Stable Ischemic Heart Disease in the Female Patient

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Atlanta, Georgia

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Sex Differences In Coronary Artery Disease - Where are We in 2016?

- Sex differences in presentation, diagnostic evaluation, management, & clinical outcomes for women with SIHD

- Recent, 30% CVD mortality decline for women
  - Increased awareness, focused clinical research, & application of guideline-directed care
  - However, declines for women, across all ages, are far less than that reported for men

**CVD Mortality Trends for Women & Men**

Sex Paradox in Chest Pain

**Angiographic Findings**
- Less Obstructive CAD
- Preserved Systolic Function / Yet more HF

**Clinical Comorbidity**
- Older, More Diabetes, HTN...Risk Factor Clustering
- More Anginal-Equivalent/Atypical Symptoms (e.g., Dyspnea)
- Higher Brain Natriuretic Peptide, C Reactive Protein

**Clinical Outcomes**
- Worsening CVD Outcomes

Guiding Principles of Radiation Safety

Justification

Optimization

American College of Cardiology Appropriate Use Criteria

<table>
<thead>
<tr>
<th>Indication</th>
<th>Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation of ischemic Equivalent (Non-Acute)</td>
<td>Nuc</td>
</tr>
<tr>
<td>Low pretest probability of CAD</td>
<td>I(5)</td>
</tr>
<tr>
<td>ECG Interpretable AND able to exercise</td>
<td>A(7)</td>
</tr>
<tr>
<td>Low pretest probability of CAD</td>
<td>A(7)</td>
</tr>
<tr>
<td>ECG uninterpretable OR unable to exercise</td>
<td>A(9)</td>
</tr>
<tr>
<td>Intermediate pretest probability of CAD</td>
<td>A(7)</td>
</tr>
<tr>
<td>ECG Interpretable AND able to exercise</td>
<td>A(7)</td>
</tr>
<tr>
<td>Intermediate pretest probability of CAD</td>
<td>A(7)</td>
</tr>
<tr>
<td>High pretest probability of CAD</td>
<td>A(7)</td>
</tr>
<tr>
<td>Regardless of ECG interpretability and ability to exercise</td>
<td>A(7)</td>
</tr>
</tbody>
</table>

I: Inappropriate; U: Uncertain; A: Appropriate

Understanding Risk-Benefit Ratio – Improve Patient Safety

- Projected Risk of Radiation is Low
- Greater Projected Risk in Women & in Younger Individuals
- Apply Risk-Benefit Decision Making
  - Test Only Appropriate Indications
  - Engage Shared Decision Making
- NIH-NHLBI Symposium: Patient-Centered Imaging - Shared Decision Making for Cardiac Imaging Procedures

Projected Incident Cancer per 10,000 Women

Coronary Mortality in Symptomatic Women With Ischemia

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-54</td>
<td>12.1</td>
<td>5.6</td>
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<tr>
<td>55-64</td>
<td>2.4</td>
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<td>1.9</td>
<td>1.7</td>
<td>1.8</td>
<td>1.7</td>
</tr>
<tr>
<td>75-84</td>
<td>2.0</td>
<td>1.8</td>
<td>1.7</td>
<td>1.9</td>
<td>2.0</td>
<td>1.9</td>
</tr>
<tr>
<td>85-89</td>
<td>1.8</td>
<td>1.7</td>
<td>1.7</td>
<td>1.9</td>
<td>2.0</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Ambulatory pts. from Finland ages 45-89 yrs. w/ No Hx CAD, (56,441 women & 34,885 men)

Source: Hemingway JAMA 2006; 295:1404-1411.

Viviany R. Taqueti, MD, MPH; Sharmila Dorbala, MD, MPH; David Wolinsky, MD; Brian Abbott, MD; Gary V. Heller, MD, PhD; Timothy Bateman, MD; Jennifer H. Mieres, MD; Lawrence M. Phillips, MD; Nanette K. Wenger, MD; Leslee J. Shaw, PhD
Prognostic Accuracy of SPECT MPI in Women

Risk-Adjusted Mortality Across Diverse Racial & Ethnic Subsets of Women Undergoing SPECT MPI

Source: Shaw JACC 2005.

