Peripartum Cardiomyopathy

Introduction

- Cardiomyopathies cause mechanical and/or electrical dysfunction that result in dilated, hypertrophic or restrictive pathophysiology. [1]
- Cardiomyopathies are dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), and Restrictive cardiomyopathy (RCM). [1]
- Imaging with echocardiography, cardiac computed tomography (CT), positron-emission tomography-CT, and cardiac magnetic resonance help in diagnose varied etiologies. [2]
- Early recognition of myocardial dysfunction prevents inappropriate prolonged therapy for heart failure and repeated hospital admissions. [2]

1)Schultheiss HP et al. Nat Rev Dis Primers. 2019; 5(1): 32.
2)Anne AV. J Indian Acad Echocardiogr Cardiovasc Imaging 2018;2:106-11

Peripartum cardiomyopathy

- Peripartum cardiomyopathy is a type of Dilated cardiomyopathy, a form of systolic heart failure affecting young women toward the end of pregnancy or in the months following delivery. [1]
- **European Society of Cardiology (ESC) Definition: i**s an idiopathic cardiomyopathy occurring towards the end of pregnancy or in the months following delivery, abortion or miscarriage, without other causes for heart failure, and with a left ventricular (LV) ejection fraction (EF) <45%. [2]
- Outcomes are variable; women may have complete recovery, persistent myocardial dysfunction and HF, or rapid deterioration. [1]

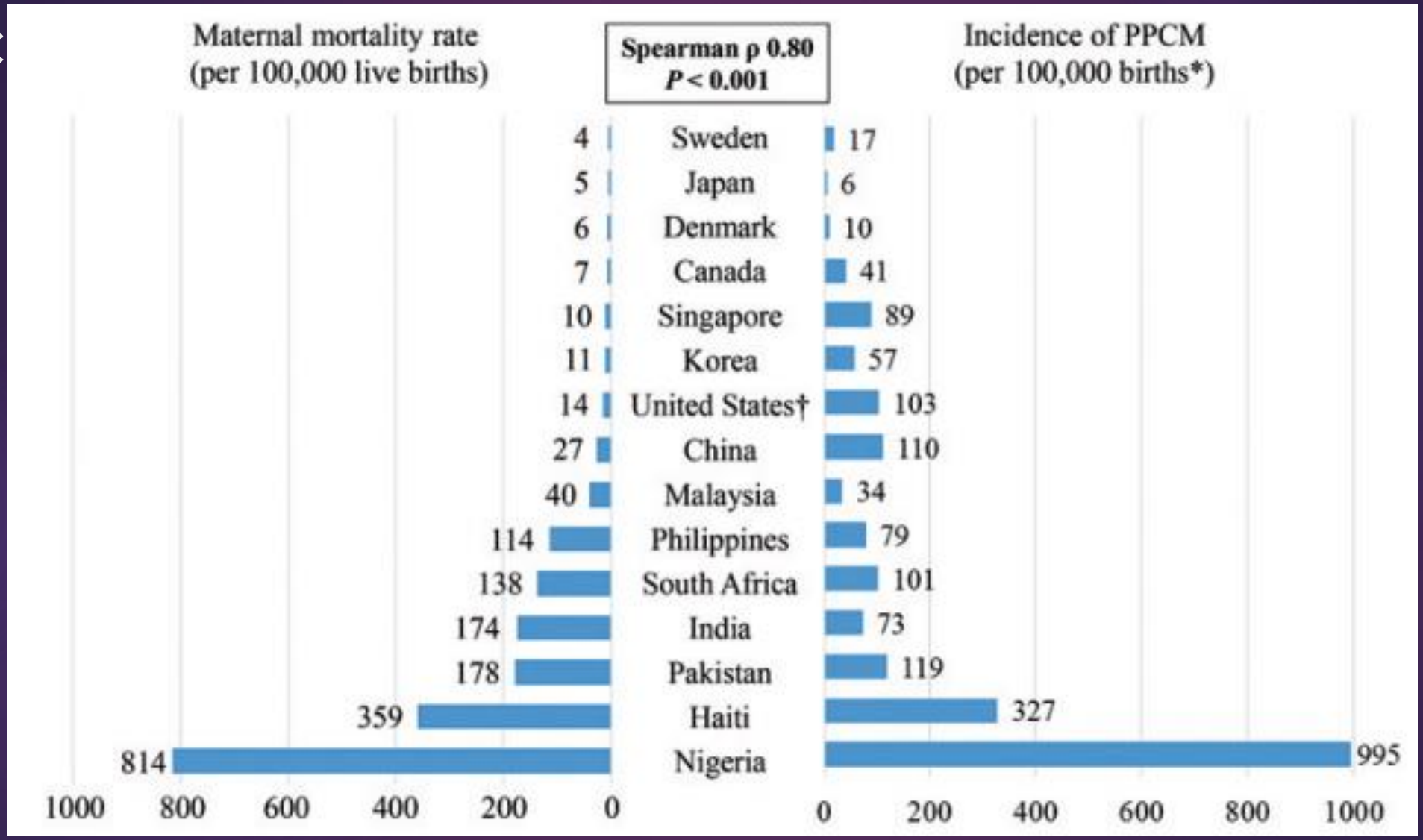
1)Davis MB et al. J Am Coll Cardiol. 2020 ;75(2):207-221
2)Bauersachs J et al. Eur J Heart Fail. 2019 s;21(7):827-84

Prevalence of peripartum cardiomyopathy worldwide

- The incidence of PPCM is highly variable by geographic region and can range from 1 in 102 to 1 in 4000 live births.
- Incidence rates in the United States are increasing overall
- There are estimated to be over 1350 new annual cases per year of PPCM in the United States.

Zagelbaum NK et al. Cardiol Rev. 2020 May/Jun;28(3):148-155

Worldwide incidence of peripartum c



*The unit of population differs among studies depending on the population representing all births, live births (excluding stillbirth), deliveries, hospitalizations, and women.

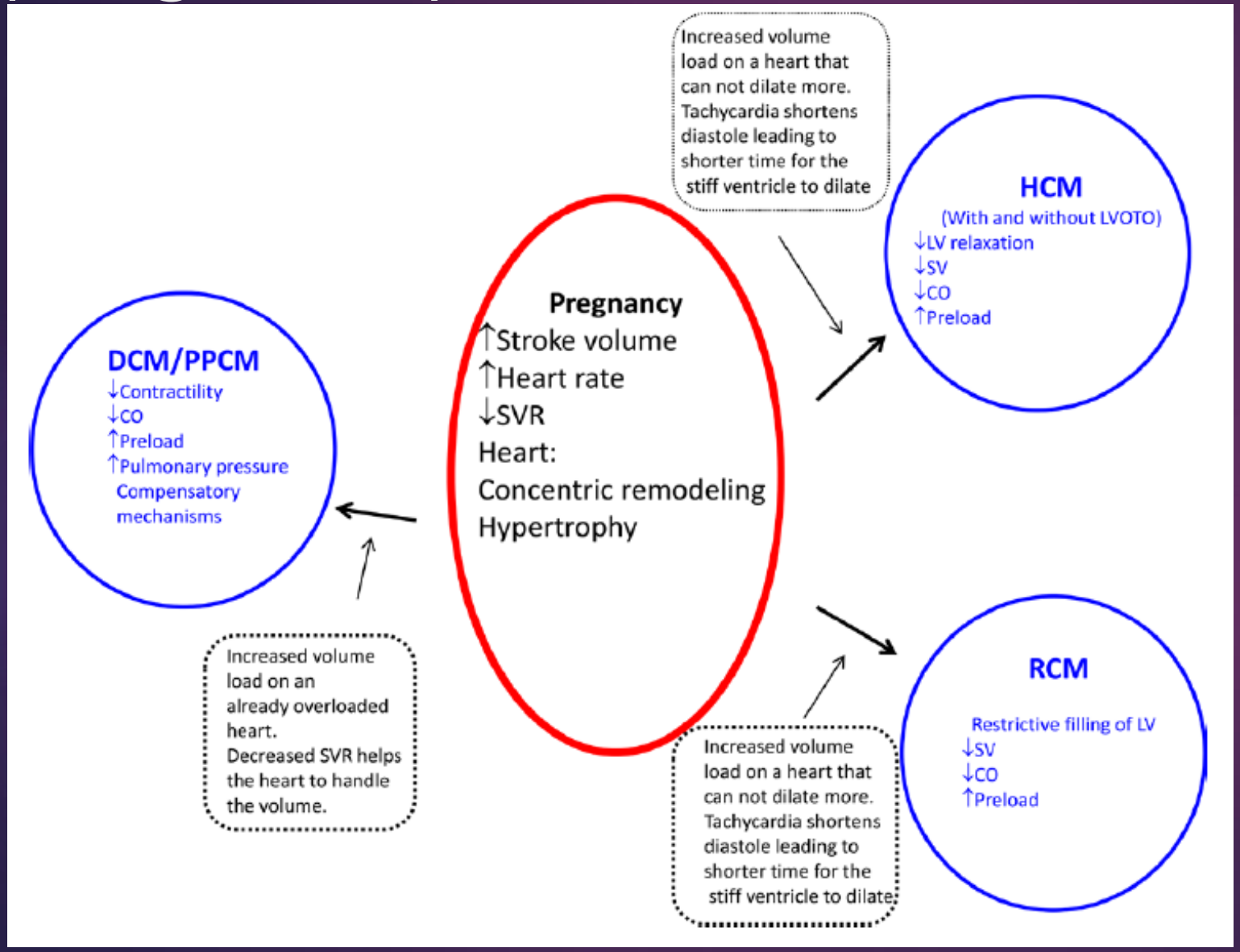
Isogai T et al. Int Heart J. 2019 May 30;60(3):503-511

Prevalence of peripartum cardiomyopathy in India

- The incidence ranges from 1:300 up to 1:15,000 (0.1% of pregnancies).
- The incidence of PPCM is one case per 1374 live births in an Indian study.
- Risk increases with increase in age

