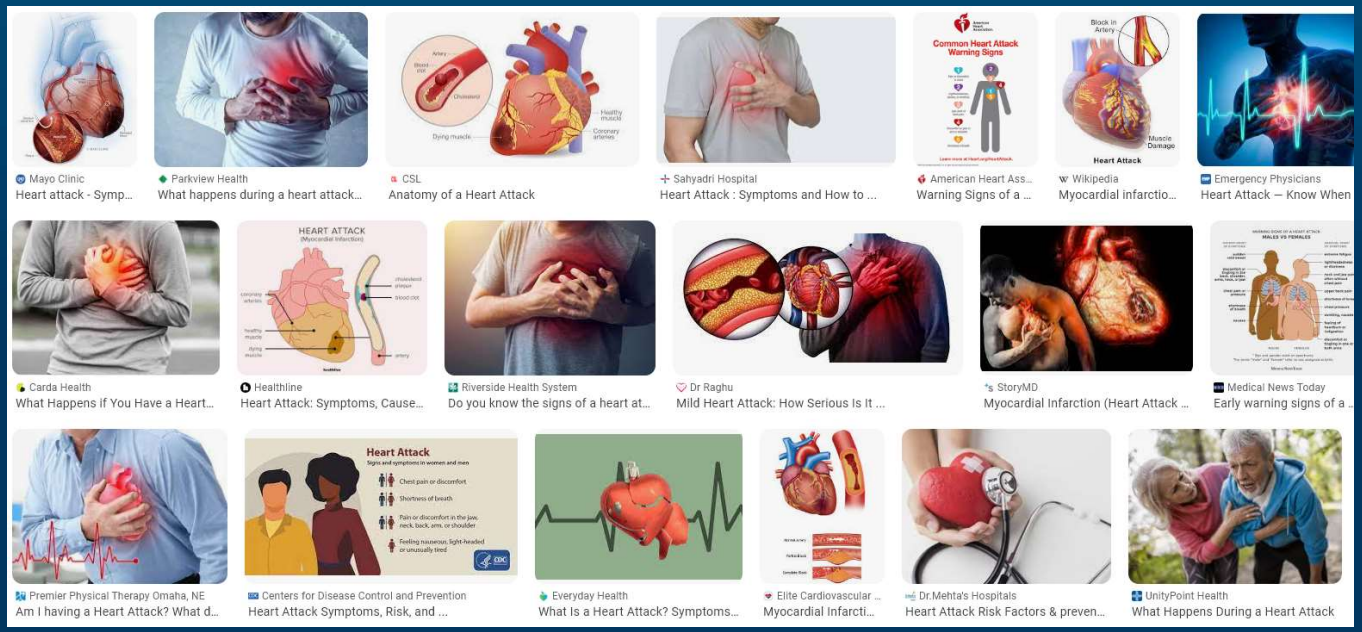
THE UNIVERSITY OF KANSAS HEALTH SYSTEM

Cardiovascular disease in Women

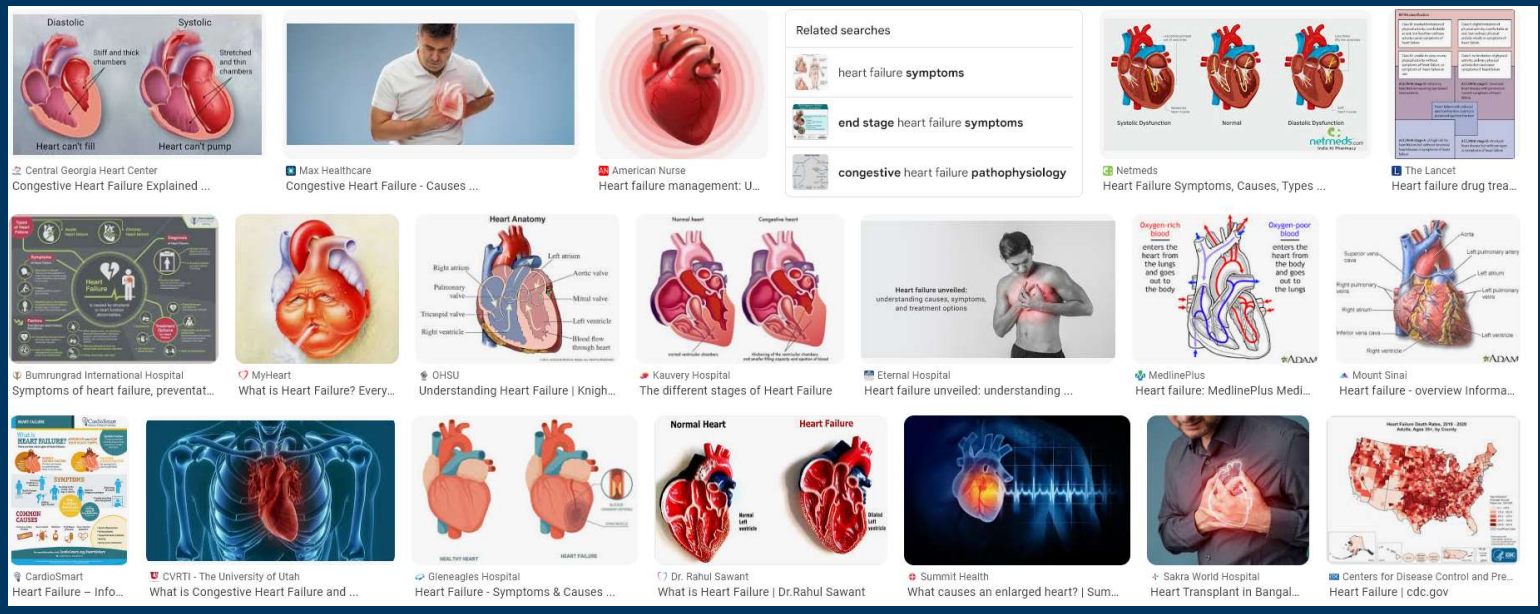
A Brief Overview with a Focus on Spontaneous coronary artery disease and peripartum cardiomyopathy.

Swathi Kovelamudi MD
Assistant Professor of Medicine,
Department of Cardiovascular Medicine.
Kansas University Medical Center.



Google image search for “heart attack”

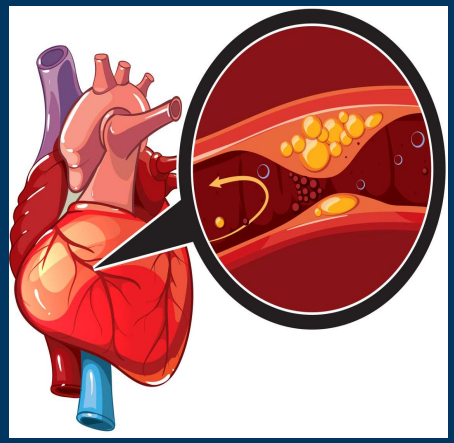
Google image search for “heart failure”

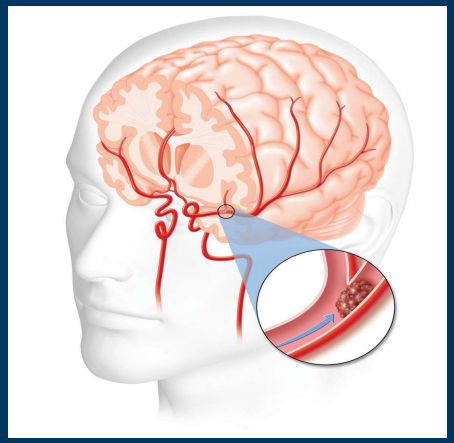


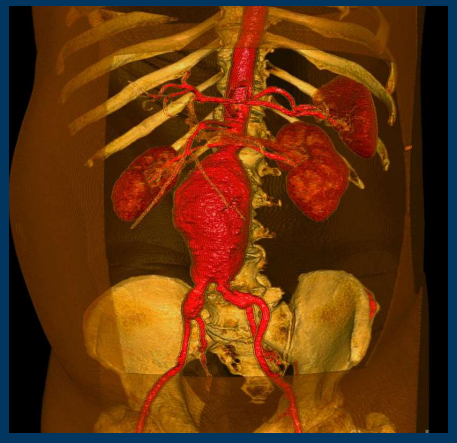
- CVD affects the **majority of adults** past the age of 60 years.
- **1 in 3** women die from CVD and **45% of women > age of 20** have CVD.

Four major diagnostic categories:

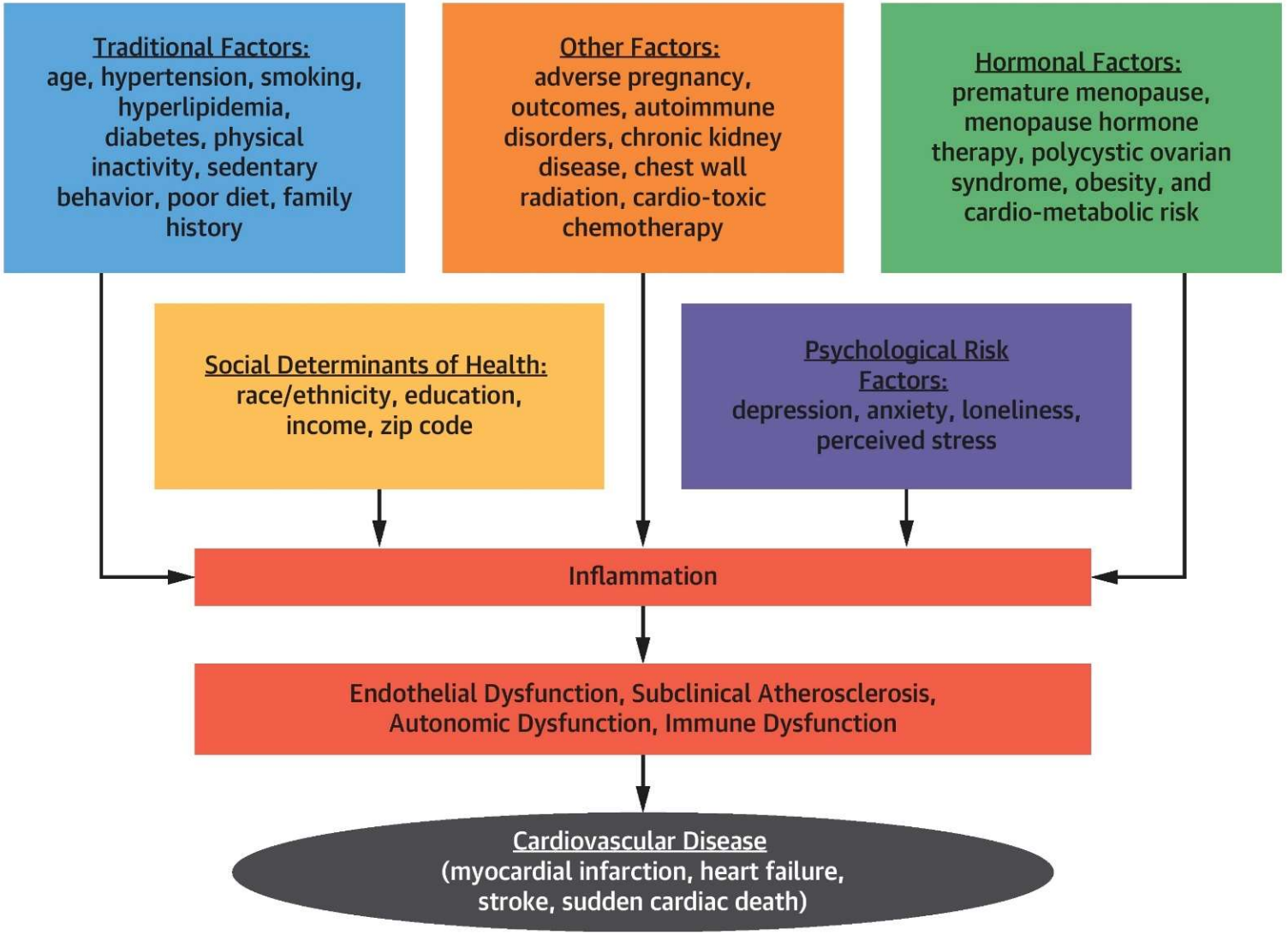
Coronary/heart disease	Cerebrovascular disease	Peripheral arterial disease	Aortic disease
• Angina/MI • Heart failure • Coronary/ cardiac death	• Stroke • Transient ischemic attack	• Limb ischemia • Intermittent claudication • Rest pain	• Atherosclerotic aortic disease • Thoracic and abdominal aneurysms.



