CORONARY ARTERY DISEASE: PATHOPHYSIOLOGY AND PRIMARY PREVENTION

BEN HUDSON

9/16/17
OBJECTIVES

• Explain the basics of the pathophysiology of CAD

• Identify risk factors and use them to predict risk of symptomatic CAD.

• Appropriate selection of non-invasive testing to further risk stratify asymptomatic patients without CAD.

• Identify effective therapies for primary prevention of CAD.
PATHOPHYSIOLOGY

Abdominal Aorta

Age, 15-18 yr (n = 568)

Age, 19-24 yr (n = 692)

Age, 25-29 yr (n = 793)

Age, 30-34 yr (n = 610)

Prevalence of Fatty Streaks, %

Prevalence of Raised Lesions, %

Right Coronary Artery

Age, 15-18 yr (n = 568)

Age, 19-24 yr (n = 692)

Age, 25-29 yr (n = 793)

Age, 30-34 yr (n = 610)

Prevalence of Fatty Streaks, %

Prevalence of Raised Lesions, %
PATHOPHYSIOLOGY

• This is not a new disease - plaques seen in Egyptian mummies.

• This is not a disease of the elderly - it starts in our teenage years.

• Plaques may not grow in a continuous fashion but may grow in “bursts”.

• Most MI’s result from lesions that do not limit flow.

• This is a disease that is still not fully understood - Why plaques form where they do, complex interplay of cell signaling, why/when plaques rupture.
Arteries have a trilaminar structure

- **Intima** - endothelial cells separated by medial layer by an internal elastic lamina. In adults there is often some thickening to include connective tissue and smooth muscle cells.

- **Media** - Concentric layers of smooth muscles cells interwoven with an elastin-rich matrix. It is bordered by the internal and external elastic lamina.

- **Adventitia** - loosely arranged collagen connective tissue. Cells are less common than other layers and are mostly fibroblasts and mast cells. Vaso vasorum and nerve endings are typically in the adventitia.
ARTERY STRUCTURE

NORMAL ARTERIAL WALL

ADVENTITIA

MEDIA:
- External elastic membrane
- Smooth muscle

INTIMA:
- Internal elastic membrane
- Endothelium

Diagram showing layers of an artery, including the adventitia, media, intima, and endothelium.
PATHOPHYSIOLOGY

- Lesion locality

- The spatial heterogeneity is difficult to explain

- Common locations of lesions include proximal portions of vessels after branch points or bifurcations suggest a hemodynamic cause.

- Others have suggested atheromas develop from being leiomyomas of the artery wall.

- Angiogenesis - plaque microcirculation
PATHOPHYSIOLOGY
PATHOPHYSIOLOGY

- MI
  - Most MI’s (2/3) occur fracture of a plaque’s fibrous cap.
  - Superficial erosion is the second most common cause of MI (25%, more common in women than men).
  - Most plaque disruptions do not cause MI.
  - It is difficult to identify the vulnerable or high-risk plaques
PATHOPHYSIOLOGY

- Risk factors and atherogenesis
  - Smoking - promotes endothelial injury, adversely effects endothelial function and promotes platelet adhesion and monocyte adhesion.
  - Diabetes - thought to enhance monocyte adhesion to the endothelium. Also reduces endothelial function and promotes a pro-thrombotic state.
  - Hypertension - damages endothelial cells which promotes lipid accumulation and stimulates suboptimal smooth muscle proliferation.
  - Hyperlipidemia - excess LDL is available to initiate atherosclerosis.
PRIMARY PREVENTION

• Why do we screen?
  
  • Ischemic heart disease is the #1 killer in America
  
  • Nearly half of men that reach middle age and a third of women will have symptomatic CAD in their lifetime.
    
    • Mortality rates and age-adjusted CAD rates have actually been on the decline but number of new cases is unchanged
      
      • Actual cases of CAD has remained stable.