Nath JD et al. J Clin Prev Cardiol 2019;8:2-5

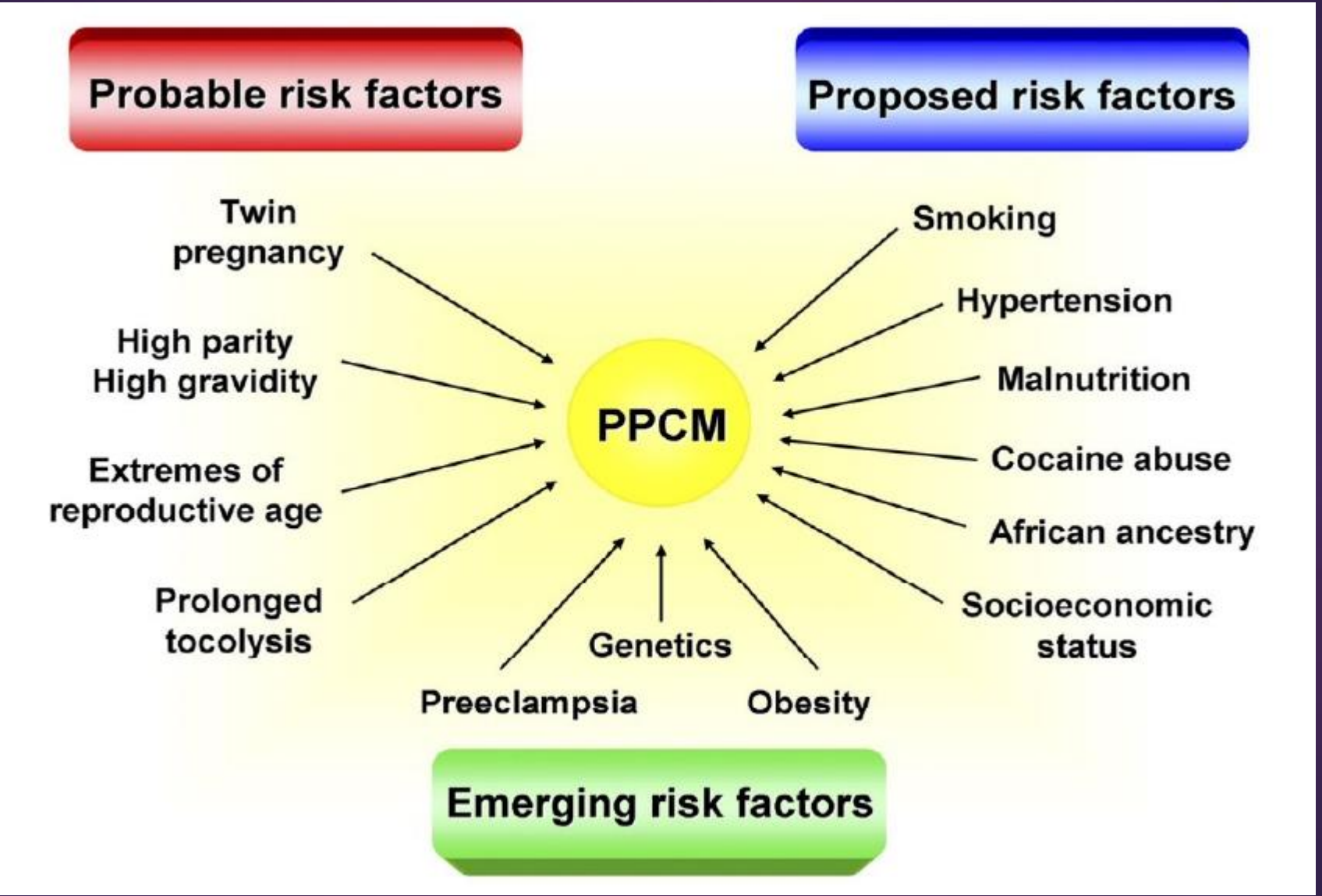
Haemodynamic changes during pregnancy and their effect on types of



DCM: dilated cardiomyopathy
CO: cardiac output
LV: left ventricle
SV: stroke volume
SVR: systemic vascular resistance.
LVOTP: left ventricular outflow tract obstruction.
PPCM: peripartum cardiomyopathy
HCM: hypertrophic cardiomyopathy
RCM: restrictive cardiomyopathy

Schaufelberger M. Heart 2019;105:1543–1551

Risk factors of Peripartum Cardiomyopathy



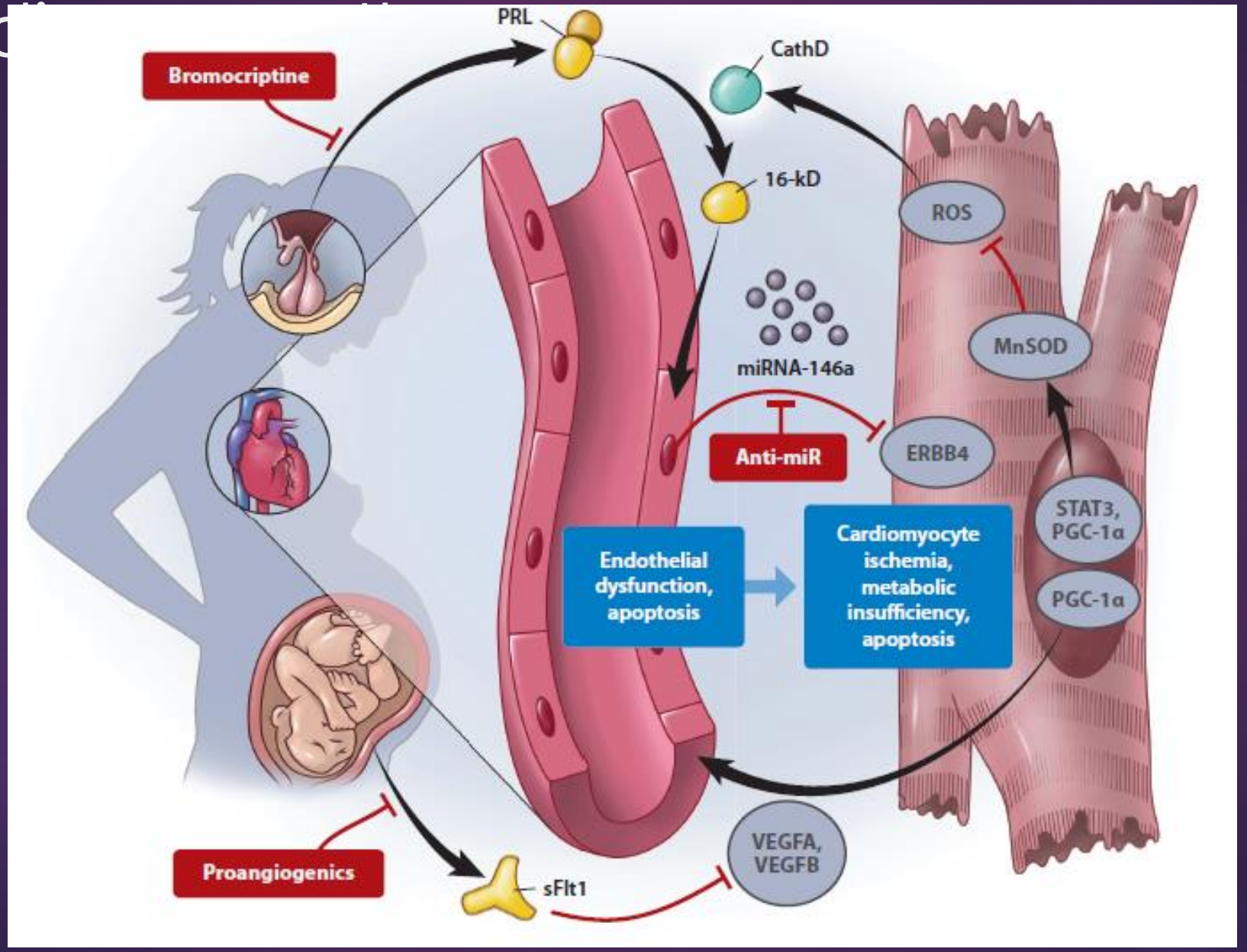
Albakri A. J Integr Cardiol, 2018 ;4(3): 1-12

Major factors involved in the development of peripartum cardiomyopathy

Pathogenesis[1]	Description[1]
Genetic factors	DCM gene mutation, MYH7, SCN5A, and PSEN2, MYH6 and TNNT2 mutations. [2]
Infectious/autoimmune factors	Infections caused by Epstein–Barr virus, human cytomegalovirus, human herpesvirus 6, and parvovirus. [2]
Factors related to angiogenesis	In Impaired cardiac protective mechanisms against anti-angiogenic factors subclinical dysfunction of cardiomyocytes may occur
Factors related to prolactin	Increased oxidative stress caused by pregnancy causes release of the prolactin-cleaving protease and cathepsin D, Cathepsin D, in turn cleaves the hormone prolactin from its 23 kDa form to its 16 kDa that is toxic to cardiomyocytes. [2]

Nguyen KA et al. Folia Cardiologica 2019; 14 (3): 315–323.
Bhandary A et al . J Clin Prev Cardiol. 2018;7:54-9.

Pathophysiology of peripartum cardi



ERBB4: avian erythroblastic leukemia viral oncogene homolog 4
MnSOD: manganese superoxide dismutase
PGC-1α: peroxisome proliferator activated receptor gamma coactivator 1 alpha
STAT3: signal transducer and activator of transcription 3 VEGF: vascular endothelial growth factor.

Arany Z. Annu Rev Med. 2018;69:165-176

Clinical presentation of peripartum cardiomyopathy

- Symptoms: Dyspnea , Orthopnea, Paroxysmal nocturnal dyspnea, Cough , Edema, Chest pain, Palpitations, Abdominal pain/discomfort, Fatigue, Exercise intolerance
- Signs : tachycardia, tachypnea, increase in jugular venous pressure, displaced apical impulse, murmurs of mitral and tricuspid regurgitation, third heart sound (S3), Right ventricular heave, Laterally displaced PMI, pulmonary oedema, hepatosplenomegaly, ascites, and peripheral edema.

