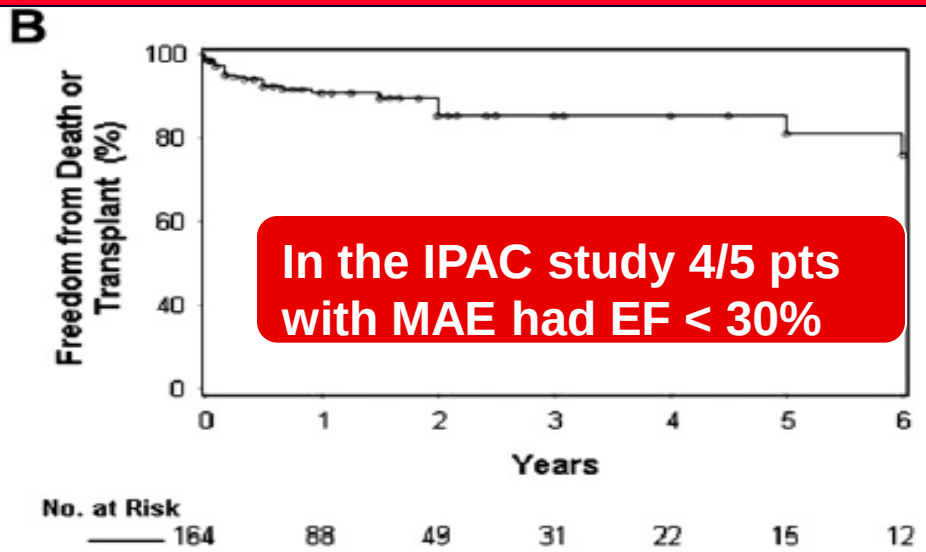
PPCM
Breast feeding

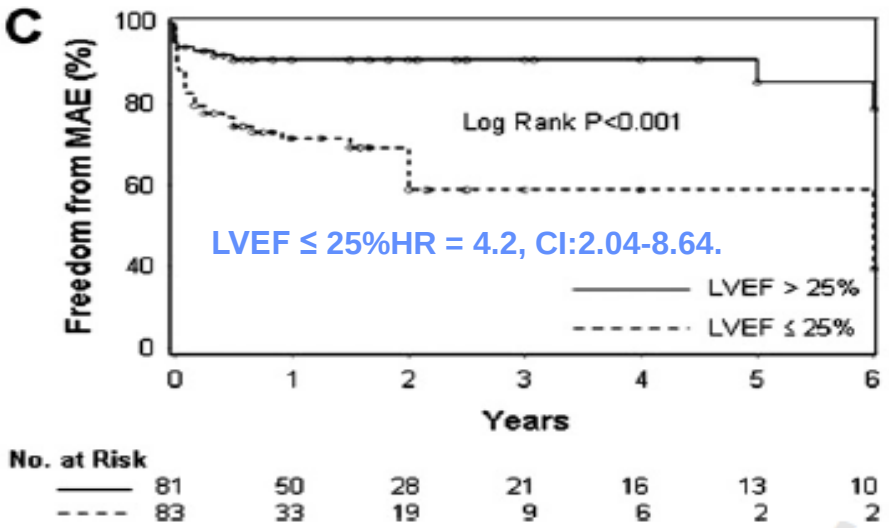
- “On the basis of the postulated negative effect of prolactin sub fragment, breast feeding is not advised in women with PPCM” (Sliwa 2010, ESC working group on PPCM)
- Higher degree of recovery of LV function in women who breast fed (Safirstein 2011).
- Most HF medications categorized as compatible with breast feeding by AAP.

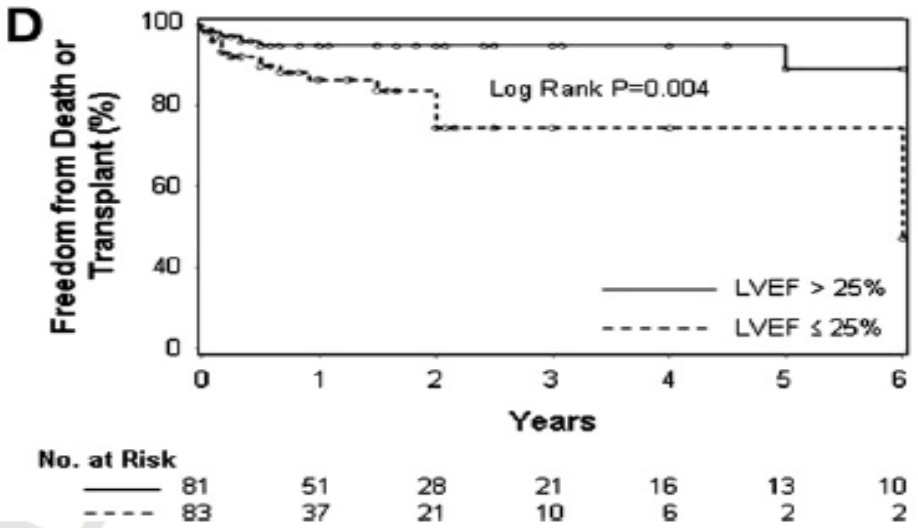
Relations Between LVEF and Major Complications

Goland, Elkayam. J Cardiac Failure 2009









Peripartum Cardiomyopathy

Therapeutic considerations during pregnancy

Safe Drugs:

- Digoxin
- Nitrates
- Hydralazine
- Heparin
- Diuretics
- Metoprolol tartrate

Unsafe Drugs:

- ACE-I
- Nitroprusside
- Amiodarone
- Warfarin

No information

- Spironolactone
- Carvedilol
- Metoprolol succinate

Peripartum Cardiomyopathy
Therapeutic considerations post partum

- ACE-I, beta blockers, aldosterone receptor antagonists.
- Anti coagulation until LV improves.
- Temporary mechanical support (IABP, LVAD) may be useful as bridge to recovery.
- Wearable or defibrillator in high risk patients (LVEF < 30%).

