Heart Failure in Pregnancy

HFCT Annual Scientific Meeting
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Modified WHO Classification of Maternal Cardiovascular Risk

WHO Pregnancy Risk Category	Risk Description	Maternal Risk Factors
I	No detectable increase in maternal mortality and no/mild increase in morbidity risk	Uncomplicated small/mild pulmonary stenosis, PDA, mitral valve prolapse
		Successfully repaired simple lesions (ASD, VSD, PDA, anomalous pulmonary venous drainage)
		Atrial or ventricular ectopic beats, isolated
II	Small increase in maternal mortality and moderate increase in morbidity risk	If otherwise well and uncomplicated:
		Unoperated ASD, VSD
		Repaired LOH
		Most arrhythmias
II–III	Moderate increase in maternal mortality morbidity risk	Mild LV impairment
		Hypertrophic cardiomyopathy
		Native or tissue valvular disease (not considered risk category I or IV)
		Marfan syndrome without aortic dilation
		Aortic dilation <45 mm in bicuspid aortic valve aortopathy
		Repaired coarctation

Modified WHO Classification of Maternal Cardiovascular Risk

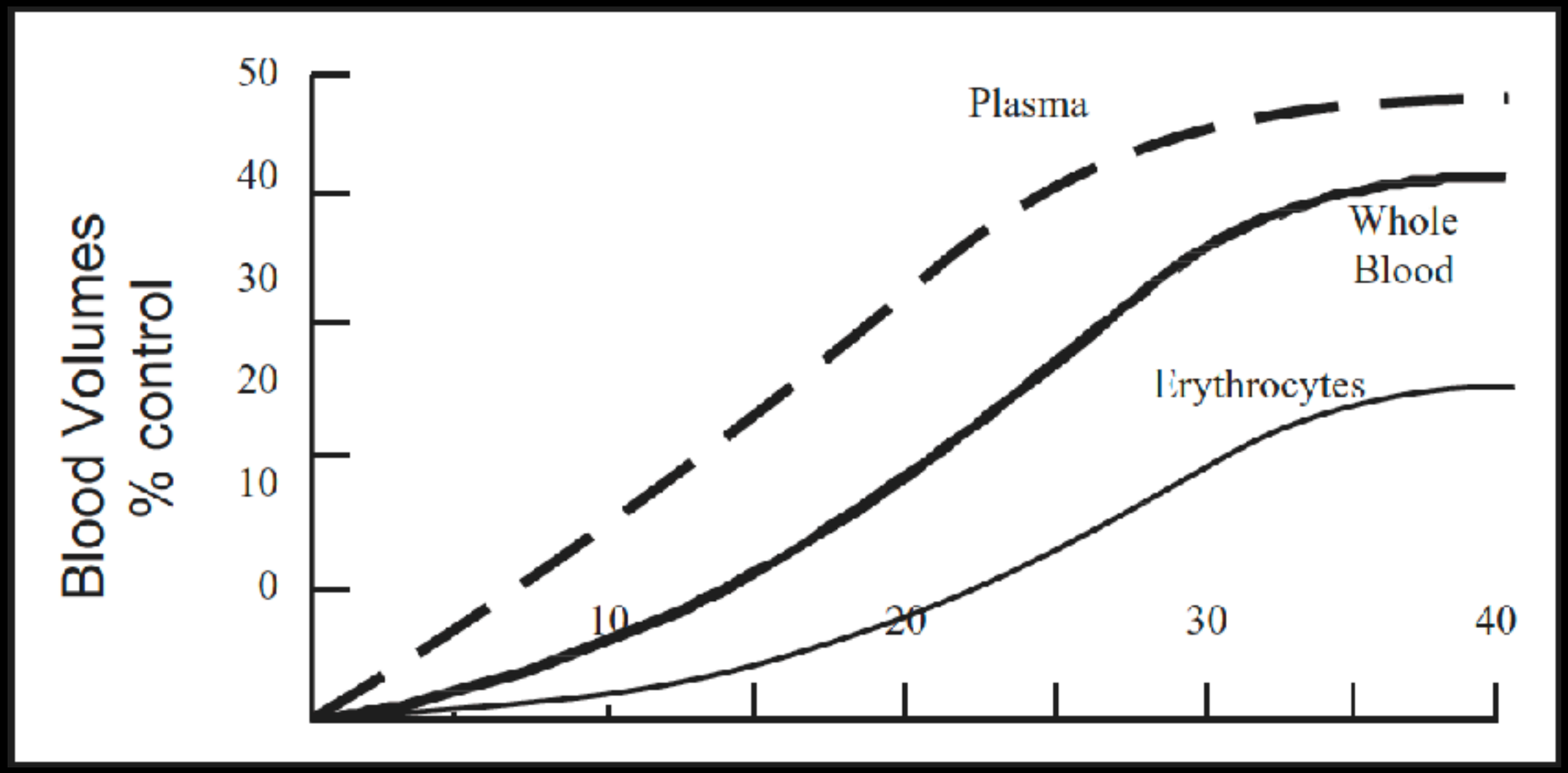
WHO Pregnancy Risk Category	Risk Description	Maternal Risk Factors
III	Significantly increased maternal mortality or severe morbidity risk. Expert counseling required. In the event of pregnancy, intensive specialist cardiac and obstetric monitoring needed throughout pregnancy, childbirth, and the puerperium.	Mechanical valve
		Systemic RV
		Fontan circulation
		Cyanotic heart disease (unrepaired)
		Other complex CHD
		Aortic dilation 40–45 mm in Marfan syndrome
		Aortic dilation 45–50 mm in bicuspid aortic valve aortopathy
IV	Extremely high maternal mortality or severe morbidity risk. Pregnancy is contraindicated. In the event of pregnancy, termination should be discussed. If pregnancy continues, care should follow class III recommendations.	Pulmonary arterial hypertension (of any cause)
		Severe systemic ventricular dysfunction (LV ejection fraction <30%, NYHA class III-IV)
		Previous peripartum cardiomyopathy with any residual impairment of LV function
		Severe mitral stenosis, severe symptomatic aortic stenosis
		Aortic dilation >45 mm in Marfan syndrome
		Aortic dilation >50 mm in bicuspid aortic valve aortopathy
		Native severe coarctation

Predictors of Cardiac Risk

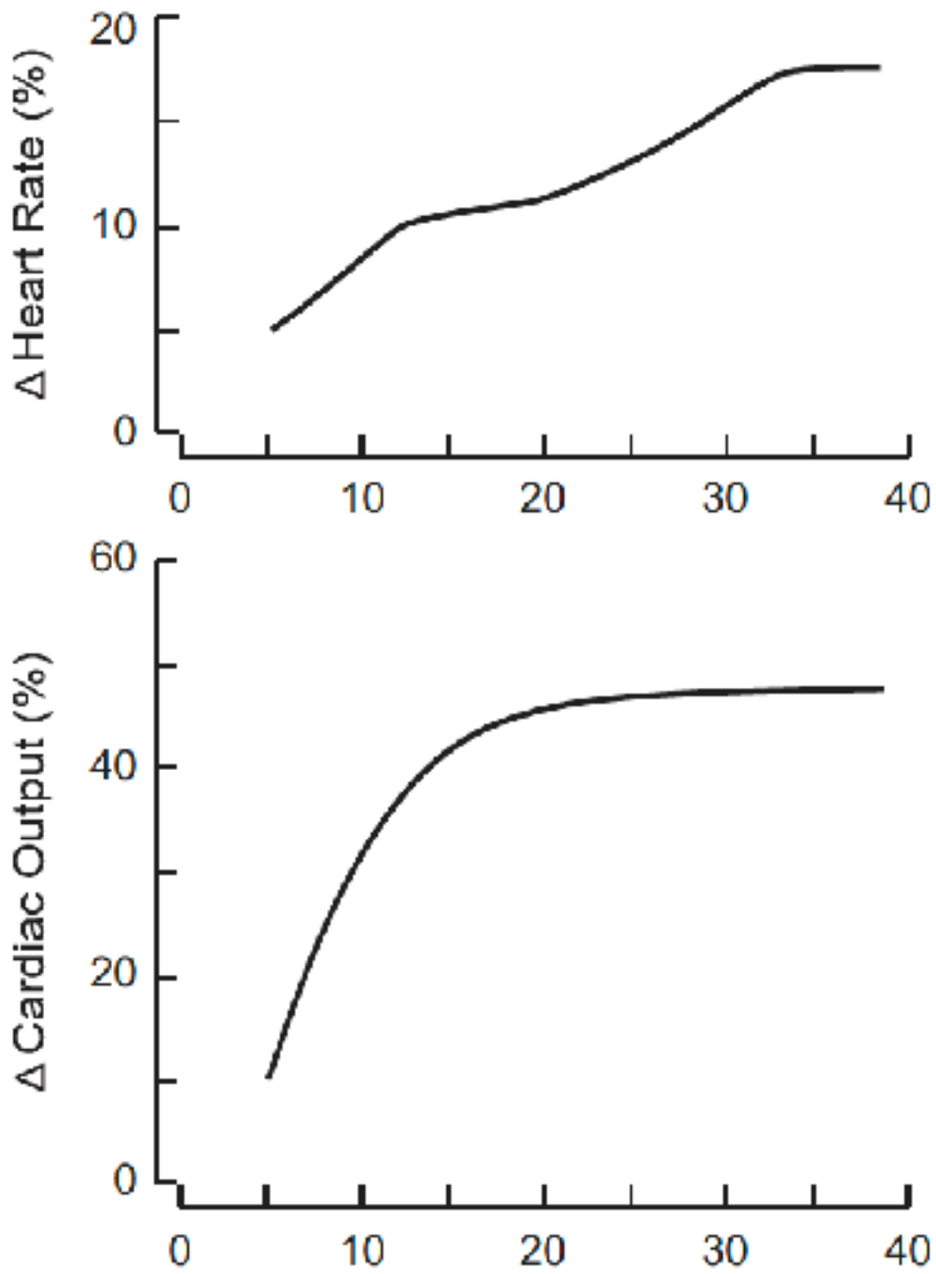
- NYHA Class III-IV
- Prior cardiac event
  - HF, TIA, stroke, or arrhythmia
- Left heart obstruction
  - Severe/symptomatic mitral stenosis; severe aortic stenosis
- LVEF <40%
- Pulmonary hypertension