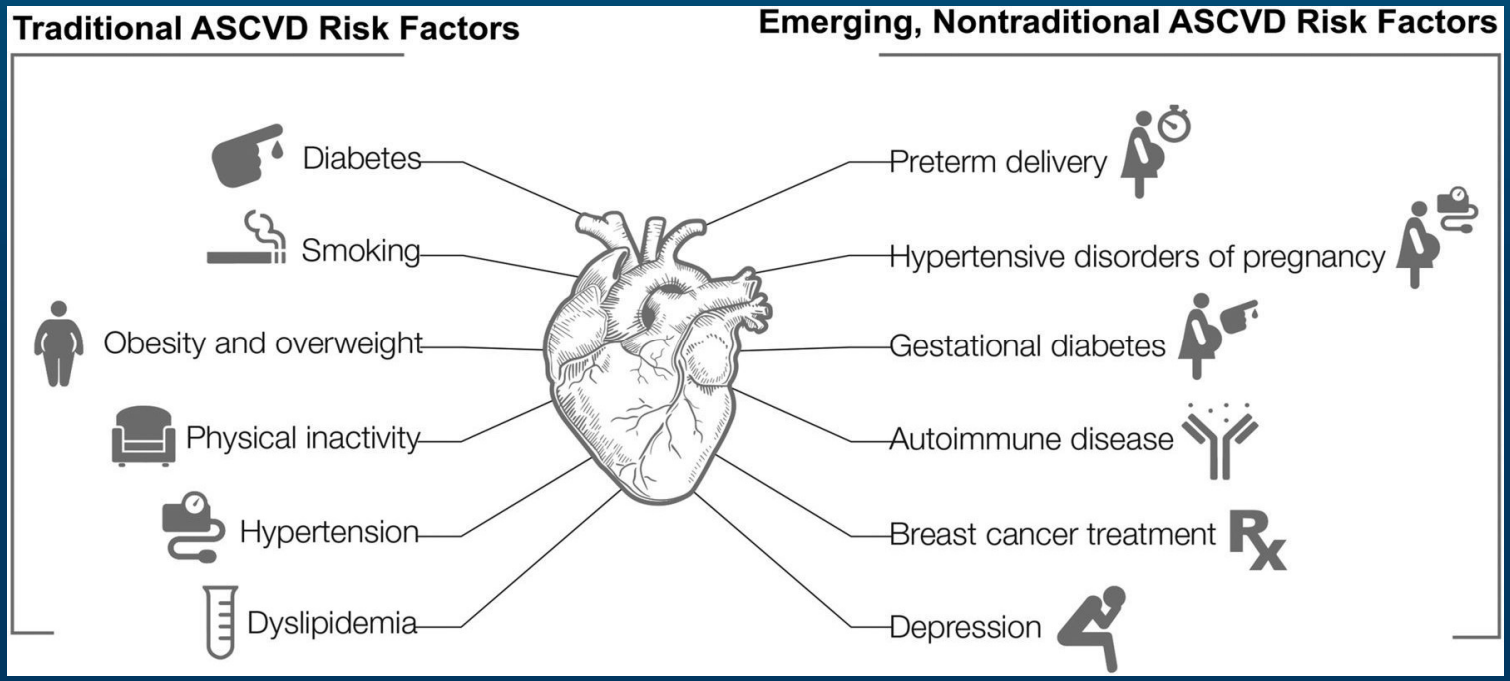




CENTRAL ILLUSTRATION: Cardiovascular Disease Risk Factors in Women

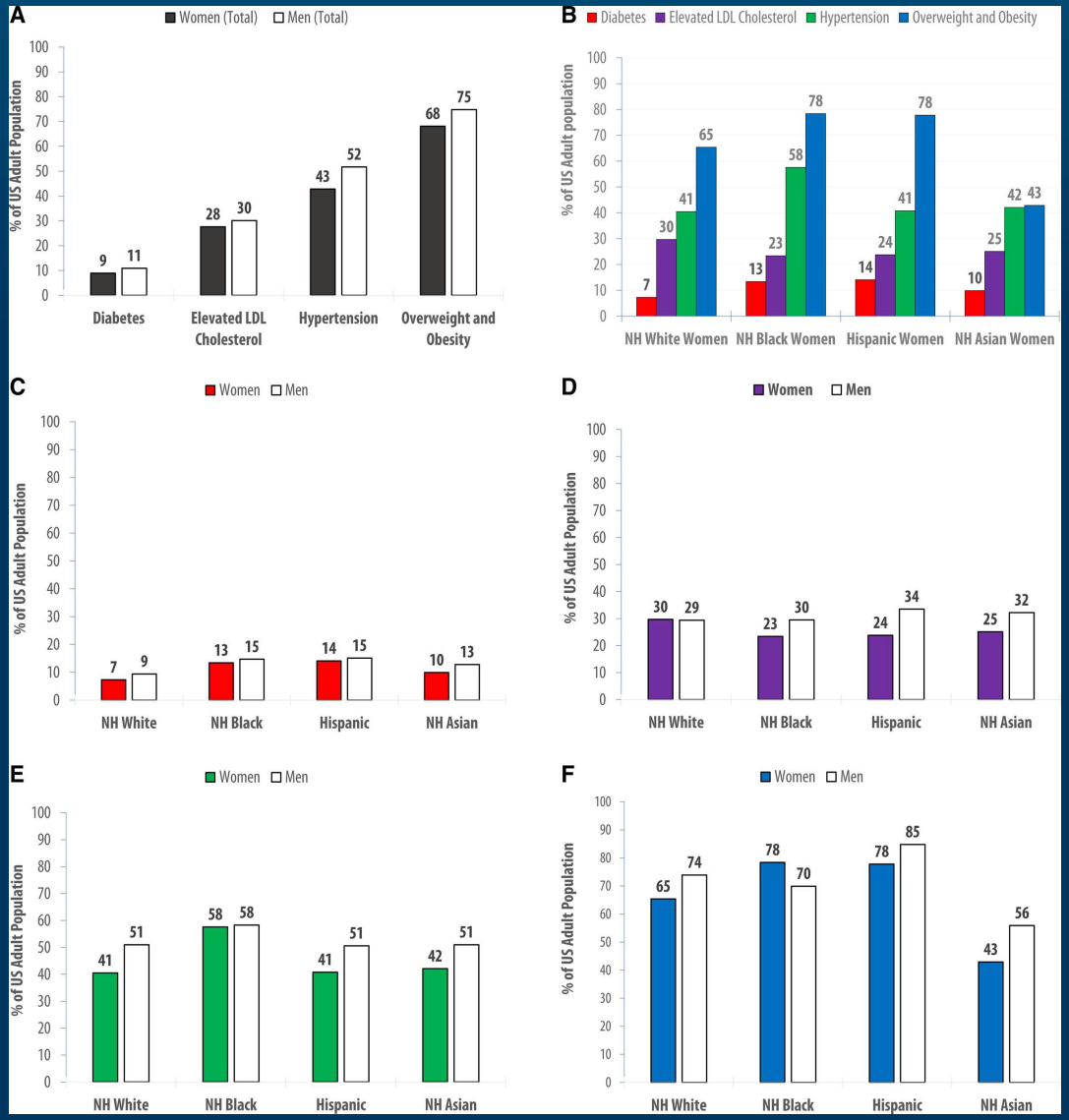


Cho, L. et al. J Am Coll Cardiol. 2020;75(20):2602-18.



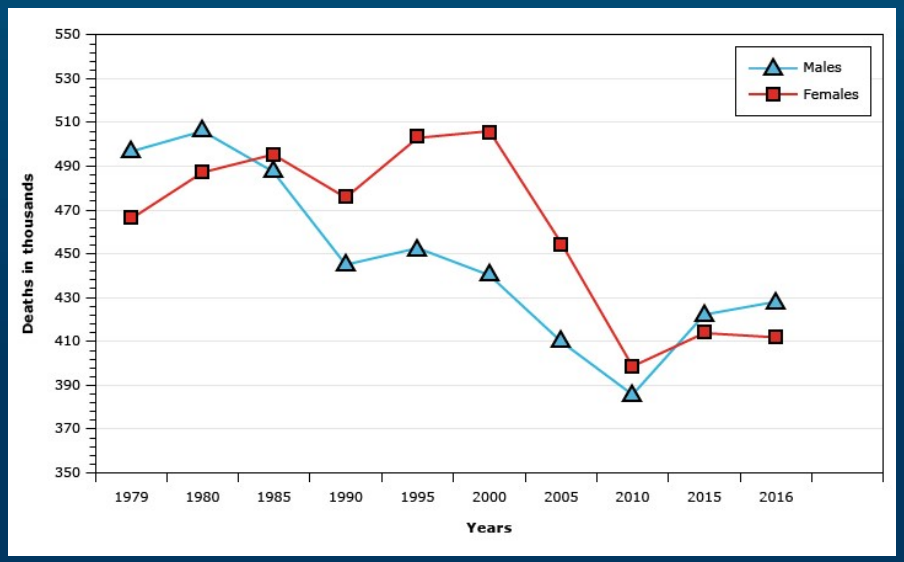
- Disproportionately affected by systemic inflammatory and autoimmune disorders - systemic lupus erythematosus, rheumatoid arthritis, and scleroderma.
  - Greatly augment the risk of CVD events.
  - SLE - 25% of women will develop pericarditis.
  - Myocarditis, coronary artery disease, increased risk of myocardial infarction, and valvular disease.

- Depression and anxiety - increased risk of CVD
- Post MI/ stroke – Increased risk of depression and anxiety.
- Chemotherapies for cancers more prevalent in women (ie, breast cancer).



Incidence of cardiovascular risk factors 2018-2019

Nanette K. Wenger. Circulation: A Presidential Advisory From the American Heart Association.

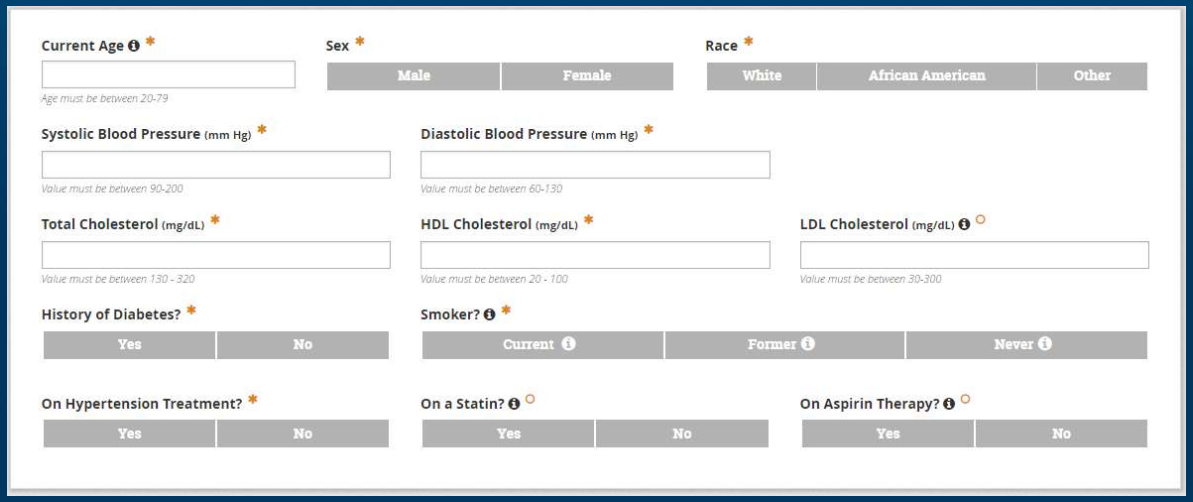


Cardiovascular disease (CVD) mortality trends for males and females (United States: 1979-2016)

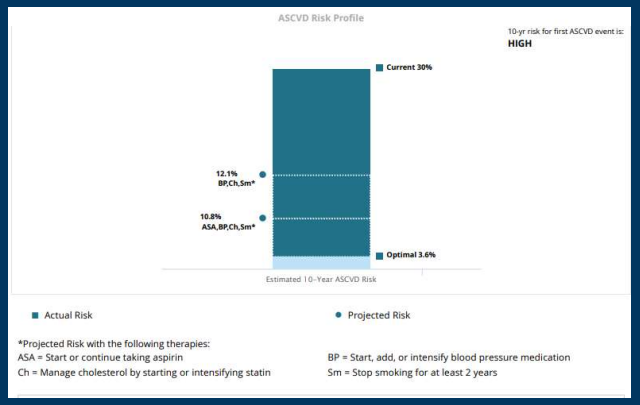
Circulation 2019.