Wearable defibrillator

LV Thrombus in PPCM

Meyer GP J Med Case Rep 2010;4:80

35 YO African woman. 4 weeks after C section. class IV. LVEF 9%.

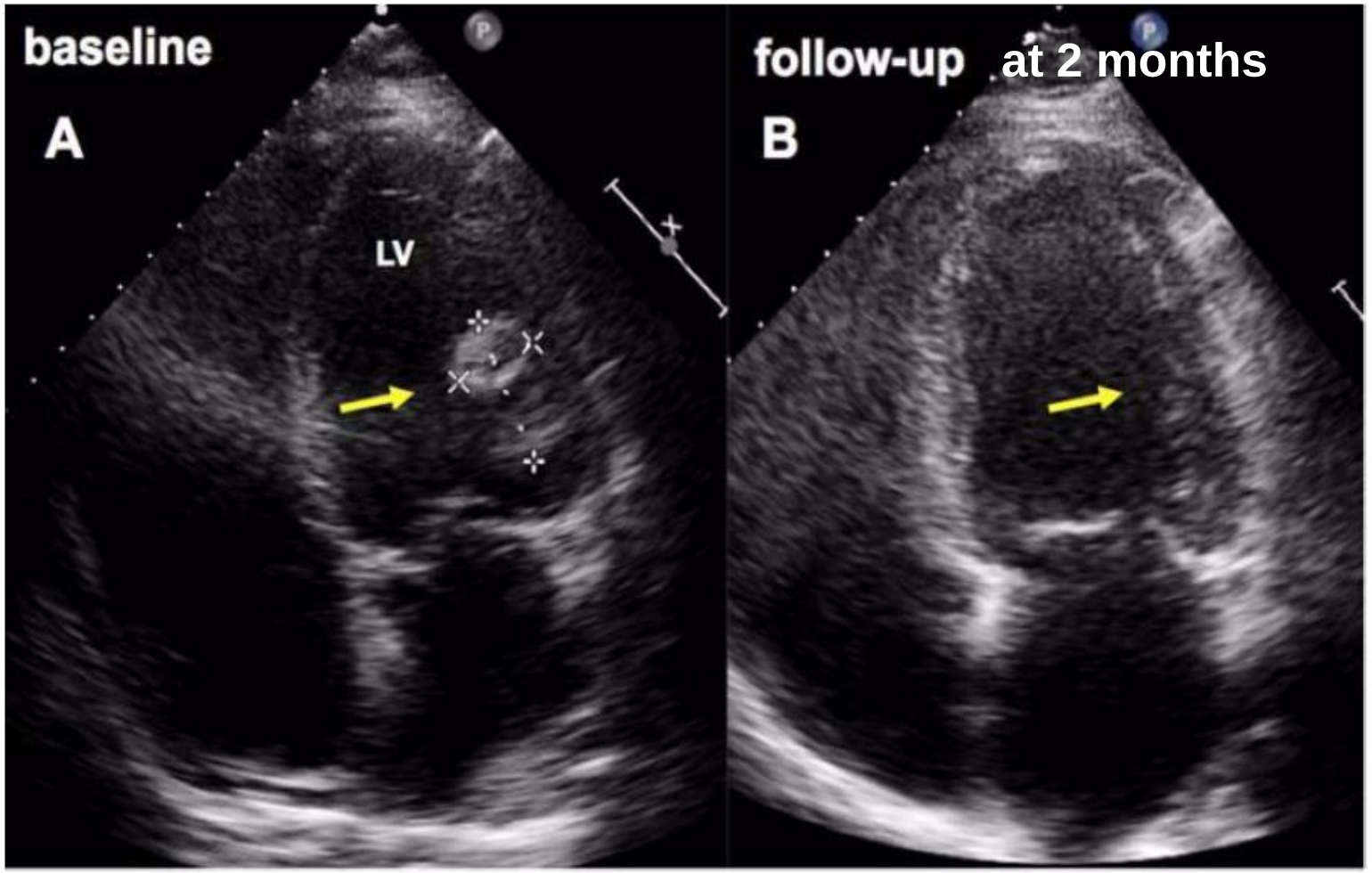


Figure 1 Four-chamber view on initial echocardiogram demonstrates a large thrombus (arrow) attached to the lateral wall of the left ventricle (LV) at baseline (A), which has completely resolved after two months (B).

32 YO F diagnosed 10 d after C section, LVEF @ 20%. 1 mo later echo showed new LV apical mural thrombus 35x20 mm, coagulation studies negative. Started on warfarin. 1 week later thrombus became mobile (fig 1) and was removed by emergency surgery. 3 d later 3 new LV thrombi (fig 2) treated successfully with AC, D/C with EF 33%, 2 y later NYHA I, EF 63%

