

Heart Disease in Women

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Leading Cause of Death

- More women die of cardiovascular disease
- ½ some form of CVD in their lifetime
- First year after a heart attack, 18% men and 23% women will die
- O.R. 2 times more likely in women <45 years of age

AHA Statistics Update Circulation. 2016
Merz et al. JACC. 2006

Public perception is still breast cancer

- AHA: 2012 telephone and on line survey to assess awareness of CVD as leading cause of mortality
- Almost doubled, 1997 30% vs 2012 56%, reverse trends for cancer
- Ethnic and racial gap remains, 30% to ~35%
- Awareness of atypical symptoms is low
- Preventative action to feel better and improve health, not for living longer.

Lori Mosca et al. Circulation. 2013;CIR.0b013e318287cf2f

Gender Bias

"...The community has viewed women's health almost with a 'bikini' approach, looking essentially at the breast and reproductive system, and almost ignoring the rest of the woman as part of woman's health..."

— Nanette Wenger, MD
2001: PBS documentary "A Woman's Heart"



Chest Pain: ER Evaluation & Treatment

- Retrospective study of 311 patients in 1994 at academic medical center
- Women more likely to present > 6hours after symptom onset
- Men more likely to receive
 - Screening EKG
 - Antiplatelet agents, Anticoagulants and Thrombolytics
 - Nitroglycerin
- Women more likely to receive
 - Anxiety medications
 - Pain medications

Lehman JB, et al 1995 Am J Cardiol; 77:641

Get With The Guidelines: Clinical Performance after MI

- GWTG-CAD Registry, 2001-2006
- 78,254 AMI patients, 39% women
- Women versus Men:
 - Older, more comorbidities
 - Less often STEMI
 - Less likely to receive aspirin or BB within 24 hours
 - Less likely to undergo invasive procedures
 - Longer reperfusion times
 - Higher death rates in STEMI patients

Jneid, H. et al. Circulation 2008;118:2803-2810

Get With The Guidelines: Age & Gender Differences in Quality of Care and Outcomes in STEMI (n=31,544)

- Quality of care lower and mortality higher in young women versus young men, 2002-2008
- Younger and Older Women were
 - Less likely to receive ACEI/ARB
 - Less likely to receive lipid-lowering therapy
 - Less likely to have a BP < 140/90 mm Hg at discharge
 - More likely to have longer door-to-balloon times
 - Less likely to receive stents

Bangalore S et al. The American Journal of Medicine 2012;125:2803-2810

Challenges Mortality

- Delays Symptom Recognition, public and healthcare
- Misdiagnosis
- Delay in Treatment
- Under-referred for LHC, PCI, CABG
- Low Adherence to GDMT
- Fewer Referrals to Cardiac Rehab

Outline

- Risk factors
- Symptoms
- Morphologic differences
 - Vessel size
 - Microvascular disease
 - Plaque characteristics in MI
- MINOCA:
 - SCAD
 - Coronary Artery Spasm
 - Mimic: Takotsubo cardiomyopathy

Major Risk Factors for CVD

Modifiable	Nonmodifiable	New Risk Factors
Hypertension	Family history	High heart rates
Hyperlipidemia	Age	Accelerated menopause
Diabetes Mellitus		High CRP
Tobacco use		Low HDL, High TG
Obesity		High Lpa
Physical inactivity		Metabolic Syndrome
High fat diet		Waist/hip >0.8 apple shape

Grundy SM, et al. *Circulation*. 1998; Grundy SM. *Circulation*. 1999
 Braunwald E. *N Engl J Med*. 1997; Grundy SM, et al. *J Am Coll Cardiol*. 1999
 Mosca et al. *Circulation* 2011

Hypertension in Women

- Gender Related Risk Factors for HTN:
 - Race/ethnicity
 - Younger women: OCP, PCOS, Pregnancy
 - Obesity, visceral fat, insulin resistance
- Rates of HTN increase as women ages
- Pregnancy related HTN and pre-eclampsia long term risk factors
- White Coat HTN
- Menopause

Menopause results in adverse changes in lipid profiles

- Lipid levels measured over time in 195 women, 10 made the transition, followed only for 6 months post.
- To eliminate effects of interindividual differences, each woman's postmenopausal values were calculated as percentages of her own mean premenopausal values.
- In 3 months after cessation of menstruation, Total-C and LDL-C rose sharply, then plateaued.
- Perimenopausal Triglyceride levels were erratic, but rose and then plateaued in 3 months post
- HDL gradually declined starting 2 years prior to menopause and then leveled off post.