Risk-Adjusted Cumulative Incidence of All-Cause Mortality

*N=2,225 women referred for SPECT-MPI followed by a mean period of 3.7 ± 1.4 years

Source: Ceci J Am Coll Cardiol Img 2011;4:880-888.
PET Prognosis Registry: Annual CAD Mortality for Stress Rb-82 PET

Women (n=2,904)  Men (n=3,133)

*% Myocardium = Summed Stress Score / (17*4)

Source: Kay JACC 2013 Nov 12;62(20):1866-76.
Coronary Flow Reserve (CFR) by Rb-82 PET

Normal

3 VD

MBF: Myocardial Blood Flow
Coronary Flow Reserve by Rb-82 PET Further Defines Microvascular Dysfunction

Normal

Diffuse / Mild CAD

Reduced Coronary Flow Reserve (CFR) on Rb-82 PET - Women Have More Nonobstructive CAD

Among Pts. with Low CFR, Women Have More Nonobstructive CAD

Women with Low CFR – Higher CAD Event Risk

*C. Unadjusted

D. Adjusted*

*Adjusted for race, pretest risk score, prior MI or PCI, diabetes, LVEF, LV ischemia, CAD severity, & early revascularization.

➔Underscores the importance of diffuse atherosclerosis & microvascular dysfunction as targets for CV risk reduction

Source: Taqueti ACC 2015.
Patient with symptoms and/or signs of ischemic heart disease (IHD)

Does patient have obstructive coronary artery disease (CAD) or nonobstructive CAD?

NONOBSURCTIVE CAD

Prevalence Women > Men
Predominantly younger, middle-aged women
Preserved LV systolic function
Possible plaque erosion with subsequent thrombus formation
Often multiple mechanisms for ischemia
Associated with heightened risk for adverse outcomes

Guideline-specific diagnosis, preventive, and/or treatment strategies
Nonobstructive CAD requires better recognition and investigation
Need to develop effective prevention, diagnosis, and treatment approaches

Angiographic CAD in Men and Women With Stable Chest Pain

11,223 ps Referred for Coronary Angiography From 1998–2009

CONFIRM Registry: COronary CTA EvaluatioN For Clinical Outcomes: An InterNational Multicenter Registry

Dynamic registry of >32,000 consecutive pts
1) 12 sites (US, Canada, Germany, Switzerland, Italy, & S. Korea)
2) +6 sites (Miami, California, Vancouver, NY, Innsbruck, Seoul)
3) +3 sites (Italy, Portugal, Poland)

Diagnosis of Obstructive CAD in Women

Mild-Modest Correlation Between Functional & Anatomic Tests

Myocardial Ischemia ≠ Anatomic Stenosis
Mechanisms of Ischemia in Symptomatic Women

Mechanisms of Myocardial Ischemia

*Epicardial Coronary Arteries*
- Atherosclerosis
  - Stable plaque
  - Vulnerable plaque
  - Plaque disruption
  - Reduction in coronary flow reserve
  - Thrombosis
  - Demand ischemia
  - Acute coronary syndromes/infarction

- Vasospastic Disease
  - Focal/Transient Vasospasm
  - Prinzmetal Angina
  - Persistent Vasospasm

- Dissection
  - Intimal tear
  - Partial obstruction
  - Clot & flap completely occluding artery
  - Acute coronary syndromes

*Coronary Microcirculation*
- Microvascular Dysfunction
  - Impairs coronary physiology and myocardial blood flow in subjects with risk factors
  - Contributes to myocardial ischemia
  - Induces severe acute ischemia ‘Takotsubo’

Source: Sanghavi Curr Atheroscler Rep 2015;17:34
Coronary Macro- and Micro-circulation

Stenosis-Ischemia Relationship is Variable

IWOS: Ischemia WithOut Stenosis
SWOI : Stenosis WithOut Ischemia

NIH Women’s Ischemia Syndrome Evaluation: Chest Pain + No Obstructive CAD

N = 100 Women with No Stenosis

79% Prevalence of Atherosclerotic Plaque

Source: Khuddus J Interven Cardiol 2010;23:511-519.
Understanding Relationship of Atherosclerotic Plaque with Myocardial Ischemia