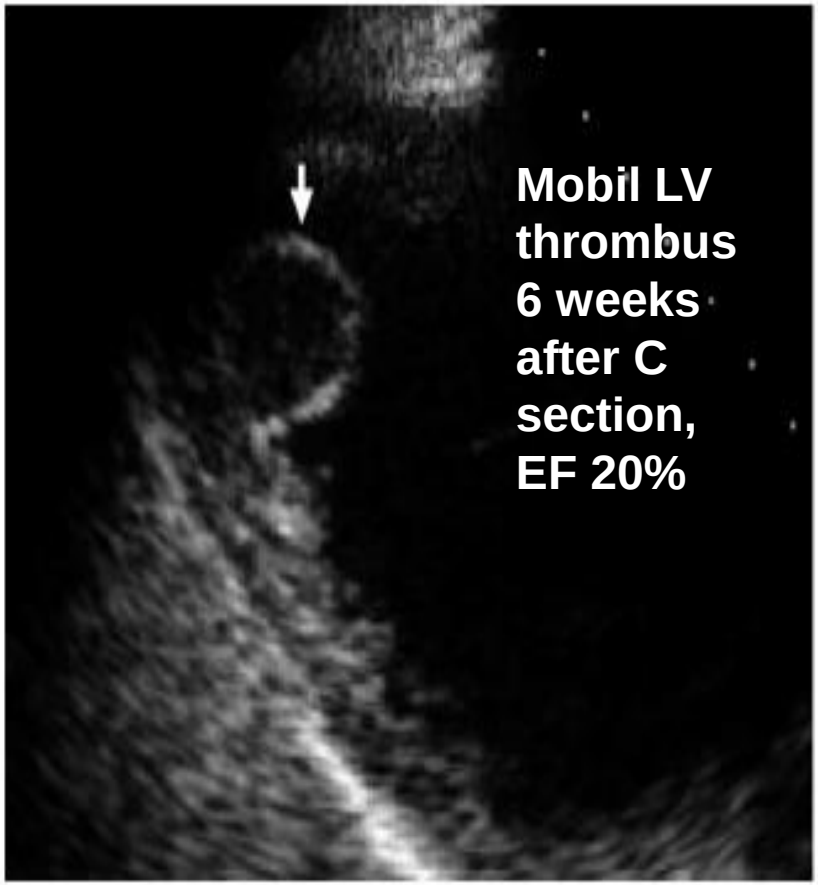


Fig 1. A long axis view of a perioperative transthoracic echocardiogram. Note the mobile mass at the apex (white arrow).

Fig 2. A short axis view of a postoperative transthoracic echocardiogram taken on postoperative day 3. Three mural thrombi were prominent (white arrows), which were neither present during intraoperative observation nor visible in an intraoperative transesophageal echocardiogram.

Shimamoto T. Circ J 2008;72:853

PPCM - Coronary embolization

Box LC. Tex Heart Inst J 2004;31:442

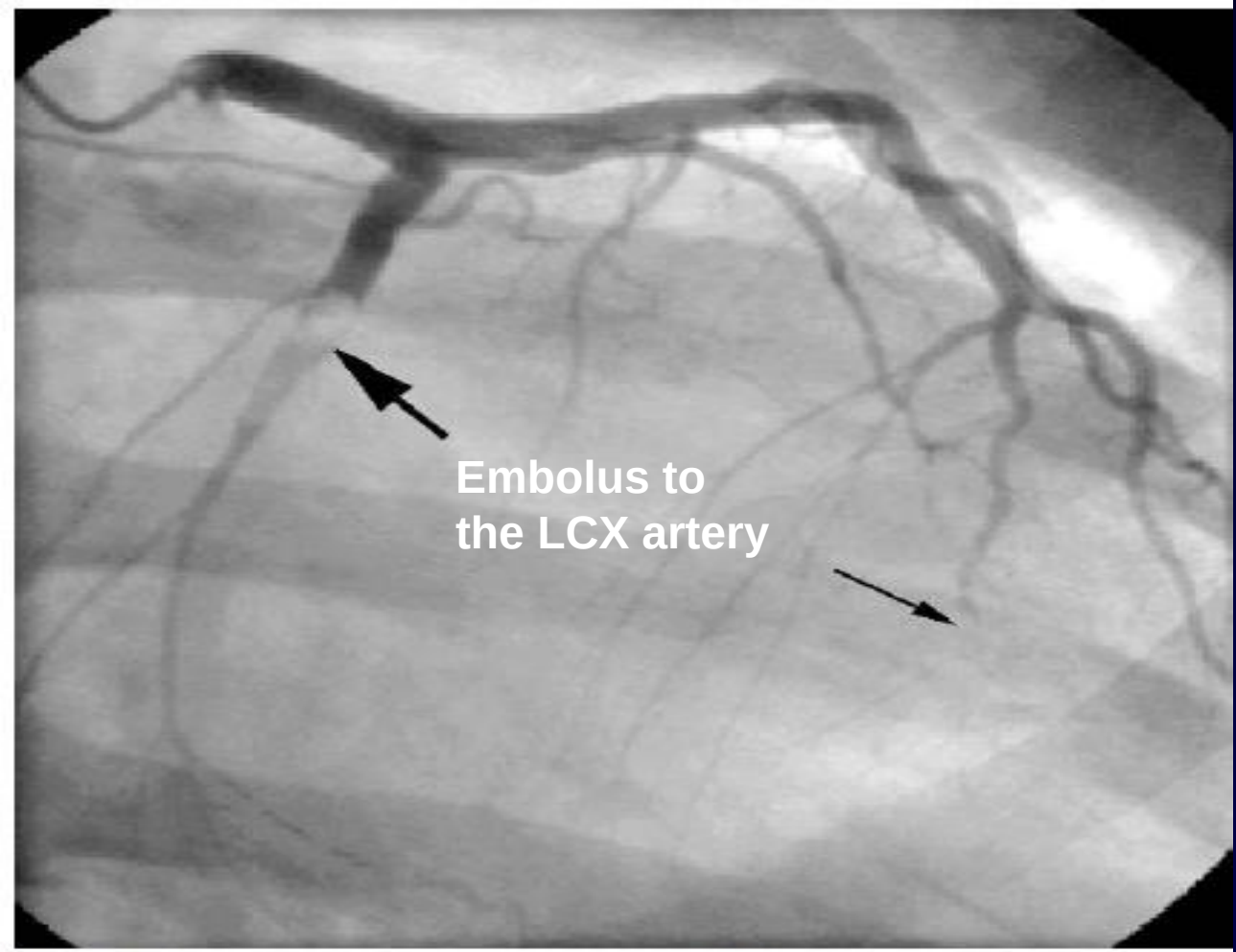
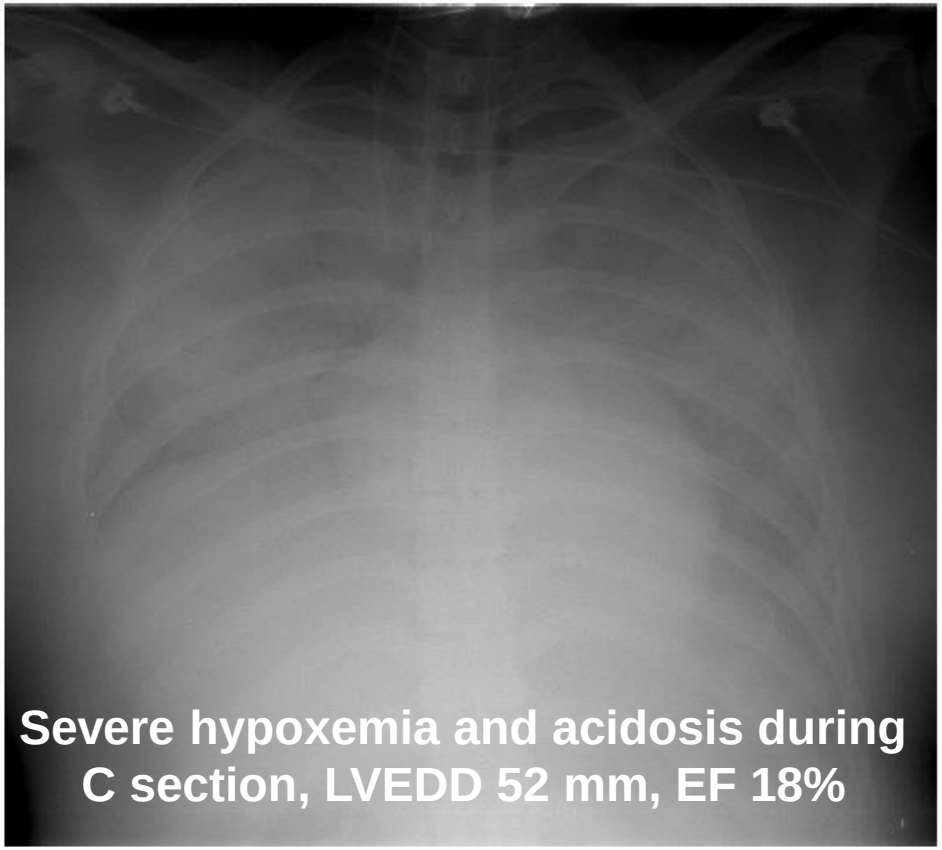