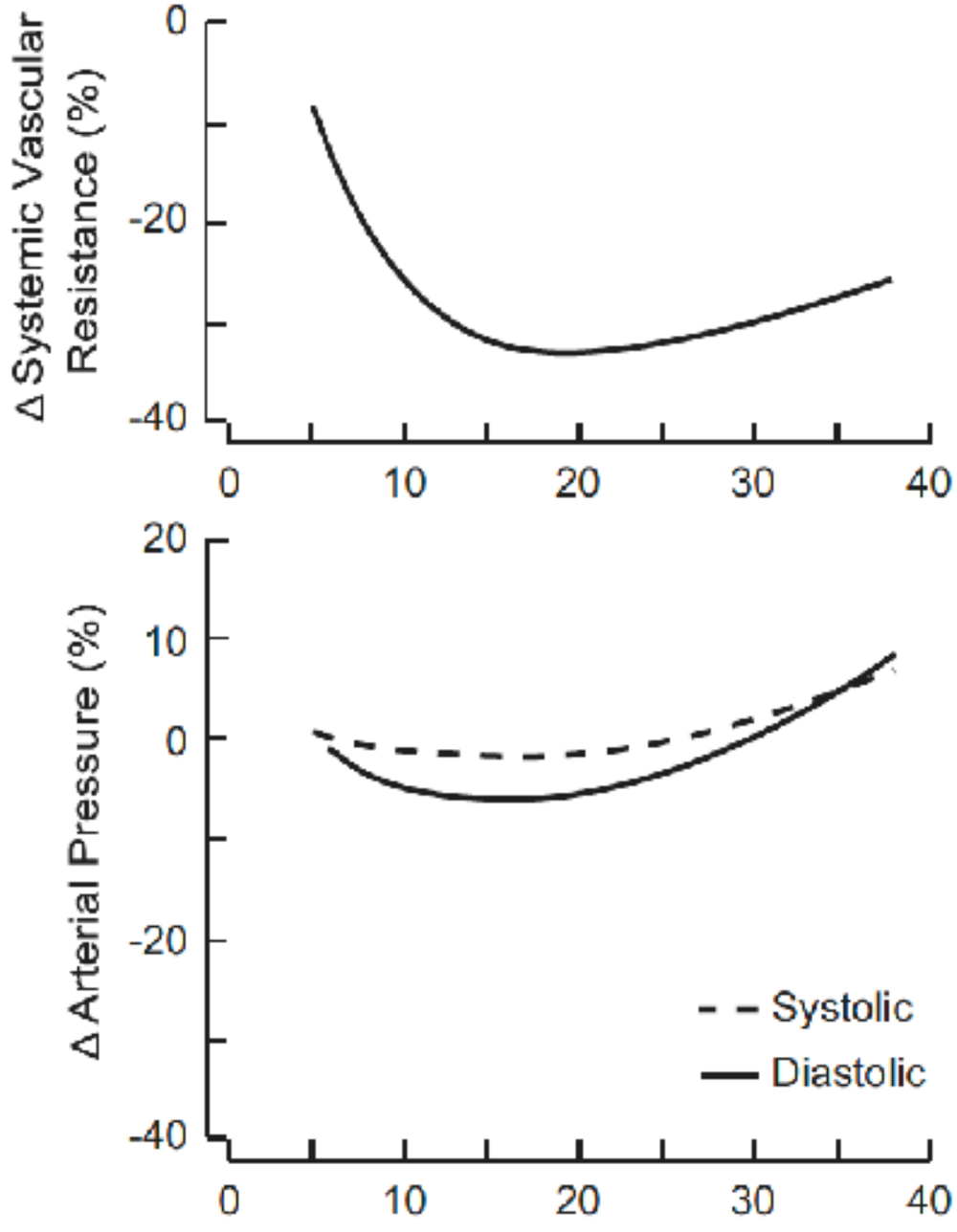
Siu et al; Circ1997; Circ2001; Stout et al Heart 2006

Blood volume increase during pregnancy



Pregnancy changes in maternal systemic hemodynamics





Mitral stenosis

MS	Mild	Moderate	Severe
Pulmonary edema	11-24 %	34-61 %	56-78 %
Atrial arrhthmias	0-7 %	10-22 %	33%

- Decompensation common (increased HR and SV, peak weeks 20-24)
- Atrial arrhythmias and HF often occur in 3rd trimester

Hemodynamic Alterations During Pregnancy

- Increased stroke volume and heart rate
- 30-50% increase in cardiac output by end 1sttrimester
- Decrease in SVR and BP
- Decreased preload due to IVC compression 3rdtrimester
- Hemodynamic changes usually resolve by 2 weeks postpartum

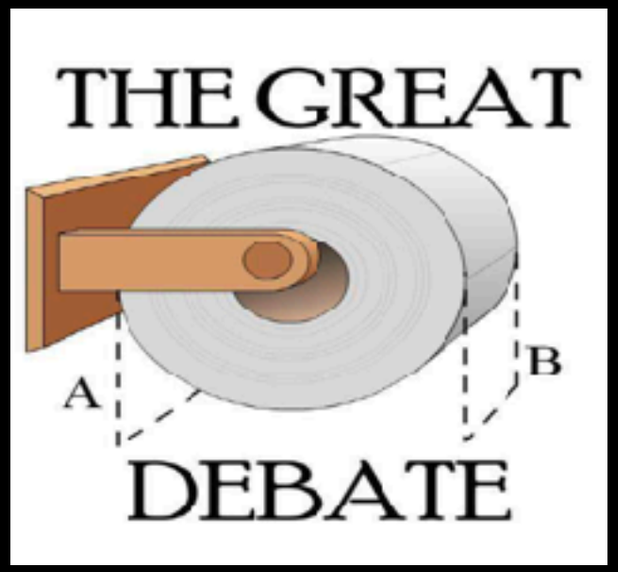
Mitral Stenosis Rx

- Mild symptomatic disease or mild-moderate asymptomatic disease ➜ MedRx
- Diuretics, β-blockade
- O_2, IV diuretics, hospitalization if pulmonary edema
- Anticoagulation if AF
- Tocolytic agents (beta-mimetics) should not be used (tachycardia-mediated increase in LAP)

Prenatal open heart surgery

- Open heart surgery is only considered if other therapies have failed because it is associated with a significant fetal mortality risk of 20% to 30%

Mode of Delivery
What is your recommendation?



1. No limitations on mode of delivery
2. Allow pushing with assisted vaginal delivery
3. No pushing with assisted vaginal delivery
4. Cesarean delivery

How to Deliver? Why all the drama?

- ↑ Cardiac output
- ↑ Heart rate
- ↑ Blood pressure
- ↑ Venous return
- ↑ Circulating blood volume with uterine contraction
- Volume loss during delivery

Overall Goals

- Minimize hemodynamic variation
- Avoid tachycardia
- Avoid hypotension

Hemodynamic Alterations During L & D

- Increased CO
- Catecholamine induced increase in SV and HR
- Abrupt changes in fluid balance
- Cessation of IVC compression
- Redistribution of blood volume from lower extremities
- Rapid volume load during delivery of placenta
- Can lead to pulmonary edema

Labor & Delivery

- Increases in:
  - Cardiac output
  - Heart rate
  - Blood pressure
  - Venous return
- Increase in preload acutely in postpartum period due to autotransfusion from uterine contraction

Hunter S, Br Heart Journ 1992

Planned cesarean vs. Planned vaginal

Morbidity	Cesarean n=46,766	Vaginal n=2,292,429	Adjusted OR (95%CI)
Overall severe morbidity	1,279 (27.3)	20,630 (9.0)	3.1 (3.0-3.3)
Hemorrhage	12 (0.3)	254 (0.1)	2.1 (1.2-3.8)
Anesthetic complications	247 (5.3)	4,793 (2.1)	2.3 (2.0-2.6)
Cardiac arrest	89 (1.9)	887 (0.4)	5.1 (4.1-6.3)
Puerperal venous thromboembolism	28 (0.6)	623 (0.3)	2.2 (1.5-3.2)
Major puerperal infection	281 (6.0)	4,833 (2.1)	3.0 (2.7-3.4)

- C/S should be reserved for obstetric indications
  - Failure to progress
  - Breech
  - Non–reassuring fetal status in labor - need to deliver fast
- Women on OACs in labor
- Marfan with aortic root 40-45 mm
- Women with acute or chronic aortic dissection

Liu et al CMAJ 2007

Vaginal delivery

- Advantage
  - Decrease blood loss (300 ml)
  - Lower risk of infection
  - Decreased risk of thrombosis

- Disadvantage
  - Valsalva
    - Inrathoracic pressure
    - venous return
  - Uterine contraction - autotransfusion

Cesarean delivery

- Advantage
  - Avoid contraction and valsalva
  - Faster
  - Safer for fetuses of mothers taking oral anticoagulants
  - May be preferred for women who are critically ill and in need of inotropic therapy or mechanical support

- Disadvantage
  - Increased blood loss (1000 cc)
  - Increased infection risk
  - Increased risk of VTE
  - Future pregnancy risk with multiple C/S
  -

Labor & Delivery - Summary

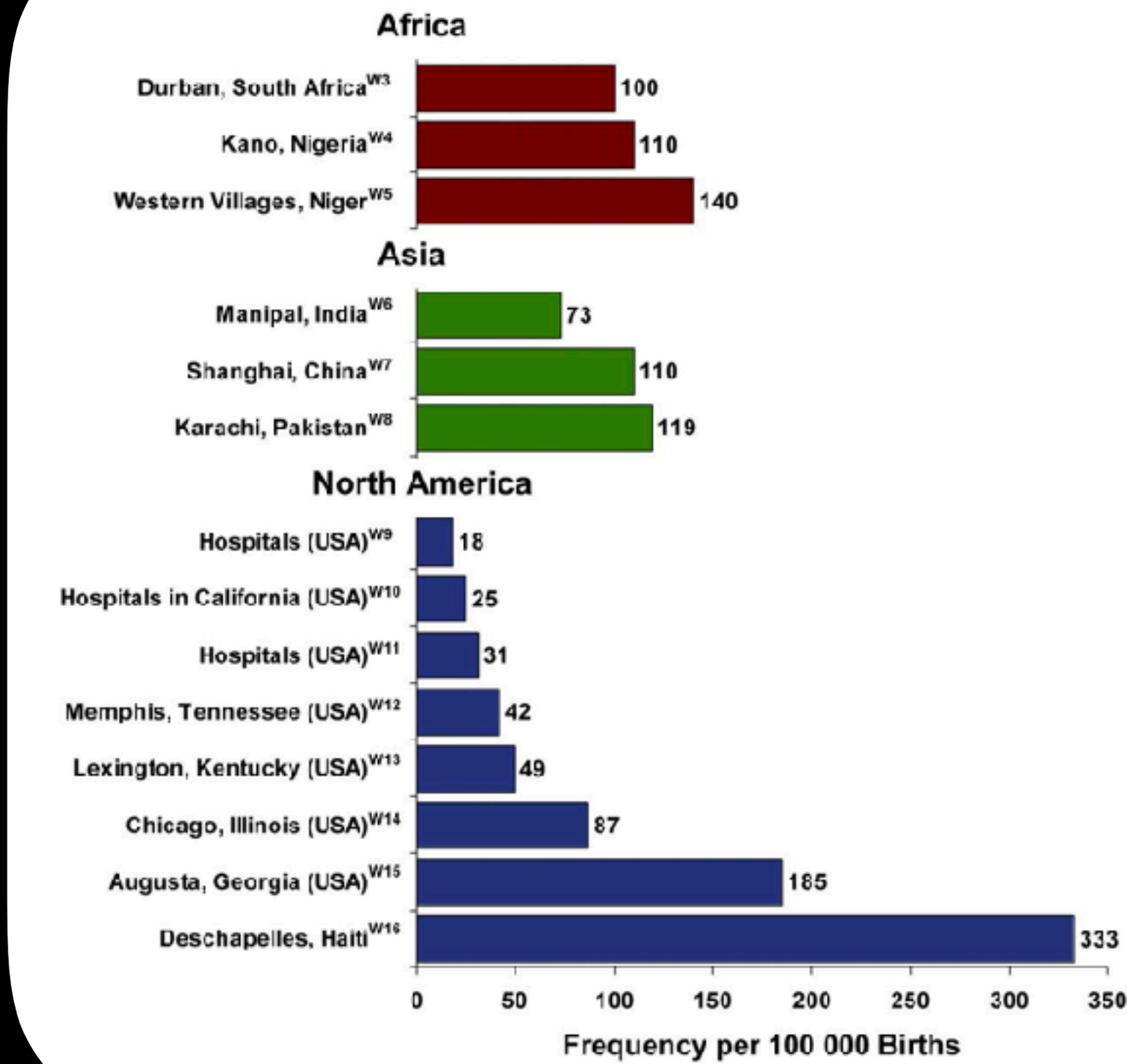
- Vaginal delivery is preferred
- Cesarean typically for obstetrical indication
- Planned induction is usually advised
- Arrhythmias , invasive BP monitoring during labor and delivery, and for 12 to 24 h post-partum in CCU
- Assisted second stage to minimize maternal expulsive effort for those in whom valsava is not recommended
  - Stenotic valves, HOCM, Aortopathy
- Good pain management - Early, slow epidural

VHD & Pregnancy

- Pre-conception counseling
- Serial clinical and echo monitoring during pregnancy
- Hemodynamic changes of pregnancy can lead to increased valve gradients on echo, with overestimation of the severity of the valve lesion
- Some may need valve intervention prior to pregnancy
- Prenatal open heart surgery is associated with 20-30% fetal mortality , should only be considered as a last resort