Stergiopoulos K et al. Trends Cardiovasc Med. 2019;29(3):164-173

Differential diagnoses of peripartum

	History	Onset	Biomarkers	Echocardiography/ cardiac MRI	Differentiation from PPCM
PPCM	No known cardiac disease, no HF signs and/or symptoms prior pregnancy	Towards the end of pregnancy and the months following delivery	Elevated natriuretic peptides	Reduced systolic LV function, LVEF < 45%	–
Myocarditis	Prior viral infection (e.g. respiratory)	Acute or subacute onset after viral infection	Elevated troponin, elevated CRP	Normal or reduced systolic LV function, typical myocardial late gadolinium enhancement pattern, pericardial effusion	Cardiac MRI (LE pattern), myocardial biopsy
Pre-existing idiopathic/ familial dilated or acquired cardiomyopathy	HF signs and/or symptoms and/or known heart disease prior pregnancy	During second trimester of pregnancy	Elevated natriuretic peptides	Reduced systolic LV function, RV dysfunction possible, typical myocardial LE pattern (DCM)	History, echocardiography, cardiac MRI (LE pattern)
Takotsubo syndrome	Chest pain, very stressful delivery or emergency due to foetal complications	Acute onset, during delivery or immediately after delivery	Elevated natriuretic peptides	Regional wall motion abnormalities with typical anatomical patterns	History, echocardiography
Pregnancy-associated myocardial infarction	Chest pain, epigastric pain	Acute onset, during pregnancy or immediately after delivery	Elevated troponin	Regional wall motion abnormalities, ischaemic myocardial scar	History, ECG, coronary angiography, cardiac MRI (LE pattern)
Pulmonary embolism	Chest pain, unilateral leg swelling, acute dyspnoea	Acute onset during pregnancy or after delivery	Elevated natriuretic peptides and/or troponin, elevated D-dimer	RV dysfunction, RV dilatation, LV function usually normal	Computed tomography, VQ scan
Amniotic fluid embolism	Chest pain during/immediately after delivery, acute dyspnoea	Acute onset during delivery or immediately after delivery	Elevated natriuretic peptides possible	Reduced RV systolic function, RV dilatation	History, echocardiography

Bauersachs J et al. Eur J Heart Fail. 2019 Jul;21(7):827-84

Differential diagnoses of peripartum cardiomyopathy

	History	Onset	Biomarkers	Echocardiography/ cardiac MRI	Differentiation from PPCM
Hypertensive heart disease/severe pre-eclampsia	Pre-existing or new-onset hypertension, proteinuria	During second trimester of pregnancy	Elevated natriuretic peptides	LV hypertrophy, diastolic dysfunction, transient LV dysfunction	History, echocardiography
Hypertrophic cardiomyopathy	Familial predisposition	During second trimester of pregnancy	Elevated natriuretic peptides	LV hypertrophy, typical myocardial late enhancement pattern, LVOTO (HOCM)	History, echocardiography, cardiac MRI (LE pattern)
HIV/AIDS cardiomyopathy	HIV infection, AIDS	During second trimester of pregnancy	Elevated natriuretic peptides	Reduced systolic LV function, LV/RV often not dilated	HIV serology/test
Pre-existing (unknown) congenital heart disease	HF signs and/or symptoms prior pregnancy, known heart disease, prior cardiac surgery	During second trimester of pregnancy	Elevated natriuretic peptides	(Corrected) congenital heart defects, cardiac shunts	History, echocardiography
Pre-existing valvular heart disease	HF signs and/or symptoms prior pregnancy, known heart disease	During second trimester of pregnancy	Elevated natriuretic peptides	Valvular stenosis or regurgitation, prosthetic heart valves	History, echocardiography

Bauersachs J et al. Eur J Heart Fail. 2019 Jul;21(7):827-84

Diagnostic criteria for Peripartum Cardiomyopathy

Demakis criteria	Echocardiographic criteria
Heart failure within last month of pregnancy up to 5 months after delivery	LVEF <45%
Absence of determinable cause for the heart failure	LVFS <30%
Absence of heart disease before the last month of pregnancy	LVEDD >2.7 cm/m2 body surface area

LVEF: left ventricular ejection fraction
LVFS: left ventricular fractional shortening
LVEDD: left ventricular end-diastolic dimension

Dinic V et al. Front Med (Lausanne). 2015; 2: 82

Diagnostic criteria for Peripartum Cardiomyopathy

All four criteria are required for PPCM diagnosis.

1. Development of HF in the last month of pregnancy or within 5 months after delivery
2. LV systolic dysfunction (LV EF < 45% by echocardiography)
3. No identifiable cause for HF
4. No recognized heart disease before the last month of pregnancy

PPCM, peripartum cardiomyopathy; HF, heart failure; LV, left ventricle; EF, ejection fraction.

Kim MJ et al. Korean J Intern Med 2017;32:393-403

Diagnosis of peripartum Cardiomyopathy

Examination	Finding
Electrocardiography	Sinus tachycardia, Sinus arrhythmia, Atrial fibrillation, Prolonged QTc interval, Repolarization abnormalities, especially T wave inversion, Bundle branch block
Laboratory diagnostics	Elevated levels of NT-proBNP, Elevated levels of cardiac enzymes (creatine kinase and TnI), Increased blood lactate values/ low pH values
Echocardiography	Decreased LVEF, Mitral regurgitation, Cardiac thrombus
Cardiac magnetic resonance imaging	Decreased LVEF, Decreased right ventricular ejection fraction, Elevated T2 ratio as a sign of cardiac oedema, Late gadolinium enhancement as a sign of myocardial fibrosis
Coronary angiography	Normal findings

Ricke-Hoch M et al. Cardiovasc Res. 2020;116(3):520-531

Diagnostic tests recommended for the peripartum cardiomyopathy

	Clinical examination	ECG	Natriuretic peptides	Echocardiography	Chest X-ray	Cardiac MRI	CT scan	Coronary angiography
Diagnosis of PPCM	X	X	X	X	X	(X)[b]	(X)[b]	(X)[b]
4-6 weeks after diagnosis	X	X	X	X				
3 months after diagnosis	X	X	X[a]	X				
6 months after diagnosis	X	X	X[a]	X		(X)[b]		
12 months after diagnosis	X	X	X[a]	X				
18 months after diagnosis	X	X	X[a]	X				
Annually for at least 5 years after diagnosis (especially if not fully recovered)	X	X	X[a]	X				

Generally, an individual approach is recommended depending on the severity of the disease and/or potential differential diagnoses.
CT, computed tomography; ECG, electrocardiogram; MRI, magnetic resonance imaging; PPCM, peripartum cardiomyopathy.
[a]May be considered depending on costs and local availability.
[b]May be considered depending on the clinical presentation and/or differential diagnoses.

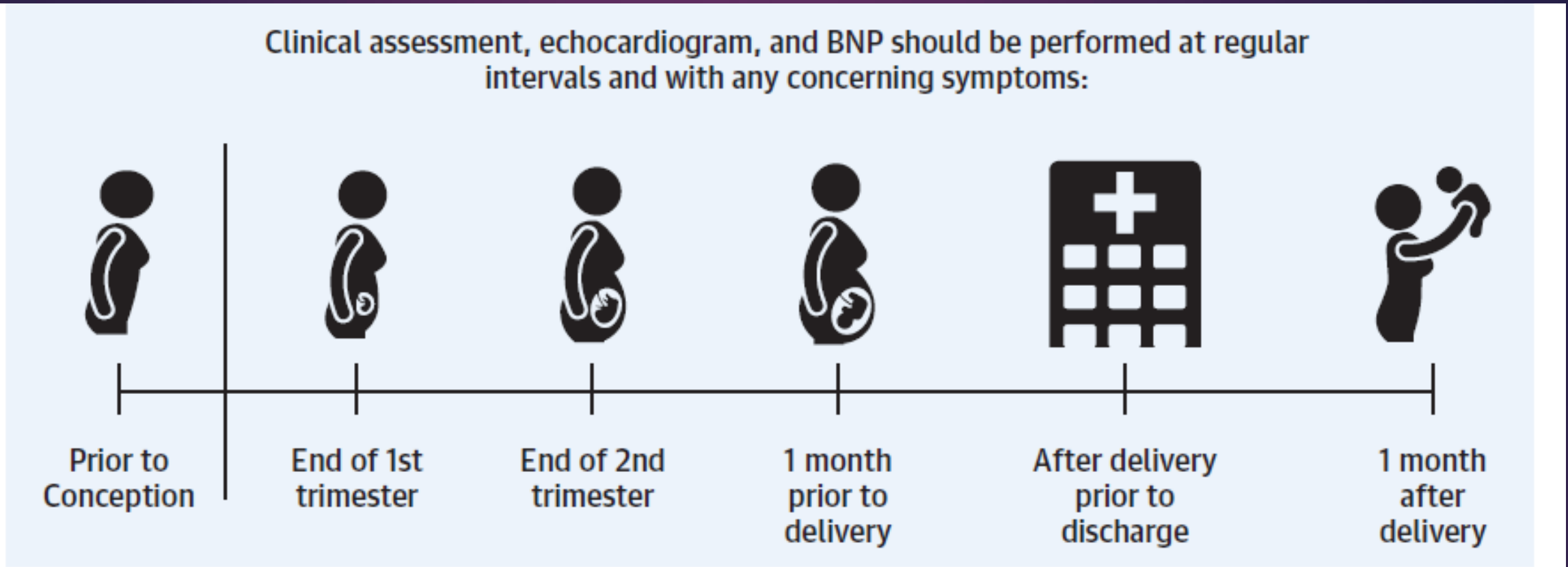
Bauersachs J et al. Eur J Heart Fail. 2019 Jul;21(7):827-84