Jensen et al. *Maturitas*. 1990;12:321-331

2011 Update: Guidelines for the Prevention of Cardiovascular Disease in Women

High Risk Population

- Clinically Manifest CHD, PVD, CVA
- Abdominal Aortic Aneurysm
- Diabetes Mellitus
- End Stage or Chronic Kidney Disease

Mosca et al. Circulation 2011

At Risk Group Population

- Cigarette smoking
- BP >120/80, or treated HTN
- Total chol > 200, HDL <50, or treated dyslipidemia
- Obesity, central adiposity
- Poor diet
- Physical inactivity
- Family history of premature CVD
- Metabolic syndrome
- Subclinical atherosclerosis: CAC, carotid plaque, CIMT
- Poor exercise capacity or abnormal HR recovery after stopping exercise
- Autoimmune disease: SLE, RA
- History of preeclampsia, gestational DM, PIH

Mosca et al. Circulation 2011

Ideal Cardiovascular Health Population

- BP 120/80, untreated
- Total cholesterol <200,
- Fasting glucose <100, untreated
- Nonsmoker or abstinence for >12 months
- BMI <25
- Physically active (>150 min/wk moderate intensity, >75 min/wk vigorous intensity, or combination)
- Healthy diet

Mosca et al. Circulation 2011

Symptoms Associated With Heart Attack

Men (Textbook)

- Crushing substernal chest pain/pressure
- Rest pain
- Pain down left arm and shoulder
- Weakness

Women (Vague)

- Pain in chest, upper back, jaw or neck
- Shortness of breath
- Flu-like symptoms: nausea or vomiting, cold sweats
- Weakness or fatigue
- Anxiety or loss of appetite

Coronary Artery Size

- IVUS of Coronary Arteries of 50 male and 25 female patients
 - Sex is an independent predictor of coronary arterial area (LM, LAD).
- Study of Transplant patients (n=86)
 - Proximal LAD vessel area increased in all groups
 - Same gender and male donor to female recipient transplanted hearts, change in vessel size was small.
 - Significant increase in vessel area in female donor to male recipient transplanted hearts
 - Potential association between coronary arterial size and host gender

Sheifer et al. Am Heart J 2001;139:649-653
Herity et al. J Am Coll Cardiol 2003

Womens Ischemia Syndrome Evaluation (WISE)

- 887 women with chest pain, abnormal stress test and underwent angiograms.
- Mean age was 58 years
- 25% had diabetes.
- No CAD (<20% stenosis) in 37%
- Minimal CAD (<50% stenosis) in 25%
- Significant CAD (≥50% stenosis) in 38%
- Therefore ~62% with none or minimal stenosis.

Sharaf et al. J Am Coll Cardiol. 2004;292A. Abstract 1119-93.

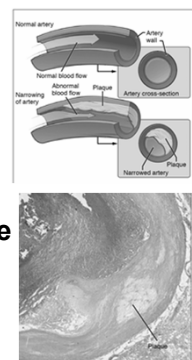
WISE Findings

- Normal or near normal coronary angiogram (luminography)
- Abnormal CFR and increased LVEDP
- IVUS: positive remodeling with diffuse atherosclerosis
- Male pattern: typical centripetal, focal lesion
- Female pattern: cellulite like
- Higher risk of future CV events in women with nonobstructive disease and persistent CP
- Newer techniques: retinal AVR, cardiac MRI

Sharaf et al. J Am Coll Cardiol. 2004;292A. Abstract 1119-93.
Johnson BD et al. Eur Heart J. 2006;27:1408-15.
Wong, T. Y. et al. JAMA 2002;287:1153-1159
Panting et al. NEJM 2002

Plaque Rupture

- Typical plaque
- More common in men
- Necrotic core
- Thin fibrous cap
- Most frequent site of rupture is the shoulder region
- Older women: HLP



Arbustini, E et al. Heart 1999;82:269-272
Burke, A. P. et al. Circulation 1998;97:2110-2116
Yahgal, et al. Atherosclerosis, 2015
By OpenStax College [CC BY 3.0 (<http://creativecommons.org/licenses/by/3.0/>)], via Wikimedia Commons.
Anatomy & Physiology, Connexions Web site. <http://cnx.org/content/col11496/1.6/>, Jun 19, 2013