PCM Timing of presentation

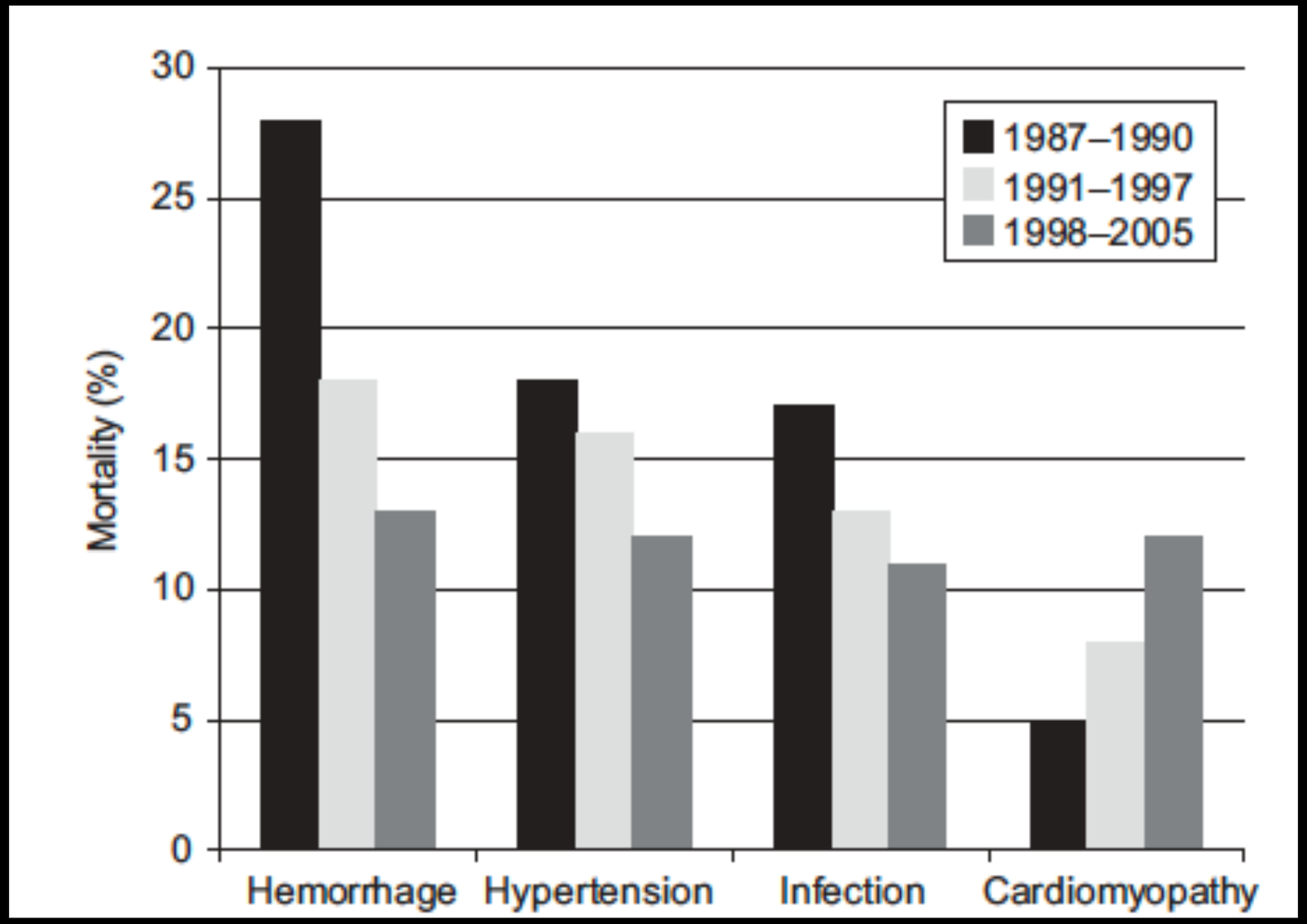
Incidence of PPCM



Blauwet L A , Cooper L T Heart 2011;97:1970-1981

PPCM

Rising proportion of peripartum maternal deaths in US



Cunningham. Obstet Gynecol 2012

Diagnostic criteria for peripartum cardiomyopathy

All 4 of the following:

Classic

1. Development of cardiac failure in the last month of pregnancy or within 5 months postpartum
2. No identifiable cause for the cardiac failure
3. No recognizable heart disease before the last month of pregnancy

Additional

1. Strict echocardiographic indication of left ventricular dysfunction:
   a. Ejection fraction <45%
      and/or
   b. Fractional shortening <30%
   c. End-diastolic dimension >2.7 cm/m^2

Clinical Signs and Symptoms Observed in Normal Pregnancy

Hyperventilation causing shortness of breath and dyspnea
Brisk, full carotid upstroke with distended jugular veins with prominent A and V waves
Diffuse, displaced left ventricular impulse; palpable RV impulse
Increased first heart sound; persistent splitting of second heart sound
Systolic ejection-type murmurs at the left lower sternal border over the pulmonary area
Anemia
Weight gain

HF in Pregnancy

- May mimic physiological changes occurring during pregnancy. Delayed Dx may occur.
- Ddx
  - Pre-existing HD
    - VHD
    - Congenital heart disease
    - Cardiomyopathy
  - PPCM
  - Myocarditis
  - Pregnancy-associated myocardial infarction (PAMI)
    - Spontaneous coronary artery dissection (SCAD)
  - Pulmonary embolism, amniotic liquid embolism

Cardiogenic shock

Ddx Peripartal acute dyspnea

	PPCM	Pre-existing CMP, valve disease or congenital heart disease	Pregnancy-associated myocardial infarction	Pulmonary embolism/ amniotic liquid embolism	Myocarditis
History	Most commonly post-partal onset of dyspnoea	Earlier onset (during second trimester) Sometimes family history	Retrosternal chest pain, abdominal discomfort, nausea	Pleuritic chest pain	Infection
Biomarkers	Elevated natriuretic peptides	Elevated natriuretic peptides	Elevated troponin	Elevated D-dimer, troponin, natriuretic peptides	Elevated troponin Possibly. elevated natriuretic peptides
Echocardiography	Left and/or right ventricular dysfunction	Evidence of pre-existing valve disease or congenital defect	Regional hypokinesis/akinesis	RV dysfunction, elevated RV pressure, McConnell's sign	Regional or general hypokinesis
Additional tests	Consider MRI	Consider MRI Consider genetic test	Coronary angiography	CT-scan or. V/Q scintigraphy; consider angiography	MRI Consider myocardial biopsy

CMP, cardiomyopathy; MRI, magnetic resonance imaging; PPCM, peripartum cardiomyopathy; RV, right ventricular.

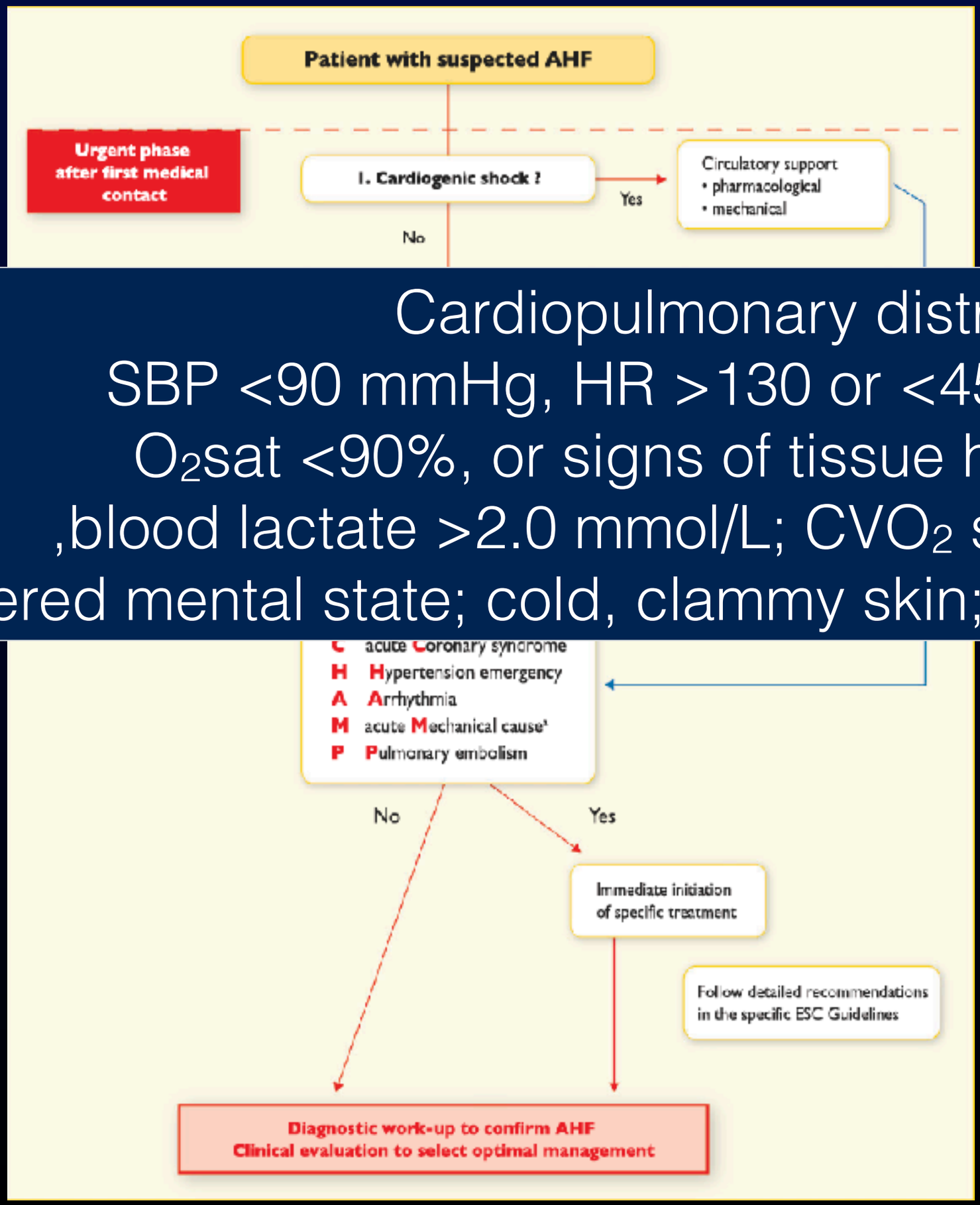
J. Bauersachs et al. Eur J Heart Fail 2016

Pregnancy is contraindicated in women with severe systemic ventricular dysfunction (left ventricular ejection fraction <30%, NYHA class III or IV)

PPCM

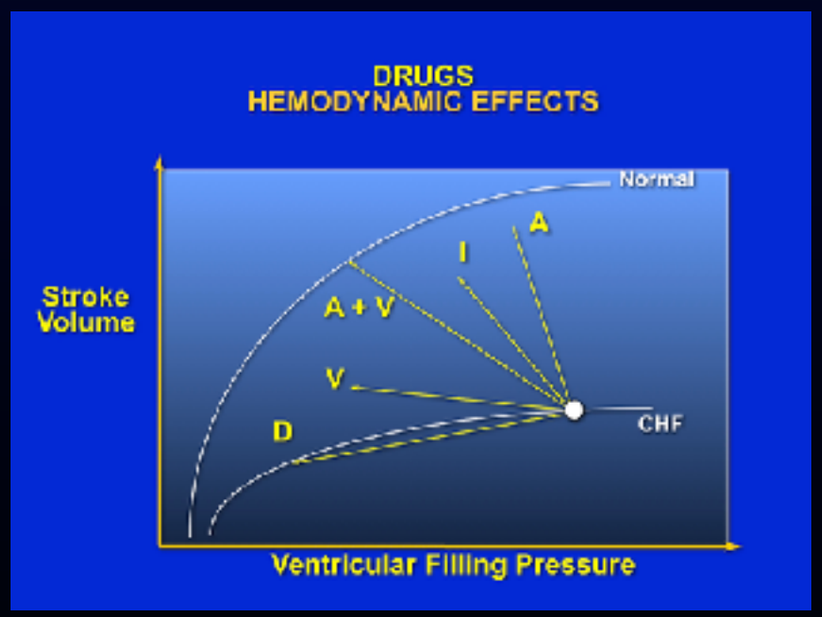
- Initial therapy includes five main elements:

1. optimization of the preload;
2. optimization of oxygenation;
3. restoration of haemodynamics with inotropes and/or vasopressors
4. urgent delivery if heart failure occurs during pre-partum
5. consideration of adjunctive therapies with bromocriptine (2.5 mg twice daily for 2 weeks followed by 2.5 mg per day for 6 weeks)

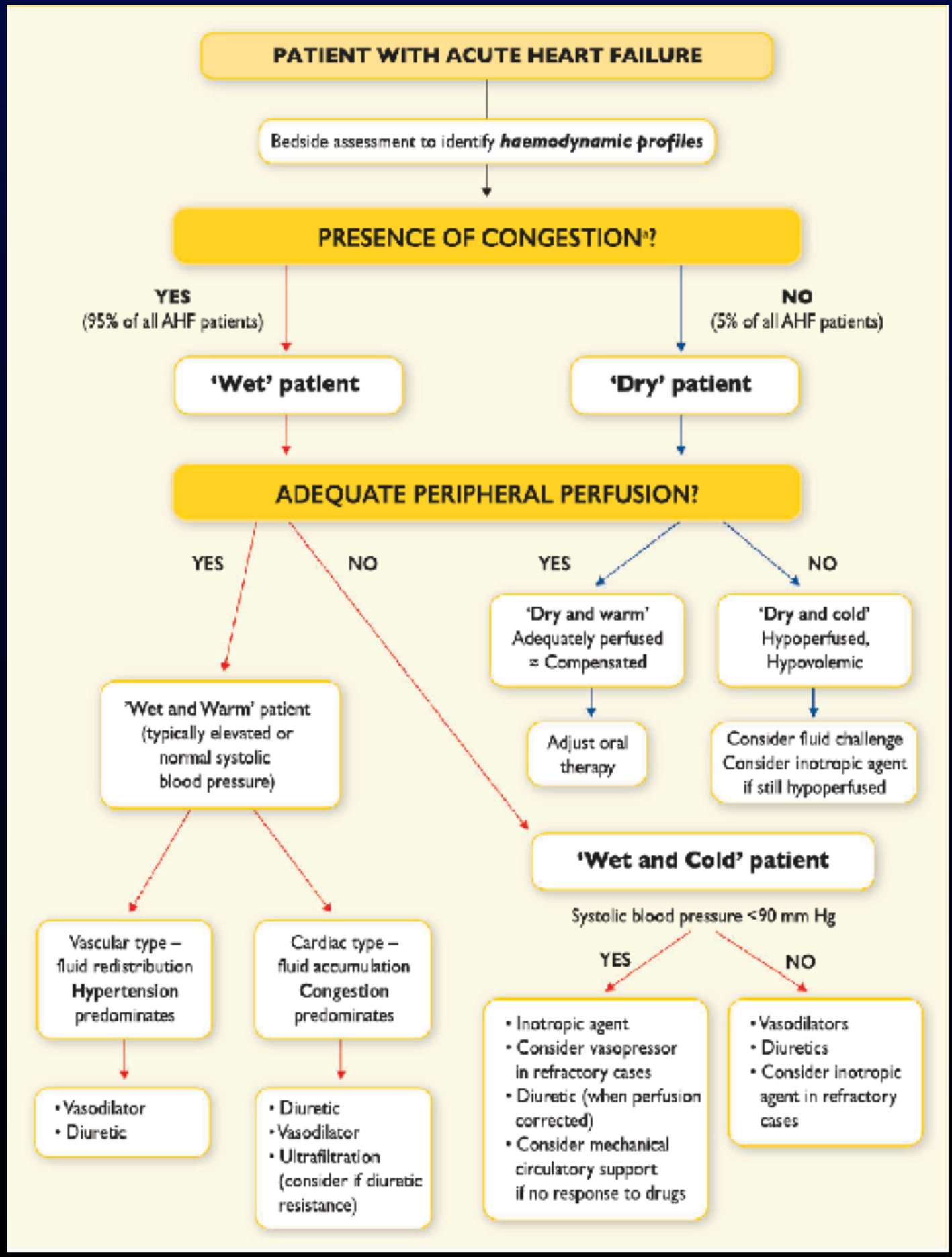


Cardiopulmonary distress
SBP <90 mmHg, HR >130 or <45, RR >25/min;
O_2sat <90%, or signs of tissue hypoperfusion
,blood lactate >2.0 mmol/L; CVO_2 saturation <60%,
altered mental state; cold, clammy skin; oliguria<0.5 mL/kg/h

ESC HF Guidelines 2016



ESC HF Guidelines 2016



AHF : Pulmonary edema

- Upright position
- 100% Oxygen
- Tight seal mask for CPAP, BiPAP
- Furosemide iv
- Continuous fetal monitoring by OB to direct delivery
- Intubate and add PEEP if necessary
- +/-Nitroglycerine/Nitroprusside (beware uterine atony)

AHF in PPCM

- Young & critically ill
- Therapeutic interventions need always to consider the health of both the mother and the foetus
- High mortality
- Time frame and extent of recovery are unpredictable
- Ventricular arrhythmias
- Cardio-embolic complications

Peculiarities in the management of AHF caused by PPCM

- Multidisciplinary approach
- Avoidance of HF drugs with foetal toxicity during pregnancy and breastfeeding
- Bromocriptine (2.5 mg twice daily for 2 weeks, followed by 2.5 mg per day for 6 weeks)
- Anticoagulation
- Levosimendan (0.1 μg/kg/min for 24 h) instead of catecholamines as first-line inotropic drug.
- Early evaluation of mechanical circulatory
- Wearable cardioverter-defibrillator devices

FDA Drug Classification

Category	Definition
A	Adequate a… controlled human studies hav… to demonstrate a risk to the fetus… trimester of pregnancy (… no evidence of risk in later tri…
B	Animal … fai… …k to the fetus and there are … …nant women OR Animal studies… …quate and well-controlled studies… …demonstrate a risk to the fetus in any trimester…
C	Animal reproducti… …effect on the fetus and there are no a… …umans, but potential benefits ma… …despite potential risks.
D	There is … human fe… …rse reaction data from inve… …rketing experienc… …umans, but potential … warrant use of the drug … women despite potential ri…
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

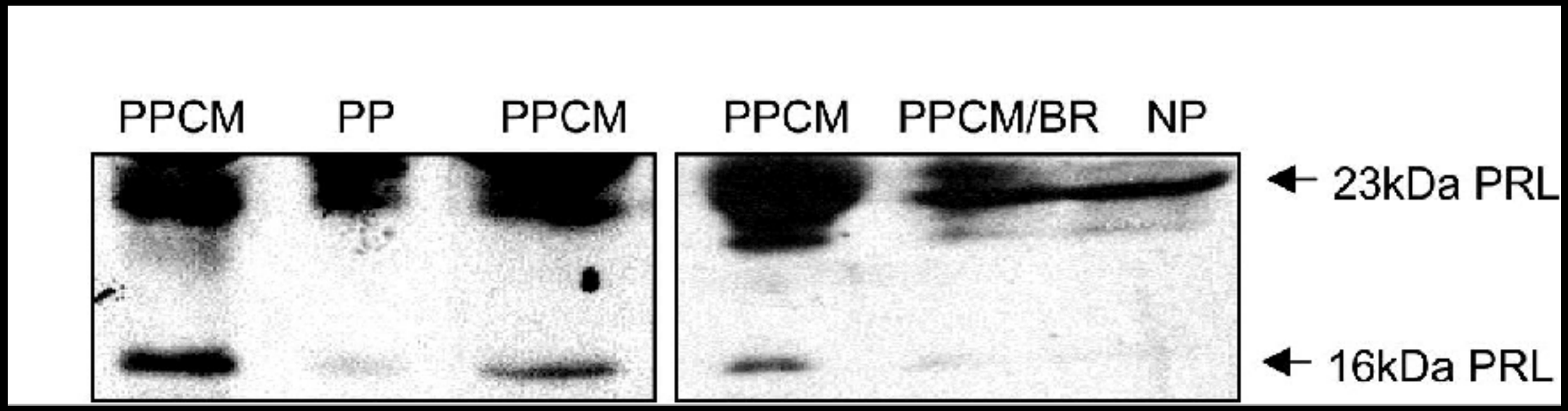
	 Pregnancy	Lactation 
ACEi	🚫	Enalapril -ok
ARB	🚫	🚫
β-blockers	✅	✅
MRA	🚫	🚫
Hydralazine	✅	✅
Nitrates	✅	✅
Digoxin	✅	✅
Diretics	✅	✅

Drug	Indication
ACE-inhibitors and Angiotensin-II receptor blocker (ARBs)	Contraindicated because of serious renal and other foetal toxicity (I-C). AT1-receptor blockers probably cause similar toxicity.
Hydralazine and long acting nitrates	It is believed that this combination can be used safely, instead of ACE-inhibitors/ARBs, in patients with PPCM.
Beta-blockers	Not shown to have teratogenic effects. Beta-1 selective drugs preferred because beta-2 receptor blockade can have an anti-tocolytic action.
Diuretics	Should be used sparingly as can cause decreased placental blood flow
Furosemide and hydrochlorothiazide	Most frequently used
Aldosterone antagonists	Spironolactone thought to have antiandrogenic effects in first trimester. Eplerenone - effects on the human foetus uncertain, avoid during pregnancy.

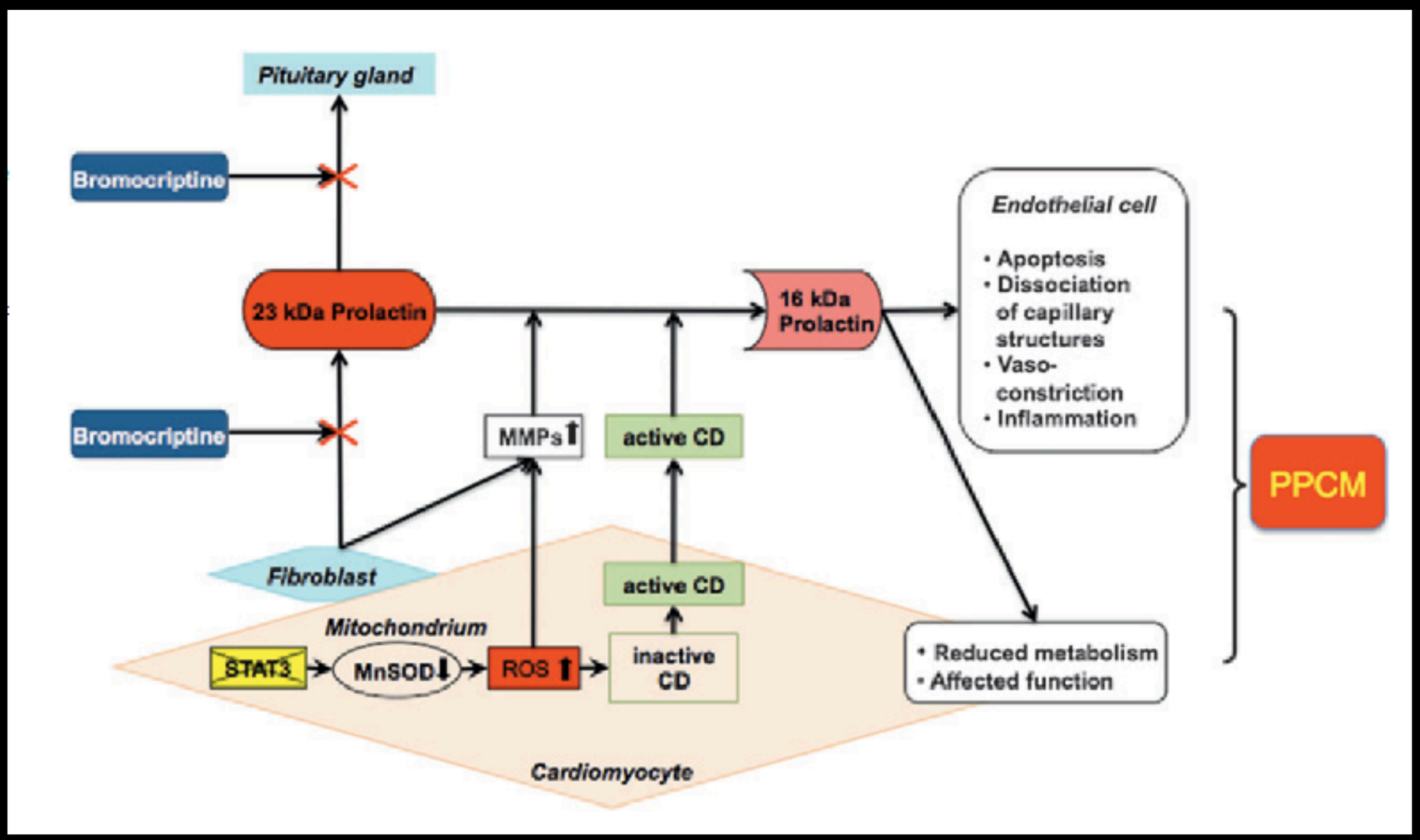
Medications for peripartum cardiomyopathy