Fig. 1 *An embolus is present in the left circumflex artery (large arrow) and the distal left anterior descending coronary*

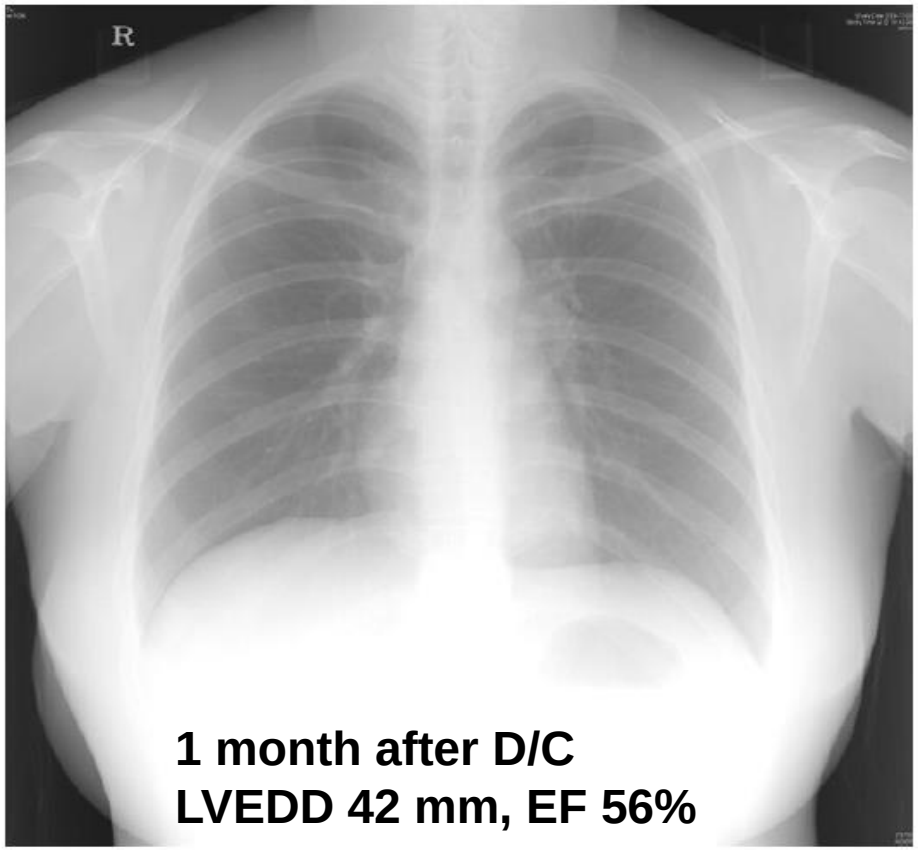
Extracorporeal Membrane Oxygenation in a Patient With Peripartum Cardiomyopathy

(Ann Thorac Surg 2007;84:262–4)



Severe hypoxemia and acidosis during C section, LVEDD 52 mm, EF 18%

Fig 1. Severe pulmonary edema was shown in the chest x-ray taken at admission.



1 month after D/C LVEDD 42 mm, EF 56%

Fig 2. Chest x-ray taken during an outpatient visit (1 month after discharge).

18 YO G1 developed tachycardia and hypertension with severe hypoxemia (PO_2 30%) and acidosis during C section which was not corrected with Inotropic support and 100% oxygen. LVEF 18%. ECMO was use successfully for 24 h, Pt. extubated on day 4 and was D/C home on day 12 with LVEDD of 42 from 52 mm and LVEF of 56%.

