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

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 > 6 hours 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


## 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

<table>
<thead>
<tr>
<th>Modifiable</th>
<th>Nonmodifiable</th>
<th>New Risk Factors</th>
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</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Family history</td>
<td>Age</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td></td>
<td>Accelerated menopause</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td></td>
<td>High CRP</td>
</tr>
<tr>
<td>Tobacco use</td>
<td></td>
<td>Low HDL, High TG</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td>High Lpa</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td></td>
<td>Metabolic Syndrome</td>
</tr>
<tr>
<td>High fat diet</td>
<td></td>
<td>Waist/hip &gt;0.8 apple shape</td>
</tr>
</tbody>
</table>

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.

Mosca et al. Circulation 2011
**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

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### 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

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### 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

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### 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

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.

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

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

References:

- Sheifer et al. Am Heart J 200;139:649-653
- Horig et al. J Am Coll Cardiol 2001
- Panting et al. NEJM 2003
- Arbustini, E et al. Heart 1999;82:269-272
- 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


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**50 Consecutive SCD Cases: Post-Mortem Analysis**

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

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

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**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

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**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
## 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 ischeia

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

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

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

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

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**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

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**Optimal Treatment of SCAD**

- Stenting
- CABG
- Conservative Therapy

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**Long-Term Outcomes after SCAD**

<table>
<thead>
<tr>
<th>Free of Recurrent SCAD</th>
<th>Survival 7.7% mortality</th>
</tr>
</thead>
</table>

10 yr recurrence 29%  
median time 2.8 yrs  
most new vessel  
all females

<table>
<thead>
<tr>
<th>Free of MACE</th>
<th>47.4 % MACE</th>
</tr>
</thead>
</table>

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

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 provacative 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

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: catecolamine 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

<table>
<thead>
<tr>
<th>Emotional</th>
<th>Physical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>Postsurgical</td>
</tr>
<tr>
<td>Interpersonal conflict</td>
<td>Acute resp failure</td>
</tr>
<tr>
<td>Job issues</td>
<td>Infection</td>
</tr>
<tr>
<td>Financial issues</td>
<td>Stroke</td>
</tr>
<tr>
<td>Bad News</td>
<td>Seizure</td>
</tr>
<tr>
<td>Anger</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Panic</td>
<td>Chemotherapy</td>
</tr>
</tbody>
</table>

11% of patients with no identifiable stressful event

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

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

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.