• We have treatment options to decrease risk of developing symptomatic CAD.
PRIMARY PREVENTION

• When should we start screening?
  • Guidelines say we should assess traditional risk factors starting at age 20.
  • Estimate 10 year risk starting at age 40.
  • Estimate lifetime risk risk starting at age 20.
PRIMARY PREVENTION

- Traditional risk factors
  - Smoking
  - Diabetes
  - Hypertension
  - Hyperlipidemia
**PRIMARY PREVENTION**

- Traditional risk factors - it's complicated...

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**Table 1. Men and Women With at Least 1 Clinically Elevated Major CHD Risk Factor by Cohort, CHD Outcome, Sex, and Baseline Age**

<table>
<thead>
<tr>
<th></th>
<th>CHA†</th>
<th></th>
<th></th>
<th>MRFIT†</th>
<th></th>
<th>FHS</th>
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<tbody>
<tr>
<td></td>
<td>CHD</td>
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<td></td>
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<td>No CHD</td>
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<tr>
<td></td>
<td>Death</td>
<td>Death‡</td>
<td></td>
<td>Death</td>
<td>Death‡</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>P Value§</td>
<td></td>
<td>P Value§</td>
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<td></td>
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<tr>
<td>No.</td>
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<td>10,862</td>
<td>1,442</td>
<td>19</td>
<td>29</td>
<td>185</td>
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<tr>
<td>% (95% CI)</td>
<td>95.0</td>
<td>(92.2-97.8)</td>
<td>72.7</td>
<td>(71.9-73.6)</td>
<td>88.0</td>
<td>(86.3-89.7)</td>
<td>&lt;.001</td>
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**Men Aged 18-39 Years**

<table>
<thead>
<tr>
<th>No.</th>
<th>1068</th>
<th>8026</th>
<th>17,416</th>
<th>212</th>
<th>167</th>
<th>767</th>
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<tbody>
<tr>
<td>% (95% CI)</td>
<td>92.7</td>
<td>(91.1-94.3)</td>
<td>80.6</td>
<td>(79.7-81.4)</td>
<td>87.0</td>
<td>(86.5-87.5)</td>
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**Men Aged 40-59 Years**

<table>
<thead>
<tr>
<th>No.</th>
<th>25</th>
<th>7715</th>
<th>NA</th>
<th>NA</th>
<th>NA</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>% (95% CI)</td>
<td>92.0</td>
<td>(81.1-100)</td>
<td>57.5</td>
<td>(56.4-58.6)</td>
<td>NA</td>
<td>NA</td>
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</table>

**Women Aged 18-39 Years**

<table>
<thead>
<tr>
<th>No.</th>
<th>465</th>
<th>7,188</th>
<th>NA</th>
<th>NA</th>
<th>NA</th>
<th>NA</th>
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</thead>
<tbody>
<tr>
<td>% (95% CI)</td>
<td>93.8</td>
<td>(91.6-96.0)</td>
<td>75.9</td>
<td>(74.9-76.9)</td>
<td>NA</td>
<td>NA</td>
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</table>

**Women Aged 40-59 Years**

<table>
<thead>
<tr>
<th>No.</th>
<th>94</th>
<th>933</th>
<th>NA</th>
<th>NA</th>
<th>NA</th>
<th>NA</th>
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</thead>
</table>

**Abbreviations:** CHA, Chicago Heart Association Detection Project in Industry; CHD, coronary heart disease; CI, confidence interval; FHS, Framingham Heart Study; MI, myocardial infarction; MRFIT, Multiple Risk Factor Intervention Trial; NA, not applicable.

*Data are expressed as those in each indicated CHD outcome stratum with at least 1 clinically elevated risk factor (serum cholesterol ≥240 mg/dL [≥6.22 mmol/L], diastolic blood pressure ≥90 mm Hg or systolic blood pressure ≥140 mm Hg, current antihypertensive or cholesterol-lowering medication, current smoking, or diabetes). Age range in the FHS is 34 to 59 years and in MRFIT is 35 to 57 years.