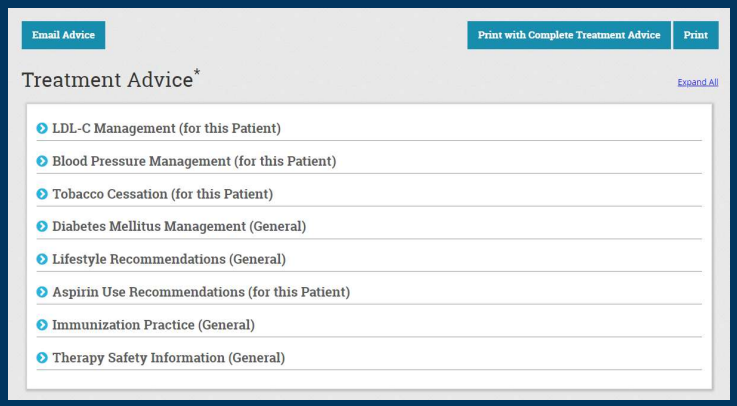
Appropriate risk stratification:

ACC ASCVD risk calculator plus



tools.acc.org/ascvd-risk-estimator-plus





- Integrating women-specific risk factors in the quantitative risk assessment across the life span is necessary, and the AHA is currently evaluating approaches to do so.
- In the interim, in situations when the risk category remains uncertain, clinicians may discuss with women the option to add coronary calcium imaging to further stratify risk and provide additional insight to an agreed-on care plan.
- Sex Differences in Cardiovascular Medication Prescription in Primary Care: A Systematic Review and Meta-Analysis

Zhao M et.al;. J Am Heart Assoc. 2020 Jun

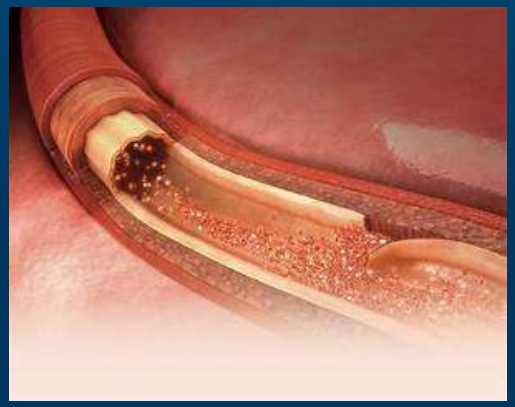
Patients at high risk or with established CVD in primary care. - women were less likely to have a prescription for aspirin, statins, or ACE inhibitors but more likely to have a prescription for diuretics.

SPONTAEOUS CORONARY ARTERY DISSECTION

Definition:

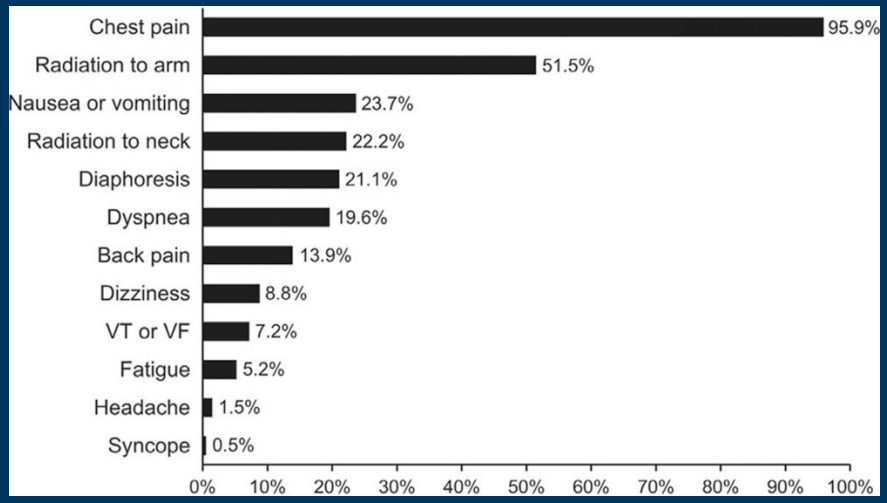
- Non-traumatic, non-iatrogenic and non-atherosclerotic epicardial coronary artery dissection.

*External high-energy traumatisms (eg, traffic accident), direct vessel instrumentation or complicated atherosclerosis should be excluded.



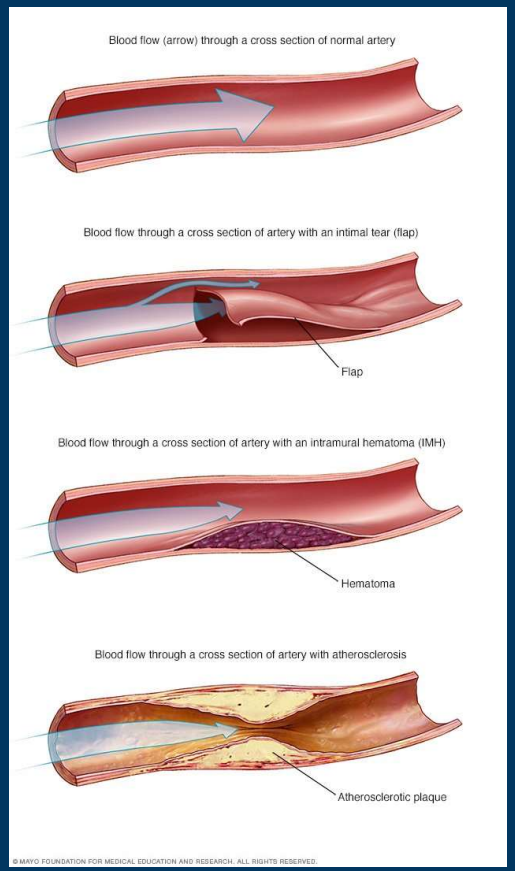
Clinical presentation :

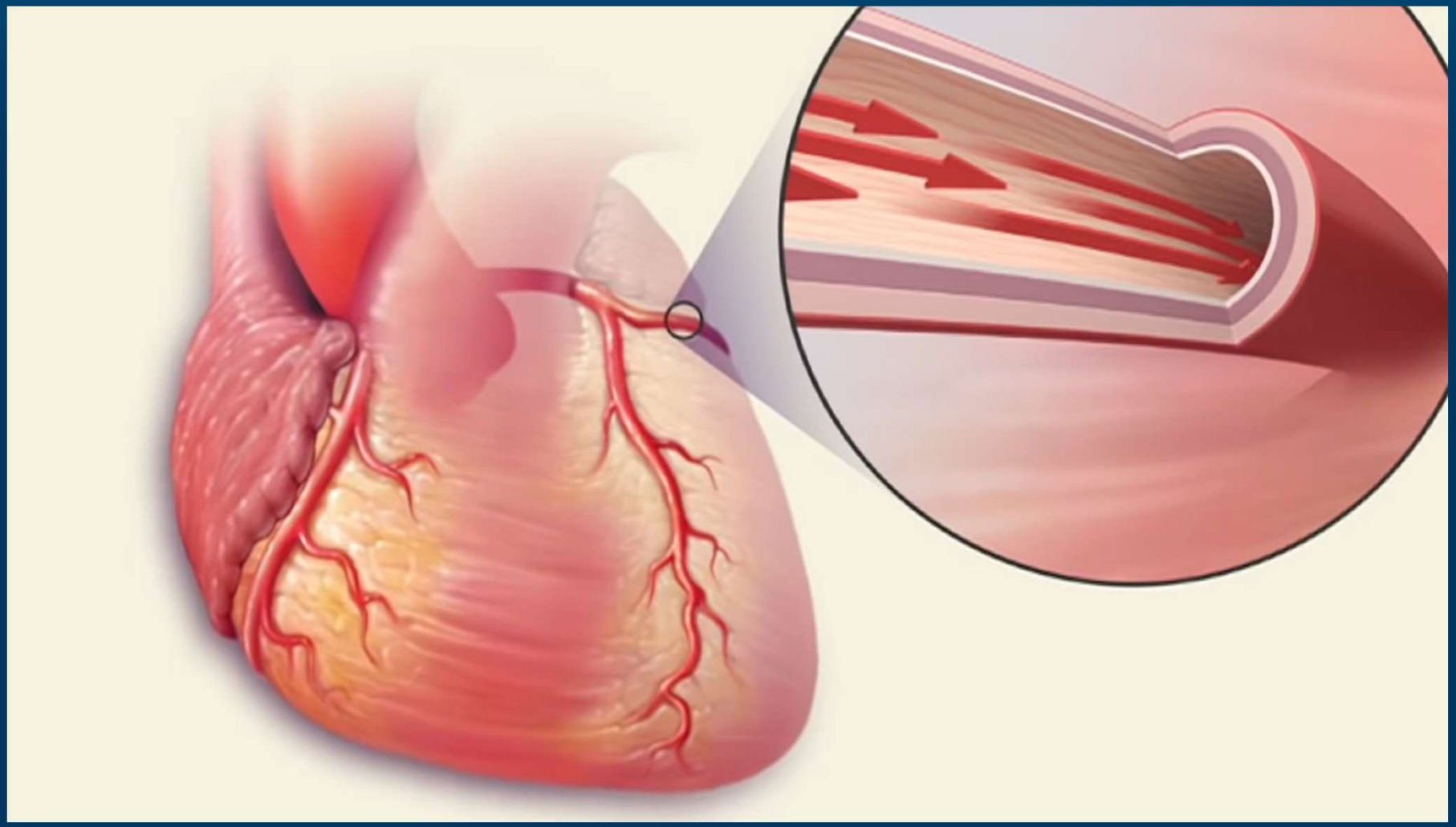
1. Acute coronary syndrome
   - → 26% - 87% STEMI
   - → 13% - 67% NSTEMI
   - → 2%-5% - shock
2. Arrhythmia
3. Sudden cardiac death.



Pathophysiology

- Acute and spontaneous separation of the coronary artery wall layers → Generation of an intramural space (false lumen)
- May or may not be communicated with the true lumen through an intimal tear (flap fenestration)
- Compression of the true lumen of a coronary artery due to hematoma within the vessel wall.
- Majority may be related to an “outside-in” mechanism whereby the hematoma arises *de novo* in the media.





Epidemiology:

- True prevalence of SCAD remains uncertain -> underdiagnosed condition.

Missed diagnoses:

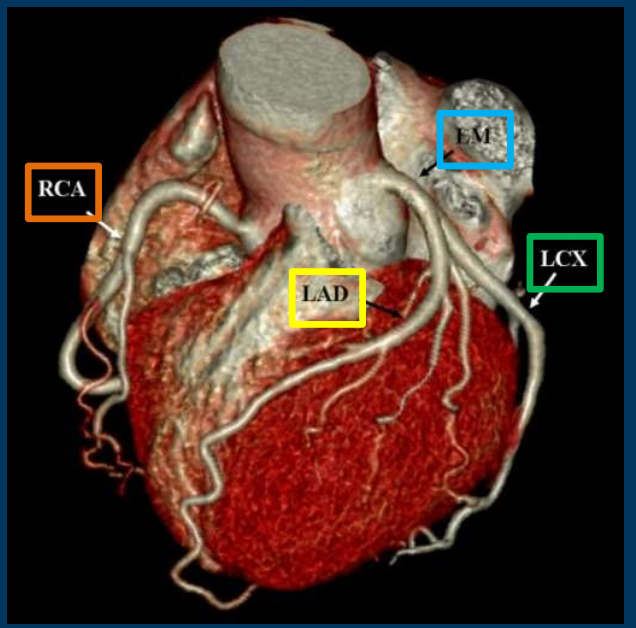
→ low suspicion of ACS in young women even in the presence of classic presenting symptoms
→ limitations of current coronary angiographic techniques
→ lack of clinician familiarity with the condition.
→ most commonly occurs in patients with few or no traditional cardiovascular risk factors.

