Coronary Heart Disease in Women and underrepresented populations

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Disclosures

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CCMC Ethics credit is approved for this course. The CCMC Code of Professional Conduct will be referenced in this presentation. View the CCMC Code of Professional Conduct here.
1964 – AHA held the first conference on women and heart disease

Featuring Paul Dudley White

“Hearts and Husbands”

It was basically about How to Care for Your Man

“This session has vital importance for the wives of men suffering from any heart disease”
2016 – AHA releases the first scientific statement on myocardial infarction in women
Heart Disease is the #1 Cause of Death in Women

Centers for Disease Control and Prevention, 2013 data

- **Heart Disease**: 289,758
- **Cancer**: 163,200
- **Lung Disease**: 42,100
- **Alzheimer’s Disease**: 23,500
- **Diabetes**: 21,200

Breast cancer: 39,620
Heart Disease in Women

• **Ischemic heart disease in women**
  • biology, risk factors, response to therapy

• **Ischemic syndromes of particular importance to women**
  • MINOCA, Microvascular Dysfunction, SCAD

• **Heart failure syndromes of particular importance to women**
  • Takotsubo cardiomyopathy
Women have less obstructive CAD

Patients undergoing elective angiography for angina

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Percent of patients with &gt;50% stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td></td>
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<tr>
<td>50-59</td>
<td></td>
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<tr>
<td>60-69</td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td></td>
</tr>
<tr>
<td>&gt;79</td>
<td></td>
</tr>
</tbody>
</table>

Women have less obstructive CAD

ACC-National Cardiovascular Data Registry™. J Am Coll Cardiol. 2006
CAD develops differently in women

MEN

Focal
Stenosis

WOMEN

Diffuse
atherosclerosis

A large amount of atherosclerosis can hide
CAD develops differently in women

MEN
Plaque rupture

WOMEN
Plaque erosion

Focal Stenosis
Diffuse atherosclerosis

Men have “classic” symptoms
Women have “atypical” symptoms

- Chest pain or discomfort
- Unusual upper body discomfort
- Light-headedness or sudden dizziness
- Shortness of breath
- Diaphoresis
- Unusual or unexplained fatigue
- Nausea

The Heart Truth Campaign, NHLBI
Risk Factors for Heart Disease

- Smoking
- Diabetes
- Hypercholesterolemia
- Hypertension
- Obesity/Overweight
- Physical inactivity
- Family history
- Age

Risk Factors of particular importance to women

- Auto-immune disease
- Breast cancer treatments
- SAD Risk factors (Stress, Anxiety and Depression)
- Pregnancy Complications
  - Pre-term delivery
  - Pregnancy induced hypertension
  - Gestational diabetes
Reproductive Hormone transition times are high risk for women’s CV systems

- Puberty
  - Boys grow taller and thinner; girls grow taller and heavier

- Pregnancy
  - A “stress test” for the cardiovascular system

- Menopause
  - The menopause “bump”
Pregnancy – a Stress Test for the heart

Preeclampsia with preterm delivery
- 8 x ↑ risk of future death CVD
- 5 x ↑ risk of future stroke

Preeclampsia with full term delivery
- 3 x ↑ risk of future death CVD

Gestational diabetes
- ~30 % ↑ risk of future death CVD
- 20-60% will develop type 2 DM within 5-16 yrs

Menopause

Loss of estrogen puts women at higher risk for developing CVD

Before the onset of menopause, women have \( \sim 1/5 \) the rate of heart disease as men

10 years after menopause, rate of MI equals that of men

The Menopause Bump
Blood Pressure Levels by Age

Men

Women

PP=Pulse Pressure.

Lipid Changes Peri-Menopause

Pre and post menopause changes

Cross-sectional study of 3,636 women (40–59 years old)

<table>
<thead>
<tr>
<th>Variable</th>
<th>PRE</th>
<th>POST</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>49.7</td>
<td>55.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Activity (METS)</td>
<td>5502</td>
<td>2458</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>26.9</td>
<td>28.1</td>
<td>0.001</td>
</tr>
<tr>
<td>% BF</td>
<td>34.1</td>
<td>36.2</td>
<td>0.001</td>
</tr>
<tr>
<td>HTN (%)</td>
<td>55.2%</td>
<td>60.4%</td>
<td>0.01</td>
</tr>
<tr>
<td>LDL-c</td>
<td>121.6</td>
<td>132.2</td>
<td>0.001</td>
</tr>
<tr>
<td>HDL-c</td>
<td>63.7</td>
<td>62.5</td>
<td>NS</td>
</tr>
<tr>
<td>TG</td>
<td>100.8</td>
<td>113.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Glucose</td>
<td>92.0</td>
<td>95.8</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Ghrelin (discovered in 1999) is a hormone that stimulates appetite.

