Primary Prevention of Heart Disease:

What works? What doesn’t?

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Objectives

1. To review current challenges for atherosclerotic cardiovascular disease (ASCVD) prevention, with a focus on the impact in women
2. Aspirin for the prevention of ASCVD
   Secondary prevention
   Primary prevention
   Sex differences
   Guideline recommendations
3. Statins for the prevention of ASCVD

Cardiovascular disease is the leading cause of death in women and men (US: 1979–2009)

Mozaffarian et al, Circulation 2015;131:e29-e322
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Impact of ASCVD in Women

- Single largest killer of women in US
- One in 30 women will die of breast cancer, vs. one in 3 will die from CVD
- One woman dies from CVD every minute
- CVD deaths in women = all deaths from cancer, lung disease, and Alzheimer disease combined

Impact of ASCVD in Women

- Black women ~ 40% more likely to die from CVD compared with White women
- Death rate in US women ages 35-54 is increasing, possibly due to obesity
- Two thirds of women who die suddenly had no prior symptoms (vs. ~ half of men)
- More women than men will have a second heart attack after their first heart attack

Impact of ASCVD in Women

- More strokes than coronary heart disease (CHD) in women (opposite in men)
- Gestational diabetes (2-10% of pregnancies): increases risk of future diabetes by 30 to 60%
- Unique risk factors for stroke in women:
  - pregnancy
  - hormone therapy
  - more hypertension at ≥ age 65

Lifetime Risk of ASCVD Death for Women by Risk Factors at Age 45

4 Major Risk Factors:
- Smk, DM, TC>240, BP>160/100
- Optimal Risk Factors:
  - Non-smk, non-DM, TC<180, BP<120/80

Berry et al. NEJM 2012;366:321-9
Awareness lagging among women that heart disease is their leading cause of death


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Aspirin: Mechanism of Action

Platelets are central to coronary thrombosis

Aspirin Evidence: Secondary Prevention of ASCVD

Antithrombotic Trialists’ (ATT) Collaboration
Meta-analysis of 16 randomized trials of aspirin (N=17,000 participants, 3306 serious vascular events)

- ↓ 31%, nonfatal MI
- ↓ 20%, major CHD events
- ↓ 19%, total stroke
- ↓ 19%, any serious vascular event

(Results similar in men and women)


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Aspirin Evidence: Primary Prevention

- The role of aspirin in primary prevention has not been as clear, particularly among women.
- The assessment of the benefits of aspirin in primary prevention is more complicated, since the absolute risks of vascular events are lower than in secondary prevention while complication rates (eg., bleeding) are comparable.

Aspirin Evidence: Primary Prevention

Antithrombotic Trialists’ (ATT) Collaboration
Meta-analysis of 95,456 low risk patients randomized to aspirin (100 mg every other day to 500 mg daily) vs. placebo for 4 to 20 years

<table>
<thead>
<tr>
<th>Event</th>
<th>Number of Events - Aspirin vs. Control</th>
<th>Rate ratio (95% CI) (Aspirin vs. Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major coronary event</td>
<td>934 vs. 1115</td>
<td>0.82 (0.79-0.89)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>596 vs. 756</td>
<td>0.77 (0.69-0.86)</td>
</tr>
<tr>
<td>CHD mortality</td>
<td>372 vs. 393</td>
<td>0.95 (0.82-1.10)</td>
</tr>
<tr>
<td>Stroke</td>
<td>655 vs. 682</td>
<td>0.95 (0.85-1.06)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>116 vs. 89</td>
<td>1.32 (1.00-1.75)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>367 vs. 397</td>
<td>0.86 (0.74-1.00)</td>
</tr>
<tr>
<td>Unknown cause</td>
<td>222 vs. 226</td>
<td>0.97 (0.80-1.18)</td>
</tr>
<tr>
<td>Vascular death</td>
<td>619 vs. 637</td>
<td>0.97 (0.87-1.09)</td>
</tr>
<tr>
<td>Any serious vascular event</td>
<td>1675 vs. 1885</td>
<td>0.88 (0.82 vs 0.94)</td>
</tr>
<tr>
<td>Major extracranial bleed</td>
<td>355 vs. 215</td>
<td>1.54 (1.30-1.82)</td>
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Aspirin reduces the risk of ischemic events, but with a higher rate of bleeding