Biomarkers raising the suspicion of Peripartum cardiomyopathy

Biomarker	Relevance
NT-proBNP	Commercial marker for screening of PPCM but nonspecific – also elevated in preeclampsia, pulmonary embolism and heart failure
16-kDa Prolactin	Pathophysiologic factor for PPCM but diagnostic accuracy requires confirmation
Interferon a	Elevated plasma levels in PPCM patients but diagnostic accuracy requires further evaluation
Asymmetric Dimethylarginine	Marker for endothelial dysfunction and cardiac risk
Cathepsin D	Increased activity in plasma of PPCM patients
Soluble fms-like tyrosine kinase-1	Increased activity in plasma of PPCM patients
MicroRNA-146a	Pathophysiologic factor for PPCM but diagnostic accuracy requires further evaluation

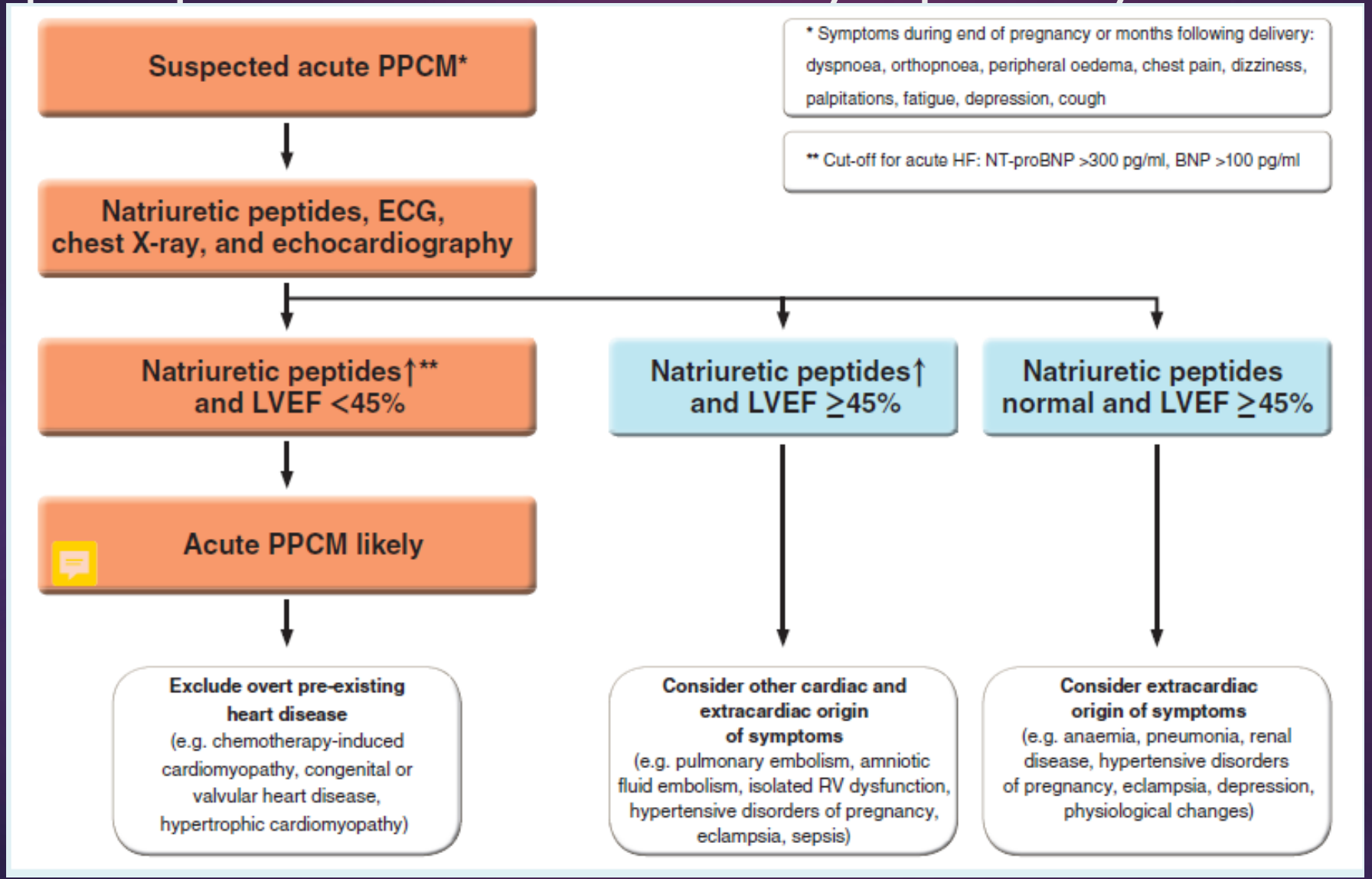
Albakri A et al. J Integr Cardiol, 2018; 4(3): 9-12

Serial monitoring of BNP during pregnancy



Proposed outline for serial testing during a subsequent pregnancy. BNP = brain natriuretic peptide.

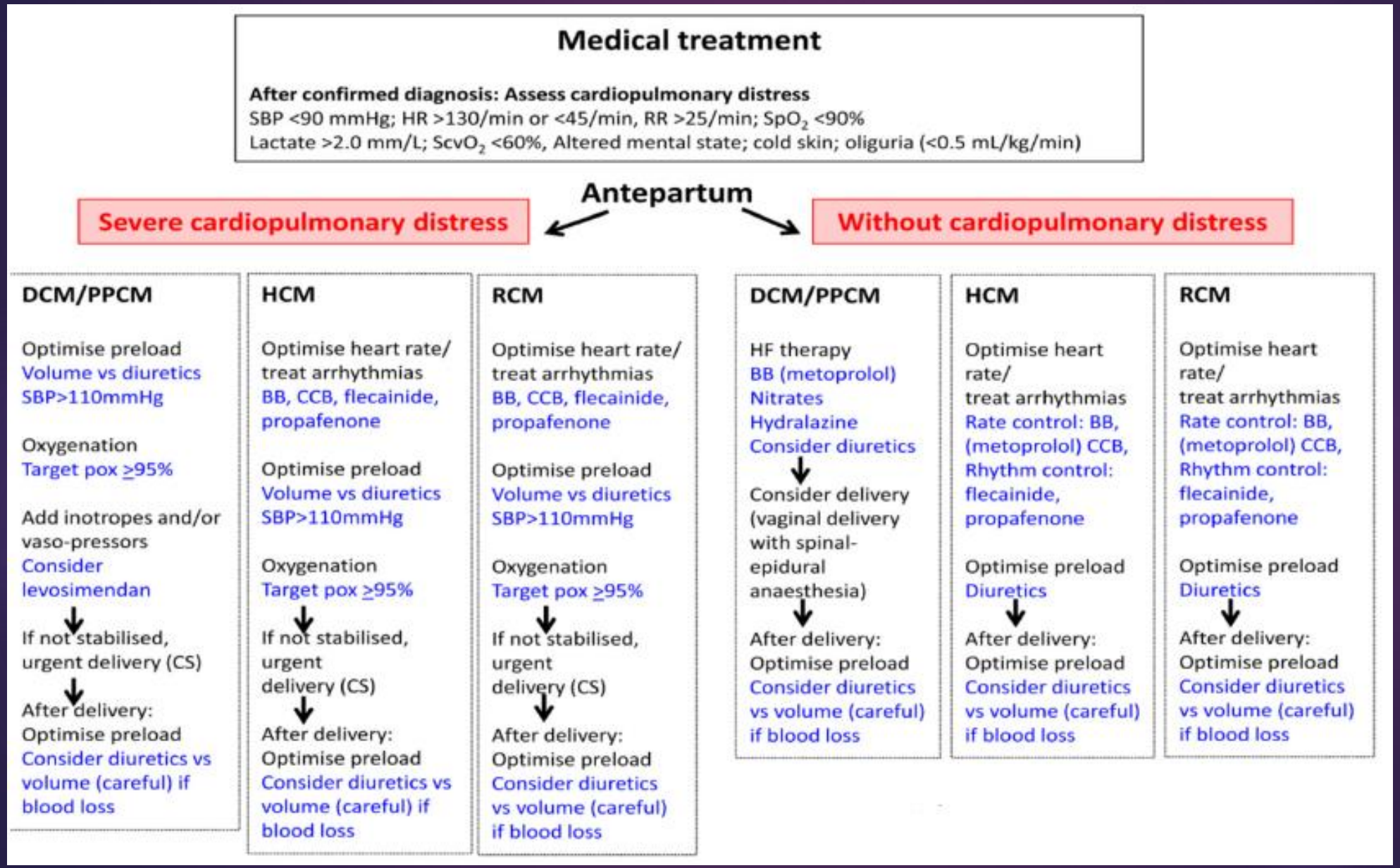
Diagnostic algorithm with suspected peripartum cardiomyopathy



PPCM: peripartum cardiomyopathy . BNP : B-type natriuretic peptide
HF: heart failure; LVEF: left ventricular ejection fraction
NT-proBNP : N-terminal pro-B-type natriuretic peptide
RV: right ventricular.