PPCM

New Concepts in Pathophysiology and Management

The Oxidative Stress Hypothesis:
Rational for the use of Bromocriptine for the treatment of PPCM

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

Denise Hilfiker-Kleiner,[1,*] Karol Kaminski,[1] Edith Podewski,[1] Tomasz Bonda,[1] Arnd Schaefer,[1] Karen Sliwa,[3] Olaf Forster,[3] Anja Quint,[1] Ulf Landmesser,[1] Carola Doerries,[1] Maren Luchtefeld,[1] Valeria Poli,[4] Michael D. Schneider,[5] Jean-Luc Balligand,[6] Fanny Desjardins,[6] Aftab Ansari,[7] Ingrid Struman,[8] Ngoc Q.N. Nguyen,[8] Nils H. Zschemisch,[1] Gunnar Klein,[1] Gerd Heusch,[9] Rainer Schulz,[9] Andres Hilfiker,[1,2] and Helmut Drexler[1]

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DOI 10.1016/j.cell.2006.12.036

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

Imbalance Between Oxidative Stress and Antioxidants lead to PPCM

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

- Pregnancy, mostly because of the mitochondria-rich placenta, is a condition that favors oxidative stress.
- STAT3 (Signal Transducers and Activators of Transcription 3) is involved in cardiac protection from oxidative stress, by up regulation of antioxydative enzymes (manganese superoxide dismutase - MnSOD). Megoro, Circ 2001

Bromocriptine as treatment of PPCM

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

- In addition STAT3 plays an important roll in promoting myocardial angiogenesis.
  Hilfiker, Circ Res 2004
- Female mice with cardiomyocite-specific knockout of STAT3 developed PPCM. Hilfiker, Cell 2007

Bromocriptine in the treatment of PPCM
Hilfiker-Kleiner et al. Cell 2007;128:589

- In the absence of STAT3, oxidative stress enhances the expression of cardiac cathepsin D (A protease) which cleaves the nursing hormone Prolactin to a 16 kDa form.

  Corbacho, J Endocrinol 2002

Bromocriptine in the treatment of PPCM
Hilfiker-Kleiner et al. Cell 2007;128:589

- 16 kDa Prolactin causes apoptosis, capillary dissociation, vasoconstriction and impaired myocyte metabolism which lead to myocardial dysfunction.
  Tabruyn, Mol Endocrinol 2003.
- Treatment with bromocriptine , an inhibitor of prolactin , prevents the development of PPCM.
  Hilfiker, Cell 2007

PPCM
Bromocriptine

Luck of STAT3 (Signal Transducers and Activators of Transcription) results in deacresed Mn SOD

↓

↑Superoxide production →Cardiac cathepsin D expression

↓

Generates cleaved form of PROLACTIN (16 kDa)
Anti-angiogenic
Pro-apoptotic

↓

Endothelial cell apoptosis, capillary dissociation,Vasoconstriction.