Ghrelin levels increase in peri-menopause

Therapeutic Approaches in IHD

Invasive Management vs. Medical Management
Aspirin Effects by sex

Myocardial Infarction

- BDT, 1988: Aspirin Better
- PHS, 1989: Aspirin Better
- TPT, 1998: Aspirin Better
- HOT, 1998: Aspirin Better
- PPP, 2001: Aspirin Better
- Combined: Aspirin Better

Aspirin Better
Placebo Better

Stroke

- BDT, 1988: Aspirin Better
- PHS, 1989: Aspirin Better
- TPT, 1998: Aspirin Better
- HOT, 1998: Aspirin Better
- PPP, 2001: Aspirin Better
- Combined: Aspirin Better

Aspirin Better
Placebo Better

- HOT, 1998: No Difference
- PPP, 2001: No Difference
- WHS, 2005: No Difference
- Combined: No Difference

Aspirin Better
Placebo Better

Aspirin Better
Placebo Better

Aspirin Better

Meta-analysis of Primary Prevention Statin Trials in Women

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>RR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFCAPS/TexCAPS</td>
<td>1998</td>
<td>0.67</td>
<td>(0.34-1.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MEGA</td>
<td>2006</td>
<td>0.73</td>
<td>(0.49-1.10)</td>
<td></td>
</tr>
<tr>
<td>JUPITER</td>
<td>2008</td>
<td>0.54</td>
<td>(0.37-0.80)</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td>0.63</td>
<td>(0.49-0.82)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Women tend to fare worse after PCI

Men fare worse

Women fare worse

Major adverse cardiac event
Death
Myocardial Infarction
CABG
Repeat PCI
Repeat revascularization
Target lesion revascularization
Target vessel revascularization

Young women have especially poor outcomes

Women < 50 years of age do especially poorly after PCI

- Major adverse cardiac event
- Death
- Myocardial Infarction
- CABG
- Repeat PCI
- Repeat revascularization
- Target lesion revascularization
- Target vessel revascularization

Men fare worse\[\text{\textcolor{cyan}{Men fare worse}}\]

Women fare worse\[\text{\textcolor{magenta}{Women fare worse}}\]

Heart Disease in Women

- **Ischemic heart disease in women**
  - biology, risk factors, response to therapy

- **Ischemic syndromes of particular importance to women**
  - MINOCA, Microvascular Dysfunction, SCAD

- **Heart failure syndromes of particular importance to women**
  - Takotsubo, peripartum cardiomyopathy HFpEF

- **The link between breast cancer and heart disease**
What is MINOCA?

### Table 1. Definition of MINOCA

1. **Acute myocardial infarction (AMI) criteria**
   - Clinical evidence of AMI including any of the following:
     - Symptoms – chest pain criteria
     - ECG – new changes including ST segments, LBBB, pathological Q waves
     - Myocardial perfusion imaging – new loss of viable myocardium
     - Left ventricular functional imaging – new regional wall motion abnormality

2. **Non-obstructive coronary arteries**
   - No stenosis ≥50% on coronary angiography

3. **No clinically overt cause for AMI presentation**

   \[ LBBB = \text{left bundle branch block}; \text{MINOCA} = \text{MI with non-obstructive coronary arteries}. \]
Clinical Presentation
55-year old female presented with sudden onset of central chest pain for 2 hours.

Troponin T (Reference Range <29ng/L)
Initial: 99 ng/L
6 Hours: 301 ng/L

ECG
ST elevation in V3-V5

1. Acute Myocardial Infarction
Women are more likely to have MINOCA

Mortality is high in patients with MINOCA

Almost 4% of MINOCA patients are dead at 1 year
Treatment of MINOCA

Statins, ACE/ARBs and βblockers improve outcomes in MINOCA. Dual antiplatelet therapy does not.
MINOCA – Cardiac MR Diagnoses

- Coronary spasm
- Coronary thromboembolism
- Coronary dissection
- Microvascular dysfunction

Pasupathy et. al. Circulation 131:861 2015
The microvasculature is important

Epicardial coronary arteries (>500 µm) are where we focus most of our attention

Microvessels (<500 µm) are much more abundant and carry most of myocardial blood flow

Image from Prof. P Camici
Microvascular disease (MVD)

Microvascular dysfunction (MVD) can cause ischemic heart disease.

Microvascular dysfunction (MVD) is more common in women.

MVD may be influenced by hormonal fluctuations and by cardiac risk factors (especially diabetes).