Bauersachs J et al. Eur J Heart Fail. 2019 Jul;21(7):827-84

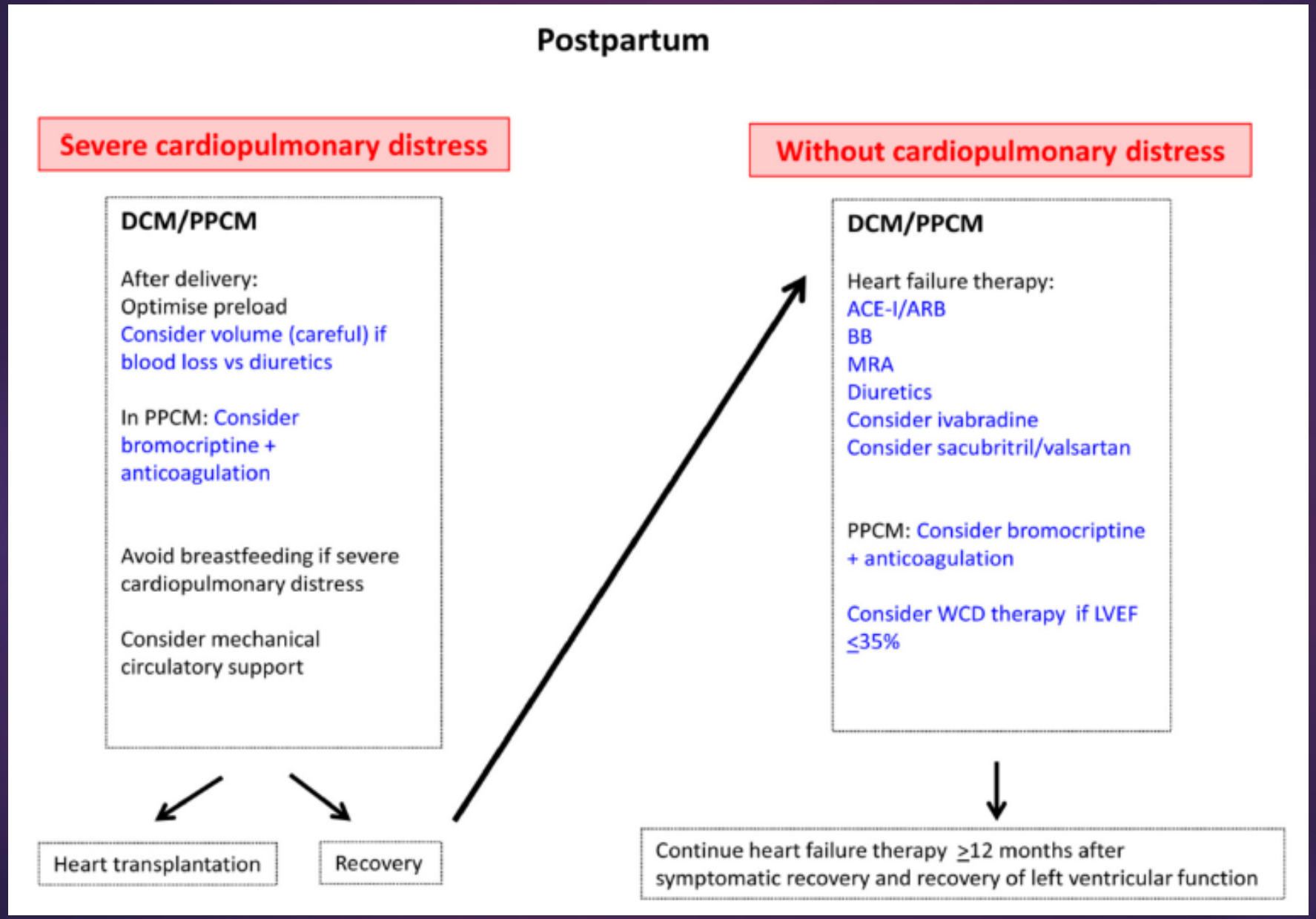
Treatment of cardiomyopathies



ACE-I/ARB : ACE inhibitor /angiotensin receptor blocker
BB, beta-blocker
CCB: calcium channel blocker
MRA: mineral corticoid receptor antagonist;
CS: Caesarean section
DCM: dilated cardiomyopathy HCM: hypertrophic cardiomyopathy
PPCM: peripartum cardiomyopathy
HR: heart rate
ScvO2: central venous oxygen saturation

Schaufelberger M.. Heart. 2019 ; 105 (20) : 1543-51.

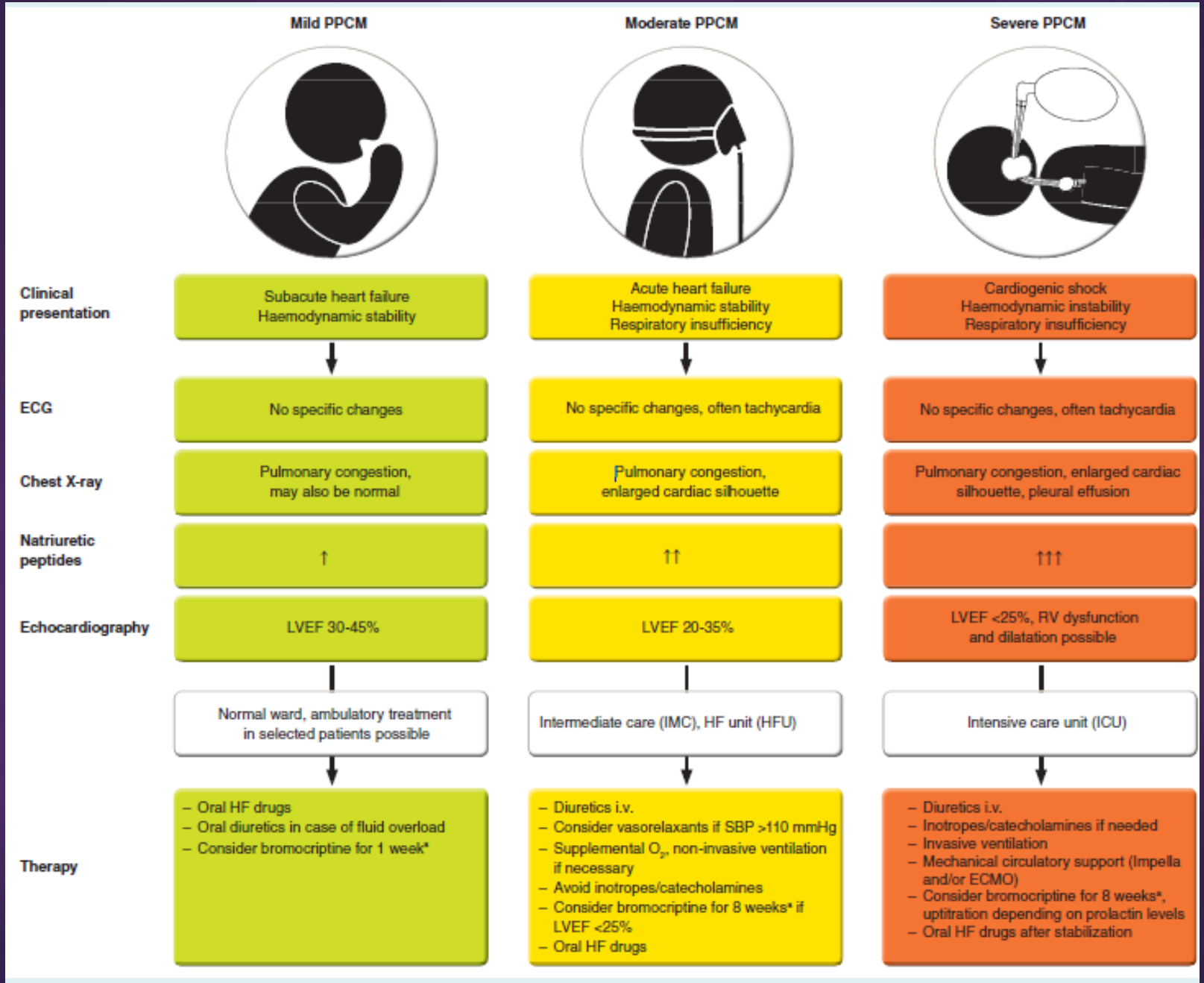
Treatment of cardiomyopathies



DCM: dilated cardiomyopathy PPCM: peripartum cardiomyopathy
WCD: wearable cardioverter defibrillator.

Schaufelberger M.. Heart. 2019 ; 105 (20) : 1543-51.

Grades of peripartum cardiomyopathy



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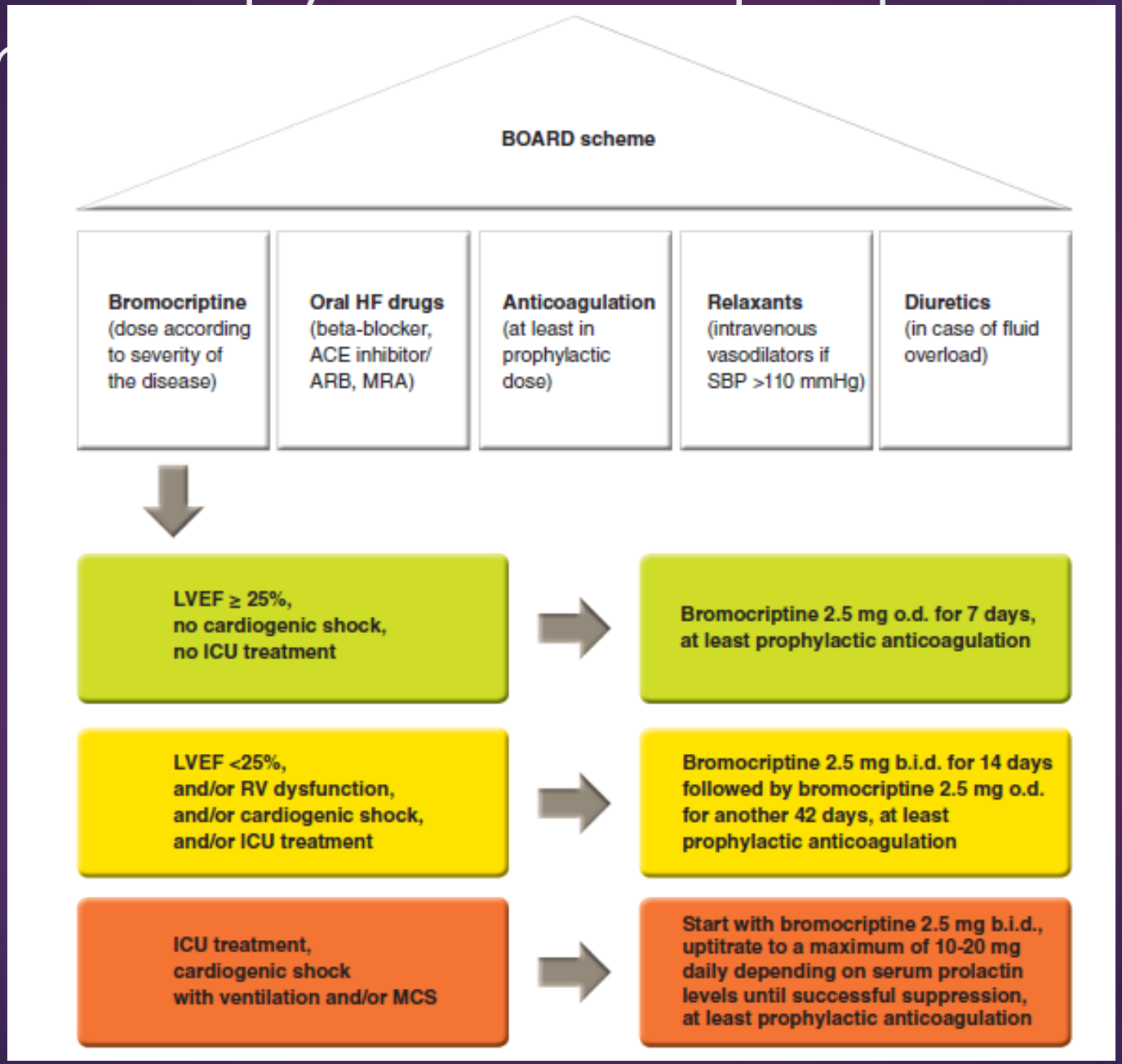
BOARD therapy for acute peripartum cardior