Plaque Erosion

- More frequent in Young Women
- Associated with cigarette smoking
- Fibrous cap is absent
- Exposed intima
- Smooth muscle and proteoglycans
- Can be missed on angiogram

Burke, A. P. et al. Circulation 1998;97:2110-2116

50 Consecutive SCD Cases: Post-Mortem Analysis

	Plaque Rupture N=28	Plaque Erosion N=22	P value
Male:Female	23:5	11:11	0.03
Age (years)	53 ± 10	44 ± 7	<0.02
%stenosis	78 ± 12	70 ± 11	<0.03
Occlusive:nonocclusive thrombus	43:57	18:82	0.08
Concentric:eccentric	46:54	18:82	0.07
Smooth muscle cells	33	95	<0.0001

Andrew Farb et al. Circulation. 1996;93:1354-1363

Gender and Extent of Coronary Atherosclerosis

- 697 patients (24% women) with ACS enrolled in PROSPECT study.
- Three-vessel IVUS after treatment of the culprit lesion
- Women were older and had higher rates of insulin requiring DM, HTN, renal insufficiency, CHF
- Women: Less Extensive CAD, Less plaque rupture, Similar plaque burden.
- Highest risk of MACE: PB>70% in men and TCFA in women

Lansky et al. JACC 2012

MINOCA: MI with Non-obstructive CAD

- Higher rates in women versus men in ACS trials, ≈20% or greater excess of normal or nonobstructive arteries in women vs men
- MINOCA: 63% lower in-hosp mortality and 41% lower 12 month mortality
- Guarded prognosis (6.7% vs 4.7%)
- Causes of MINOCA: Acute coronary artery spasm or plaque disruption, SCAD, Takotsubo cardiomyopathy, microvascular disease

Diagnosis of MINOCA:

1. Positive cardiac biomarkers
2. Clinical evidence of infarction:
 - Symptoms
 - New EKG findings, New Q waves
 - New LV systolic dysfunction
3. Cath
4. Consider MRI
5. Exclude other causes of troponin elevation

Case 1

- 49 year old Caucasian female
- Substernal chest discomfort, radiation to shoulder and jaw, worse with exertion, nausea, mild dyspnea, day prior had exertional weakness
- PMHx: thyroid disorder, nonsmoker
- Unremarkable exam
- Normal EKG

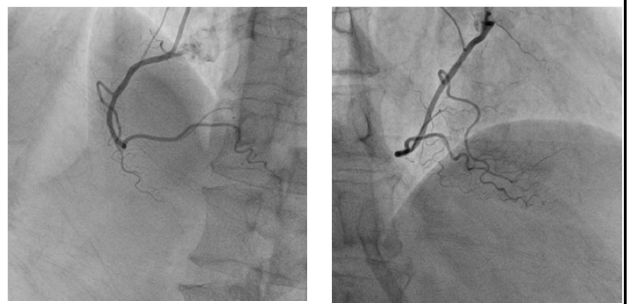
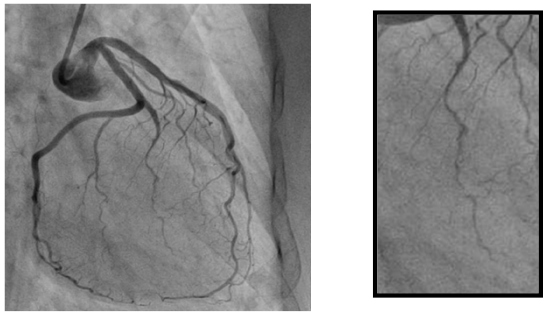
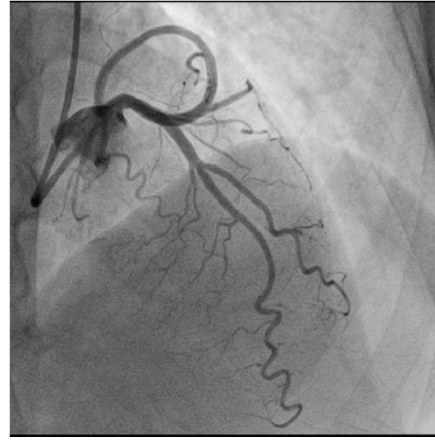
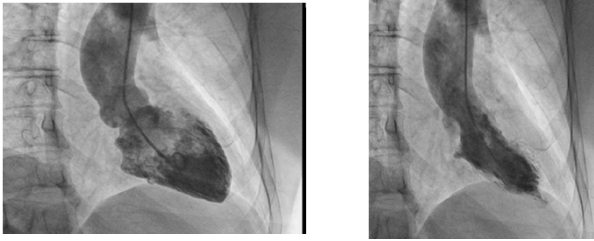
What Would You Do Next?