**Measures of Positive Remodeling (PR) & Low Attenuation Plaque (LAP)**

<table>
<thead>
<tr>
<th>Angiographic Diameter Stenosis Severity, %</th>
<th>FFR</th>
<th>No. of Lesions (% in Subgroup) (% in Entire Cohort)</th>
<th>Possible Histologic Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt; 0.80</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>50-70</td>
<td>&gt; 0.80</td>
<td>402 (65) [13]</td>
<td>2FNP with moderate luminal stenosis</td>
</tr>
<tr>
<td></td>
<td>≤ 0.80</td>
<td>218 (35) [18]</td>
<td>2FPP with moderate luminal stenosis</td>
</tr>
<tr>
<td>71-90</td>
<td>&gt; 0.80</td>
<td>104 (20) [8]</td>
<td>2FNP with moderate to severe luminal stenosis</td>
</tr>
<tr>
<td></td>
<td>≤ 0.80</td>
<td>450 (40) [33]</td>
<td>2FPP with moderate to severe luminal stenosis</td>
</tr>
</tbody>
</table>

**Events in Patients with <75% Stenosis**

NIH-NHLBI PROspective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) Trial: Prognosis in Women & Men by CCTA & Stress Test Findings

Women w/ Positive CCTA Higher Relative Hazard for Events vs. Positive Stress Test (p=0.028)

HR 5.86, p<0.001
HR 2.27, p=0.011

Working Model of Imaging Targets Identifying IHD Risk in Women

Interplay of Risk Across Imaging Target Types
- May Necessitate Multimodality Approaches

Nonobstructive High Risk Atherosclerotic Plaque
Stenosis 31-49%

High Risk Atherosclerotic Plaque
- Plaque burden (volume, area)
- Plaque composition (mixed, non-CAC, CAC)
- “Lipid dense” intra-plaque core
- Arterial remodeling (+, -, interm.)

Flow / Perfusion /WM Δs

* Early Manifestations (Subendo. Ischemia)
* Near- & Long-term Prognosis
...

High Risk Atherosclerotic Plaque
- Unknown Factors
- ? Metabolic Alterations
- CMD Factors
- ...

Source: Baldassarre J Am Coll Cardiol Img 2016;9:603-617.
CAD Imaging in Women - 2016

Angiographic Findings
More Nonobstructive CAD
Potential for Atherosclerotic Plaque to Cause Ischemia

Nuclear MPI in Women
• Considerable Evidence Supports the Utility of SPECT & PET MPI
• Impaired Coronary Flow Reserve May Detect Underlying Vascular Abnormalities Including in the Microvasculature
• Use of CCTA Detects Stenosis + Plaque

Advantages:
1. From typically acquired CCTA
2. No additional image acquisition
   – No excess radiation
3. No modification to imaging protocols
   – Prospective or retrospective ECG gating
4. No administration of adenosine or other medications

Disadvantages:
1. High Cost ($1,200-$1,500)
2. Requires Remote Read (~6-8 hrs)
3. Good Image Quality

$\text{FFR}_{\text{CT}} = 0.72$
(can select any point on model)
Mild Nonobstructive Stenosis & Adverse Events

2,583 patients with CCTA ≤50% stenosis (Follow-up: 3.1 years)

>6-fold higher mortality for patients with 3-vessel mild CAD

Age- and Gender-Stratified Prognosis
23,854 patients w/o known CAD, 2.3 year f/u

CONFIRM Registry: COronary CTA Evaluation For Clinical Outcomes: An International Multicenter Registry
The Stenosis-Ischemia Relationship is Far From Perfect

IWOS: Ischemia WithOut Stenosis
SWOI : Stenosis WithOut Ischemia

American Heart Association Statement:
Noninvasive Testing in the Evaluation of Women with Suspected Ischemic Heart Disease

