Stable Ischemic Heart Disease

Ivan Anderson, MD
RIH VH Cardiology
Outline

• Review of the vascular biology of atherosclerosis
• Why not just cath everyone with angina?
• Medical management of ischemic cardiomyopathy
• Who is appropriate for an interventional strategy (angiography +/- percutaneous coronary intervention)
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LDL is Oxidized in the Vascular Wall and its Oxidized Constituents are Released by Lp-PLA₂
Atheroma Formation
Vascular Injury and Repair and EPCs

- Smoking
- Hypertension
- Hypercholesterolemia
- Age
- Diabetes

- Vascular injury
- EPCs
- Vasa Vasorum
- DES
- Inflammation & oxidative stress

Endothelial dysfunction: The risk of the risk factors
Epigenetic Approach to Epidemiology.

A Genomewide association studies

Example 1. Detected genetic coding variant
- Disease phenotype (e.g., rheumatoid arthritis)
- Cooperative or disease-risk gene
- Mechanistic connection

Example 2. Detected heritable genetic variant (SNP)
- Disease phenotype (e.g., diabetes)
- Cooperative or disease-risk gene

B Epigenome-wide association studies

Environmental exposures and aging, meQTL
- Disease phenotype (e.g., diabetes and rheumatoid arthritis)
- Hypothetical disease-risk gene
- Hypothetical disease-risk gene

C Integrated genomewide and epigenome-wide association studies

Example 1. Environmental exposures and aging, SNP, meQTL
- Hypothetical disease-risk gene
- Hypothetical disease-risk gene

Example 2. Haplotype block 1, Haplotype block 2
- Hypothetical disease-risk gene
- Hypothetical disease-risk gene
- Hypothetical disease-risk gene

D Cancer

Environmental exposures and aging, SNP, meQTL or CmMe
- Somatic genetic variant
- Hypothetical disease-risk gene

Fatty Deposits are in Orange and Red

Thoracic Aorta

Abdominal Aorta

Right Coronary Artery

Increasing Age from teens to mid 30s

JAMA 281:727, 1999
Obstructive Lesions Have Evidence of Multiple Plaque Rupture Events Histologically

Stenosed Coronary Artery

Plaque Rupture Events

A

Number of prior ruptures, healed rupture sites

Mean % stenosis

Circulation. 2001;103:934-940
Coronary Flow with Normal Epicardial Coronary Arteries and in Disease

Large ability to change coronary flow as pressure elevates

Limited ability to change coronary flow with high-grade stenosis
Dog Experiment

Am J Cardiol 1974; 33(1):87-94
Pressure Drop as a Function of % Stenosis

Am J Cardiol 1974; 33(1):87-94
Exposure time of mismatch in myocardial oxygen supply/demand
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HEART STENT ALERT
New research reveals this common procedure on coronary arteries is often unnecessary

$5.6 BILLION
The projected global market for stents in 2020

$30,000
The average cost of the procedure, before insurance

THE COMMON STENT
is made of stainless steel or a cobalt-chromium alloy.

15.45 MILLIMETERS
The average length of a bare metal stent (0.6 inches)

850,000 PATIENTS
The number who receive stent implants
JAMA 2011: 12% of PCI Inappropriate