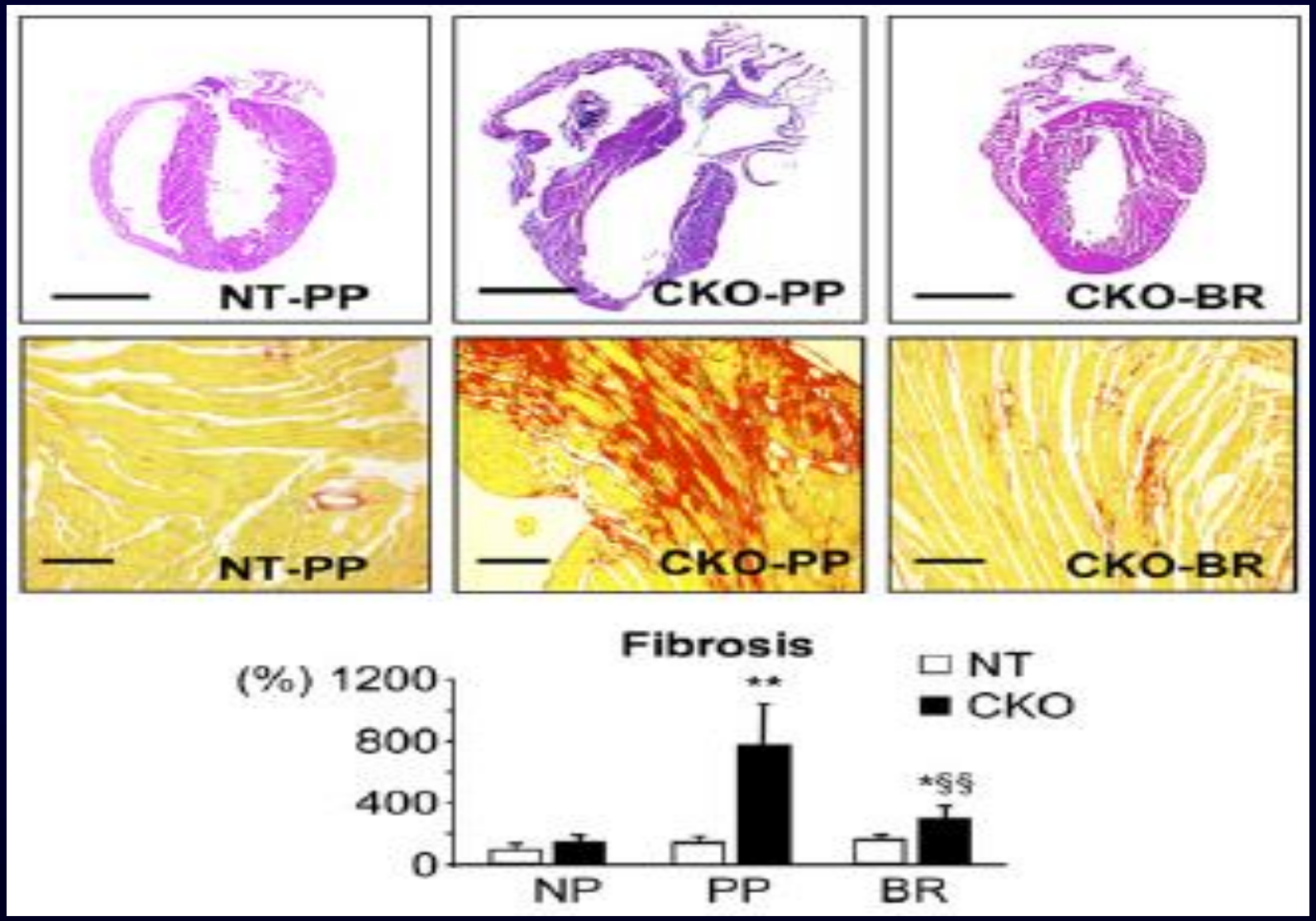
▼

Impaired microcirculation and myocardial dysfunction

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

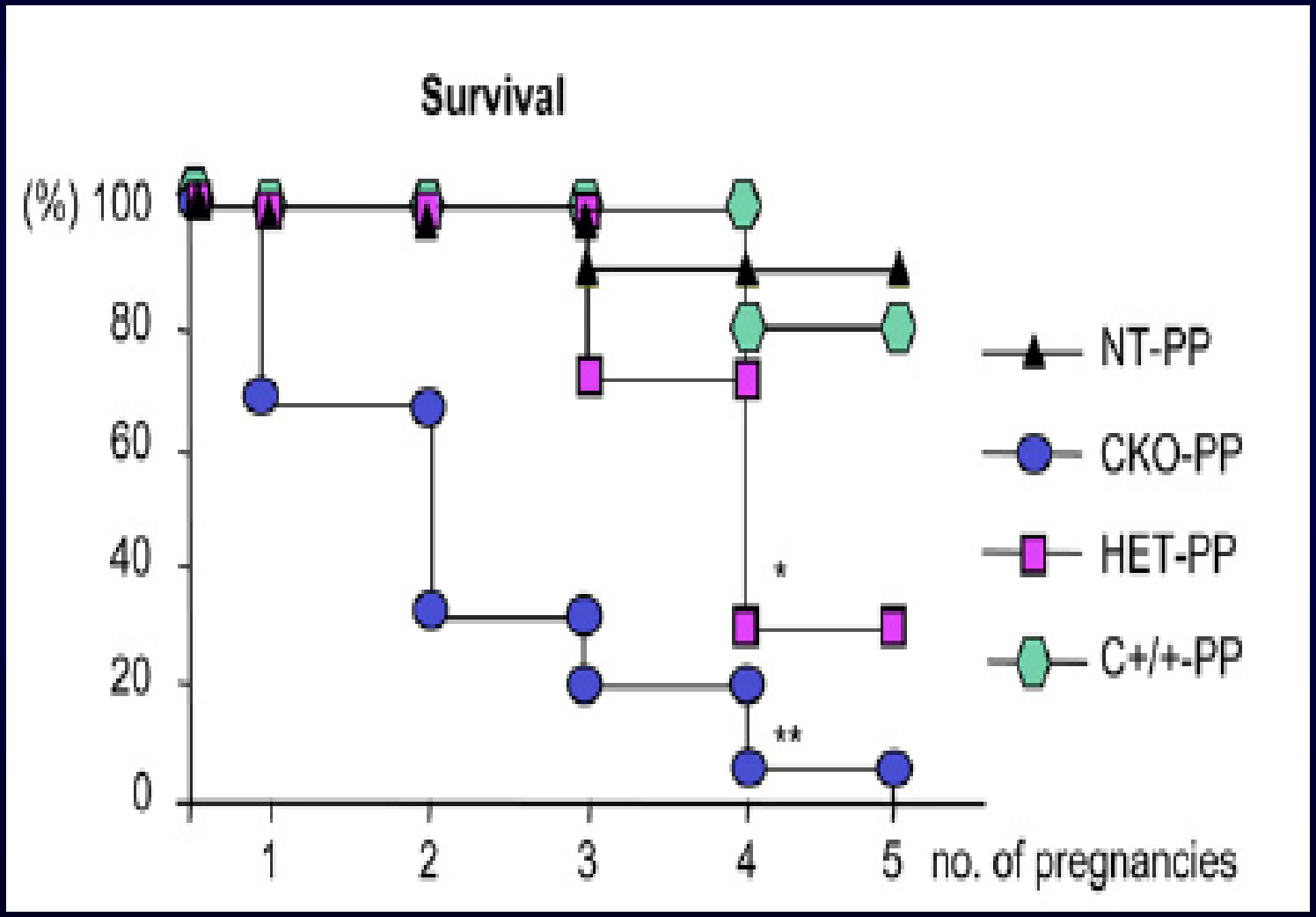
A Cathepsin D-Cleaved 16 kDa Prolactin Mediates PPCM