Bauersachs J et al. Eur J Heart Fail. 2019 Jul;21(7):827-84

Chronic drug treatment in peripartum cardiomyopathy patients after delivery

Drug	Persisting heart failure and absence of complete LV recovery	Complete and sustained recovery (LVEF > 55% and NYHA functional class I)
Beta-blocker	Essential for all patients in standard or maximally tolerated dosages	Continue all drugs (beta-blocker, ACEI/ARB/ARNI, MRA) for at least 12–24 months after full recovery, individual approach/discuss with patient. Discontinue stepwise and monitor symptoms and LV function: 1. MRA 2. ACEI/ARB/ARNI 3. Beta-blocker
ACEI	Essential for all patients in standard or maximally tolerated dosages	
ARB	Recommended in patients who do not tolerate ACEI	
ARNI	Recommended in patients with LVEF < 40% who are symptomatic despite maximal dosages of beta-blocker, ACEI/ARB and MRA	
MRA	Recommended in patients with LVEF < 40%, preferably eplerenone due to less hormonal side effects and less blood pressure reduction compared to spironolactone	
Ivabradine	Recommended in patients in sinus rhythm with a persisting heart rate > 70 b.p.m. at rest despite maximal tolerated beta-blocker up-titration	Discontinue if heart rate < 50 b.p.m. and/or in case of complete recovery
Diuretics	Recommended in patients with fluid overload	Taper dose/discontinue if no signs of fluid overload, maintain only if part of antihypertensive therapy

ACEI: angiotensin-converting enzyme inhibitor
ARB : angiotensin receptor blocker;
ARNI: angiotensin receptor–neprilysin inhibitor;
LV: left ventricular;
LVEF: left ventricular ejection fraction
MRA: mineralocorticoid receptor antagonist;
NYHA: New York Heart Association

Bauersachs J et al. Eur J Heart Fail. 2019 Jul;21(7):827-84

Heart Failure Medications: Indications and Safety in Pregnancy and During Lactation

MEDICATION	DURING PREGNANCY	POTENTIAL ADVERSE EFFECTS	INDICATIONS	DURING LACTATION
HEART FAILURE MEDICATIONS				
Loop diuretics	Yes	Caution for hypovolemia or hypotension that may lead to decreased placental perfusion	For signs and symptoms of congestion and fluid overload.	Yes, but over-diuresis can lead to decreased milk production.
Beta blockers (metoprolol tartrate used most commonly)	Yes	IUGR; fetal bradycardia and hypoglycemia	For standard treatment of HF; consider treatment of women with subsequent pregnancy.	Yes
Hydralazine/nitrates	Yes	Caution with hypotension	Use for afterload reduction during pregnancy (instead of ACE-I/ARB) when needed.	Yes, but ACE-I/ARB typically chosen post-partum
Digoxin	Yes	No associated congenital defects	Can be used with symptomatic heart failure and/or systolic dysfunction during pregnancy, or afterwards per guidelines.	Yes

	Data or experience to support use
	Caution with using this medication
	Data is limited or inconclusive

Davis MB et al. J Am Coll Cardiol. 2020 ;75(2):207-221

Heart Failure Medications: Indications and Safety in Pregnancy and During Lactation

MEDICATION	DURING PREGNANCY	POTENTIAL ADVERSE EFFECTS	INDICATIONS	DURING LACTATION
ACE-I/ARB	No	Anuria, oligohydramnios, fetal limb contractures, craniofacial deformation, pulmonary atresia, fetal hypocalvaria, intra uterine growth restriction, prematurity, patent ductus arteriosus, stillbirth, neonatal hypotension and death	Cannot use during pregnancy. After delivery, should be used as part of guideline-directed medical therapy for afterload reduction and LV remodeling.	Enalapril and captopril can be used
Aldosterone receptor antagonists	No	Spironolactone has been associated with antiadrenergic activity, feminization of male rat fetuses and permanent changes in reproductive tract in both sexes	As per guideline-directed medical therapy for heart failure.	Spironolactone can be used
Sacubitril-valsartan	No	Same as ACE-I/ARB	As per guideline-directed medical therapy for heart failure.	No information in human, present in rat milk
Ivabradine	Scant data in humans; would avoid due to concerns in animal studies	Scant data in humans, animal data suggest risk	As per guideline-directed medical therapy for heart failure.	No information in human, present in rat milk

	Data or experience to support use
	Caution with using this medication
	Data is limited or inconclusive

Davis MB et al. J Am Coll Cardiol. 2020 ;75(2):207-221

Anticoagulant Medications: Indications and Safety in Pregnancy and During Lactation

MEDICATION	DURING PREGNANCY	POTENTIAL ADVERSE EFFECTS	INDICATIONS	DURING LACTATION
Low molecular weight heparin	Yes	Caution at time of delivery and with neuraxial anesthesia; does not cross placenta; consider the need for monitoring anti-Xa levels	For prevention and treatment of thromboembolic complications during pregnancy and as bridge to warfarin postpartum.	Yes
Warfarin	Avoid	Warfarin embryopathy and fetopathy	For prevention and treatment of thromboembolic complications postpartum.	Yes

	Data or experience to support use
	Caution with using this medication
	Data is limited or inconclusive

Davis MB et al. J Am Coll Cardiol. 2020 ;75(2):207-221

Management of subsequent pregnancy with Peripartum cardiomyopathy

Algorithm for Subsequent pregnancy management in PPCM and LV dysfunction

- **During pregnancy**
- Base line echocardiography and BNP level prior to or during the first visit
- Follow Up for symptoms once in a month for 30 week and then once in 2 weeks until delivery
- β-blockers to be contined, switching over ACEI/ARBS/ Sacubitril/Valsartan to Hydralazine/Isosorbide dinitrate
- Diuretics for volume overload

Goland S et al. Cardiac Problems in Pregnancy. 2019 Aug 26:128-54.

Algorithm for Subsequent pregnancy management in PPCM and LV dysfunction

- **During pregnancy**
- Aspirin 81 mg/daily started between 12 and 28 wk until delivery in women at increased risk of preeclampsia.
- Digoxin for symptoms improvement
- Therapeutic anti coagulation for LVEF <40%
- Wearable Defibrillator for LVEF ≤35%
- echocardiography and BNP are repeated at the end of first and second trimester, 1mo prior to estimated time of delivery, prior to discharge after the delivery, 1-mo postpartum and if symptoms worsen

Goland S et al. Cardiac Problems in Pregnancy. 2019 Aug 26:128-54.

Algorithm for Subsequent pregnancy management in PPCM and LV dysfunction

- **After the delivery**
- Enalapril and Spironolactone is started
- Anticoagulation is continued for 6 weeks
- Wearable defibrillator as a bridge to recovery or implantation of implantable cardioverter defibrillator
- Breast-feeding is allowed in stable patients.
- Close follow-up for 6 months

Goland S et al. Cardiac Problems in Pregnancy. 2019 Aug 26:128-54.

Algorithm for Subsequent pregnancy management in PPCM and recovered LV function (≥50%)

- Baseline echocardiography and BNP level prior to or at first visit during pregnancy
- Follow-up for symptoms once in 1–2mo for 30 weeks and then every 2 weeks until delivery
- ACEi/ARBs are discontinued, β-blockers are continued
- Echocardiogram and BNP levels are repeated 1–2mo after discontinuation of RAAS medication to reassess LV function
- No drug therapy in patients who are not on medications

Goland S et al. Cardiac Problems in Pregnancy. 2019 Aug 26:128-54.

Algorithm for Subsequent pregnancy management in PPCM and recovered LV function (≥50%)

- Aspirin 81 mg/d started between 12 and 28 weeks until delivery in women at increased risk of preeclampsia
- Echocardiogram and BNP are repeated at the end of second trimester, 1 month prior to estimated time of delivery, prior to discharge, 1 month postpartum or at any time if symptoms worsen
- Breast-feeding can be allowed
- Close follow-up for 6 months

Goland S et al. Cardiac Problems in Pregnancy. 2019 Aug 26:128-54.