†Nonfatal events were not measured in the CHA or MRFIT cohorts.

‡Includes participants who did not die or who died of other causes during follow-up; excludes nonfatal MI in the FHS.

§Calculated by χ² or Fisher exact test comparing those with a CHD event vs all others within the sex-cohort-age stratum.
PRIMARY PREVENTION

• How to screen?

• ASCVD/Pooled cohort recommended as the screening calculator of choice by ACC/AHA
PRIMARY PREVENTION

- Other risk factors
- Metabolic syndrome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large waist circumference</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&gt;102 cm (40 in)</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;88 cm (35 in)</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>Women</td>
<td>&lt;50 mg/dL</td>
</tr>
<tr>
<td>High triglycerides</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>≥130 mm Hg systolic or ≥85 mm Hg diastolic</td>
</tr>
<tr>
<td>Impaired fasting glucose level</td>
<td>≥110 mg/dL</td>
</tr>
</tbody>
</table>
PRIMARY PREVENTION

- Other risk factors
- Metabolic syndrome
### PRIMARY PREVENTION

- Risk scores aren’t perfect...

#### Table 3. Ten-Year CHD Risk Profile

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>LDL Cholesterol (mg/dl)</th>
<th>Total % Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;100</td>
<td>100–129</td>
</tr>
<tr>
<td>2+ risk factors 10-year risk &gt;20%</td>
<td>2 (1%)</td>
<td>11 (5%)</td>
</tr>
<tr>
<td>2+ risk factors 10-year risk 10%–20%</td>
<td>6 (3%)</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>2+ risk factors 10-year risk &lt;10%</td>
<td>12 (5%)</td>
<td>22 (10%)</td>
</tr>
<tr>
<td>0–1 risk factor</td>
<td>31 (14%)</td>
<td>33 (15%)</td>
</tr>
<tr>
<td>Total (% cohort)</td>
<td>51 (23%)</td>
<td>78 (35%)</td>
</tr>
</tbody>
</table>
PRIMARY PREVENTION

• Other tests/risk factors that may be helpful to risk stratify low/intermediate risk patients
  
  • Family history of premature CAD (men <55 or women <65)
  
  • Elevated coronary artery calcium score
  
  • Elevated hs-CRP
  
  • ABI <0.9
PRIMARY PREVENTION

• Other screening tests
  
  • EKG - reasonable in just about everyone
  
  • Stress testing
    
    • ETT - Reasonable in asymptomatic patients if intermediate risk, particularly if initiating an exercise program.
    
    • Nuclear imaging or stress echo - generally not recommended in asymptomatic individuals as a screening tool for CAD.
    
    • Transthoracic echo - generally not recommended in asymptomatic individuals as screening for CAD. May have a role when hypertensive heart disease is suspected.
    
  
  • Coronary CTA - Not recommended in asymptomatic individuals
PRIMARY PREVENTION

• Advanced lipoprotein analysis…
  • Discriminating between small, dense LDL and large, less dense LDL.
  • Apolipoprotein B levels predict CV risk better than LDL
  • Non-HDL cholesterol
  • Lipoprotein (a) - a type of LDL that has a strong correlation to excess risk of CVD.
PRIMARY PREVENTION

• Advanced lipoprotein analysis...
  
  • Discriminating between small, dense LDL and large, less dense LDL.

  LITTLE OR NO DATA THAT THESE ADD INCREMENTAL BENEFIT TO RISK ANALYSIS OR THAT TARGETED TREATMENT CHANGES OUTCOMES.

  • Apolipoprotein B levels predict CV risk better than LDL
  
  • Non-HDL cholesterol

  ROUTINE MEASUREMENT IS NOT RECOMMENDED.

  • Lipoprotein (a) - a type of LDL that has a strong correlation to excess risk of CVD.
PRIMARY PREVENTION

- Management - Life’s simple 7!