The microcirculation has the greatest impact on coronary blood flow.
**Spontaneous Coronary Artery Disease (SCAD)**

First described in 1931

A non-atherosclerotic form of acute coronary syndrome

Underdiagnosed and often not considered in younger women presenting with chest pain

Previously considered rare, SCAD now recognized to cause 2–4% of all ACS, 24–36% of MIs in women <50y, and the most common cause of pregnancy-associated MI

Significant association with fibromuscular dysplasia

- ? Generalized vasculopathy
The Canadian SCAD (CanSCAD) a prospective, observational study

750 SCAD patients from Canada (20 centers) and the US (2 centers)

Average age was 51.8 years
89% were female
55% were postmenopausal
Only 4.5% were peripartum
33.9% had NO cardiac risk factors

Presented at the European Society of Cardiology conference in Munich, Germany August 2018
The Canadian SCAD (CanSCAD) study through 2018

50.3% reported high or severe levels of emotional stress
28.9% reported unusually intense physical stress
9.8% reported Isometric stress >50 lb. weight lifting
32.5% had a history of migraines
31.1% had *fibromuscular dysplasia*
  ◦ 27.7 % renal arteries
  ◦ 21.0 % femoral and/or iliac
  ◦ 29.5 % cerebrovascular
  ◦ 7.1% had cerebral aneurysms

Presented at the European Society of Cardiology conference in Munich, Germany August 2018
SCAD should be treated conservatively
Long term outcomes of SCAD are poor

Long term outcomes are poor in SCAD with high recurrent CV event rates
Heart Disease in Women

- **Ischemic heart disease in women**
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- **Heart failure syndromes of particular importance to women**
  - Takotsubo cardiomyopathy

- **The link between breast cancer and heart disease**
Takotsubo: Stress and the heart
Northridge earthquake and Cardiac Deaths

Number of Cardiac Deaths

January 1991

January 1992

January 1993

January 1994

Cardiac Deaths and World Cup soccer in Germany

“Stress” is an Important Cardiovascular Risk Factor in women

TAKOTSUBO CARDIOMYOPATHY

Non-atherosclerotic form of acute myocardial infarction
Cardiomyopathy with apical sparing (resembling a “takotsubo”)
Preceding emotional stressor (“lifetime crisis”) or physical trigger
90% post-menopausal females

Takotsubo

- Broken Heart Syndrome
- Stress Cardiomyopathy
Takotsubo outcomes similar to ACS outcomes

- 1,613 patients enrolled in the International Takotsubo Registry.
- 90% women
- Takotsubo patients had similar long-term mortality to ACS patients
### Urinary stress hormone levels Women vs. Men

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Female n=348</th>
<th>Male n=306</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking Status, %</td>
<td>59/34/7</td>
<td>38/49/13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic Blood Pressure, mmHg</td>
<td>67.4 ± 9.62</td>
<td>73.5 ± 9.52</td>
<td>0.00001</td>
</tr>
<tr>
<td>Blood pressure medications, %</td>
<td>49</td>
<td>39</td>
<td>0.0134</td>
</tr>
<tr>
<td>BMI, kg/m2</td>
<td>29.6 ± 5.9</td>
<td>28.0 ± 4.5</td>
<td>0.0014</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>56.6 ± 15.80</td>
<td>46.3 ± 14.45</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### Urinary Catecholamines

<table>
<thead>
<tr>
<th>Catecholamines</th>
<th>Female</th>
<th>Male</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE, (ln ng/ creatinine mg/dl)</td>
<td>29.1(23.1-40.6)</td>
<td>24.2(17.9-32.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EPI, (ln ng/ creatinine mg/dl)</td>
<td>2.3(1.4-3.0)</td>
<td>2.4 (1.5-3.3)</td>
<td>0.4200</td>
</tr>
<tr>
<td>DA, (ln ng/ creatinine mg/dl)</td>
<td>242.919</td>
<td>198.4(158.5-250.5)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
“We wanted to make the stress test as realistic as possible.”
Underrepresented Minorities
Death rates by race-ethnicity

Centers for Disease Control and Prevention, National Center for Health Statistics. WONDER Online Database 2014
Disparities in heart disease death rates

Black have higher heart disease death rates than white.
This has been true since 1970
The gap is not closing
Disparities in heart disease death rates
Heart disease mortality is increasing in Black men.
CVD Mortality by Ethnic Group, in California

South Asians

South Asians

- Bangladesh, Bhutan, India, Nepal, Pakistan, Sri Lanka
- 1.6 billion individuals *(one-fifth of all humans!)*

Migration:

- **1890s-1920s**: First wave, mainly from the Indian State of Punjab occurred
- **1960s**: Second wave with passage of the 1965 immigration and nationality act (INA).
  - A total of 20,000 highly skilled professionals and 25,000 physicians emigrated from India to the US.
- **1980s**: Third wave: Family reunification, allowing for parents and extended families of the settled professionals, to emigrate to the U.S.
South Asians in the United States

Total US Population: 1,678,765

- California: 314,819 (18.8%)
- New York: 251,724 (15%)
- Texas: 129,365 (15%)
- Florida: 70,740 (4.2%)
- Pennsylvania: 57,241 (3.4%)
- Virginia: 48,815 (3.4%)
- New Jersey: 169,180 (10.1%)
- Maryland: 49,909 (3%)
South Asians in the U.S.