Incidence: 1% to 4% of ACS cases.

- Occurs overwhelmingly in women (<10% reported cases in men)
- Cause of ACS in up to **35% of MIs in women ≤50 years of age**
- Most common cause of pregnancy-associated MI (43%)
- Average age of women with SCAD ranges from 45 to 53 years (cases reported from 2nd to 8th decade)
- Men → presented with SCAD at a slightly younger age than

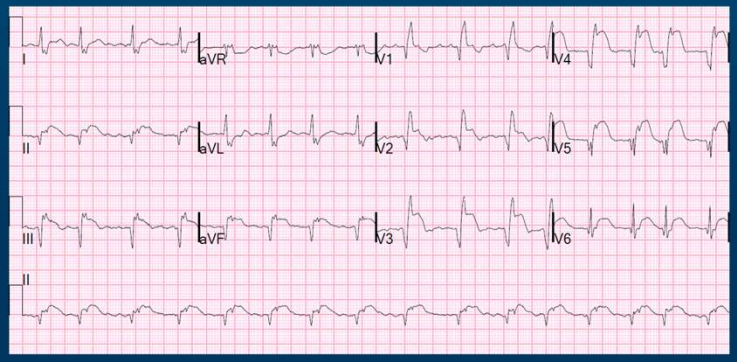
Coronary distribution of SCAD:

- LAD (32%–46%)
- **Left anterior descending and diagonal and septal branches (45% to 61%)**
- **Circumflex and ramus and obtuse marginal branches (15% to 45%)**
- **Right coronary artery and acute marginal, posterior descending and posterolateral branches (10% to 39%)**
- **Left main artery (~ 4%) of cases**
- In the majority of cases → mid to distal segments of coronary arteries
- <10% of cases → proximal left anterior descending, circumflex, right coronary, left main.
- Multivessel SCAD occurs in 9% to 23% of cases.

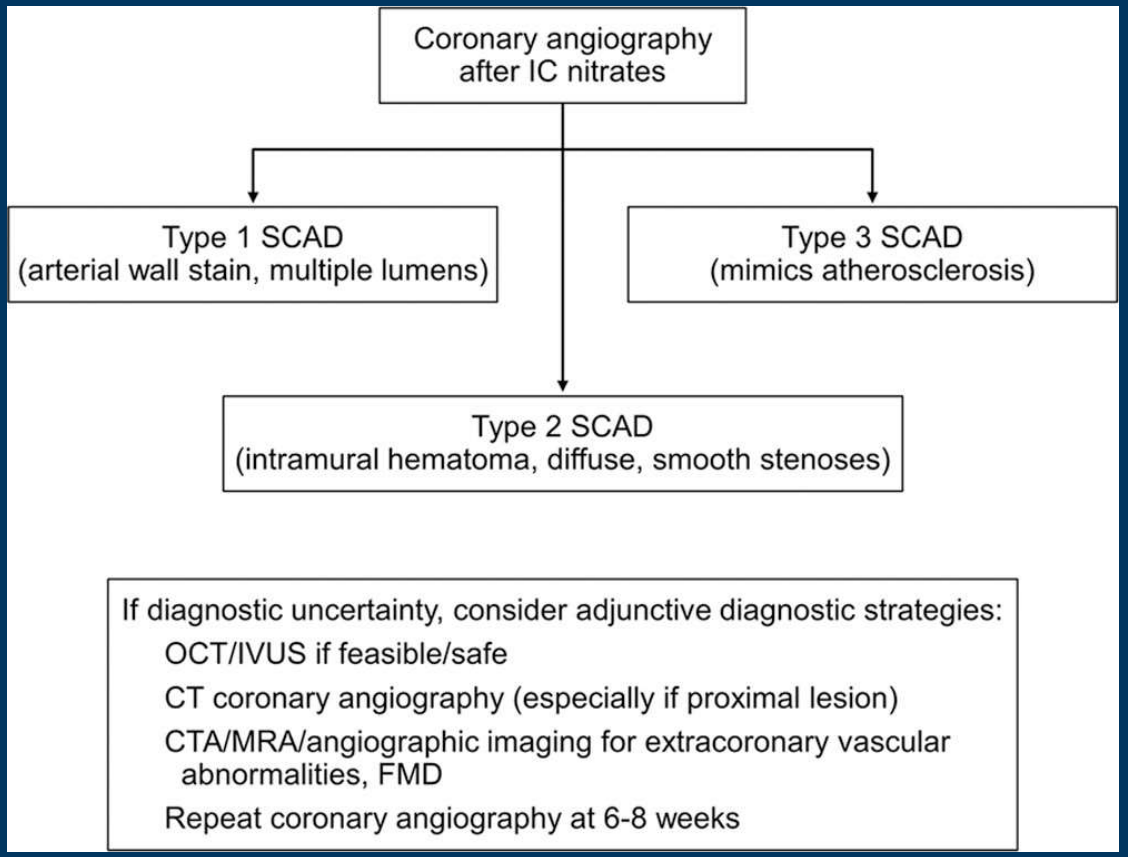


Diagnosis

- At risk of receiving alternative diagnoses and of being **discharged** after emergency department evaluation.
- Relatively young, absence of atherosclerotic risk factors, do not fit the expected phenotype of an atherosclerotic patient with MI.
- Accurate diagnosis of SCAD in the early stages of ACS presentation is important because management and investigation are different from those for atherosclerotic forms of coronary artery disease.
- Patient demographics - young age, female sex, and few or no conventional cardiovascular risk factors.
- Once SCAD is suspected, coronary angiography should be performed as early as feasible, especially in the setting of ST-segment–elevation MI.

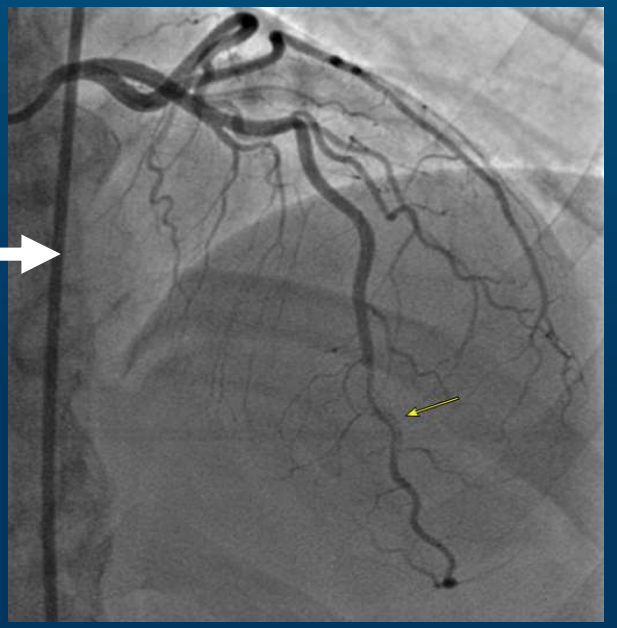


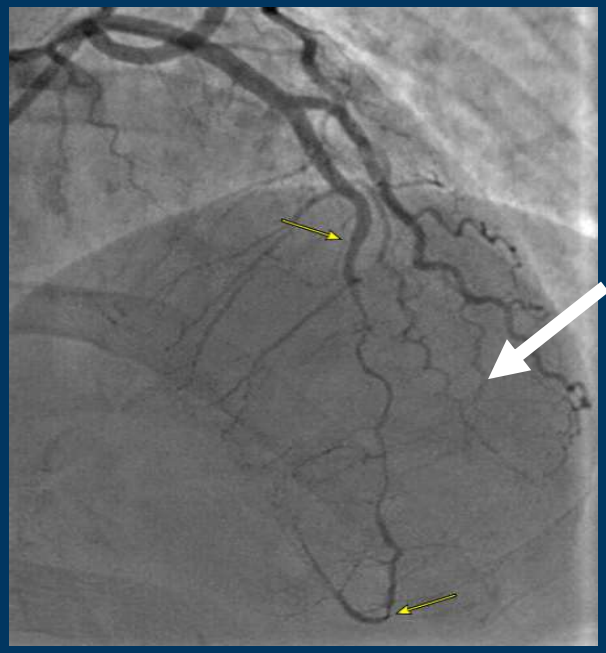
Troponin
CBC
BMP
Echocardiogram



Saw angiographic SCAD classification

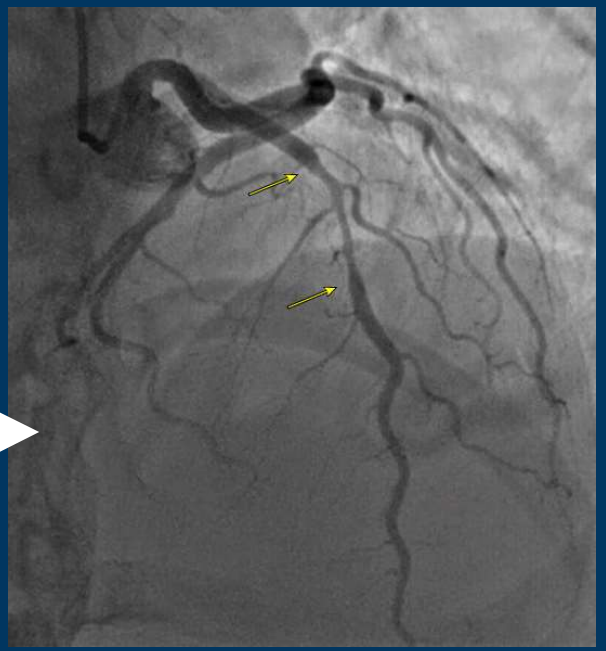
Type 1 – Pathognomonic contrast dye staining of arterial wall with multiple radiolucent lumen, with or without the presence of dye hang-up or slow contrast clearing.





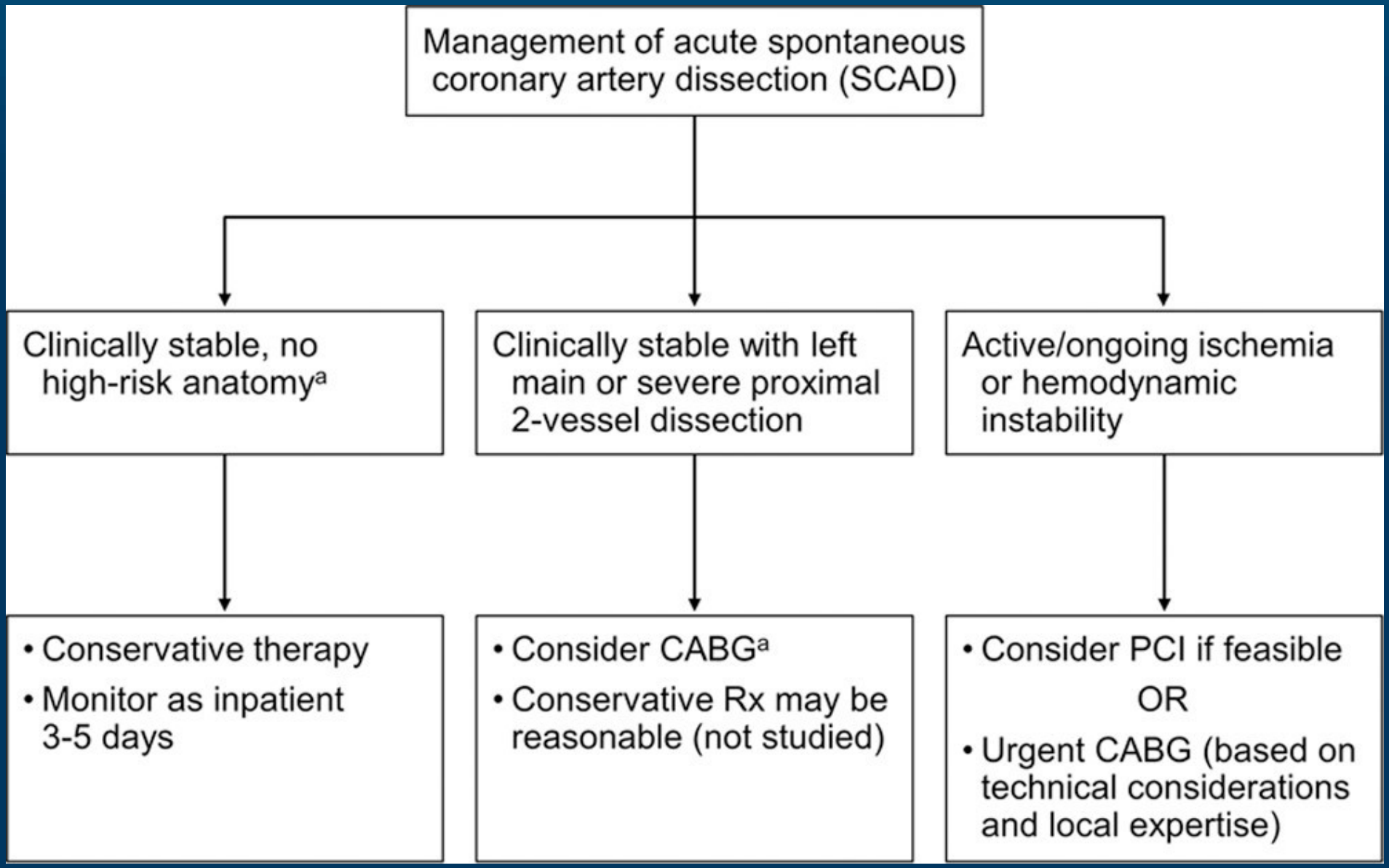
Type 2 – Diffuse long and smooth stenosis that can vary in severity from mild stenosis to complete occlusion

Type 3 – Mimics atherosclerosis with focal or tubular stenosis, requires OCT or IVUS to differentiate the cause.