THE AMERICAN HEART ASSOCIATION’S “LIFE’S SIMPLE 7” STEPS

Get Started Now

GET ACTIVE
CONTROL CHOLESTEROL
EAT BETTER
MANAGE BLOOD PRESSURE
LOSE WEIGHT
REDUCE BLOOD SUGAR
STOP SMOKING
PRIMARY PREVENTION

- Management - Life’s simple 7!

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<table>
<thead>
<tr>
<th>No. of ideal metrics, n (%)</th>
<th>Total, N = 9364</th>
<th>Women, n = 6918</th>
<th>Men, n = 2446</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6 (0.06)</td>
<td>5 (0.07)</td>
<td>1 (0.04)</td>
</tr>
<tr>
<td>1</td>
<td>200 (2)</td>
<td>158 (2)</td>
<td>42 (2)</td>
</tr>
<tr>
<td>2</td>
<td>907 (10)</td>
<td>641 (9)</td>
<td>266 (11)</td>
</tr>
<tr>
<td>3</td>
<td>2122 (23)</td>
<td>1464 (21)</td>
<td>658 (27)</td>
</tr>
<tr>
<td>4</td>
<td>2925 (31)</td>
<td>2015 (29)</td>
<td>910 (37)</td>
</tr>
<tr>
<td>5</td>
<td>2124 (23)</td>
<td>1674 (24)</td>
<td>450 (18)</td>
</tr>
<tr>
<td>6</td>
<td>1020 (11)</td>
<td>906 (13)</td>
<td>114 (5)</td>
</tr>
<tr>
<td>7</td>
<td>60 (1)</td>
<td>55 (1)</td>
<td>5 (0.2)</td>
</tr>
</tbody>
</table>

Summary categories of ideal metrics, n (%)

- 0–1: 206 (2) 163 (2) 43 (2)
- 2–5: 8078 (86) 5794 (84) 2284 (93)
- 6–7: 1080 (12) 961 (14) 119 (5)
PRIMARY PREVENTION

• Management - Life’s simple 7!
### Primary Prevention

- Management - Life’s simple 7!

#### Incidence Rate and Hazard Ratios of Cardiovascular Disease According to the Number of Ideal Cardiovascular Health Metrics, ARIC, 1987–2007

<table>
<thead>
<tr>
<th>Number of Ideal Metrics</th>
<th>Total Sample</th>
<th>African Americans</th>
<th>Whites</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of CVD Cases</td>
<td>Incidence Rate <strong>†</strong> (95% CI)</td>
<td>Hazard Ratio <strong>††</strong> (95% CI)</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>23</td>
<td>3.9</td>
<td>(2.6–5.9)</td>
</tr>
<tr>
<td>5</td>
<td>127</td>
<td>6.4</td>
<td>(5.4–7.5)</td>
</tr>
<tr>
<td>4</td>
<td>354</td>
<td>8.6</td>
<td>(7.8–9.6)</td>
</tr>
<tr>
<td>3</td>
<td>735</td>
<td>12.0</td>
<td>(11.2–12.9)</td>
</tr>
<tr>
<td>2</td>
<td>946</td>
<td>16.0</td>
<td>(15.0–17.1)</td>
</tr>
<tr>
<td>1</td>
<td>699</td>
<td>21.9</td>
<td>(20.3–23.6)</td>
</tr>
<tr>
<td>0</td>
<td>159</td>
<td>32.1</td>
<td>(37.5–33.5)</td>
</tr>
<tr>
<td>Overall</td>
<td>3,063</td>
<td>13.3</td>
<td>(12.8–13.8)</td>
</tr>
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</table>
• Management - Exercise