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



Effect of Bromocriptine for 3 month post delivery

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

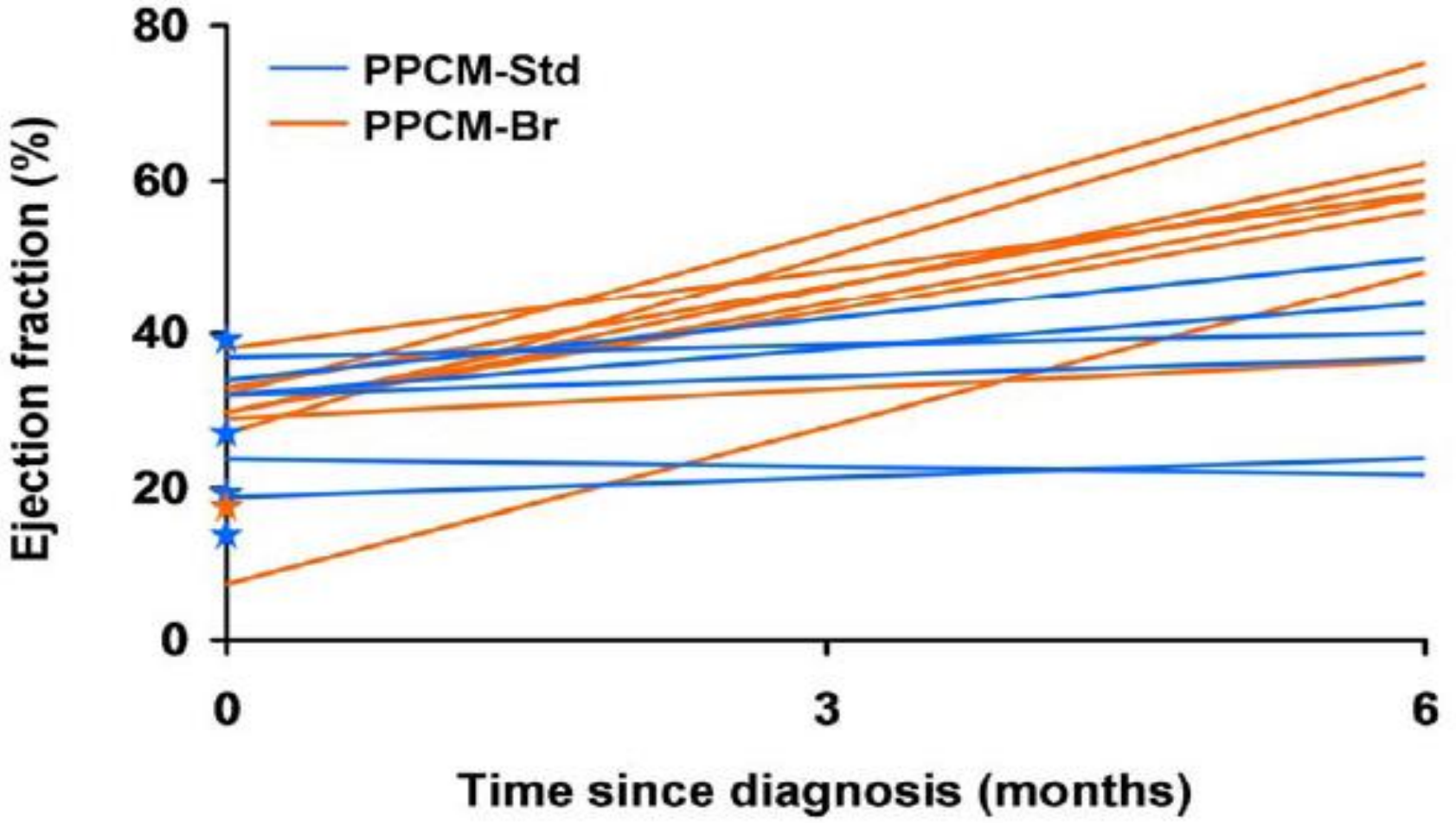
Cardiac dimensions and function in patients with subsequent pregnancies with (n=6) or without (n=6) BR treatment