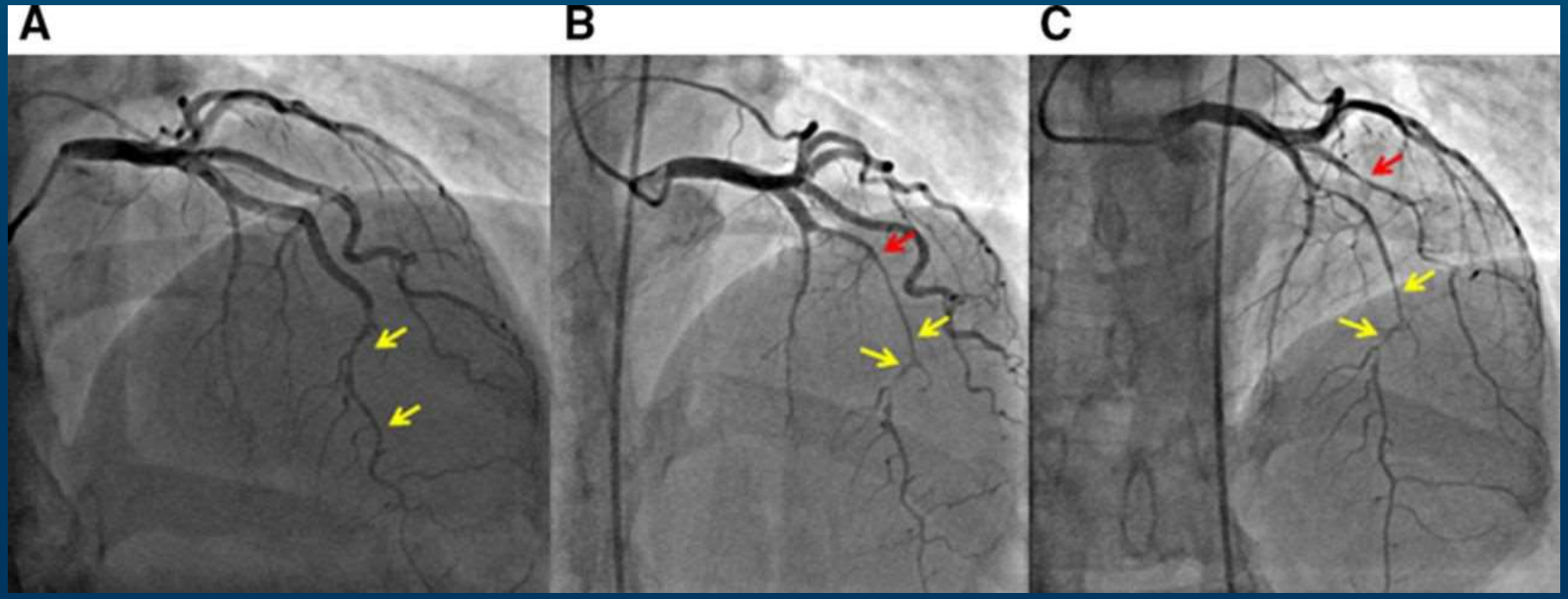


Management pearls:

- Thrombolytics should be avoided.
- Percutaneous coronary intervention → higher complication rates and suboptimal outcomes, including risk of iatrogenic dissection or propagation of hematoma.
- Minimal ongoing ischemia / distal coronary involvement / preserved coronary flow, instrumentation is avoided.
- **95% of conservatively treated patients with SCAD will heal within 30 days.**
- Early reinfarction can occur (6.1-17.5%) and longer length of stay may be preferred.
- Most recurrent chest pain is nonischemic.
- **Medical management:** Standard heart failure medications → left ventricular dysfunction, and hypertension should be treated. **Statins are not indicated** for treatment of SCAD.
- Post-SCAD chest pain is common and may persist for many months. Serial electrocardiography and biomarker assessment, noninvasive cardiac computed tomography angiography. .
- **Nitrates** may be effective, but are often limited by hypotension and migraines.
- Due to the association of SCAD with **fibromuscular dysplasia**, arterial imaging from head to pelvis to identify significant extracoronary vascular abnormalities is recommended.
- Recurrent SCAD → 10-30% of patients.
- **Contraception** should be discussed with patients. Levonorgestrel (subdermal implants / intrauterine devices) reduce menstrual blood loss →beneficial for women with increased bleeding related to dual antiplatelet therapy.
- After SCAD, **pregnancy is often discouraged**, but women who strongly desire pregnancy should receive thorough preconception counseling.



2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization:



32-year-old woman presenting with non–ST-segment–elevation myocardial infarction and left anterior descending (LAD) spontaneous coronary artery dissection (SCAD) managed conservatively

Three days later, she had recurrent chest pain with repeat angiogram showing dissection progression. Again, she was conservatively managed

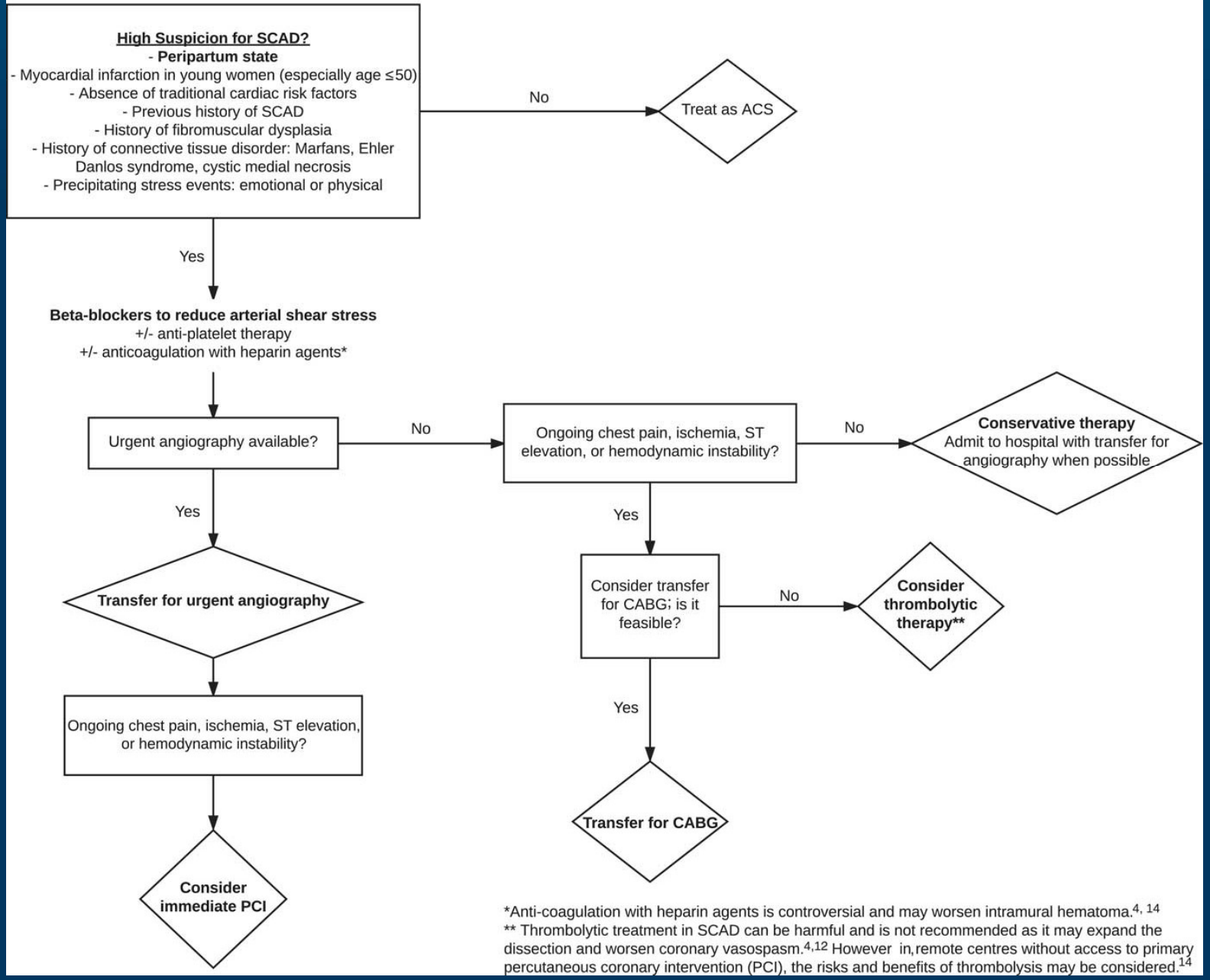
Recurrent chest pain, progressed SCAD and ST-elevation during angiography → Emergent CABG

- In patients with ongoing ischemia, vessel occlusion, or patient instability, selective revascularization may be necessary.
- Unlike other forms of ACS, routine revascularization for patients with SCAD may not confer the same benefit.
- PCI wires may propagate the dissection, and balloons and stents can extend the hematoma and lead to vessel occlusion.
- CABG onto a dissected vessel or one with a propensity to dissect is challenging, and as many as 30% of patients have acute graft closure.

Pregnancy associated SCAD

- Most common cause of pregnancy-associated MI and is reported as the cause of MI in 24% to 35% of all women younger than 50 years.
- Can be seen at any trimester in pregnancy and up to months postpartum, the majority of cases have been reported in the third trimester or early postpartum period defined as within 6 weeks of delivery.
- Abnormal electrocardiogram (ECG) changes, elevated troponins, and regional wall motional abnormalities on echocardiography are all diagnostic findings of PASCAD, which can be ultimately confirmed with coronary angiography.
- Failure to immediately address this condition can lead to acute heart failure, cardiogenic shock, and death.