Category	Drug	Dosage	Comment
ACEI	Captopril	Start with 6.25 mg tid Titrate up to 25–50 mg tid	Contraindicated during pregnancy
	Enalapril	Start with 1.25 mg bid Titrate up to 10 mg bid	Contraindicated during pregnancy
	Ramipril	Start with 1.25 mg bid Titrate up to 5 mg bid	Lack of data during pregnancy
ARB	Candesartan	Start with 2 mg qd Titrate up to 32 mg qd	Contraindicated during pregnancy and lactation
	Varsartan	Start with 40 mg bid Titrate up to 160 mg bid	Contraindicated during pregnancy and lactation
MRA	Spironolactone	Start with 12.5 mg qd Titrate up to 50 mg qd	Contraindicated during pregnancy and lactation
β-Blocker	Extended-release metoprolol	Start with 0.125 mg qd Titrate up to 0.25 mg qd	Rare risk of bradycardia or respiratory distress in newborn
	Carvedilol	Start with 3.125 mg bid Titrate up to 25 mg bid	Same as metoprolol
Vasodilator	Hydralazine	Start with 10 mg tid Titrate up to 40 mg tid	
	Nitroglycerin	Start with 10–20 μg/min IV Titrate according to BP	Risk of hypotension
Diuretics	Hydrochlorothizide	12.5–50 mg qd	Risk of uteroplacental circulatory insufficiency
	Furosemide	20–80 mg qd-bid (oral or IV)	Risk of uteroplacental circulatory insufficiency
Inotropics	Digoxin	0.125–0.25 mg qd	Risk of drug toxicity
	Dobutamine	2.5–10 μg/kg/min	
	Milrinone	0.125–0.5 μg/kg/min	
Prolactin inhibition	Bromocriptine	2.5 mg bid for 2 weeks, then 2.5 mg qd for 2 weeks	Risk of thrombosis

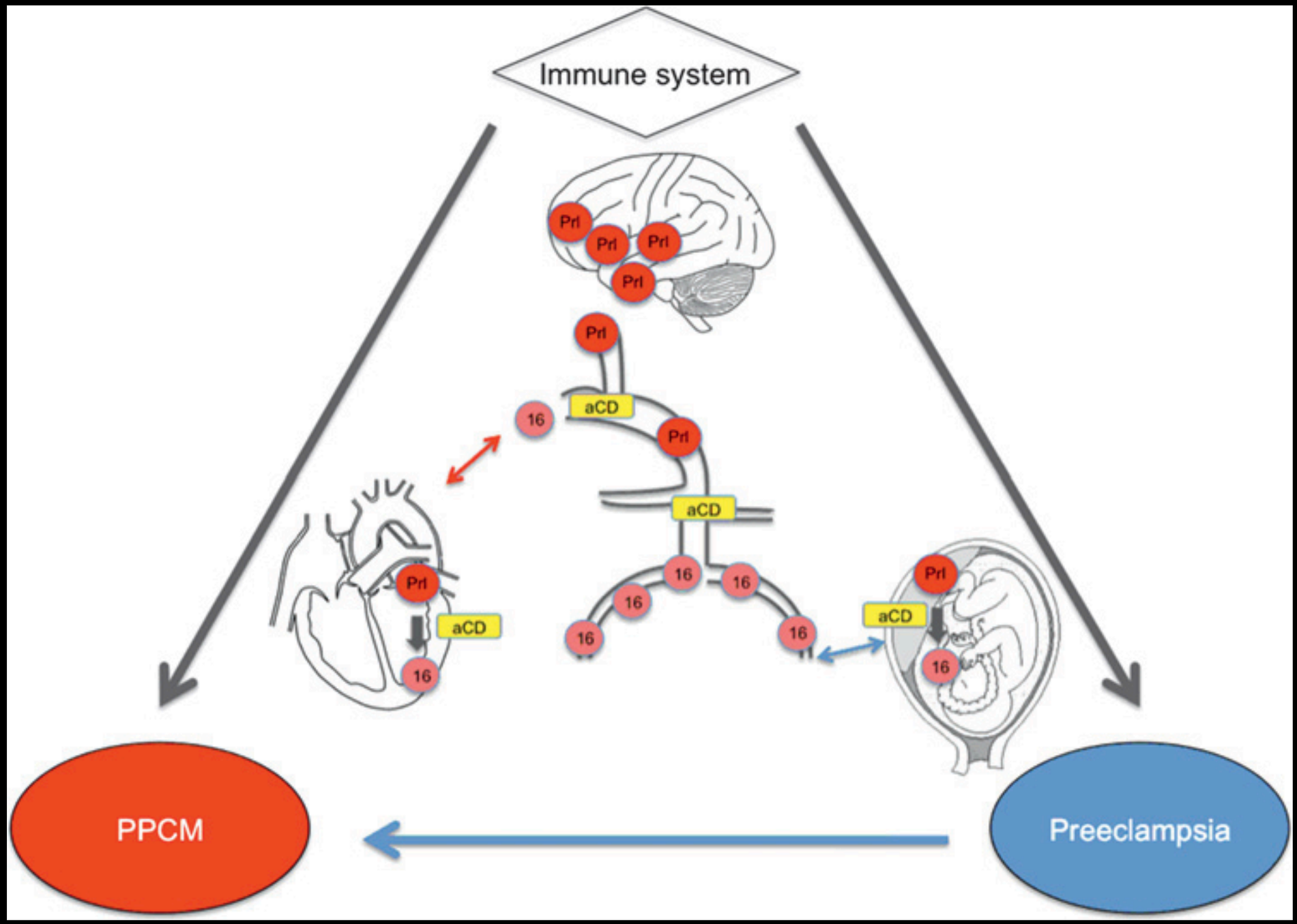
Prolactin 16KD fragment: elevated in PPCM and eliminated by bromocriptine



Hilfiker-Kleiner et al, Cell, 2007

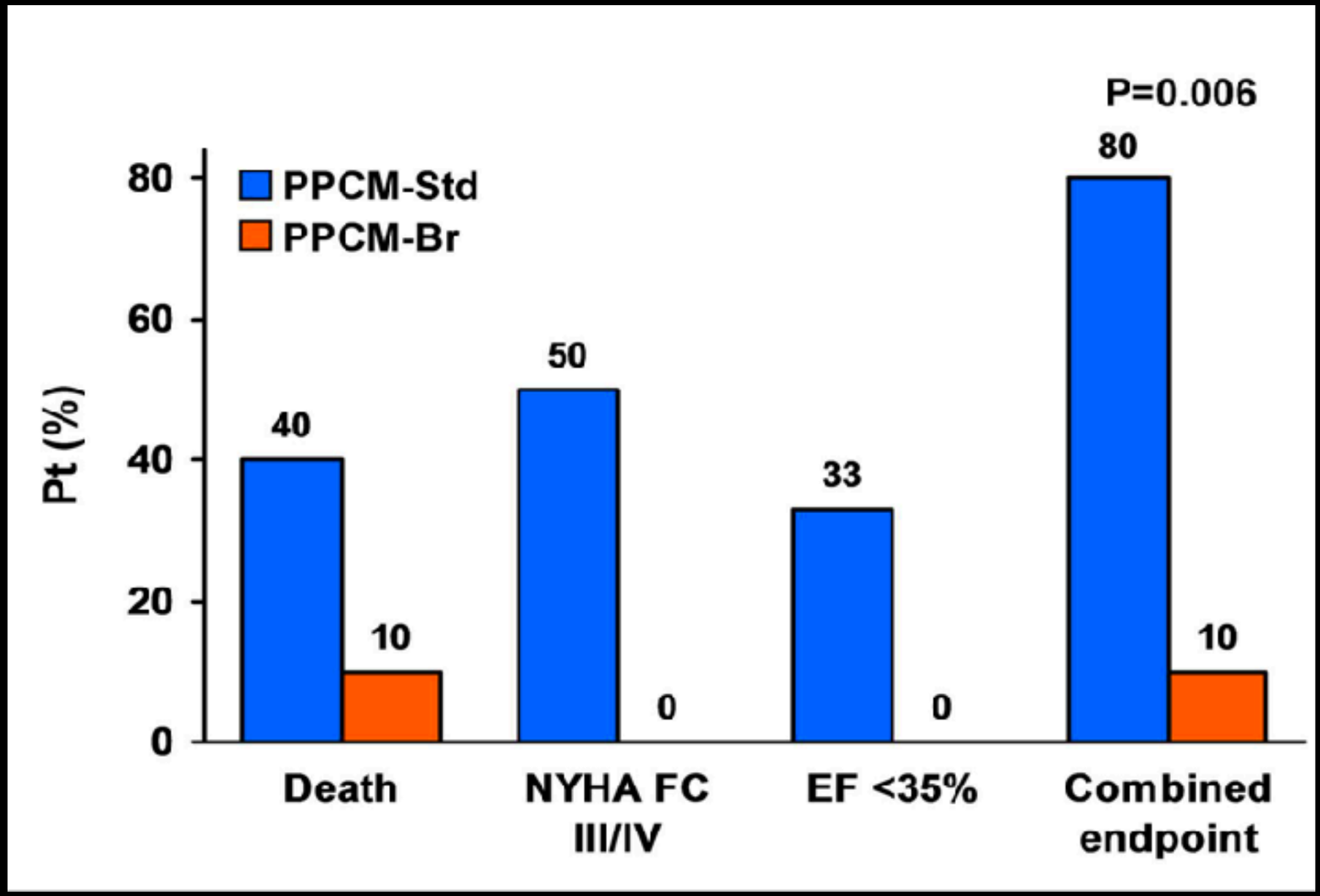


Yamac et al. Heart 2010;96:1352e1357



Yamac et al. Heart 2010;96:1352e1357

Evaluation of Bromocriptine in the Treatment of Acute Severe Peripartum Cardiomyopathy A Proof-of-Concept Pilot Study