**Figure 3.** Meta-analysis of All-Cause Mortality and CHD/CVD for Individuals With Low vs High CRF

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Individuals or Events</th>
<th>Crude RR (95% CI)</th>
<th>Favors</th>
<th>Adjusted RR (95% CI)</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slattery and Jacobs, 1988</td>
<td>NA NA NA NA</td>
<td>1.23 (1.17 - 1.30)</td>
<td></td>
<td>1.47 (1.39 - 1.55)</td>
<td></td>
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<tr>
<td>Hein et al., 1992</td>
<td>976 994 78 47</td>
<td>1.43 (1.18 - 1.73)</td>
<td></td>
<td>1.53 (1.26 - 1.80)</td>
<td></td>
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<tr>
<td>Alpert et al., 2008</td>
<td>NA NA NA NA</td>
<td>1.50 (1.26 - 1.76)</td>
<td></td>
<td>1.76 (1.07 - 1.47)</td>
<td></td>
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<tr>
<td>Villeneuve et al., 1998</td>
<td>321 3935 8 80</td>
<td>1.52 (0.72 - 2.19)</td>
<td></td>
<td>1.22 (0.58 - 2.57)</td>
<td></td>
</tr>
<tr>
<td>Stevens et al., 2002 [men]</td>
<td>NA NA 260 64</td>
<td>1.59 (1.18 - 2.14)</td>
<td></td>
<td>1.92 (1.43 - 2.59)</td>
<td></td>
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<tr>
<td>Farrell et al., 2002</td>
<td>1657 4521 75 57</td>
<td>1.75 (1.22 - 2.53)</td>
<td></td>
<td>1.25 (0.87 - 1.80)</td>
<td></td>
</tr>
<tr>
<td>Stevens et al., 2002 [women]</td>
<td>NA NA 208 33</td>
<td>1.84 (1.24 - 2.72)</td>
<td></td>
<td>2.23 (1.50 - 3.30)</td>
<td></td>
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<tr>
<td>Emond et al., 1993</td>
<td>420 487 106 24</td>
<td>1.86 (0.90 - 3.80)</td>
<td></td>
<td>1.38 (0.67 - 2.83)</td>
<td></td>
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<tr>
<td>Kannel et al., 1996</td>
<td>3436 7343 197 81</td>
<td>2.04 (1.55 - 2.68)</td>
<td></td>
<td>1.42 (1.08 - 1.87)</td>
<td></td>
</tr>
<tr>
<td>Stevens et al., 2004</td>
<td>NA NA 77 24</td>
<td>2.13 (1.34 - 3.39)</td>
<td></td>
<td>2.58 (1.62 - 4.09)</td>
<td></td>
</tr>
<tr>
<td>Laukkanen et al., 2008</td>
<td>410 410 124 39</td>
<td>2.48 (1.66 - 3.71)</td>
<td></td>
<td>1.83 (1.22 - 2.73)</td>
<td></td>
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<tr>
<td>Savoca and Muto, 1997</td>
<td>1793 1889 96 17</td>
<td>2.56 (1.47 - 4.47)</td>
<td></td>
<td>2.38 (1.36 - 4.14)</td>
<td></td>
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<tr>
<td>Eriksson et al., 1998</td>
<td>357 357 97 37</td>
<td>2.62 (1.80 - 3.72)</td>
<td></td>
<td>2.09 (1.47 - 2.98)</td>
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<tr>
<td>Arraz et al., 1992</td>
<td>833 801 36 12</td>
<td>2.70 (1.36 - 5.35)</td>
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<td>2.17 (1.09 - 4.30)</td>
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<tr>
<td>Gulati et al., 2004</td>
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<td>1.89 (1.25 - 2.86)</td>
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<tr>
<td>Myers et al., 2002</td>
<td>NA NA NA NA</td>
<td>4.52 (3.00 - 6.83)</td>
<td></td>
<td>2.96 (1.97 - 4.46)</td>
<td></td>
</tr>
</tbody>
</table>