Approach for suspected SCAD in a peripartum patient



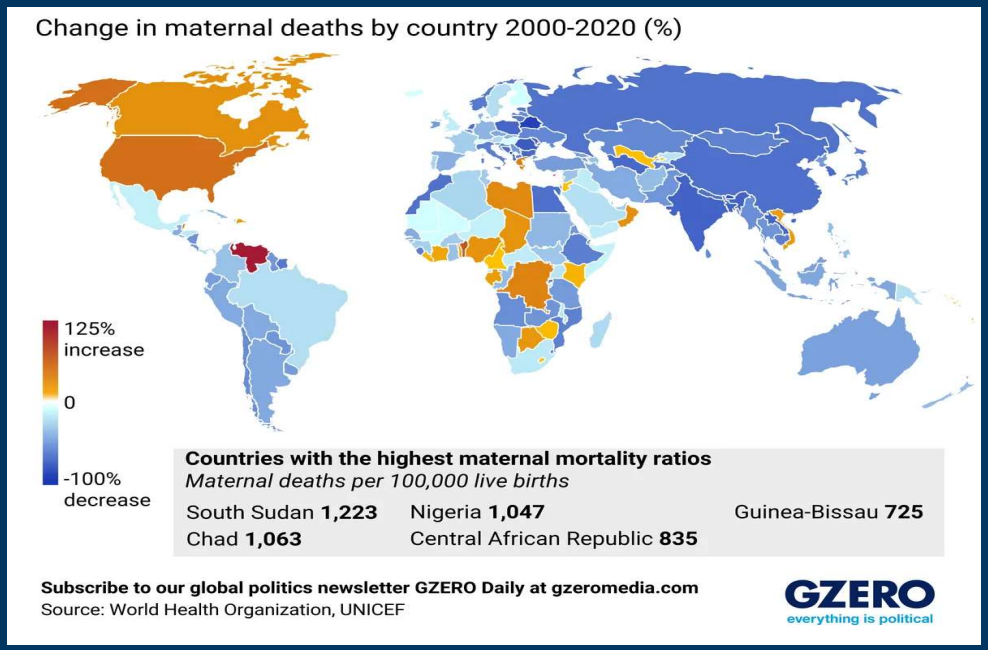
*Anti-coagulation with heparin agents is controversial and may worsen intramural hematoma.[4, 14]

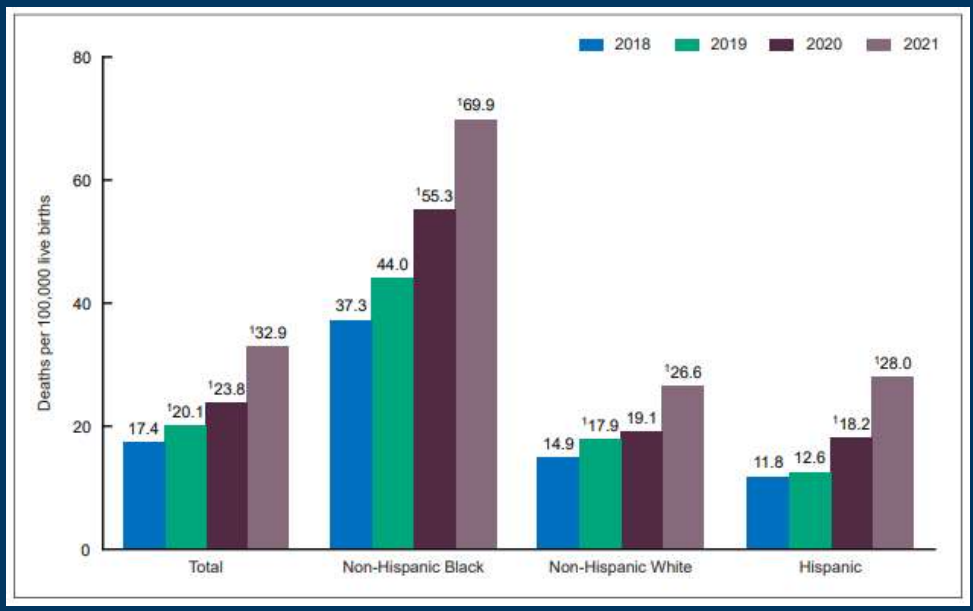
** Thrombolytic treatment in SCAD can be harmful and is not recommended as it may expand the dissection and worsen coronary vasospasm.[4,12] However in remote centres without access to primary percutaneous coronary intervention (PCI), the risks and benefits of thrombolysis may be considered.[14]

PERIPARTUM CARDIOMYOPATHY

Definition:

- Maternal heart failure with systolic dysfunction (left ventricular ejection fraction, <45%)
- Develops in the last month of pregnancy or in the first 5 months after delivery.
- In the absence of known preexisting cardiac dysfunction.





Maternal mortality in the US, 2018-2021

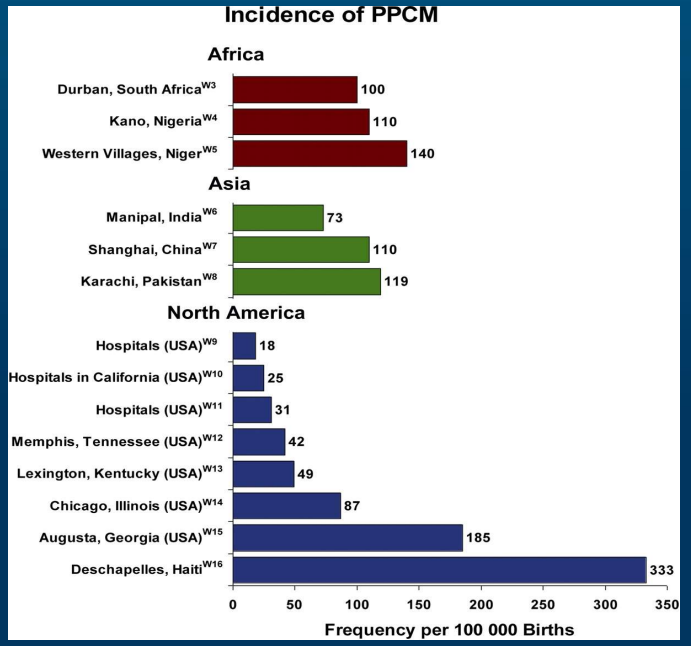
Epidemiology:

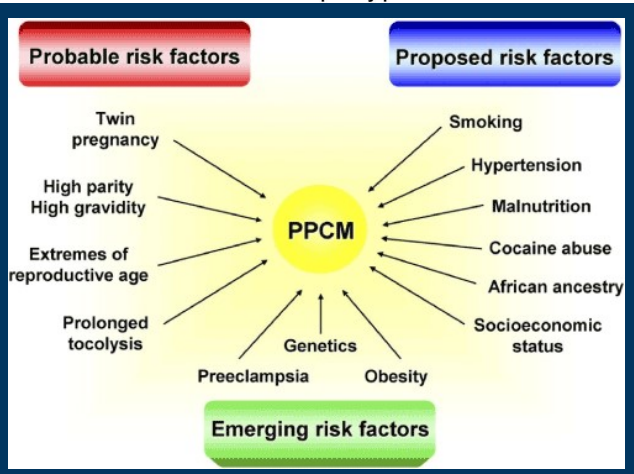
INCIDENCE:

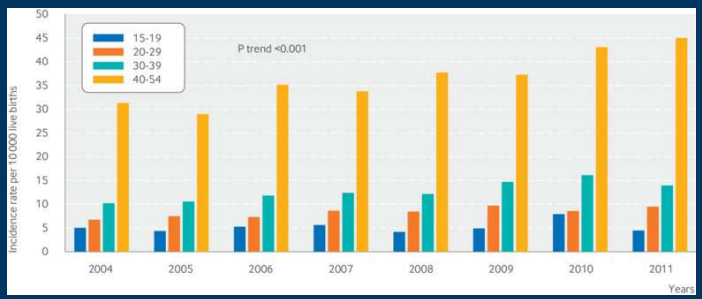
- Global incidence is varied.
- Nigeria : 1 in 100 deliveries
- Haiti: 1 in 300 deliveries
- USA: 1 in 1,000 to 1 in 4,000
- Japan : 1 in 20,000
- Maternal cardiovascular deaths in California
- (2002 – 2006): PPCM → leading cause (23%)

INTRINISIC RISK FACTORS:

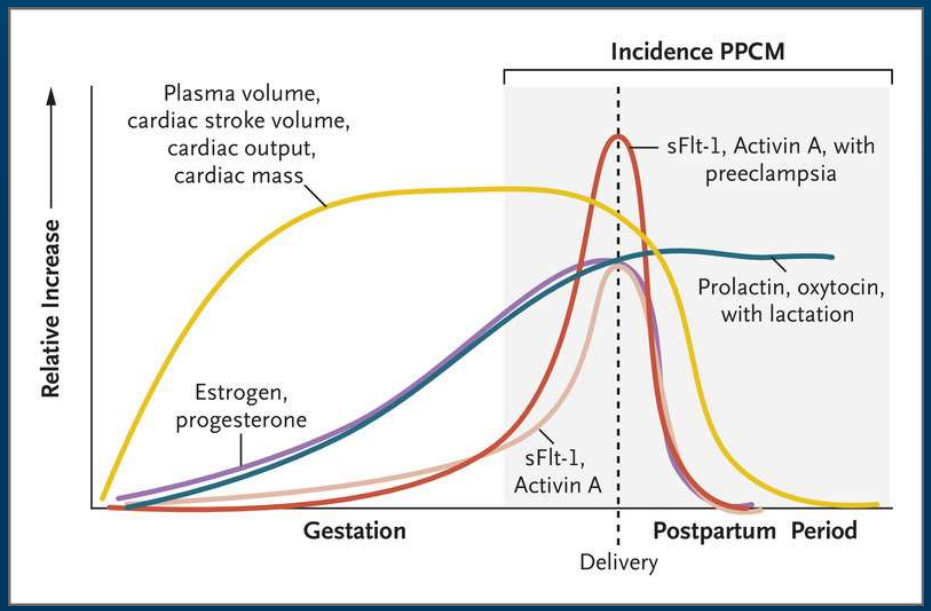
- African ancestry (>40% of cases of PPCM in the US).
- Pre-eclampsia - 22% of women with PPCM
- Other hypertensive disorders - 37% of women with PPCM
- Multigestational pregnancies - 7% to 14.5% of women with PPCM
- Older maternal age : 50% of cases of PPCM occur in women age >30 years
- Age >40 years : odds ratio of 10 of developing the disease compared with women age <20 years

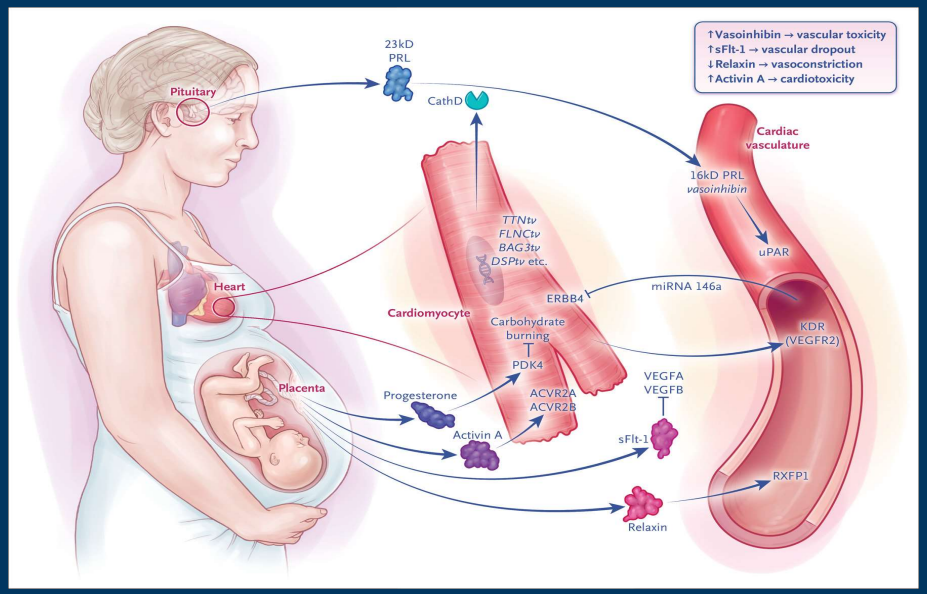






ETIOLOGY:





Vasculohormonal model of pathogenesis

Intrinsic cardiac factors in susceptible women.

↓

Imbalances in peripartum hormones.

↓

Cardiovascular dysfunction and heart failure.