1. Do Nothing
2. Treat with Anxiolytics
3. Treat with Cardiac Medications
4. Stress Test
5. Cardiac Catheterization

ER Course

- Diagnosed with atypical chest discomfort and low risk profile for CAD
 - Clopidogrel and beta-blocker therapy
 - Stress test
- Subsequently troponin mildly elevated so decision to take to the cath lab

LV Gram



What Would You Do Now?

1. Medical Management:
 - Cardiac medications
 - Anxiolytics
2. Stress Test +/- PCI
3. GI Evaluation
4. Do Nothing

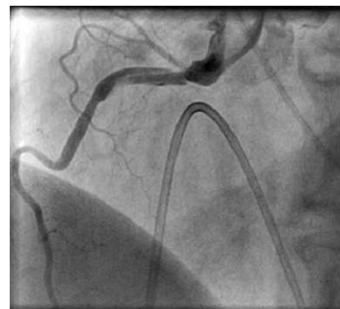
Recurrent Chest Pain What Would You Do Now?

1. Medical Management:
 - Cardiac medications
 - Anxiolytics
2. EKG
3. Stress Test +/- Cath
4. GI Evaluation
5. Do Nothing

Post-Cath

- Vagal reaction in recovery area: atropine and iv fluids
- Chest pain persisted
- EKG with ST elevation inferiorly

What Do You Do Now?



1. Do Nothing
2. Anxiolytic
3. PCI
4. CABG

Spontaneous Coronary Artery Dissection (SCAD)

- Primary dissection: spontaneous
- Secondary Dissection: extension from aortic root dissection or consequence of an insult
- Dissection: separation of layers of arterial wall, false and true lumens
 - Planes: between intima and media or media and adventitia
 - Hemorrhage in false lumen and then thrombosis compresses true lumen and then ischemia

Vrints C J M Heart 2010;96:801-808

SCAD

- Mean age 30-45 yrs, range 30-70
- >70% women
- ~11% of women <50 presenting with STEMI or ACS
- ~30% in postpartum period, within 2 weeks
 - Risk Factors: advanced age, multiparity
 - SCAD not exclusive cause of AMI
- LAD most frequently involved in autopsy and angiographic series, 60% of cases, multiple vessel involvement as well
- Some present with SCD or ventricular arrhythmias

Vrints C J M Heart 2010;96:801-808

Predisposing Arteriopathies

- Atherosclerosis
- Nonatherosclerotic
 - Fibromuscular dysplasia
 - Multiple pregnancies
 - Connective tissue disorders
 - Systemic inflammatory conditions
- Idiopathic

Precipitating Stress Events

- Intense exercises
- Intense emotional stress
- Labor and delivery
- Intense Valsava type activities
- Recreational drugs
- Intense hormonal therapy

Vrints C J M Heart 2010;96:801-808

SCAD Imaging

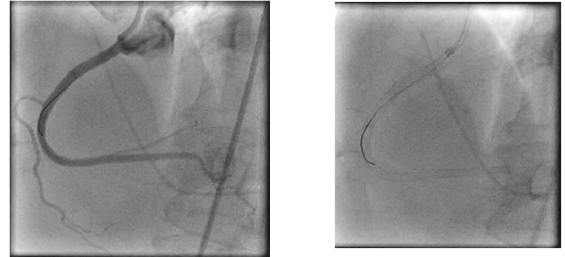
- Careful intubation of the coronary arteries
- IVUS
- OCT
- Double Lumen, entry point
- Compressive hemorrhage

Types of SCAD

- **Type 1: Intimal Tear, contrast dye staining of arterial wall with radiolucent lumen, slow contrast clearing**
- **Type 2: Diffuse, smooth narrowing, No Response to IC NTG, OCT or IVUS shows intramural hematoma**
- **Type 3: Mimics Atherosclerosis with focal or tubular stenosis**

Jacqueline Saw et al. Circ Cardiovasc Interv. 2014;7:645-655

6 Stents placed, peak troponin 63



Echo: EF 45%, moderate HK of inferoposterior segments, mild MR

What is Her Prognosis?