Antithrombotic Trialists’ Collaboration. Lancet 2009;373:1449-60
Aspirin Evidence: Primary Prevention

Effect of antiplatelet treatment on vascular events

Rate Ratios for Vascular Events

Non-fatal MI
Stroke
Vascular Mortality
Major GI and extracranial bleeds
Serious Vascular Events

Antiplatelet Better
Antiplatelet Worse

P=0.0001

Antithrombotic Trialist Collaboration. Lancet 2009;373:1849

Aspirin Evidence: Dose and Efficacy

Indirect comparisons of aspirin doses on vascular events in high-risk patients

Aspirin Dose | No. of Trials (%) | Odds Ratio for Vascular Events
---|---|---
800-1800 mg | 34 | 19
180-325 mg | 19 | 28
75-150 mg | 12 | 32
<75 mg | 3 | 11
Any aspirin | 66 | 23

Antithrombotic Trialist Collaboration. BMJ 2002;324:71-86

Aspirin Evidence: Primary Prevention

2015 U.S. Preventive Task Force Services updated meta-analysis

<table>
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<tr>
<th>Outcome</th>
<th>No. trials</th>
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<th>Summary Relative Risk</th>
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<td>Nonfatal MI</td>
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<td>114,734</td>
<td>0.78 (0.71-0.87)</td>
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<td>Nonfatal stroke</td>
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<td>99,655</td>
<td>0.95 (0.85-1.06)</td>
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<tr>
<td>CVD mortality</td>
<td>11</td>
<td>118,445</td>
<td>0.94 (0.86-1.03)</td>
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<td>Total mortality</td>
<td>11</td>
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Guirgis-Blake JM et al. 2015  www.uspreventiveservicestaskforce.org

Aspirin Evidence: Primary Prevention

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Guirgis-Blake JM et al. 2015  www.uspreventiveservicestaskforce.org
Bleeding risks with aspirin

Risk factors for bleeding
- Age
- Male sex
- GI hospitalization
- Excess alcohol use
- Current smoking
- Hypertension
- Diabetes
- Liver / renal disease
- Concomitant meds (NSAIDs, anticoagulants)

Proton Pump Inhibitors (PPIs) may decrease risk of GI bleeding on aspirin

Whitlock E et al. 2015  www.uspreventiveservicestaskforce.org

GI: Gastrointestinal

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Aspirin in Primary Prevention: Sex differences?

Aspirin Evidence: Primary Prevention in Men

22,071 men randomized to aspirin (325 mg every other day) followed for an average of 5 years

Physicians’ Health Study (PHS)

End point Relative Risk (95% CI) P value
CV Mortality 0.95 (0.80–1.13) NS
Myocardial infarction
Fatal 0.34 (0.15–0.75) 0.007
Nonfatal 0.59 (0.47–0.74) <0.00001
Total 0.56 (0.45–0.70) <0.00001
Stroke
Fatal 1.51 (0.54–4.28) 0.43
Nonfatal 1.20 (0.91–1.59) 0.20
Total 1.22 (0.93–1.60) 0.15

Aspirin reduces the risk of MI among men in the PHS

G=Confidence Interval, CV=Cardiovascular, MI=Myocardial infarction, NS=Non-significant

The Women's Health Study: Subgroup Analyses, Primary Endpoint of Major CV Event

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Aspirin (N=19,934)</th>
<th>Placebo (N=19,942)</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>45–54 (24,025)</td>
<td>163</td>
<td>161</td>
<td>1.01</td>
<td>0.81-1.26</td>
<td>0.92</td>
</tr>
<tr>
<td>55–64 (11,754)</td>
<td>183</td>
<td>186</td>
<td>0.98</td>
<td>0.80-1.20</td>
<td>0.84</td>
</tr>
<tr>
<td>≥65 (4,097)</td>
<td>131</td>
<td>175</td>
<td>0.74</td>
<td>0.59-0.92</td>
<td>0.008</td>
</tr>
</tbody>
</table>