Figure 1. Table 3. Key Variables in Classifying Appropriateness for Nonacute Percutaneous Coronary Interventions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (N=144737)</th>
<th>Appropriate (n=72911)</th>
<th>Uncertain (n=54988)</th>
<th>Inappropriate (n=16833)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No symptoms</td>
<td>20,607 (14.2)</td>
<td>4305 (5.9)</td>
<td>7239 (13.2)</td>
<td>9063 (53.8)</td>
<td></td>
</tr>
<tr>
<td>CCS class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>I</td>
<td>17,709 (12.2)</td>
<td>4407 (6.0)</td>
<td>11,136 (20.3)</td>
<td>2,166 (12.9)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>48,853 (33.8)</td>
<td>13,606 (18.7)</td>
<td>29,890 (54.4)</td>
<td>5,337 (31.8)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>45,486 (31.4)</td>
<td>39,636 (54.4)</td>
<td>5,675 (10.3)</td>
<td>175 (1.0)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>12,062 (8.3)</td>
<td>10,957 (15.0)</td>
<td>1,048 (1.9)</td>
<td>77 (0.5)</td>
<td></td>
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<tr>
<td>Noninvasive ischemia evaluation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>29,665 (20.1)</td>
<td>7,312 (14.0)</td>
<td>10,779 (35.6)</td>
<td>11,574 (71.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>39,049 (26.9)</td>
<td>17,757 (34.0)</td>
<td>16,691 (55.1)</td>
<td>4,601 (28.4)</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>29,971 (20.4)</td>
<td>27,158 (52.0)</td>
<td>2,813 (9.3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>None performeda</td>
<td>48,052</td>
<td>20,684</td>
<td>24,705</td>
<td>663</td>
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</tr>
<tr>
<td>No. of antianginal medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>0</td>
<td>40,549 (28.0)</td>
<td>15,726 (21.5)</td>
<td>17,697 (32.2)</td>
<td>7,126 (42.3)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>65,906 (45.5)</td>
<td>28,696 (39.4)</td>
<td>28,196 (51.3)</td>
<td>9,015 (53.5)</td>
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</tr>
<tr>
<td>2</td>
<td>31,547 (21.8)</td>
<td>23,311 (32.0)</td>
<td>7,626 (13.9)</td>
<td>607 (3.8)</td>
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<tr>
<td>&gt;2</td>
<td>6,735 (4.7)</td>
<td>5,179 (7.1)</td>
<td>1,466 (2.7)</td>
<td>90 (0.5)</td>
<td></td>
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<tr>
<td>Coronary artery stenoses</td>
<td>496</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1</td>
<td>72,219 (49.0)</td>
<td>29,851 (40.9)</td>
<td>31,849 (57.9)</td>
<td>9,519 (62.5)</td>
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<tr>
<td>2</td>
<td>47,792 (33.0)</td>
<td>24,469 (33.6)</td>
<td>18,030 (32.8)</td>
<td>5,323 (31.4)</td>
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<tr>
<td>3</td>
<td>24,726 (17.1)</td>
<td>18,591 (25.5)</td>
<td>5,100 (9.3)</td>
<td>1,026 (6.1)</td>
<td></td>
</tr>
<tr>
<td>Presence of proximal LAD stenosis</td>
<td>496</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
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<tr>
<td>1</td>
<td>38,554 (26.6)</td>
<td>28,168 (38.6)</td>
<td>9,379 (17.1)</td>
<td>1,017 (6.0)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CCS, Canadian Cardiovascular Society; LAD, left anterior descending artery.
*These percutaneous coronary interventions were matched to indications in the appropriate use criteria (18-21 or 46-47) that did not require prior noninvasive stress evaluation.

499,676 PCIs (978 sites) included in hospital-level analysis
Potential Harm with Revascularization

- CABG or PCI should not be performed with the sole intent to improve survival in patients with stable ischemic heart disease with:
  - Insignificant coronary stenosis (<70% or FFR > 0.80)
  - Only mild ischemia on non-invasive testing or subtend only a small area of viable myocardium
  - Involve only the RCA or Circumflex
Nuclear Substudy of the COURAGE Trial – Improved Survival with >5% Ischemia Reduction

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**Percutaneous Coronary Intervention + Optimal Medical Therapy**

*n=159*

- 33.3% with ≥5% Ischemia Reduction
  - *p=0.0004*

- 8.2% (7.2%-9.3%)
  - *p=0.63*

- 5.5% (4.7%-6.3%)

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**Optimal Medical Therapy**

*n=155*

- 18.9% with ≥5% Ischemia Reduction
  - *p<0.0001*

- 8.6% (7.5%-9.8%)

- 8.1% (6.9%-9.4%)

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Changes by treatment were adjusted by index ischemia. Dotted lines indicate no significant reduction in ischemia. Solid lines indicate ≥5% reduction in myocardial ischemia.

**Stent Group**

**Medical Rx**

*Circulation. 2008;117:1283-1291*
Long-Term Survival with CABG, PCI, and Medical Therapy
Long-Term Survival with CABG, PCI, and Medical Therapy

<table>
<thead>
<tr>
<th>Coronary Anatomy</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Stenoses ≥ 75%</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Number of Stenoses ≥ 95%</td>
<td>0</td>
<td>1</td>
<td>0-1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Any LAD Location</td>
<td>±</td>
<td>N</td>
<td>±</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>≥ 75% Stenosis Proximal LAD</td>
<td>N</td>
<td>N</td>
<td>±</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>≥ 95% Stenosis Proximal LAD</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

≥ 95% Left Main Stenosis

Relative Prognostic Weight

No Coronary Disease

Long-Term Survival with CABG, PCI, and Medical Therapy

Least Blockages

Most Blockages

5%

20%

25+%

Endothelial Dysfunction After Stenting
Risk of Mortality with Dual Antiplatelet Therapy

~5% ↑ in mortality w DAPT
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Determinants of Myocardial Oxygen Demand
Medical Therapy – Anti-anginals

• Beta blocker: 3 years after ACS, every with EF ≤40%, possibly lifelong (potent anti-anginal)
• Calcium channel blockers (DHB and non-DHB): for symptom relief
• Long-acting nitrates: for symptom relief
• Sublingual nitroglycerin for immediate relief
• Ranolazine with or without beta blockers
• External counterpulsation (EECP)
  • (DHB = dihydropyridine)
Medical Therapy – Other