Sliwa. Circulation, 2010

Bromocriptine use in a German Registry Impact on Outcomes

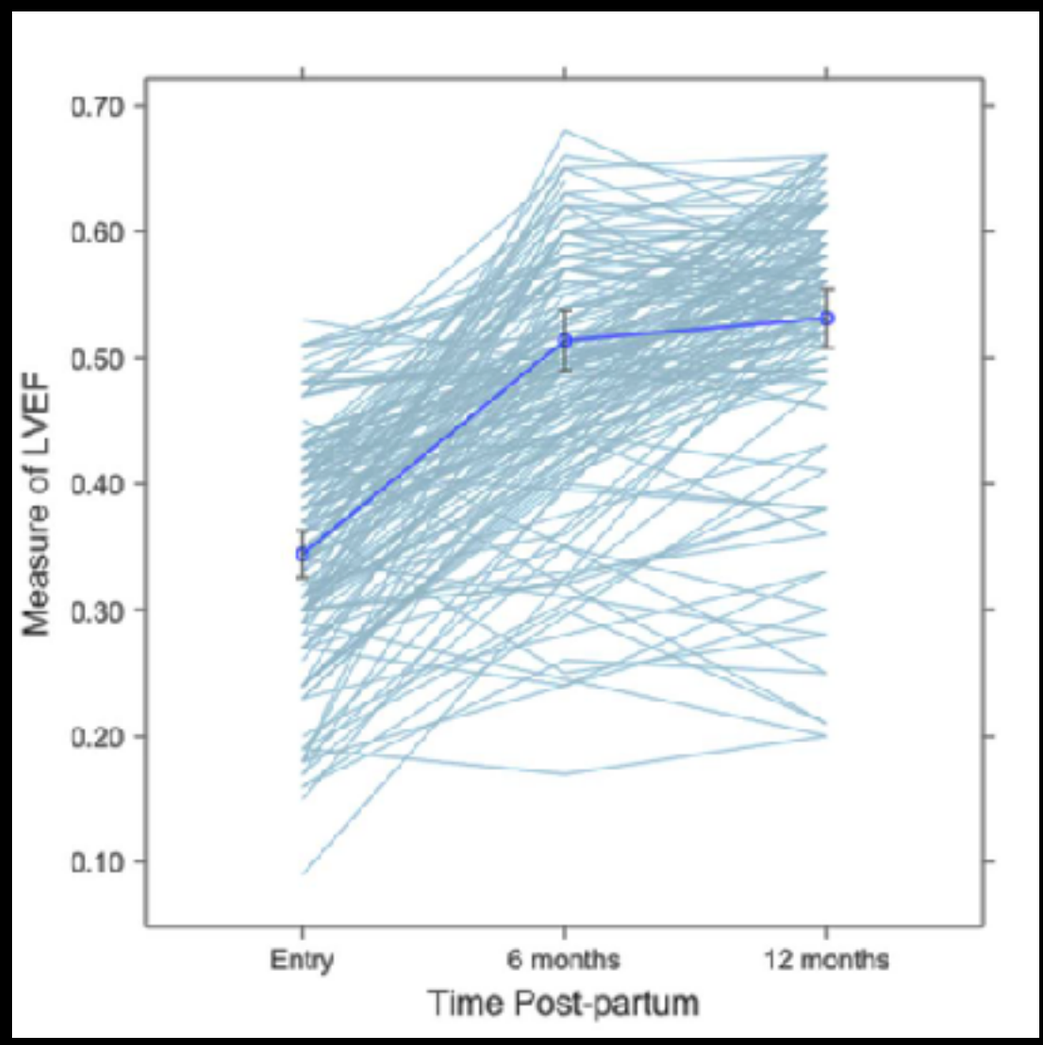
	Improver (Δ LVEF>10 EF units)	Full Recovery LVEF (≥55%)	Non-improver
All (n=96)	82 85%	45 47%	14
Bromo (n=64)	59 92%	30 47%	5
No Bromo (n=32)	23 72%	15 47%	9

- Overall events in 9% (transplants/LVAD/death) with no significant difference by treatment

Haghikiaet al, Basic Card Res,2013

Myocardial Recovery in IPAC study of 100 women from North American Peripartum Cardiomyopathy Network

- IPAC Recovery:
  - D10 EF in 80%
  - final LVEF>55% in 57%
  - Events in 7% (6/91) by one year (Tx/LVAD/ Death)Only 1 of 100 treated with bromocriptine IPAC

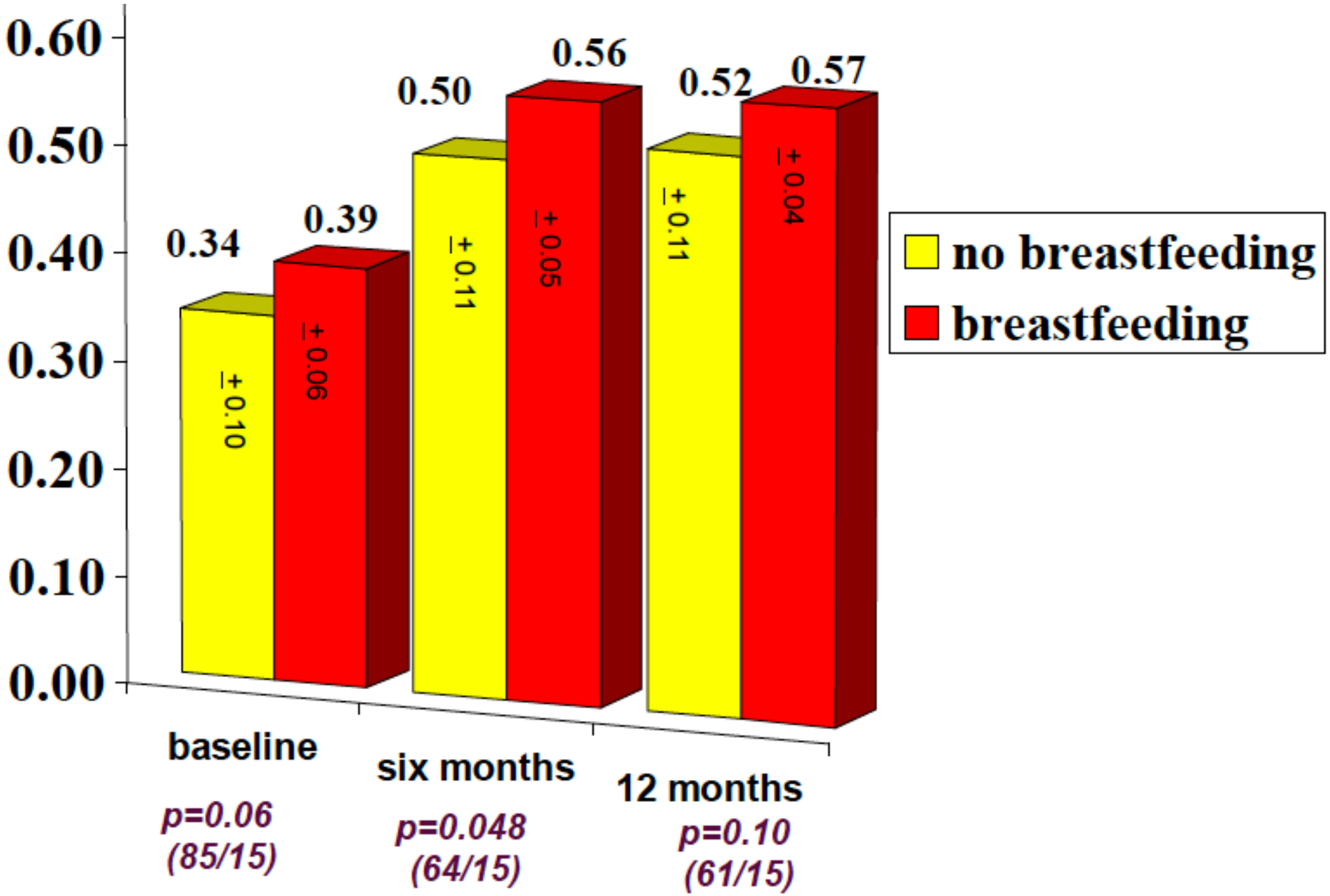


McNamara et al, JACC 2015

Breastfeeding ?

- Yes
- No

IPAC: LVEF at entry, 6 month and 12 months by breastfeeding (Marino, Koczo, ACC 2017)



V KA vs UFH in Pregnancy

Anticoagulation	Thromboembolic Risk	Maternal Mortality	Fetal Anomalies
VKA throughout	3.9%	1.8%	6.4%
UFH 1st trimester, then VKA	9.2%	4.2%	3.4%
UFH throughout	33%	15%	0%

Chan et. al., Arch Intern Med, 2000

LMWH

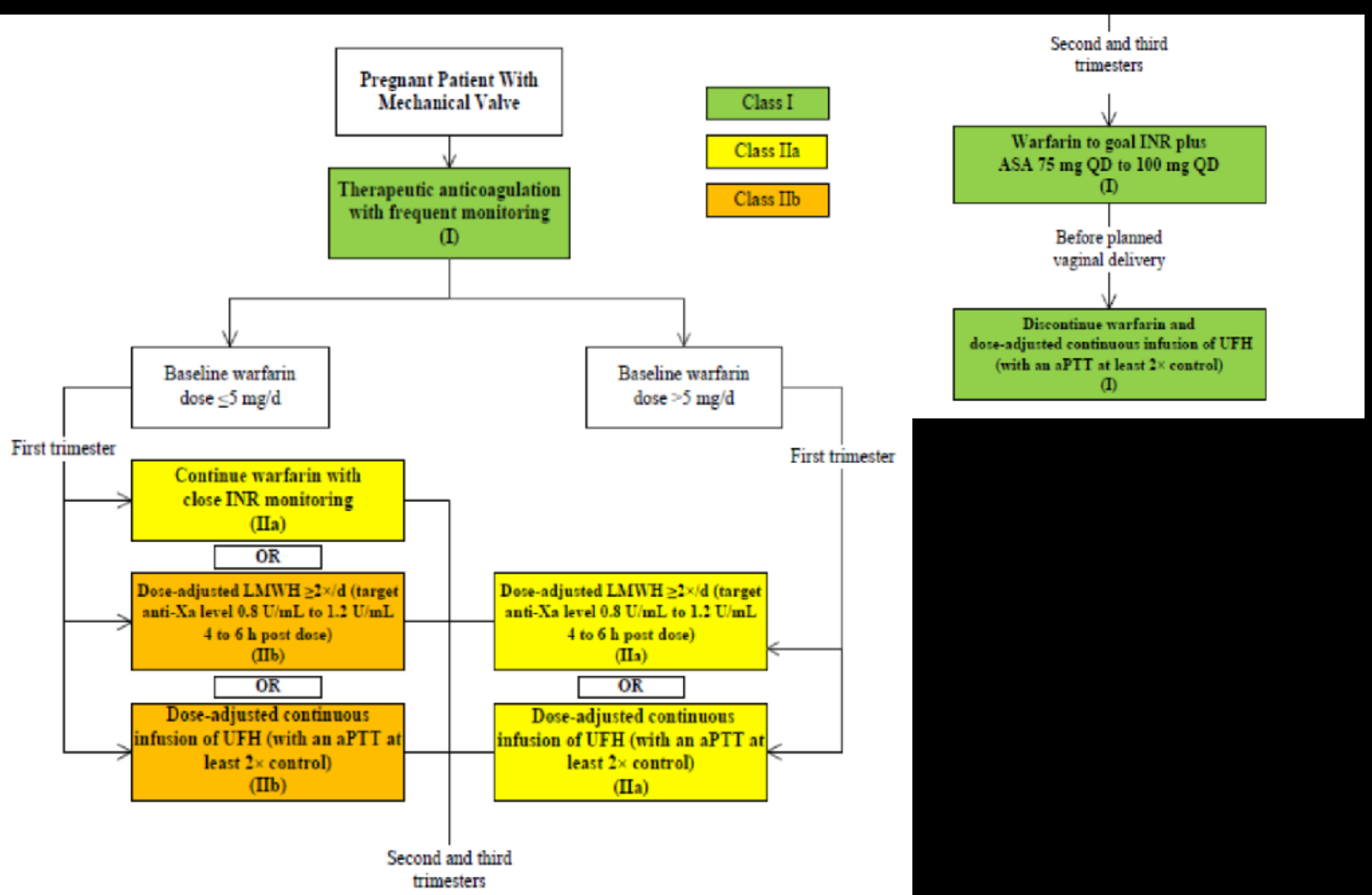
- Decreased risk of fetal anomalies
- Increased maternal risk of thrombosis
- Increased risk with inadequate monitoring

Anticoagulation	Thromboembolic Risk
VKA throughout	0-2%
LMWH 1st trimester, then VKA	3.5-16%
LMWH throughout	7 50%

- James et al, JMFM, 2006; Abildgaard et al, Thrombo Res, 2009; Basude et al, BJOG 2012