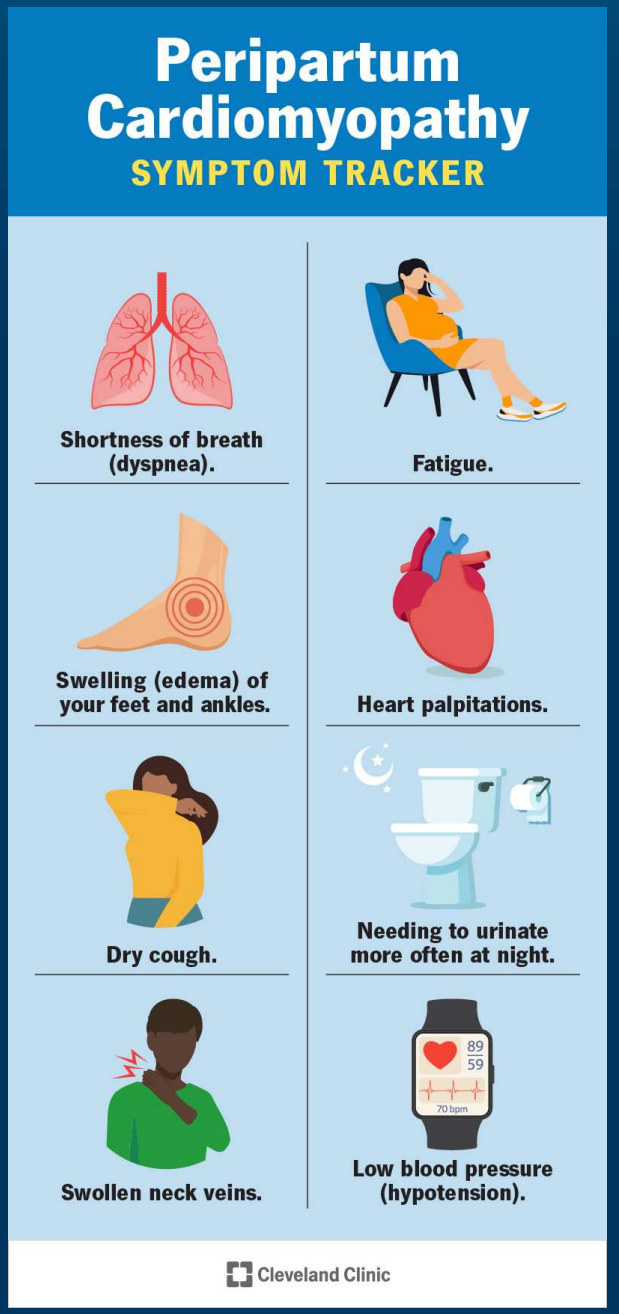
Genetic factors - cluster of families with PPCM. 10% of women with PPCM have the same genes found in dilated and alcoholic cardiomyopathy.

Pro-inflammatory state - Increased levels of cytokines (TNF-alpha and interleukin-6) have been found in patients with PPCM.

Autoimmune response - high levels of antibodies against certain cardiac tissue →autoimmune myocarditis

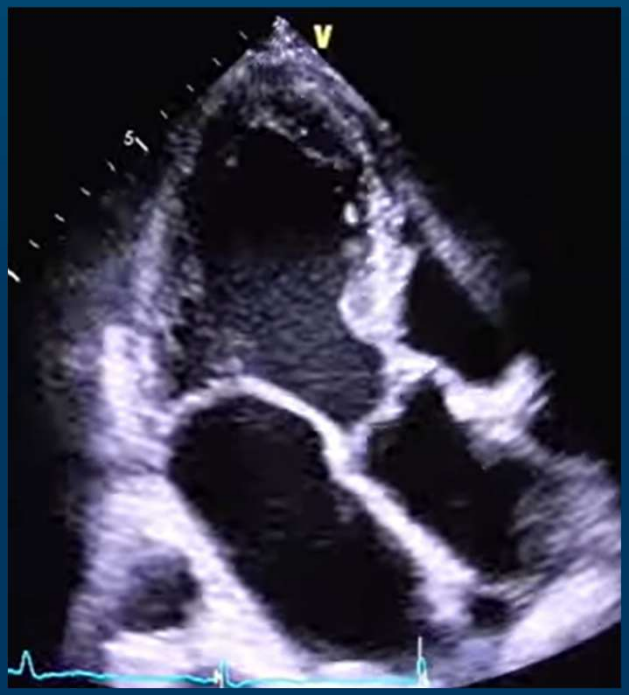
Clinical presentation:

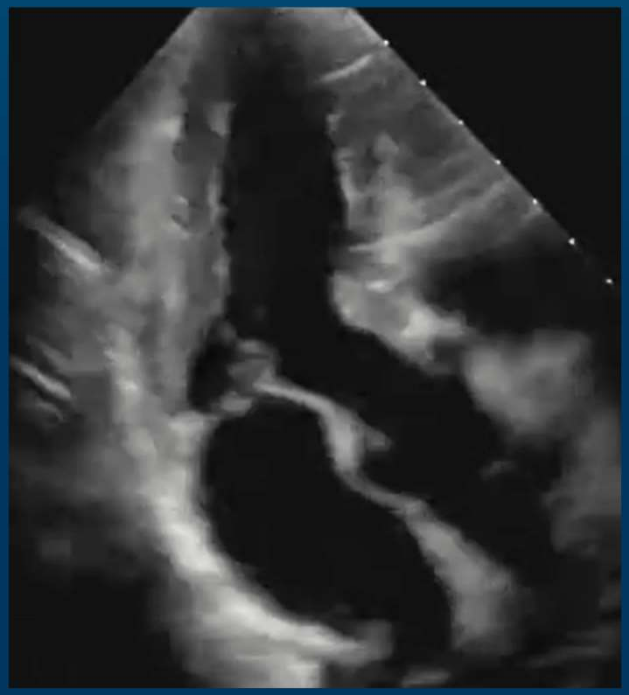
- Majority of women with PPCM are diagnosed after delivery, typically in the first month postpartum.
- Frequent delays in diagnosis
- → under-recognition of this disease.
- → overlap in signs and symptoms of normal pregnancy.
- Most common:
- Shortness of breath on exertion
- Fatigue
- Orthopnea
- Paroxysmal nocturnal dyspnea.
- Edema
- Chest tightness.
- Minority → cardiogenic shock, severe arrhythmias, thromboembolic complications.
- Delays in diagnosis are associated with increased incidence of preventable complications and worse outcomes

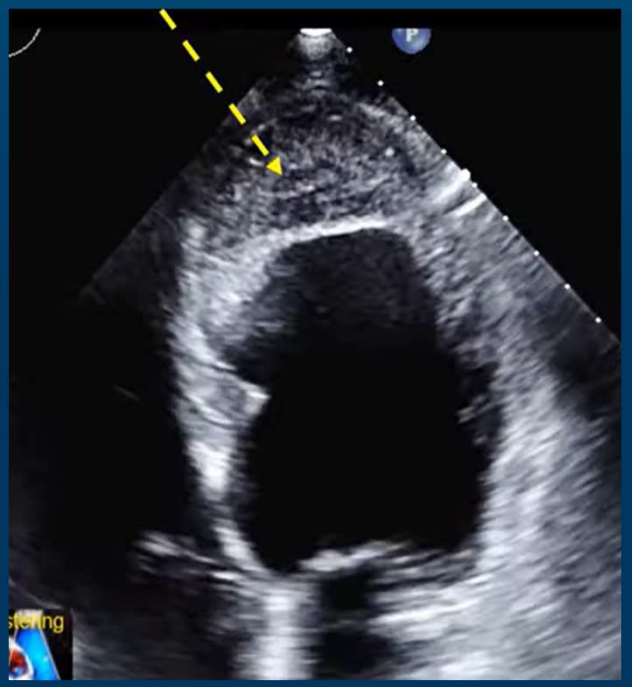


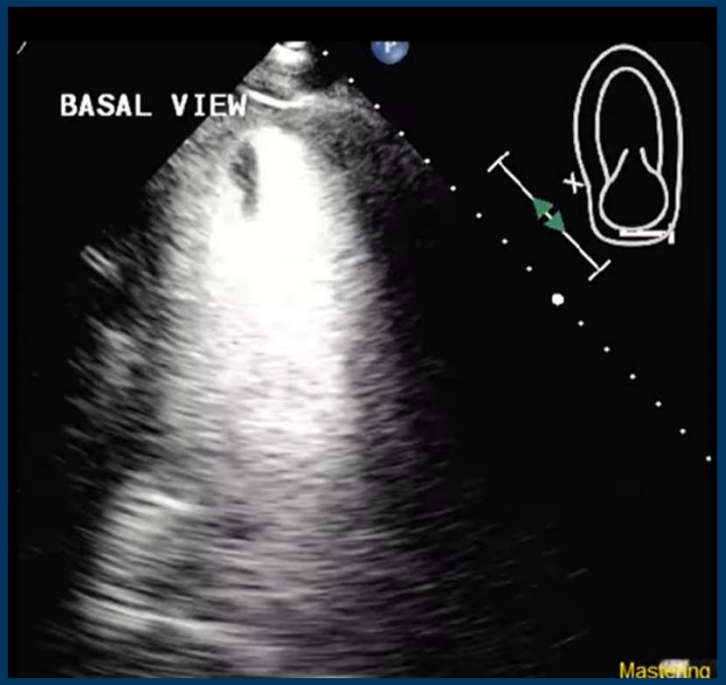
Diagnosis:

- Diagnosis of exclusion
- Echocardiography
  → Systolic function :LVEF is typically <45%
  →LV and right ventricular dilatation and/or dysfunction,
  →functional mitral and/or tricuspid regurgitation
  → pulmonary hypertension
  → left atrial or biatrial enlargement
  → Intracardiac thrombus (particularly when the LVEF is severely reduced)
- Brain natriuretic peptide (BNP) and N-terminal pro-BNP → Markedly elevated.
- (No significant change during normal pregnancy, mildly elevated in pre-eclampsia)
- ECG → non specific
- Chest x-rays → pulmonary venous congestion, enlarged cardiac silhouette.
- Cardiac magnetic resonance imaging → echocardiogram is inadequate, but gadolinium is avoided during pregnancy.
- Endomyocardial biopsy is only indicated if there is suspicion for an alternative diagnosis, such as giant cell myocarditis, that would necessitate a different management plan.








BASAL VIEW

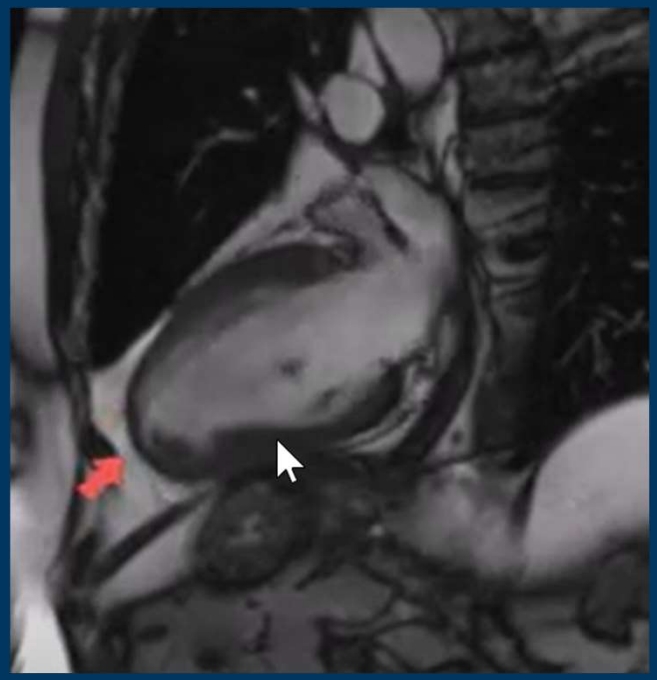
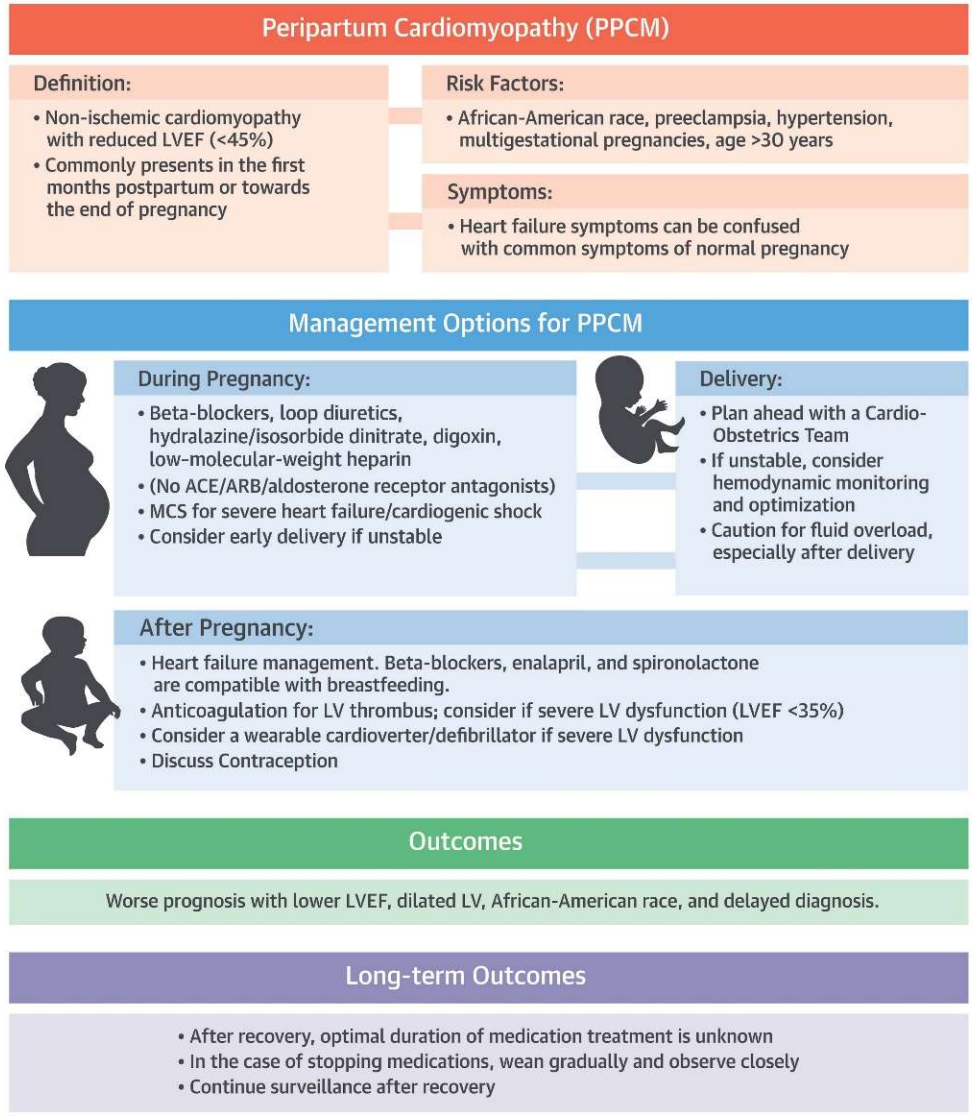