Index IHD Risk Estimate

No Resting ST Segment Abnormalities

Initial ETT Strategy

Assess Routine ADL or DASI

Not Limited

Abnml or Indeterminate Ex ECG

Selective Imaging Strategy

Limited

Resting ST Segment Abnormalities or Functional Disability

Initial Imaging Strategy

Stress Imaging

Intermediate-High IHD Risk

CCTA

Intermediate IHD Risk

Standardized Reporting of Low to High Risk Abnormalities

Low Risk

Abnormal but Non-High Risk

High Risk

Initial SIHD Management Per Clinical Practice Guidelines

ADL=Activities of Daily Living; DASI: Duke Activity Status Index
Source: Mieres Circulation 2014;130:350-379.
Comparison of FFR Between Women & Men

Suggests that A Higher Cutoff of 0.80 May be Preferable for Women

Source: Jing Circ Cardiovasc Interv 2013;6:662-670
An FFR-guided strategy resulted in similar risk reduction for death, MI, & repeat revascularization in women & men.

Comparison of FFR Between Women & Men

Suggests that A Higher Cutoff of 0.80 May be Preferable for Women

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An FFR-guided strategy resulted in similar risk reduction for death, MI, & repeat revascularization in women & men.

**FFR\textsubscript{CT} Examples**

CCTA | FFR\textsubscript{CT} | Invasive angiography | FFR

>50% diameter stenosis | FFR\textsubscript{CT} 0.74 → Ischemia | >50% diameter stenosis | FFR 0.74 → Ischemia

>50% diameter stenosis | FFR\textsubscript{CT} 0.85 → No ischemia | >50% diameter stenosis | FFR 0.84 → No Ischemia
FFR Can Now Be Derived from CCTA (FFR\textsubscript{CT})

1. **Image-Based Modeling** – Segmentation of patient-specific arterial geometry
2. **Heart-Vessel Interactions** – Allometric scaling laws relate caliber to pressure and flow
3. **Microcirculatory resistance** – Morphometry laws relate coronary dimension to resistance
4. **Left Ventricular Mass** – Lumped-parameter model couples pulsatile coronary flow to time-varying myocardial pressure
5. **Physiologic Conditions** – Blood as Newtonian fluid adjusted to patient-specific viscosity
6. **Induction of Hyperemia** – Compute maximal coronary vasodilation
7. **Fluid Dynamics** – Navier-Stokes equations applied for coronary pressure

Which Women May Benefit from FFR_{CT}?

Symptomatic patients undergoing initial testing by CCTA

- Apical lateral ischemia
- High grade LAD stenosis
- High grade LCx stenosis
- No sig. RCA dx

Symptomatic patients undergoing CCTA with equivocal or discordant stress testing

Patients with equivocal CCTA

Patients with ischemia and multiple stenoses

- Apical lateral ischemia
- High grade LAD stenosis
- High grade LCx stenosis
- No sig. RCA dx
**FFR_{CT} for Intermediate Stenoses**

<table>
<thead>
<tr>
<th>FFR_{CT}</th>
<th>Accuracy (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCTA stenosis ≥50%*</td>
<td>56.1 (43.3-68.3)</td>
<td>90.3 (74.2-98.0)</td>
<td>25.7 (12.5-43.3)</td>
<td>51.9 (37.8-65.7)</td>
<td>75.0 (42.8-94.5)</td>
</tr>
<tr>
<td>FFR_{CT} ≤ 0.80 (95% CI)</td>
<td>86.4 (75.7-93.6)</td>
<td>90.3 (74.2-98.0)</td>
<td>82.9 (66.4-93.4)</td>
<td>82.4 (65.5-93.2)</td>
<td>90.6 (75.0-98.0)</td>
</tr>
<tr>
<td>FFR_{CT} ≤ 0.75 (95% CI)</td>
<td>83.3 (72.1-91.4)</td>
<td>77.3 (64.6-92.2)</td>
<td>86.4 (72.6-94.8)</td>
<td>73.9 (51.6-89.8)</td>
<td>88.4 (74.9-96.1)</td>
</tr>
</tbody>
</table>