*P for interaction by age = 0.05 for total CVD and 0.03 for MI

**Major CV Event** = Nontatal MI, nonfatal stroke, cardiovascular death
Women’s Health Study: Subgroup Analyses, Age ≥65 years

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Aspirin</th>
<th>Placebo</th>
<th>RR (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major CV Event†</td>
<td>131</td>
<td>175</td>
<td>0.74 (0.59–0.92)</td>
<td>0.008</td>
</tr>
<tr>
<td>Total MI</td>
<td>41</td>
<td>62</td>
<td>0.66 (0.44–0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Total Stroke</td>
<td>68</td>
<td>86</td>
<td>0.78 (0.57–1.08)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

44 Fewer Major CV Events
16 Additional GI Hemorrhages Requiring Transfusion

† Major CV Event = nonfatal MI, nonfatal stroke, cardiovascular death

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2010 Aspirin Recommendations for Patients with Diabetes Mellitus (ADA/AHA/ACC)

- Use aspirin 75 to 162 mg/day for secondary ASCVD prevention
- Consider aspirin 75 to 162 mg/day for primary ASCVD prevention in diabetic patients at increased risk
  - Those at risk for ASCVD (10-year risk >10%)—men >50 yrs, women >60 yrs, with >1 additional risk factor (family history of premature ASCVD, HTN, smoking, dyslipidemia, albuminuria)
- Not sufficient evidence for aspirin for primary prevention in low risk groups

2011 AHA guidelines: CVD Prevention in women

- Aspirin (75 to 325 mg/d) in high-risk women
  - If aspirin-intolerant: substitute clopidogrel
- Aspirin (81 mg/d or 100 mg every other day) in at-risk women ≥65 years is reasonable if BP is controlled and benefit outweighs risk
- Aspirin in at risk women <65 years for preventing ischemic stroke may be reasonable if benefit outweighs risk
- Not Recommended: for preventing myocardial infarction in optimal risk women <65 years

Pignone M et al JACC 2010;55:2878
Mosca et al. Circulation 2011;123:1243-1262
2015 U.S. Preventive Services Task Force Draft Recommendations for low dose aspirin

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults age 50-59 yrs</td>
<td>For primary prevention of ASCVD and colorectal cancer if:</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>- ≥ 10% ASCVD risk *</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Not at increased risk of bleeding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Life expectancy of at least 10 yrs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Willing to take aspirin for at least 10 yrs</td>
<td></td>
</tr>
<tr>
<td>Adults age 60-69 yrs</td>
<td>Individualize the decision if:</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>- ≥ 10% ASCVD risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Not at increased risk of bleeding</td>
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<td></td>
<td>- Willing to take aspirin for at least 10 yrs</td>
<td></td>
</tr>
<tr>
<td>Adults &lt; 50 yrs</td>
<td>Insufficient evidence</td>
<td>I</td>
</tr>
<tr>
<td>Adults ≥ 70 yrs</td>
<td>Insufficient evidence</td>
<td>I</td>
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*Pooled Cohort Equations available at [http://my.americanheart.org/cvriskcalculator](http://my.americanheart.org/cvriskcalculator)

Guiruis-Blake JM et al. 2015 www.uspreventiveservicestaskforce.org

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2013 Cholesterol Guidelines

- New Equations* for ASCVD risk assessment
  - Stroke included, in addition to MI
  - Separate equations for blacks
- 4 Statin benefit groups
  - Adults with clinical ASCVD
  - Adults with LDL-C ≥ 190 mg/dL
  - Adults 40 to 75 yrs of age with diabetes
  - Adults ≥ 7.5% estimated 10-yr risk of ASCVD
- No LDL-C or non-HDL-C treatment targets