- Asian Americans 2010 Census
  - Chinese (3.79 million)
  - Filipino (3.41 million)
  - **Indian (3.18 million)**
  - Vietnamese (1.73 million)
  - Korean (1.7 million)
  - Japanese (1.3 million)
- 2010 U.S. Census: 3,863,963 South Asians
  - 6% are age 65 or older
- Largest numbers of South Asians are in New York, New Jersey, Michigan, Texas and Illinois
Cardiovascular Disease in South Asians

High rates of CAD for South Asians
  ◦ higher hospitalization and mortality rates from CAD
  ◦ Average 10 years earlier first event than other race/ethnicities

Heart Failure Younger age of onset
  ◦ Higher risk of ventricular arrhythmias and lower risk of AF
  ◦ More ischemic etiology responsible for HF
Risk Factors - Type 2 Diabetes Mellitus

- **South Asians**
  - Higher odds of diabetes compared to whites and Latinos
  - Not significantly different from African Americans and Chinese Americans
  - Approximately 33% of participants have pre-DM, 25% DM
  - South Asians develop DM 5–10 years earlier and at a lower BMI
  - Migrant SAs more insulin-resistant than white Europeans across the life course and potentially experience β-cell exhaustion at a younger age
Traditional Risk Factors – Obesity

The Skinny-Fat Phenotype

Undermuscled in the shoulders, upper chest, arms, and upper back and back in general - what I call the "Halo" and "Wings" - which makes for more of an "A" build rather than an "X" build, a very ectomorph build for muscle mass, but...

Fat Deposits typically in the lower chest, love handles, and belly area

http://anthonymychal.com
Emerging Risk Factors

Lipoprotein (a)

- LDL-like particle and the specific apolipoprotein(a) [apo(a)], covalently bound to the apoB of the LDL like particle
- Correlated with atherogenic activity and CVD outcomes with large genetic determination
- Multiple U.S. cohorts demonstrate elevated levels in South Asians when compared to white controls
- Correlation of Lp(a) has relationship to CAD severity in South Asians\textsuperscript{23,24}
Atherosclerotic Cardiovascular Disease in South Asians in the United States: Epidemiology, Risk Factors, and Treatments

A Scientific Statement From the American Heart Association

ABSTRACT: South Asians (from Bangladesh, Bhutan, India, the Maldives, Nepal, Pakistan, and Sri Lanka) make up one quarter of the world's population and are one of the fastest-growing ethnic groups in the United States. Although native South Asians share genetic and cultural risk factors with South Asians abroad, South Asians in the United States can differ in socioeconomic status, education, healthcare behaviors, attitudes, and health insurance, which can affect their risk and the treatment and outcomes of atherosclerotic cardiovascular disease (ASCVD). South Asians have higher proportional mortality rates from ASCVD compared with other Asian groups and non-Hispanic whites, in contrast to the finding that Asian Americans (Asian Indian, Chinese, Filipino, Japanese, Korean, and Vietnamese) aggregated as a group are at lower risk of ASCVD, largely because of the lower risk observed in East Asian populations. Literature relevant to South Asian populations regarding demographics and risk factors, health behaviors, and interventions, including physical activity, diet, medications, and community guidelines, is summarized. The evidence to date is that the biology of ASCVD is complex but is no different in South Asians than in any other racial/ethnic group. A majority of the risk in South Asians can be explained by the increased prevalence of known risk factors, especially those related to insulin resistance, and no unique risk factors in this population have been found. This scientific statement focuses on how ASCVD risk factors affect the South Asian population in order to make recommendations for clinical strategies to reduce disease and for directions for future research to reduce ASCVD in this population.

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On behalf of the American Heart Association:
Council on Epidemiology and Prevention; Cardiovascular Disease and Stroke in Women and Special Populations Committee of the Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Stroke Council
Conclusion

- Sex, race, and ethnicity matter in cardiovascular disease
- Heart disease is the No. 1 killer of women, and its signs and symptoms may differ from men.
- Many underrepresented populations are at higher risk for CHD
- Understanding the unique risk factors, pathophysiology, and response to therapy for patients at greatest risk will greatly improve cardiovascular outcomes
Why we need to prevent cardiovascular disease

If we keep on doing what we've always done... we'll keep on getting what we've always gotten...