**Overall**

Crude RR (95% CI): 2.00 (1.66 - 2.42); $P = 0.001$

Adjusted RR (95% CI): 2.70 (1.97 - 3.42); $P = 0.001$

**CHD/CVD**

Crude RR (95% CI): 1.18 (1.18 - 1.26); $P = 0.001$

Adjusted RR (95% CI): 1.35 (1.26 - 1.46); $P = 0.001$

Features of the graph include:
- **Crude Mortality**
- **Adjusted Mortality**
- **CHD/CVD**
- **Overall**

The graph provides a comprehensive view of the meta-analysis results for both crude and adjusted mortality, as well as CHD/CVD, with significance levels indicated for each category.
PRIMARY PREVENTION

- Management - Exercise
PRIMARY PREVENTION

- Management - Exercise
PRIMARY PREVENTION

• Management - smoking cessation
  • Recommendation is complete cessation and avoidance of 2nd hand smoke.
  • Smoking cessation decreases risk of CAD by ~33%
  • Best results with cessation are a combination of counseling and pharmacologic therapies which is more effect than either therapy alone.

• Proven drug therapies include:
  • Nicotine replacement
  • Varenicline
  • Bupropion
PRIMARY PREVENTION

- Management - smoking cessation
PRIMARY PREVENTION

• Management - Normal weight

• Goal BMI 18-25 and waist circumference <40in in men and 35in in women.

• Weight loss of 5-10% of body weight can have profound impact on other risk factors (i.e. reduction in risk of diabetes).
PRIMARY PREVENTION

- Management - Glucose control
PRIMARY PREVENTION

- Management - Glucose control
PRIMARY PREVENTION

• Management - Diet
  • Decreased processed foods
  • Limit sugars and foods with added sugars
  • Limit refined grains
PRIMARY PREVENTION

- Management - Mediterranean Diet

![Graphs showing primary end point and total mortality comparisons between different diet groups.](image)
PRIMARY PREVENTION

- Management - Lipid control...

Definitions of High- and Moderate-Intensity Statin Therapy (See Table 5)

- High:
  - Daily dose lowers LDL-C by approx. ≥50%

- Moderate:
  - Daily dose lowers LDL-C by approx. 30% to <50%

Clinical ASCVD

- LDL-C ≥190 mg/dL
  - Yes: High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)
  - No: High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)

LDL-C ≥190 mg/dL

- Diabetes Type 1 or 2
  - Yes: Moderate-intensity statin

- Age 40-75 y
  - Yes: Moderate-to-high intensity statin
  - No: Yes

Estimate 10-y ASCVD Risk with Pooled Cohort Equations*

- ≥7.5% estimated 10-y ASCVD risk and age 40-75 y
  - Yes: Moderate-to-high intensity statin

- No: Yes
PRIMARY PREVENTION

• Management - Lipid control

• Are risk calculators helpful in deciding when to initiate a statin?

• It identifies those at high risk that need priority in risk reduction

• But are they really the best tool we have to identify those that will benefit from statins?
PRIMARY PREVENTION

- Management - Lipid control
  - Statins in patients on hemodialysis
    - Multiple studies show no difference in MACE comparing statin to placebo.
      - Slight trend to significance in reduction of cardiac events (excluding stroke)
    - Statins in patients with ischemic and non-ischemic cardiomyopathy (EF ~30%)
      - Two large studies showed no reduction in MACE or hospital admission
PRIMARY PREVENTION

• Management - Lipid control

• What to add to statins?

  • Fibrates - No effect on mortality

  • Niacin - AIM-HIGH trial, adding niacin to simvastatin was not beneficial

  • Fish oil - majority of trials show no benefit on MACE outcomes

  • Ezetimibe - IMPROVE-IT trial showed a 2% decrease in event rate when added to simvastatin.

  • PCSK9 inhibitors - outcome data looks promising. Indications include familial hypercholesterolemia and LDL >100 in those with CVD on max statin and/or ezetimibe therapy. Problem - EXPENSIVE
PRIMARY PREVENTION

• Management - Aspirin