• Aspirin: lifelong, 75-162 mg PO daily
• Plavix (clopidogrel) 75 mg PO daily if ASA allergic
• ACE-I: esp if
  – DM
  – EF ≤ 40%
  – Hypertension
  – CKD

Circulation. 2012;126:e354-e471
Treat Co-morbidities

• Smoking cessation
• Diet
• Exercise
Class III (Can Cause Harm)

- Estrogen in postmenopausal women
- Vitamin C, E, beta-carotene
- Treatment of elevated homocysteine with folate, B6 or B12
- Chelation therapy
- Garlic, CoQ10, selenium, chromium
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Cath ‘em

• ≥ 1 significant coronary stenosis and angina despite maximal medical therapy or contraindication to medical therapy

• High-risk test characteristics
  – > 5% area of ischemia on nuclear stress test
  – Large, reversible anterior defect
  – Depressed left ventricular ejection fraction
  – High risk based on score calculators (e.g. EuroScore)
<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>Hazard ratio (95% CI)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 1 year increment)</td>
<td>1.03 (1.01 to 1.05)</td>
<td>0.001</td>
</tr>
<tr>
<td>Sex (female v male)</td>
<td>1.19 (0.79 to 1.79)</td>
<td>0.40</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.40 (1.55 to 3.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.12 (1.29 to 3.48)</td>
<td>0.002</td>
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<tr>
<td>Hyperlipidaemia</td>
<td>1.00 (0.63 to 1.58)</td>
<td>0.99</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>1.53 (1.00 to 2.36)</td>
<td>0.05</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>3.24 (1.72 to 6.13)</td>
<td>0.002</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>2.98 (1.98 to 4.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptom severity:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II versus class I</td>
<td>2.34 (1.37 to 4.00)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Class III versus class I</td>
<td>3.44 (1.80 to 6.55)</td>
<td></td>
</tr>
<tr>
<td>Symptom duration &gt;6 months</td>
<td>0.60 (0.39 to 0.94)</td>
<td>0.03</td>
</tr>
<tr>
<td>Signs of heart failure</td>
<td>2.67 (1.56 to 4.57)</td>
<td>0.001</td>
</tr>
<tr>
<td>Body mass index &gt;30</td>
<td>0.82 (0.49 to 1.37)</td>
<td>0.43</td>
</tr>
<tr>
<td>Tertiary education</td>
<td>0.78 (0.40 to 1.52)</td>
<td>0.46</td>
</tr>
<tr>
<td>Investigative variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>1.50 (0.66 to 3.43)</td>
<td>0.34</td>
</tr>
<tr>
<td>Q wave</td>
<td>2.37 (1.38 to 4.06)</td>
<td>0.002</td>
</tr>
<tr>
<td>ST or T wave changes</td>
<td>2.26 (1.50 to 3.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischaemic ECG changes†</td>
<td>2.27 (1.50 to 3.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Result of individual stress tests:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive exercise ECG‡ (n=2299)</td>
<td>1.44 (0.80 to 2.61)</td>
<td>0.22</td>
</tr>
<tr>
<td>Positive stress echocardiogram‡ (n=119)</td>
<td>1.24 (0.24 to 6.40)</td>
<td>0.80</td>
</tr>
<tr>
<td>Positive perfusion scan‡ (n=420)</td>
<td>3.55 (0.77 to 16.47)</td>
<td>0.07</td>
</tr>
<tr>
<td>Result of any stress test‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive test</td>
<td>1.50 (0.82 to 2.73)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No test done</td>
<td>4.42 (2.50 to 7.82)</td>
<td></td>
</tr>
<tr>
<td>Echocardiography (before events):</td>
<td></td>
<td></td>
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<tr>
<td>Abnormal left ventricular function†</td>
<td>5.21 (3.19 to 8.49)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Euro Heart Score
Oh, crap! Was that TODAY?
Questions
**STEP 1**
Inflation initiates retrograde pulse wave

**STEP 2**
Inflation of lower thigh cuffs 50ms later

**STEP 3**
Inflation of upper thigh cuffs 50ms later

**STEP 4**
Deflation facilitates cardiac unloading
Diastolic Augmentation
↑ Coronary Perfusion

Unassisted Systole

Assisted Systole

Unassisted Aortic End-Diastolic Pressure

Balloon Inflation

mm Hg
Mechanisms of Improved Vascular Endothelial Function with EECP

- Increased coronary perfusion pressure
- Decreased peripheral resistance
- Recruitment of collaterals
- Attenuation of oxidative stress and proinflammatory cytokines
- Promotion of angiogenesis and vasculogenesis
- Peripheral training effect
Endothelial dysfunction and Atherosclerosis

- The Endothelial Organ
  - One of the largest organs in the body (weighs 1.8 kg in a 70 kg person, maybe 2nd to the skin)
  - A 70 kg person has ~ 1 trillion endothelial cells
  - The endothelial surface is the size of ~ 6 tennis courts