Clinical trials

Efficacy of Bromocriptine in peripartum cardiomyopathy with and right ventricular dysfunction

- Aim: To assess the effect of short term and long term Bromocriptine on RV dysfunction in peripartum cardiomyopathy.
- Methods: 40 patients with PPCM were included, with 24 patients having reduced RV ejection fraction (RVEF < 45%).
- Patients were administered Bromocriptine for short-term at the dose of 2.5 mg for 7 days (*n* = 10) compared with long-term treatment at the dose of 5 mg for 2 weeks followed by 2.5 mg for another 6 weeks (*n* = 14) for 8 weeks totally in addition to heart failure therapy.
- Assessment:

(1) change from baseline (Δ delta) in RVEF

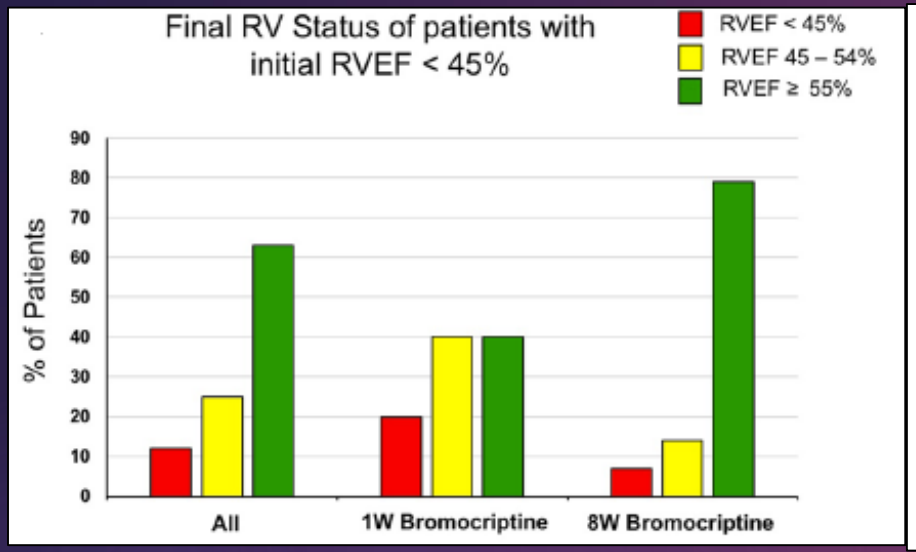
(2) change from baseline in left ventricular EF (LVEF)

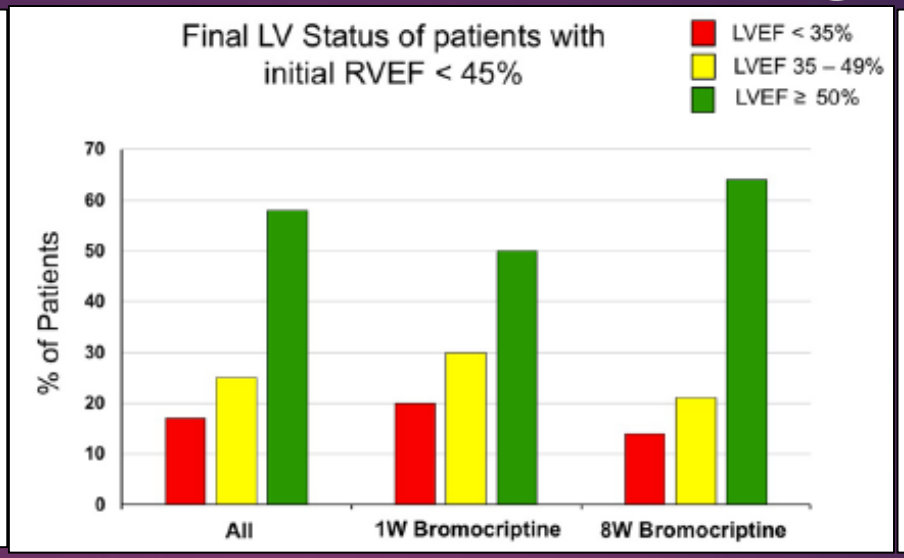
(3) Rate of patients with full LV recovery (LVEF ≥ 50%)

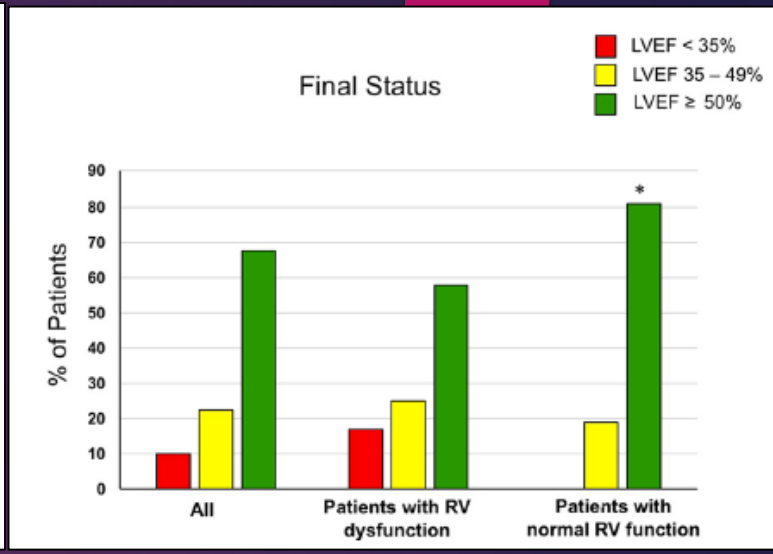
(4) rate of patients with full RV recovery (RVEF ≥ 55%) at 6-month follow-up as assessed by cardiac magnetic resonance imaging.

Haghikia A et al. Clin Res Cardiol. 2019;108(3):290-297

Efficacy of Bromocriptine in peripartum cardiomyopathy with normal and right ventricular







- Results: RVEF increased from 38 ± 7 to 53 ± 11% with a delta-RVEF in the 1 week group, and from 35 ± 9 to 58 ± 7% % in the 8 weeks group (Δ RVEF 1 week vs 8 weeks: $p = 0.118$).
- LVEF increased from 25 ± 8 to 46 ± 12% in the 1 week group, and from 22 ± 6 to 49 ± 10% in the 8 Weeks group (Δ LVEF 1W vs 8W: $p = 0.211$).
- Full LV recovery was seen in 50% of the 1 Week group and in 64% of the 8 Week group ($p = 0.678$). Full RV recovery was observed in 40% of the 1 Week group and in 79% of the 8 Week group and significant recovery at 6 months follow up. (p= 0.027)

Conclusion: Bromocriptine treatment in PPCM patients with RV involvement was associated with a high rate of full RV and LV recovery

Haghikia A et al. Clin Res Cardiol. 2019;108(3):290-297

Clinical trials

- A study done by Sliwa K et al showed that Pentoxiphylline 400 mg thrice daily showed improvement in left ventricular functions in patients with Peripartum Cardiomyopathy. [1]

- A study by Boskurt B revealed that Intravenous immunoglobulin improved the ejection fraction markedly reduced the levels of inflammatory cytokines in peripartum cardiomyopathy. [2]

1)Sliwa K et al. Eur J Heart Fail 2002;4:305-9.
2)Bozkurt B et al. J Am Coll Cardiol 1999;34:177-180

Novel markers and targets

A novel marker of persistent left ventricular systolic dysfunction in patients with peripartum cardiomyopathy: monocyte count- to- HDL cholesterol ratio

Firdevs Aysenur Ekizler[1,2*] and Serkan Cay[1,2]

Abstract

Background: Peripartum cardiomyopathy (PPCM) is a rare but potentially life-threatening complication of pregnancy. There is limited data regarding the predictors of persistent left ventricular (LV) systolic dysfunction. Recently, monocyte-to-high density lipoprotein (HDL) cholesterol ratio (MHR) has emerged as a novel indicator of inflammation and oxidative stress. We aimed to assess the predictive value of MHR on LV recovery in patients with PPCM.

Methods: A total of 64 patients with PPCM who admitted to our tertiary reference hospital between 2009 and 2017 were retrospectively analyzed in this study. Demographic and clinical data, laboratory parameters and echocardiographic findings were recorded. The duration of follow-up was at least 12 months after diagnosis for all participants. Recovery of LV systolic function was defined as the presence of LV ejection fraction (LV EF) > 45%. Univariate analysis was used to determine the significant predictors of persistent LV systolic dysfunction (non-recovery). A receiver operating characteristic (ROC) curve was used to establish the cut-off values for predictors.

Results: The mean follow-up duration was 72.1 ± 5.5 months. Of the 64 patients, 35 (55%) had persistent LVSD at their last follow-up while 29 (45%) showed LV EF improvement. The baseline MHR levels were significantly higher in the non-recovery group ($P < 0.001$). In univariate analysis, increased MHR levels (odds ratio:1.17; 95% confidence interval, 1.01–1.35; $P < 0.001$) significantly predicted LV non-recovery. Using a cut-off level of 9.73, MHR predicted persistent LV systolic dysfunction with a sensitivity of 89% and specificity of 79%. Besides, lower baseline LVEF increased WBC and CRP levels were identified as predictors of LV non-recovery.

Conclusions: Our data firstly indicated that elevated MHR was a significant predictor of persistent LV systolic dysfunction in PPCM. The MHR might contribute to determining high-risk patients with PPCM.

Keywords: Left ventricular recovery, Marker, Monocyte-to-HDL cholesterol ratio, Peripartum cardiomyopathy

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Global Left Ventricular Strain at Presentation Is Associated with Subsequent Recovery in Patients with Peripartum Cardiomyopathy

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Background: Peripartum cardiomyopathy (PPCM) is a serious complication of pregnancy associated with variable degrees of left ventricular (LV) recovery. The aim of this study was to test the hypothesis that global LV strain at presentation has prognostic value in patients with PPCM.