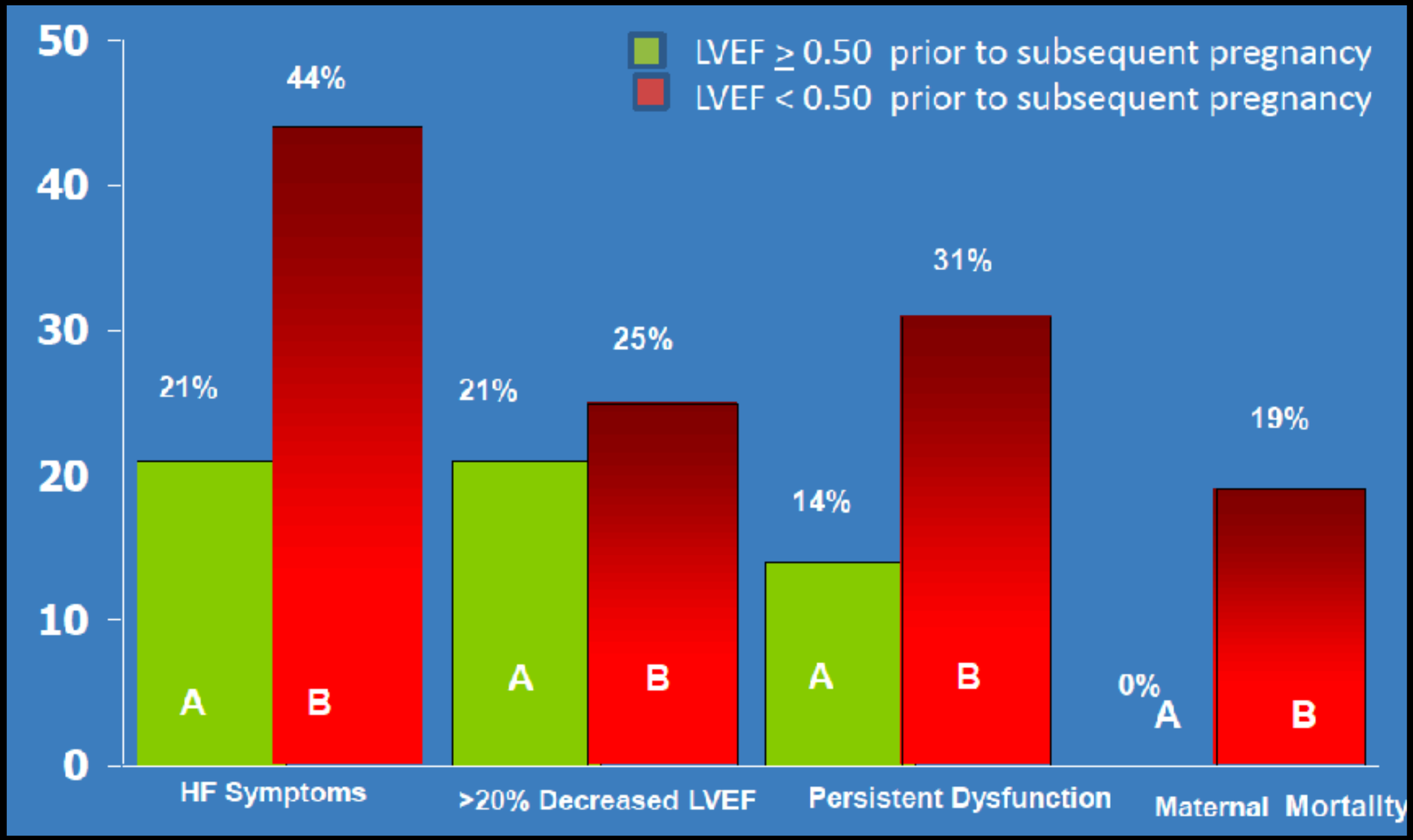
Anticoagulation

- Heparin
  - Does not cross placenta
  - Maternal thrombocytopenia or osteoporosis
  - Increased thromboembolic risk
- Warfarin
  - Spontaneous abortions
  - Embryopathy
  - Dose related (>5mg per day)
  - At risk weeks 6-12 of gestation
- LMWH
  - Reports of fatalities in pregnant women with mechanical valves
  - May be related to lack of adequate anti-Xalevels


Pregnant Patient With Mechanical Valve
Therapeutic anticoagulation with frequent monitoring (I)
Class I
Class IIa
Class IIb
Baseline warfarin dose ≤5 mg/d
Baseline warfarin dose >5 mg/d
First trimester
Continue warfarin with close INR monitoring (IIa)
OR
Dose-adjusted LMWH ≥2×/d (target anti-Xa level 0.8 U/mL to 1.2 U/mL 4 to 6 h post dose) (IIb)
OR
Dose-adjusted continuous infusion of UFH (with an aPTT at least 2× control) (IIb)
First trimester
Dose-adjusted LMWH ≥2×/d (target anti-Xa level 0.8 U/mL to 1.2 U/mL 4 to 6 h post dose) (IIa)
OR
Dose-adjusted continuous infusion of UFH (with an aPTT at least 2× control) (IIa)
Second and third trimesters
Second and third trimesters
Warfarin to goal INR plus ASA 75 mg QD to 100 mg QD (I)
Before planned vaginal delivery
Discontinue warfarin and dose-adjusted continuous infusion of UFH (with an aPTT at least 2× control) (I)

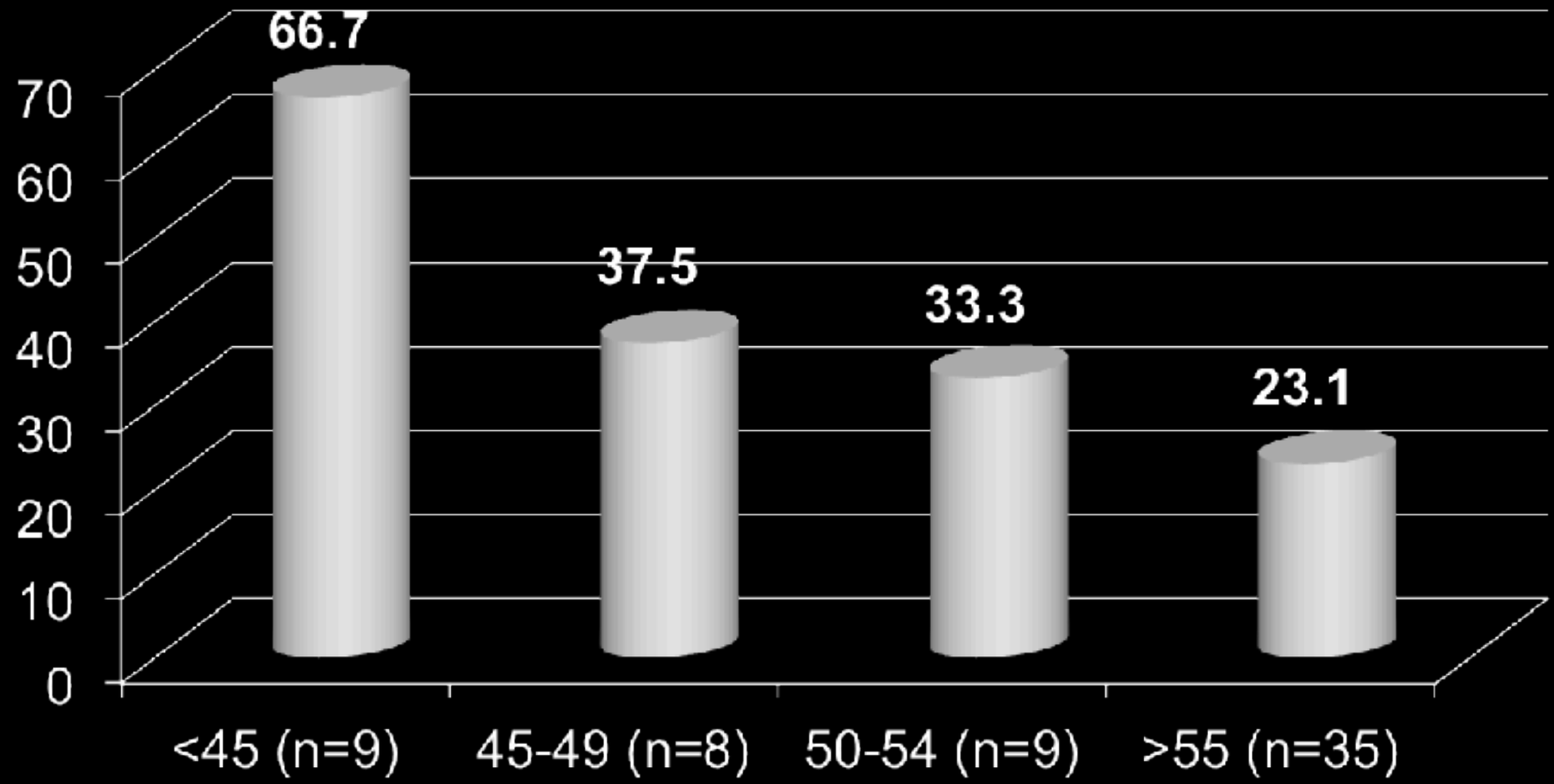
ACC VHD 2014

Maternal Complications Associated With Subsequent Pregnancy



Elkayam et al NEJM 2001;344:1567

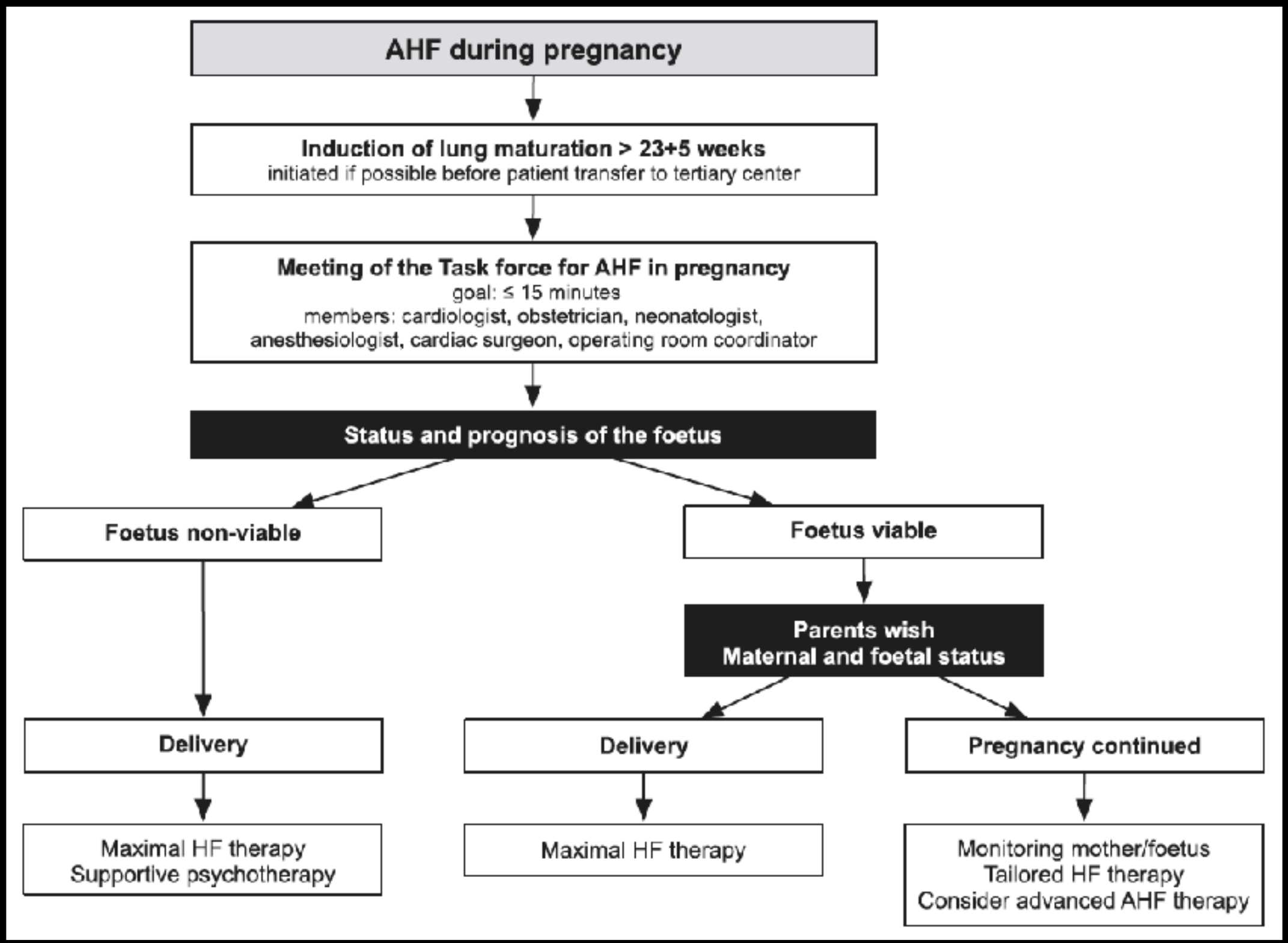
Rate of relapse/worsening heart failure among 61 post-PPCM pregnancies, 2003-2009.