Nonobstructive CAD in Women

- In the Setting of Symptomatic IHD, Consider The Burden of Nonobstructive CAD
  - If Stress-Induced Ischemia, May Consider CAC to Understand Plaque Burden
  - Moderate-Severe Ischemia, Nonobstructive CAD Observed in ~15-20%
- Consider Microvascular Angina in the Differential for All Women
- Reduced Coronary Flow Reserve May Further Refine Diagnostic Evaluation – Define Coronary Microvascular Dysfunction
- Treatment Evidence is Lacking But Reasonable Preventive & Symptom-Guided Care

Treatment Trials

<table>
<thead>
<tr>
<th>Small Trials</th>
<th>Mostly Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited Management Recommendations</td>
<td></td>
</tr>
</tbody>
</table>
Relative Hazard for MACE in Men & Women With Stable Angina & Nonobstructive Angiographic CAD

HRs (95% CI) for Patients with Nonobstructive CAD vs. Asymptomatic Women & Men

<table>
<thead>
<tr>
<th>MACE</th>
<th>Events, n</th>
<th>Model 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Model 2&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women/men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>Reference population</td>
<td>302/256</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Normal coronary arteries</td>
<td>156/127</td>
<td>1.34 (1.08–1.66)</td>
<td>1.50 (1.19–1.89)</td>
</tr>
<tr>
<td>Diffuse non-obstr. CAD</td>
<td>87/132</td>
<td>1.62 (1.25–2.10)</td>
<td>1.79 (1.43–2.25)</td>
</tr>
</tbody>
</table>

All-cause mortality

<table>
<thead>
<tr>
<th></th>
<th>Events, n</th>
<th>Model 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Model 2&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference population</td>
<td>356/298</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Normal coronary arteries</td>
<td>105/103</td>
<td>0.97 (0.77–1.23)</td>
<td>1.30 (1.02–1.65)</td>
</tr>
<tr>
<td>Diffuse non-obstr. CAD</td>
<td>66/95</td>
<td>1.31 (1.00–1.71)</td>
<td>1.33 (1.05–1.69)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Adjusted for Age

<sup>b</sup> Adjusted for Age, BMI, Diabetes, Smoking, & Statin / Antihypertensive Medication Use

Source: Jespersen Eur Heart J 2012;33:734-744.
Potential Evaluation Algorithm for Women with Nonobstructive CAD

Index Testing Strategy

Stress Ischemia

- Normal Coronaries
  - Rule-Out Artifact
  - Guideline-Directed Medical Therapy (GDMT) – Intensity May Vary By Extent Nonobstructive CAD
  - Consider Microvascular Angina

Mild or Diffuse Epicardial Atherosclerosis

- Consider Non-Coronal Causes*
  - ↓ PET Flow Reserve
  - High Risk for Progressive Dz

Anatomy Documented Nonobstructive CAD

- Normal Coronaries

Mild or Diffuse Epicardial Atherosclerosis

- Modify Risk with Preventive Care / Symptom-Guided Care

↓ PET Flow Reserve* - Evaluate Non-Coronal Causes 1st; Adding PET in the Setting of Normal Coronaries May be Considered in Women with Persistent CP
Cascade of Mechanisms & Manifestations of Ischemia

Exposure Time of Mismatch in Myocardial Oxygen Supply / Demand

- Near Term Prolonged
- Progressive Manifestations of Ischemia
  - Decreased Segmental Perfusion
  - Diastolic Dysfunction
  - Micro-Infarction/ Fibrosis
  - Altered Metabolism
  - ↓ Subendocardial Perfusion
  - Endothelial & Microvascular Dysfxn

Source: Fihn JACC 2012;60(24):e44-e164.
Younger Women (<55 years)

- Only 2 deaths in 829 women <55 years of age (0.2%, p=0.063)