Mortality: STD Tx 3/6, BR 0/6

	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*

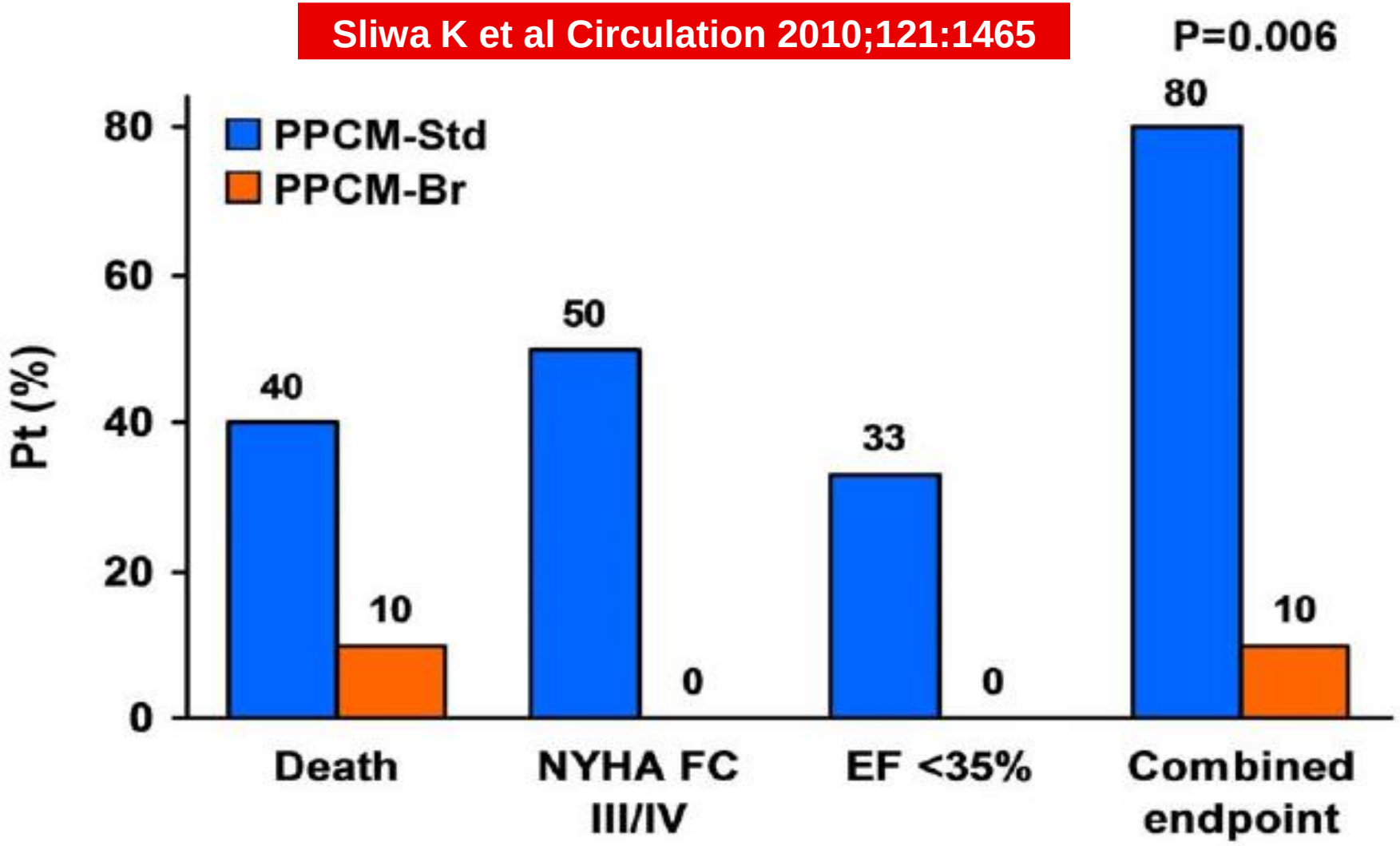
Bromocriptine in The Treatment of PPCM

Sliwa K et al Circulation 2010;121:1465



Bromocriptine in The Treatment of PPCM

Sliwa K et al Circulation 2010;121:1465



Evaluation of Bromocriptine in the Treatment of Acute Severe Peripartum Cardiomyopathy

A Proof-of-Concept Pilot Study

Table 4. Comparison of NYHA Functional Class in PPCM-Br and PPCM-Std Patients at Baseline and 6 Months

Sliwa K et al Circulation 2010;121:1465

	PPCM-Br at Baseline (n=10), n (%)	PPCM-Br at 6 mo (n=9), n (%)	PPCM-Std at Baseline (n=10), n (%)	PPCM-Std at 6 mo (n=6), n (%)	*P**
NYHA functional class					0.008
I	0	9 (100)	0	0	
II	5 (50)		5 (50)	3 (50)	
III/IV	5 (50)		5 (50)	3 (50)	

*Comparing the change from baseline to 6 months in PPCM-Br and PPCM-Std patients.

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

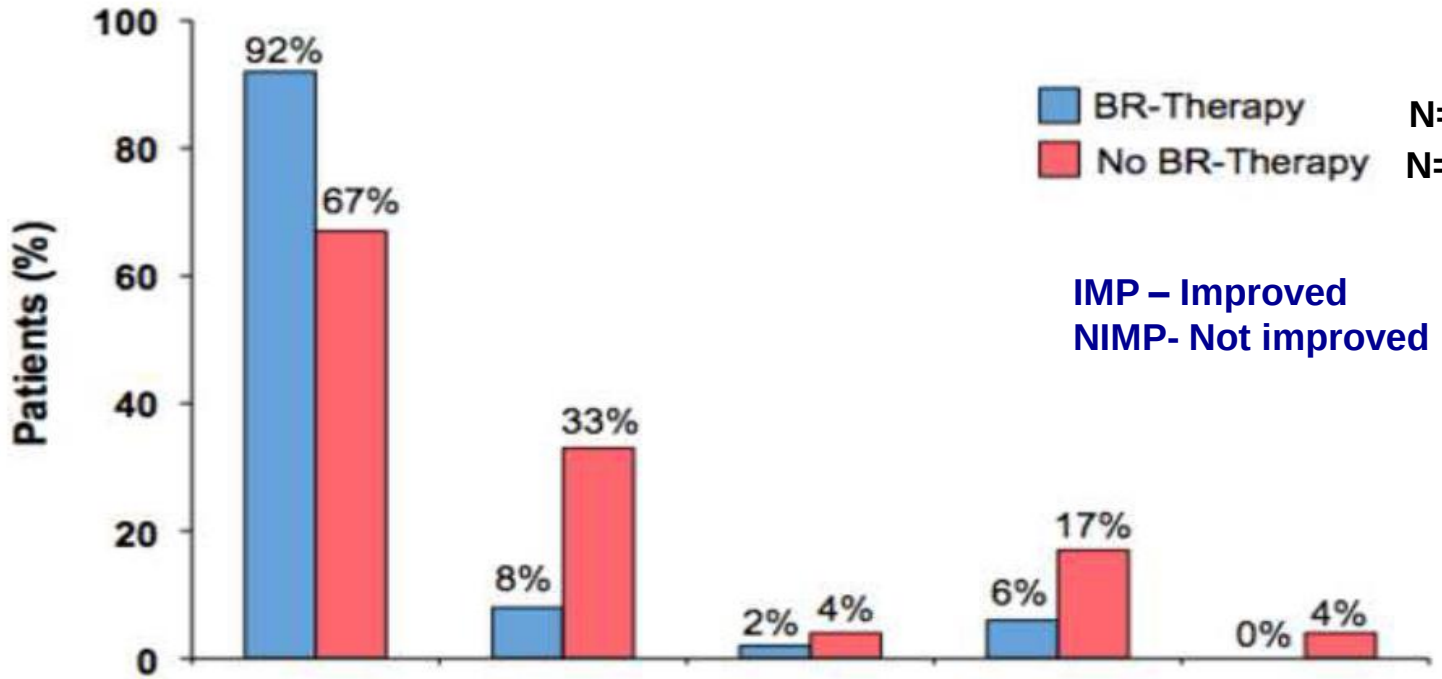
Elkayam U, Goland S, Circulation 2010;121:1463

- Small study.
- Very high mortality rate in controls.
- No LV recovery in any of the controls.
- Data may not be applicable to non-African patients.
- Safety? (Seizures, stroke, AMI)

German cohort of patients with PPCM

Haghikia a et al 2012

Figure 3



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

Summary

- PPCM may be associated with an imbalance between enhanced oxidative stress and blunted induction of antioxidant enzymes, leading to detrimental conversion of prolactin to its anti-angiogenic derivative 16 kDa.
- Inhibition of prolactin release with bromocriptin may be effective in some patients.

Summary

The efficacy and safety of bromocriptine for the treatment of PPCM needs to be evaluated in a prospective study before it can become standard therapy.