1. Unchanged
2. Better than someone with prior PCI
3. Similar than someone with prior PCI
4. Worse than someone with prior PCI

Prognosis

- Overall mortality in peripartum group 38%
- In-hospital mortality 3%
- Low rate of recurrence
- Strongest predictors of death
 - Female sex
 - Absence of early treatment

MAYO Experience of SCAD

- 1979-2011, 87 patients, majority single vessel
- 82% female, Mean age 42.6 ± 10
- 39 PCI, 24 of which were successful, 15 were unsuccessful of which 1 death
- 4 CABG
- 13 lytics: 4 CABG, 3 PCI and 6 conservative
- 31 no revascularization: 2 deaths

Tweet M S et al. Circulation 2012;126:579-588

Contemporary Data from Canada

- 168 SCAD Patients, 92% women, Type 2 SCAD most common
- 28 (17%) initially treated with PCI and then 3 with CABG
- 1 with CABG, 5 with lytics of which 3 subsequent PCI
- 134 (80%) no revascularization initially, subsequently 1 CABG, 2 PCI and rest conservative
 - 4.5% in-hospital recurrent MI
 - Majority spontaneously healed

Jacqueline Saw et al. Circ Cardiovasc Interv. 2014;7:645-655

Optimal Treatment of SCAD

- Stenting
- CABG
- Conservative Therapy

Long-Term Outcomes after SCAD

Free of Recurrent SCAD	Survival	7.7% mortality
10 yr recurrence 29%		
median time 2.8 yrs		
most new vessel	Free of MACE	47.4 % MACE
all females		

Tweet M S et al. Circulation 2012;126:579-588

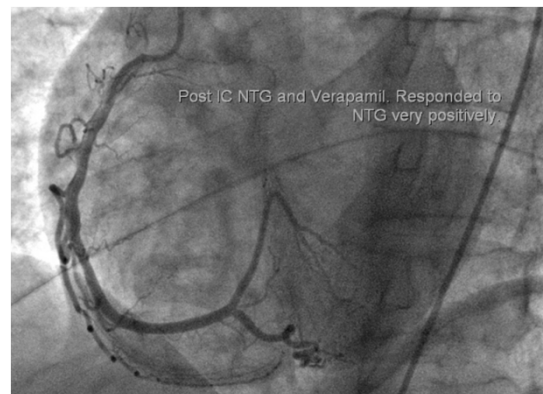
Compared to Atherosclerotic Patients SCAD vs PCI

- **Atherosclerotic Risk Factors of PCI Control vs SCAD Cases**
 - Similar age (mean in low to mid 40's)
 - Low percentage of men, 19% both
 - Higher rates of HLP 44% vs 14%), HTN (44% vs 19%), smoking (57% vs 28%), diabetes (19% vs 3%) in the PCI group vs SCAD
- Survival at 10 years is lower in the PCI group
- Freedom from MI or MI & CHF is similar

Tweet M S et al. Circulation 2012;126:579-588

Case 2

- 62 year old female
- Smoker
- Found down on way back from bathroom
- CPR-AED
- Taken to local hospital



Coronary Artery Spasm

- **First described in 1959**
- **Multifocal spasm**
- **Risk Factors:**
 - **Smoking**
 - **Excess alcohol**
 - **Drugs**
 - **Inflammation**
 - **Oxidative stress**
 - **Ethnicity**
- **Pathophysiologic Mechanism Less Understood**

Diagnostic Options

- **EKG**
- **Holter monitoring**
- **Exercise testing**
- **Coronary angiogram with provocative testing**

Treatment Options

- **Medications: Calcium channel blockers, long acting nitrates, magnesium**
 - **Avoid beta-blockers**
- **Lifestyle: quit smoking**
- **Intervention (PCI or CABG): rarely beneficial**
- **AICD**

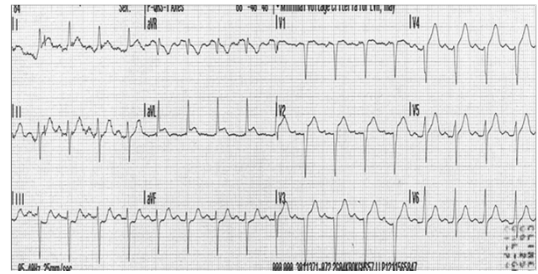
Follow up

- **Recurrent Event within one month, transferred her care to OSU**
- **AICD placed**
- **CCB**
- **Thereafter no further events**