- Target Selection of Appropriate Candidates

Source: Kay JACC 2013 Nov 12;62(20):1866-76.
### Post-Stress Testing

**Primary Endpoint (Clinical) – 1 Year**

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Direct ICA</th>
<th>Selective ICA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE (primary)</td>
<td>69 (4.6%)</td>
<td>33 (4.6%)</td>
<td>36 (4.6%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>4 (0.3%)</td>
<td>2 (0.3%)</td>
<td>2 (0.3%)</td>
<td>1.00</td>
</tr>
<tr>
<td>UA</td>
<td>17 (1.1%)</td>
<td>8 (1.1%)</td>
<td>9 (1.1%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Urgent / Emergent Revascularization</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>-</td>
</tr>
<tr>
<td>CV hospitalization</td>
<td>64 (4.3%)</td>
<td>31 (4.3%)</td>
<td>33 (4.2%)</td>
<td>1.00</td>
</tr>
<tr>
<td>CV Death</td>
<td>3 (0.2%)</td>
<td>1 (0.1%)</td>
<td>2 (0.3%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Stroke</td>
<td>4 (0.3%)</td>
<td>2 (0.3%)</td>
<td>2 (0.3%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

ICA= Invasive Coronary Angiography
Selective ICA= Index Coronary CT Angiography + Selective ICA
MACE= Major CAD Events
The CONSERVE Trial

Coronary Computed Tomographic Angiography for Selective Cardiac Catheterization Relation to Cardiovascular Outcomes and Economics


Severance Cardiovascular Hospital, Yonsei University Health System, Seoul, South Korea; Dalio Institute of Cardiovascular Imaging, Weill Cornell Medical College and New York-Presbyterian Hospital; MDDX; CARE Hospital and FACTS Foundation; Inje University, Ilsan Paik Hospital; Centro Cardiologico Monzino, IRCCS; Pusan National University Hospital; Korea University Guro Hospital; Gangneung Asan Hospital; Ajou University Hospital; Kangwon National University Hospital; Chung-Ang University Hospital; Wonju Severance Hospital; Cardiology Associates of Mobile; Gangnam Severance Hospital; Yeungnam University Hospital; Walter Reed Medical Center; Quanta Diagnostico Nuclear, Curitiba-PR; Institute of Cardiology; University of Minnesota, Minneapolis; VU Medical Center; Asan Medical Center, University of Ulsan College of Medicine; Myongji Hospital, Seonam University College of Medicine; Emory University School of Medicine
Mechanisms of Ischemia in Symptomatic Women

Mechanisms of Myocardial Ischemia

Epicardial Coronary Arteries
- Atherosclerosis
  - Stable plaque
  - Vulnerable plaque
  - Reduction in coronary flow reserve
  - Plaque disruption
  - Thrombosis
- Vasospastic Disease
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- Microvascular Dysfunction
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2,583 patients with CCTA ≤50% stenosis (Follow-up: 3.1 years)

>6-fold higher mortality for patients with 3-vessel mild CAD

Reduced Coronary Flow Reserve (CFR) on Rb-82 PET - Women Have More Nonobstructive CAD

Among Pts. with Low CFR, Women Have More Nonobstructive CAD

Proposed Pathophysiologic Link Between Abnormal Coronary Flow Reserve, Ischemia/Injury, & Outcomes

Symptomatic IHD → Reduced CFR → Microvascular Ischemia

Heart Failure/MACE → Symptom Frequency/ Stability

Low level Myocardial Injury/Fibrosis → Diastolic Dysfunction

Defining a Unique Female-Specific Profile

MACE= Major Adverse CAD Events

Sex-Differences in Trial / Registry Findings

- Understand the Statistical Power Limitations of Current Sex-Specific Evidence
- Likely Many Female Phenotypes!
- Understanding Comparative Evidence for Procedures
- As the Male Model is So Different, Is This Our Best Comparator?

Causal Inference

<table>
<thead>
<tr>
<th>Cause precedes effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause covaries with effect</td>
</tr>
<tr>
<td>Alternate explanations implausible</td>
</tr>
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Coronary Mortality in Symptomatic Women With Ischemia

Coronary Mortality Compared with Sex-Specific General Population

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<td>2.5</td>
<td>2.5</td>
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</tr>
<tr>
<td>65-74</td>
<td>1.7</td>
<td>1.8</td>
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<tr>
<td>75-84</td>
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<td>2.0</td>
<td>1.9</td>
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<tr>
<td>85-89</td>
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<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Ambulatory pts. from Finland ages 45-89 yrs. w/ No Hx CAD, (56,441 women & 34,885 men)