*Pooled Cohort Equation available at [http://my.americanheart.org/cvriskcalculator](http://my.americanheart.org/cvriskcalculator)

Goff et al JACC 2014;63:2935-59

Stone et al JACC 2014;63:2889-934

2013 Prevention Guidelines

ASCVD RISK ESTIMATOR

The information to estimate ASCVD risk (2013):
- age, sex, race, TC, HDL-C, SBP, BP Rx, diabetes, smoking
- 10-yr risk of MI, fatal or nonfatal stroke, CHD death
- Lifetime risk

Prior (ATP III, 2001):
- Age, sex, TC, HDL-C, SBP, BP Rx, smoking
- 10-yr risk of MI, CHD death

*Pooled Cohort Equation available at [http://my.americanheart.org/cvriskcalculator](http://my.americanheart.org/cvriskcalculator)
4 Groups of High Risk Individuals

- **High Risk**
  - Clinical ASCVD*
  - LDL ≥ 190 mg/dL, age ≥ 21 years
  - Primary prevention – Diabetes: age 40-75 y, LDL 70-189 mg/dL
- **Primary prevention**
  No diabetes, ≥ 7.5% 10-year ASCVD risk, age 40-75 years, LDL 70-189 mg/dL

*Acute coronary syndrome, MI, angina, coronary or other arterial revascularization, stroke, TIA, atherosclerotic peripheral arterial disease (PAD)

Individuals Not in a Statin Benefit Group

- Family history of premature ASCVD*
- High lifetime risk
- LDL-c ≥ 160 mg/dL
- hs-CRP ≥ 2 mg/L
- CAC score ≥ 300 or ≥ 75th percentile
- Ankle brachial index (ABI) < 0.9

* onset <55 y first degree male or <65 first degree female

Statin Evidence: Primary Prevention in Women

- 13,154 Women; 240 CVD events
- Year
  - APCAPS/TexCAPS
  - MEGA
  - JUPITER
- RR 95% CI Placebo Statin
  - 0.67 (0.49-1.11) 21496 14499
  - 0.73 (0.49-1.09) 562718 402838
  - 0.54 (0.37-0.80) 703375 393428
- ALL
  - 0.63 (0.49-0.82) P<0.001

Topics discussed

1. Reviewed current challenges for atherosclerotic cardiovascular disease (ASCVD) prevention, with a focus on the impact in women
2. Reviewed evidence on aspirin for the prevention of ASCVD
   - Secondary prevention
   - Primary prevention
   - Sex differences
   - Guideline recommendations
3. Reviewed evidence on statins for the prevention of ASCVD

Mora S et al., Circulation 2010;121:1099
Thank you!

### Ongoing aspirin trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Analysis</th>
<th>Study population</th>
<th>Study outcomes</th>
<th>Study results</th>
</tr>
</thead>
<tbody>
<tr>
<td>APRO</td>
<td>Randomized, double-blind, placebo-controlled trial</td>
<td>Randomized, double-blind, placebo-controlled trial</td>
<td>Age ≥ 50 and no prior cardiovascular disease</td>
<td>All-cause mortality, myocardial infarction, stroke, ischemic heart disease</td>
<td>10,000 vs 10,000, no difference</td>
</tr>
<tr>
<td>ASA-CHD</td>
<td>Randomized, double-blind, placebo-controlled trial</td>
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<td>All-cause mortality, myocardial infarction, stroke, ischemic heart disease</td>
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<td>ASCEND</td>
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**Notes:**
- **APRO:** A Prospective Randomized Controlled Trial in Aspirin-Related Heart Disease
- **ASA-CHD:** Aspirin in the Young Heart Disease Prevention Trial
- **ASCEND:** Aspirin in Community-Acquired Stroke Prevention Endpoints Evaluation

*Devar et al. JAMA 2015;313(22):2258-2266*