Case 3

- 84 years old female
- Hx of tachycardia and HTN
- At beauty salon, developed dizziness
- Subsequently chest pressure 5/10, radiating to bilateral arms, no relief with NTG sublingual
- No other associated symptoms
- Unremarkable exam

EKG



Labs

- Troponin <0.01, peak 0.39
- CK 37, peak 80/13.6/17
- Cath normal coronary arteries
- Echo showed apical ballooning

MRI

Abnormal patient



Index patient

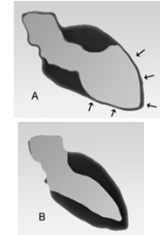


Confusing Nomenclature

- Takotsubo Cardiomyopathy
- Ampulla Cardiomyopathy
- Transient Apical Ballooning Syndrome
- Stress Induced Cardiomyopathy
- Broken Heart Syndrome

Takotsubo Cardiomyopathy

- Tako means octopus, Tsubo means pot
- Short neck round flask-like LV apical ballooning



By J. Heuser JHeuser (Own work) [GFDL (<http://www.gnu.org/copyleft/fdl.html>) or CC-BY-SA-3.0 (<http://creativecommons.org/licenses/by-sa/3.0/>), via Wikimedia Commons
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Pathophysiologic Basis of Transient LV Apical Ballooning

- Dynamic midventricular obstruction secondary to basal hypercontractility
- Multiple epicardial vasospastic angina
 - Provocative vasospasm confirmed only in limited cases
- Microvascular spasm or impaired circulation causing ischemia (stunned myocardium)
- Enhanced sympathetic activity: catecholamine exposure

The Broken Heart Syndrome

- Postmenopausal women
- Symptoms
 - Chest pain
 - Shortness of breath
 - Fatigue
- Mimics a heart attack
 - EKG and labs
 - No obstructive CAD

**Life threatening
but reversible
disease process!**

Stressors

Emotional	Physical
Death	Postsurgical
Interpersonal conflict	Acute resp failure
Job issues	Infection
Financial issues	Stroke
Bad News	Seizure
Anger	Abdominal pain
Panic	Chemotherapy

11% of patients with no identifiable stressful event

J Am Coll Cardiol. 2010;55(4):333-341. doi:10.1016/j.jacc.2009.08.057

Diagnostic Criteria

- **Mandatory**
 - Absence of coronary thrombosis (plaque rupture)
 - WMA extend beyond a single coronary territory
 - Rapid recovery of systolic function
- **Possible**
 - Acute trigger
 - EKG changes
 - Abnormal cardiac enzymes
 - Acute onset of symptoms

Treatment

- **Acute Period**
 - Hemodynamically stable
 - BB, ACEI/ARB, diuretics
 - Anticoagulation if akinetic apex and no contraindication
 - Hemodynamically unstable
 - IABP, pressors
- **Chronic Period**
 - Symptomatic
 - Nitrates for chest pain
 - Normalized LV function
 - ?BB, ACEI/ARB

Overall, good prognosis. If patient survives the acute phase, long-term prognosis is excellent.

- 0-8% in-hospital mortality, likely closer to 1-2%
- Recovery of LV function, typically in 1-4 weeks
- Late sudden death (rare) and recurrent disease (<10%) have been reported

Sharkey, S. W. et al. J Am Coll Cardiol 2010;55:333-341

Hospital Course

- Episode of PAF, started on warfarin



Are Women Doctors Better Than Male Doctors?

Sex Differences in Cardiac Catheterization: The Role of Physician Gender

- Cooperative Cardiovascular Project, 104,231 Medicare fee-for-service beneficiaries AMI between 1/94-2/95
- Fewer caths in women than men
 - Treated by male physicians (38.6% vs 50.8%)
 - Treated by female physicians (34.8% vs 45.8%)
- Regardless of patient sex, those treated by male physicians were more likely to undergo LHC than those treated by female physicians.
- Sex differences in cardiac procedure use: need to consider other factors and not bias by male physicians toward women

JAMA. 2001;286(22):2849-2856. doi:10.1001/jama.286.22.2849

Conclusions

- Women have smaller coronary arteries.
- Positive remodeling and diffuse atherosclerosis is present in women and can give false results on luminography.
- Microvascular disease is a cause for persistent chest pain in women, which is associated with adverse CV outcomes.
- Plaque erosion is more common in women.
- Not all coronary events are due to atherosclerosis: Does vessel improve with IC NTG? Is there abrupt taper, unusually small vessel, slow flow distally? Don't forget SCAD and vasospasm.