Source: Hemingway JAMA 2006; 295:1404-1411.
Women with Low CFR PET Have Increased CAD Events

Unadjusted Survival  Adjusted Survival*

*Adjusted for Race, Pretest Risk, Prior MI/PCI, Diabetes, LVEF, LV Ischemia, Angiographic Score Severity, & Early PCI/CABG

Underscores Importance of Diffuse Atherosclerosis & Microvascular Dysfunction in Women

Source: Taqueti Circulation (in press).
The Optimal Approach to Evaluation of CAD
Both Anatomy and Physiology

(1) Anatomic CAD concordant with ICA

(2) Effectively Prognostic Outcomes

(3) Triage and treat appropriately

(4) Identify lesions that cause ischemia.

(5) Plan revascularization strategy
NIH-NHLBI WISE: Diffuse Atherosclerosis - Common Finding - Chest Pain + No Obstructive CAD

N = 100 Women
79% Prevalence of Atherosclerosis & Preserved Lumen

Source: Khuddus J Interven Cardiol 2010;23:511-519.
## Advancing Our Understanding of Atherosclerotic Plaque & Myocardial Ischemia

<table>
<thead>
<tr>
<th>Angiographic Diameter Stenosis Severity, %</th>
<th>FFR</th>
<th>No. of Lesions (% in Subgroup) [% in Entire Cohort]</th>
<th>Possible Histologic Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt; 0.80</td>
<td>0</td>
<td>2FNP with moderate luminal stenosis</td>
</tr>
<tr>
<td>50-70</td>
<td>&gt; 0.80</td>
<td>407 (65) [33]</td>
<td>2FPP with moderate luminal stenosis</td>
</tr>
<tr>
<td></td>
<td>≤ 0.80</td>
<td>218 (35) [18]</td>
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</tr>
<tr>
<td>71-90</td>
<td>&gt; 0.80</td>
<td>104 (20) [8]</td>
<td>2FNP with moderate to severe luminal stenosis</td>
</tr>
<tr>
<td></td>
<td>≤ 0.80</td>
<td>409 (80) [23]</td>
<td>2FPP with moderate to severe luminal stenosis</td>
</tr>
</tbody>
</table>

Source: Ahmadi JAMA Cardiol 2016;54:1561-75.
NIH-NHLBI WISE: Abnormal Coronary Flow Reserve Prognosis in Symptomatic Women with Nonobstructive CAD

Nonobstructive CAD & 1-Yr Risk of MI

N=16,775  
(n=1,310 Women)

<table>
<thead>
<tr>
<th></th>
<th>No. of Events</th>
<th>No. of Patients</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td><strong>Obstructive CAD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-Vessel or left main</td>
<td>137</td>
<td>6036</td>
<td>19.5 (9.9-38.2)</td>
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<tr>
<td>2-Vessel</td>
<td>110</td>
<td>5452</td>
<td>16.5 (8.1-33.7)</td>
</tr>
<tr>
<td>1-Vessel</td>
<td>101</td>
<td>9411</td>
<td>9.0 (4.2-19.0)</td>
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<tr>
<td><strong>Nonobstructive CAD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-Vessel</td>
<td>6</td>
<td>1133</td>
<td>4.5 (1.6-12.5)</td>
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<tr>
<td>2-Vessel</td>
<td>13</td>
<td>2605</td>
<td>4.6 (2.0-10.5)</td>
</tr>
<tr>
<td>1-Vessel</td>
<td>10</td>
<td>4646</td>
<td>2.0 (0.8-5.1)</td>
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<tr>
<td>No apparent CAD</td>
<td>8</td>
<td>8391</td>
<td>1 [Reference]</td>
</tr>
</tbody>
</table>

Source: Maddox JAMA 2014;312:1754-1763.
Angiographic CAD in Men and Women With Stable Chest Pain

11,223 patients referred for coronary angiography from 1998–2009

CHD Mortality 1979 to 2011
Age Subsets <55, 55 to 64, & ≥65 years