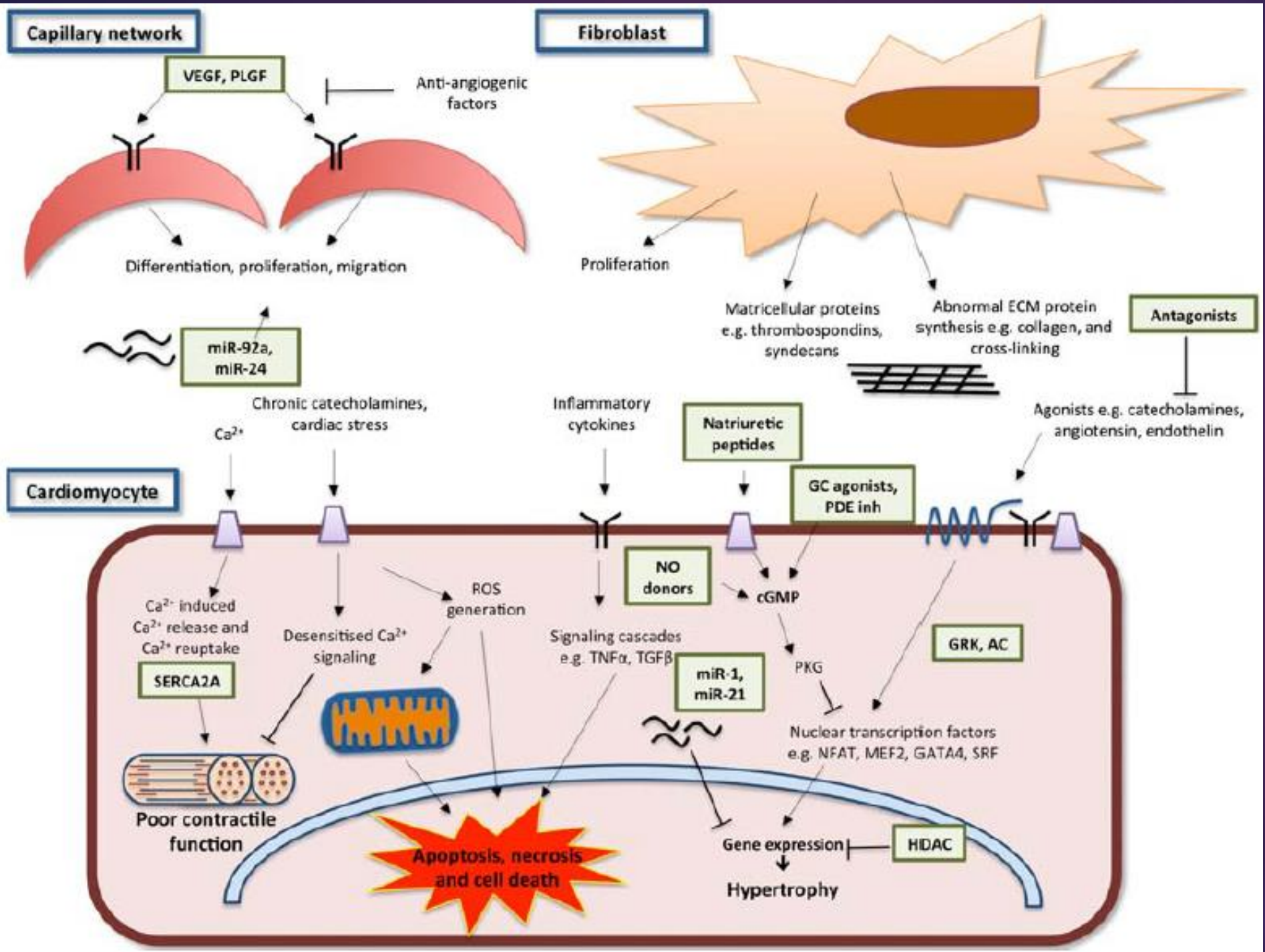
Methods: One hundred patients with PPCM aged 30 ± 6 years were enrolled in the multicenter Investigation in Pregnancy Associated Cardiomyopathy study along with 21 normal female control subjects. Speckle-tracking global longitudinal strain (GLS) and global circumferential strain (GCS) analysis was performed. The predefined primary combined outcome variable was death, transplantation, LV assist device implantation, or evidence of persistent LV dysfunction (LV ejection fraction [LVEF] < 50%) at 1 year.

Results: GLS measurement was feasible in 110 subjects: 89 of 90 patients with PPCM (99%) with echocardiographic data and all 21 control subjects. Of 84 patients (94%) with 1-year follow-up, 21 (25%) had unfavorable primary outcomes: four LV assist device placements, two deaths, and 15 patients with persistent LV dysfunction. GLS at presentation with a cutoff of 10.6% (absolute value) was specifically associated with the subsequent primary outcome with 75% sensitivity and 95% specificity. GCS at presentation with a cutoff of 10.1% was associated with the primary outcome with 78% sensitivity and 84% specificity. GLS and GCS remained significantly associated with outcomes after adjusting for LVEF (GLS odds ratio, 2.07; $P < .001$; GCS odds ratio, 1.37; $P = .005$). GLS was significantly additive to LVEF (C statistic = 0.76–0.91, net reclassification improvement = 1.32, $P < .001$).

Conclusions: GLS and GCS in patients with PPCM at presentation were associated with subsequent clinical outcomes, including death, LV assist device implantation, and evidence of persistent LV dysfunction. Strain measures may add prognostic information over LVEF for risk stratification. (J Am Soc Echocardiogr 2019;■:■-■.)

Sugahara M et al. J Am Soc Echocardiogr. 2019 ; 32 (12):1565-1573

Novel Targets in Peripartum cardiomyopathy



VEGF: vascular endothelial growth factor
PLGF: placental growth factor
SERCA2A: sarcoplasmic/ endoplasmic reticulum Ca2+ ATPase
HDAC: histone deacetylase
GRK: G-protein coupled receptor kinase
AC: adenylate cyclase
NO: nitric oxide
PDE inhibitors: phosphodiesterase inhibitors

Nabeebaccus A et al. Br Med Bull. 2016; 119(1): 99–110

Novel targets for Peripartum Cardiomyopathy

Therapy	Drug type	Hypothesized mechanism	Key trials to date	Key findings to date	Future or on-going studies
Ularitide (urodilatin)	Endogenous natriuretic peptide	Natriuresis, vasodilatation, antifibrotic and antihypertrophy effects	SIRIUS-1, SIRIUS-2	Improved haemodynamics, improved dyspnoea, reduced plasma NT-proBNP	TRUE-AHF (NCT01661634) (Phase 3) – acute decompensated heart failure
Cenderitide	Recombinant human BNP	Natriuresis, vasodilatation, antifibrotic and antihypertrophy effects	Animal studies only	Increased cGMP and reduced fibrosis in rat model of cardiac fibrosis	Number of small phase 1 trials assessing pharmacokinetics, safety and tolerance
Omecamtiv mecarbil	Direct myosin activator	Prolonged systolic ejection time	ATOMIC-AHF	Reduced dyspnoea with highest dose Reduced HR and SBP	COSMIC-HF – stable HFrEF (NCT01786512)
Neuregulin-1	Cardiac growth factor – acts via ErbB4	Regulation of cardiac structure, homeostasis and physiology	Effectiveness and safety of rhNRG-1 in chronic heart failure	Increases in LVEF and reduced LV cavity dimensions	NRG-1β (GGF-2) in HFrEF (Phase 1 (NCT01258387), rhNRG-1 (Phase 2/3) (NCT01251406)
Serelaxin	Recombinant human relaxin-2	Haemodynamic effects, reverse myocardial fibrosis	Pre-RELAX-AHF, RELAX-AHF	Improved dyspnoea, no effects on mortality/ hospitalization	RELAX-AHF-EU (NCT02064868), RELAX-AHF-2 (NCT01870778), RELAX-AHF-ASIA (NCT02007720) (all Phase 3)

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Novel targets for Peripartum

Therapy	Drug type	Hypothesized mechanism	Key trials to date	Key findings to date	Future or on-going studies
Sitaxsentan	ET_A antagonists	Systemic and pulmonary arterial vasodilatation, reduced hypertrophy	Effectiveness of sitaxsentan in HFpEF	Increased exercise tolerance, no change to echocardiographic indices of function	–
Valsartan/sacubitril	Angiotensin receptor blocker and neprilysin inhibitor	Inhibition of breakdown of natriuretic peptides and RAAS	PARADIGM-HF, PARAMOUNT-HF	20% reduction in relative risk of CV mortality and heart failure hospitalization compared with ACE inhibitor	PARAGON-HF– HFpEF (NCT01920711) (Phase 3)
Ranolazine	Metabolism modulator, Na channel modulator	Improved function, reduced arrhythmia	RALI-DHF	Improved measures of haemodynamics but no improvement of relaxation parameters or NT-pro-BNP levels	RAZE (NCT01505179)
Bendavia	Mitochondrial enhancer	Improved metabolic gene expression and reduced hypertrophy	Animal studies only	Reduced fibrosis at MI border and cardiac hypertrophy post-infarction	Bendavia in stable HFrEF (NCT02388464) and HFpEF (Mito-HFpEF) (both phase 1)
Ivabradine	I_f inhibitor	Inhibition of aldosterone signalling, reduced heart rate	SHIFT	Improved clinical outcomes (HF hospitalization and CV mortality)	EDIFY (EudraCT 2012-002742-20) (Phase 2)
Finerenone	Non-steroidal MRA	Inhibition of aldosterone signalling	ARTS (phase IIa)	Decreased NT-proBNP, improved renal profile vs. spironolactone	ARTS-HF (NCT01807221) (Phase 2b)

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Novel targets for Peripartum Cardiomyopathy

Therapy	Drug type	Hypothesized mechanism	Key trials to date	Key findings to date	Future or on-going studies
Perhexiline	Metabolism modulator	Improved myocardial energetics	Small trials in heart failure and hypertrophic cardiomyopathy	Improved energetics and symptom status	Perhexiline in patients with HFpEF (NCT00839228)
Sildenafil	cGMP phosphodiesterase V inhibitor	Improved haemodynamics and cardiac remodelling	RELAX	Possible reduction in LV systolic function, no effect on clinical or structural measurements	Sildenafil in HFpEF (EudraCT 2010-020153-14, 2011-001674-25, 2013-001659-10)
Riociguat, vericiguat	Soluble guanylate cyclase agonists	Pulmonary and systemic vasodilatation	DILATE-1, LEPHT (riociguat)	Increased stroke volume	SOCRATES-REDUCED – HFrEF (NCT01951625), SOCRATES-PRESERVED – HFpEF (NCT01951638)

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Summary

- Peripartum cardiomyopathy is a syndrome of maternal heart failure with decreased left ventricular ejection fraction affecting maternal and fetal wellbeing.
- Careful assessment of risk factors in pregnant women helps prevent PPCM.
- Early diagnosis and preservation of LVEF leads to improved prognosis.
- Therapies with bromocriptine and pentoxifylline , Intravenous immunoglobulins has shown beneficial effects.
- Novel disease specific targets like 16-kDa prolactin and its downstream mediator miR-146a and/or the VEGF system is an upcoming option for therapy or prevention in patients at risk.