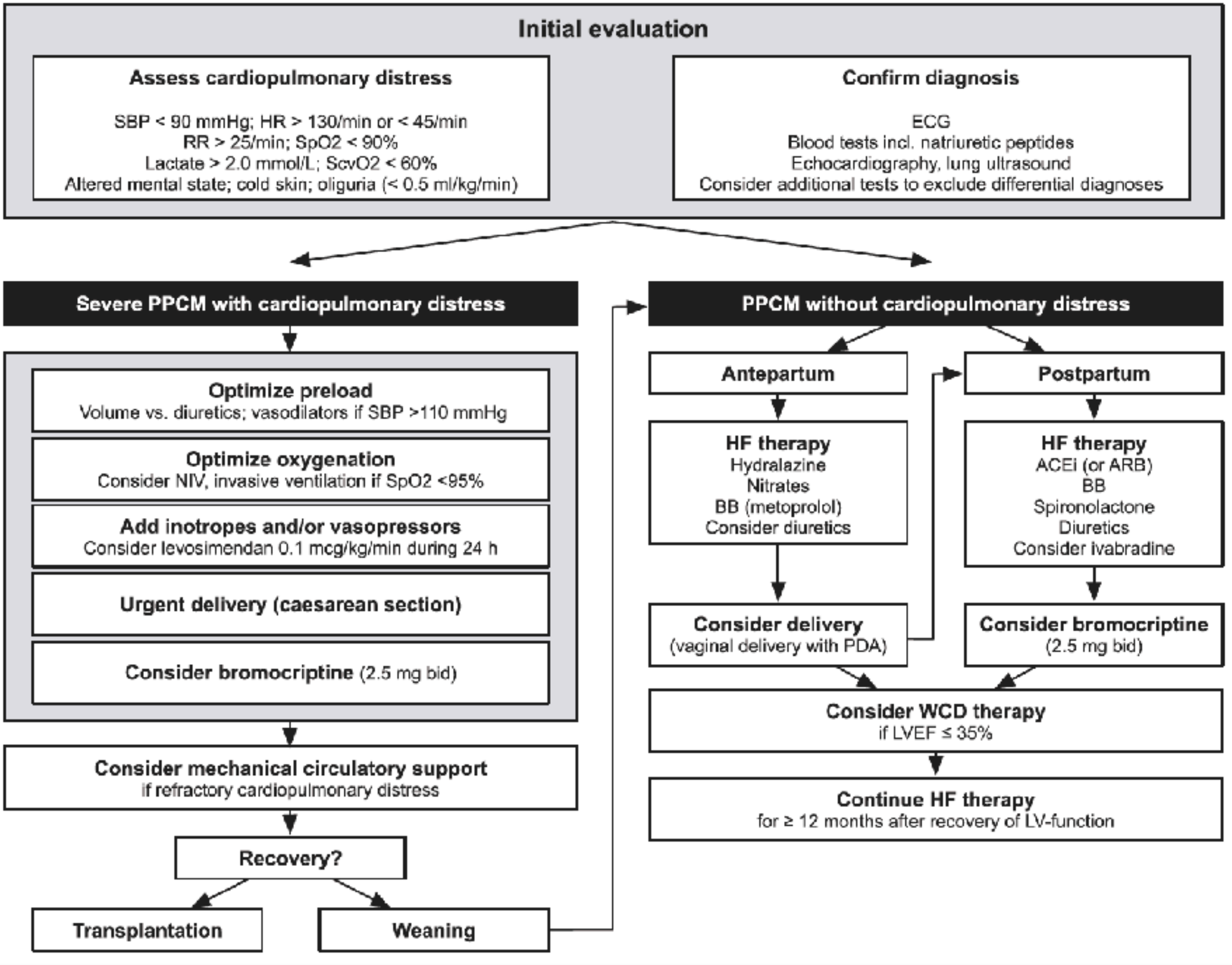
Subsequent Pregnancy in Women who Recover from PPCM

- Risk of recurrence between 20 to 25% based on retrospective data
- The impact of genomic background on the risk of recurrence of PPCM remains unknown
- Do elevations in biomarkers precede and predict possible recurrence ?

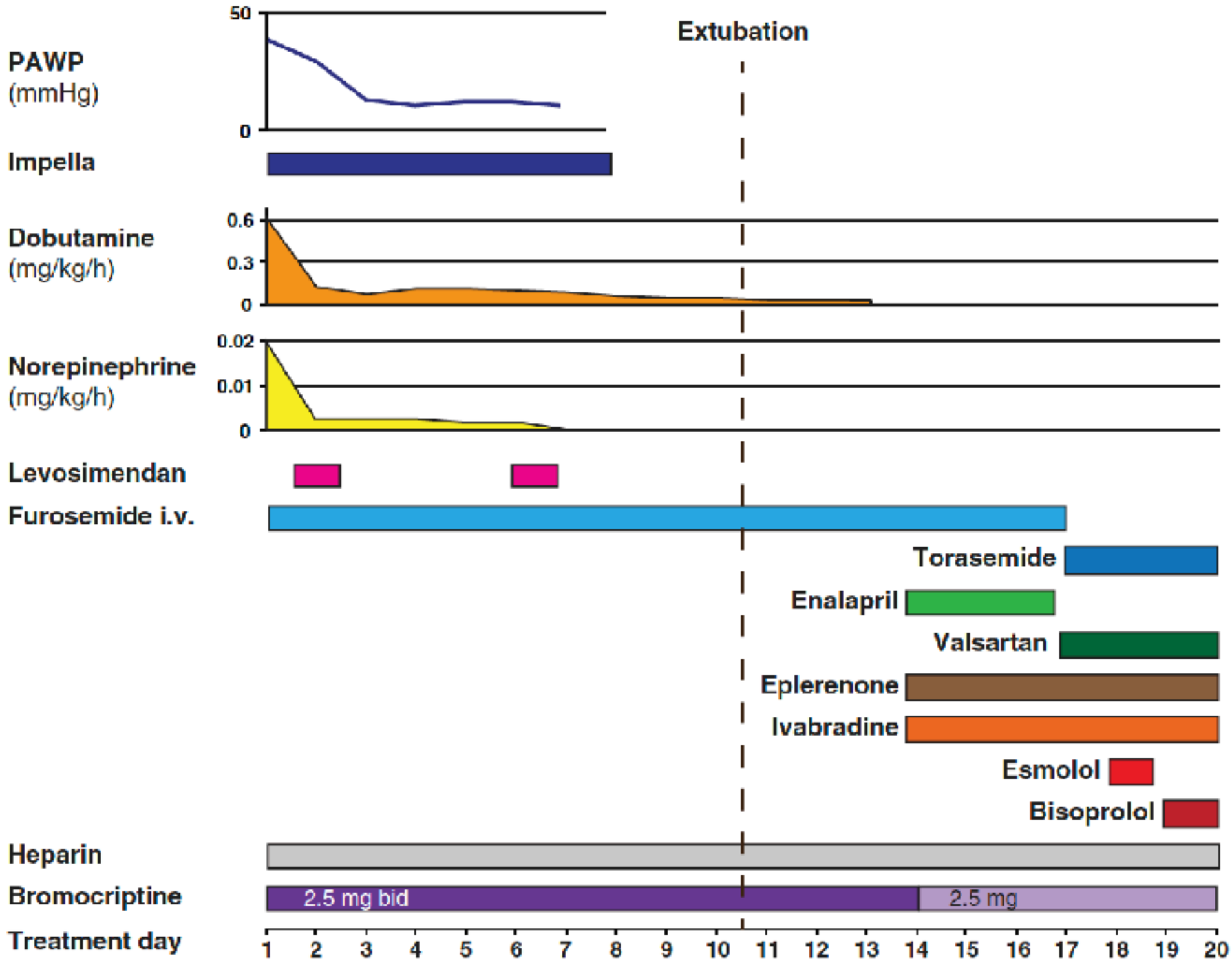
Protocol of interdisciplinary work-up for AHF



J. Bauersachs et al. Eur J Heart Fail 2016



J. Bauersachs et al. Eur J Heart Fail 2016



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Proposed strategy for HF Rx in PPCM patients *after delivery* before and after complete recovery of LV structure and function

Drug	Safety during lactation[a]	Absence of complete recovery	Complete and sustained recovery of left-ventricular structure and function (echocardiographic follow-up every 6 months)			
			6 months	6–12 months	>12 months	>18 months
β-Blocker	Bradycardia of the newborn reported in rare cases. Metoprolol is the best-studied β-blocker during lactation.	Essential for all patients. Up-titration to standard or maximally tolerated dosages.	Continue all drugs for at least 6 months after full recovery to avoid relapse	Continue β-blocker and ACE-inhibitor/ ARB for at least 6 months after stopping MRA	Continue β-blocker for at least 6 months after stopping ACE-inhibitor/ ARB	Discontinue β-blockade, ensure echocardiographic follow-up
ACE-inhibitor	Low transfer of enalapril and captopril into the breast milk.	Essential for all patients. Up-titration to standard or maximally tolerated dosages.			Reduce dosage and then discontinue ACE-inhibitor/ARB	
ARB	Very limited data on ARB during lactation and should be avoided.	Recommended for patients who cannot tolerate ACE-inhibition. Up-titration to standard or maximally tolerated dosages.				

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Drug	Safety during lactation[a]	Absence of complete recovery	Complete and sustained recovery of left-ventricular structure and function (echocardiographic follow-up every 6 months)			
			6 months	6–12 months	>12 months	>18 months
MRA	Very limited data on MRA during lactation and should be avoided	Recommended for all patients with LVEF < 40%. Eplerenone may be considered due to less hormonal side effects.			Discontinue only if complete and sustained recovery of left-ventricular structure and function	
Ivabradine	No data on ivabradine during lactation available and should be avoided.	For patients with heart rate >75/min, when β-blocker up-titration is not possible. Should be tapered when β-blocker up-titration is possible and/or heart rate is < 60/min	Continue when heart rate is >75/min despite β-blocker up-titration		Discontinue only if complete and sustained recovery of left-ventricular structure and function	
Diuretics	Thiazides are the best-studied diuretics during lactation and well tolerated. They may decrease milk production. Very limited data on furosemide and torasemide during lactation.	Only when oedema/ congestion is present. Early tapering of dose according to symptoms, even before full recovery of left-ventricular function	Continue only when symptoms (congestion/oedema) are present without diuretic therapy as part of an antihypertensive drug therapy			

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Management of PPCM diagnosed Postpartum

- Standard Heart Failure Therapy
- Anticoagulation for LV thrombus, thromboembolic events
- Consider external wearable defibrillator for high risk patients but the majority do not require.
- Bromocriptine as adjunctive therapy remains controversial

Pre-Conception Counseling Considerations: Issues to Address With the Patient

- Pregnancy risk stratification
  - Maternal cardiac risk
  - Maternal obstetric risk
  - Fetal and neonatal risks
- Long-term effects of pregnancy on the heart
- Maternal life expectancy
- Genetic consultation
- Contraception safety and efficacy
- Modification of cardiac medications
- Optimization of cardiac status
- Planning for pregnancy

Contraception

- *Talk about it!
- IUDs (Paraguardand Mirena) always safe
- Progestin implant almost always safe
- Combined Hormonal Contraceptives frequently unsafe

Conclusions

- The management of heart failure around pregnancy is challenging
- Effect of hemodynamic changes of pregnancy on clinical status
- Absence of evidence-based data
- Interdisciplinary approaches (cardiologists, intensivists, obstetricians, neonatologists, anaesthetists,cardiac surgeons)