Table 1. Differential Diagnosis of Peripartum Cardiomyopathy.*

Differential Diagnosis	Differentiating Markers
Preexisting cardiomyopathy	History, family history, prior echocardiography
Preeclampsia-induced pulmonary edema in the absence of systolic dysfunction	History, preserved ejection fraction on echocardiography, sFlt-1 and PLGF levels
Pulmonary or amniotic embolism	History, chest CT
Valvular heart disease, including rheumatic disease	History, echocardiography
Congenital heart disease that has resulted in surgical correction	History, echocardiography
Chemotherapy-induced cardiomyopathy	History, especially of treatment with doxorubicin or other anthracyclines, trastuzumab, or sorafenib
Spontaneous coronary-artery dissection	History, echocardiography, elevated troponin levels
Other causes of myocardial infarction, including MINOCA	History, echocardiography, elevated troponin levels
Myocarditis, including giant-cell myocarditis	History, endomyocardial biopsy
Takotsubo cardiomyopathy	History, apical ballooning on echocardiography
Tachycardia-induced cardiomyopathy	History, especially atrial fibrillation
Pulmonary edema resulting from prolonged tocolysis	History, preserved ejection fraction on echocardiography
Sepsis, thyrotoxicosis, and other high-output causes of heart failure	History, high output on echocardiography
Aortic dissection	History, findings on CT angiogram

* CT denotes computed tomography, MINOCA myocardial infarction with no obstructive coronary artery disease, PLGF placental growth factor, and sFlt-1 soluble fms-like tyrosine kinase 1.

CENTRAL ILLUSTRATION: Diagnosis, Management, and Outcomes for Peripartum Cardiomyopathy



Davis, M.B. et al. J Am Coll Cardiol. 2020;75(2):207-21.

Complications:

brain injury, cardiopulmonary arrest, pulmonary edema
thromboembolic complications,
mechanical circulatory support, cardiac transplantation, and death.
major adverse event preceded the diagnosis of PPCM in one-half of the patients
LV thrombus has been identified in as much as 10% to 17% of initial echocardiograms
thromboembolic complications → 5% to 9% of women.
The increased incidence of thromboembolic events in PPCM is likely related to the hypercoagulable state of pregnancy, cardiac dilatation and dysfunction, venous stasis, bed rest, and the post-operative status after cesarean section

Prognostic indicators:

LVEF <30
LV dilatation
LV thrombus (17),
right ventricular systolic dysfunction (73,74)
obesity (75).
African-American ethnicity
Concomitant pre-eclampsia
Biomarkers →troponin (78), NT-proBNP (79), and sFlt1 (39).

THE UNIVERSITY OF KANSAS HEALTH SYSTEM

Management:

- Loop diuretics
- Beta blockers
- Hydralazine/ nitrates

Anticoagulation:

AHA → when the LVEF is <30%

ESC → when LVEF ≤35%

- Choice of anticoagulant: Warfarin crosses the placenta, avoided during pregnancy for indications other than anticoagulation of mechanical heart valves.
- Low-molecular-weight heparin → preferred.
- Both warfarin and low-molecular-weight heparin are considered safe with lactation.
- Novel anticoagulants have not been studied during pregnancy or lactation and are generally avoided.

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
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
ANTICOAGULANTS				
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

Legend:

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

Labor and Delivery:

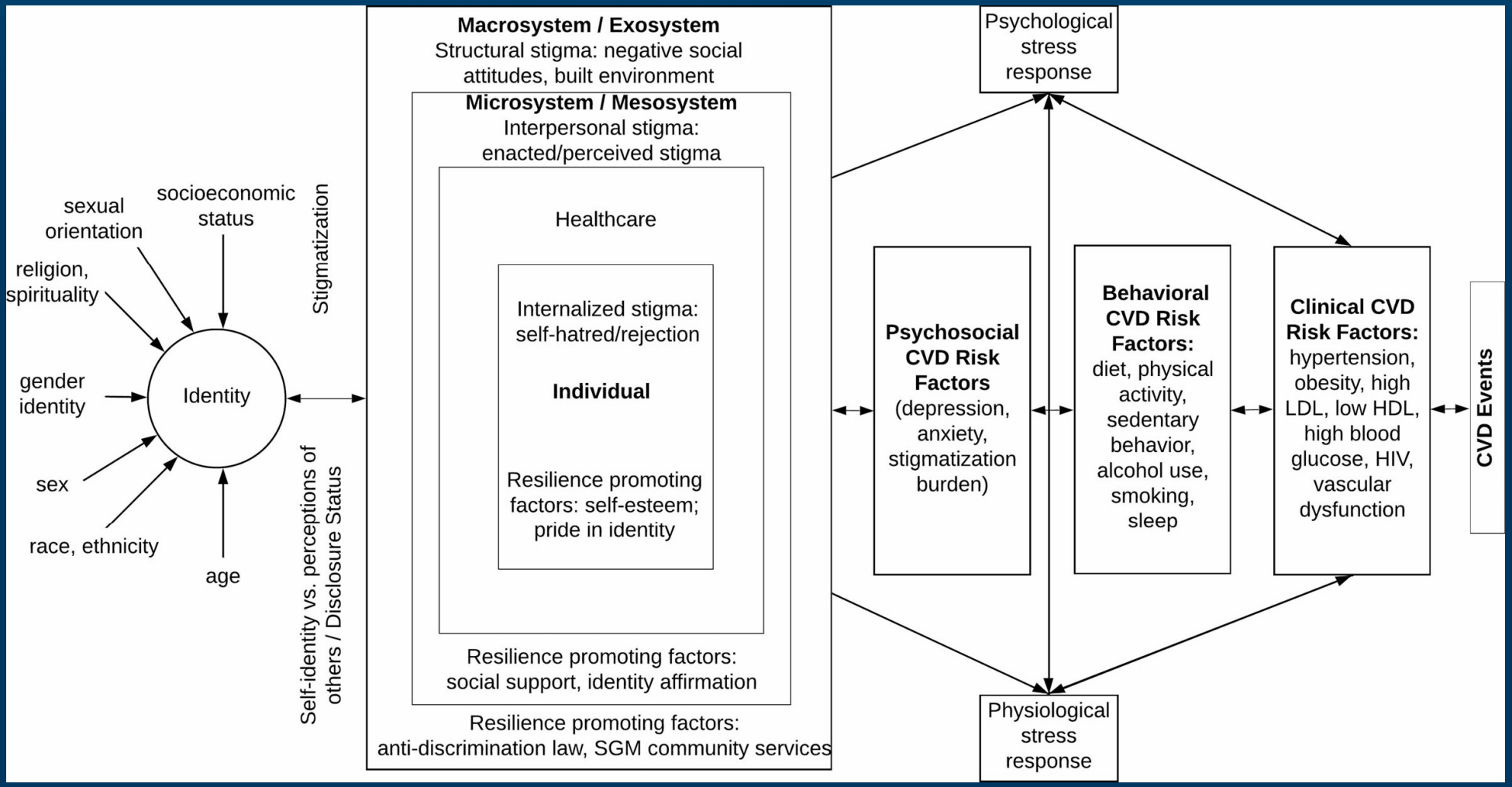
- **Stable patients are delivered vaginally unless there are obstetric reasons for cesarean section (or) patient is on warfarin.**
- **Cesarean delivery : associated with a higher incidence of hemorrhage, infection, and thromboembolic complications.**
- **Unstable patients → invasive hemodynamic optimization prior to delivery and monitoring during delivery and the early postpartum period.**
- **Following delivery, removal of caval compression by the fetus, autotransfusion due to uterine contractions, and fluid mobilization and resorption contribute to an increase in venous return.**
- **The post-partum risk of fluid overload and pulmonary edema must be anticipated.**

Contraception:

- In the early postpartum setting with severe LV dysfunction → the increased risk of thromboembolism should dissuade the use of estrogen-containing contraceptives.
- Progesterone-releasing subcutaneous implants or the Mirena intrauterine device are safe and effective choices.
- Injectable depot medroxyprogesterone acetate is less effective and is considered a second-line option. Tubal ligation and vasectomy are other options.
- Persistent LV dysfunction: the risk of a subsequent pregnancy likely outweighs any risk associated with contraception. Therefore, women should be encouraged to select the method they will use most consistently.

Cardiovascular health in the transgender population.

- AHA recognizes that transgender and gender diverse (TGD) are impacted by disparities across a variety of cardiovascular risk factors compared with their peers who are cisgender.
- cardiovascular risk factors at the individual level likely do not fully account for increased risk in cardiovascular health disparities among people who are TGD
- ≈2% of high school–aged youth[2] and 0.5% to 0.6% of adults[3] in the United States identify as TGD
- Men who are transgender had a >2-fold and 4-fold increase in the prevalence of myocardial infarction compared with men who are cisgender and women who are cisgender, respectively.
- Women who are transgender had >2-fold increase in the prevalence of myocardial infarction compared with women who are cisgender but did not have a significant increase in comparison with men who are cisgender


sexual orientation
socioeconomic status
religion, spirituality
gender identity
Identity
sex
race, ethnicity
age
Stigmatization
Self-identity vs. perceptions of others / Disclosure Status
Macrosystem / Exosystem
Structural stigma: negative social attitudes, built environment
Microsystem / Mesosystem
Interpersonal stigma: enacted/perceived stigma
Healthcare
Internalized stigma: self-hatred/rejection
Individual
Resilience promoting factors: self-esteem; pride in identity
Resilience promoting factors: social support, identity affirmation
Resilience promoting factors: anti-discrimination law, SGM community services
Psychological stress response
Psychosocial CVD Risk Factors (depression, anxiety, stigmatization burden)
Behavioral CVD Risk Factors: diet, physical activity, sedentary behavior, alcohol use, smoking, sleep
Clinical CVD Risk Factors: hypertension, obesity, high LDL, low HDL, high blood glucose, HIV, vascular dysfunction
CVD Events
Physiological stress response

THANK YOU