‘ABCDEF’ Approach for CVD Prevention: Focus on Aspirin

Roger S. Blumenthal, MD
The Kenneth J. Pollin Professor of Cardiology
Ciccarone Center for the Prevention of Cardiovascular Disease
(No Disclosures)
“ABCs” of CVD Prevention & Management

Assessment of Risk
Antiplatelet/Anticoagulant Rx
Blood pressure
Cholesterol
Cigarette Cessation
Diabetes/Glucose Management
Diet/Weight
Exercise/Education
Routine use of an ‘ABCDEF’ approach for patient management can help keep track of latest prevention-related guidelines.

Donna K. Arnett, PhD, MSPH, FAHA, Co-Chair
Roger S. Blumenthal, MD, FACC, FAHA, Co-Chair

Michelle A. Albert, MD, MPH
Andrew B. Buroker, Esq†
Zachary D. Goldberger, MD
Ellen J. Hahn, PhD, RN*
Cheryl D. Himmelfarb, PhD, RN,
Amit Khera, MD, MSc,
Donald Lloyd-Jones, MD,
J. William McEvoy, MBBCh, MEd,

Erin D. Michos, MD, MHS
Michael D. Miedema, MD,
Daniel Muñoz, MD, MPA,
Sidney C. Smith, Jr, MD, MACC
Salim S. Virani, MD, PhD
Kim A. Williams, Sr, MD
Joseph Yeboah, MD, MS,
Boback Ziaeian, MD, PhD
Assessment of CVD Risk

Shared Decision Making

Team-Based Approach to Prevention
Social Determinants of Health

- Socioeconomic factors: limit effectiveness of recommendations
- Socioeconomic disadvantages: not captured by existing CVD risk estimators
- Medicare/Medicaid developed 5 domain **screening tool:**
  - Housing instability
  - Food insecurity
  - Transportation difficulties
  - Utility assistance needs
  - Interpersonal safety
# Assessment of Cardiovascular Risk

**ASSESSMENT**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td>1. For adults 40-75 y/o, clinicians should routinely assess traditional CVD risk factors &amp; calculate 10-yr risk of ASCVD by using pooled cohort equations (PCE).</td>
</tr>
<tr>
<td>IIA</td>
<td>B-NR</td>
<td>2. For 20-39 y/o, it is reasonable to assess traditional ASCVD risk factors at least every 4 - 6 yrs.</td>
</tr>
<tr>
<td>IIA</td>
<td>B-NR</td>
<td>3. If borderline risk (5% to &lt;7.5% 10-yr ASCVD risk) or intermediate risk (≥7.5% to &lt;20%), it is reasonable to use additional risk-enhancing factors to guide decisions about preventive interventions (e.g. statin Rx)</td>
</tr>
</tbody>
</table>
Toolbox for Estimating ASCVD Risk

PCE: (Class I)
30-yr ASCVD risk: (Class IIb)

Risk-Enhancing Factors: (Class IIa)

Coronary artery calcium: (Class IIa)
Risk-Enhancing Factors

- **When** to use?
  - Uncertainty of PCE estimate
  - Or
    - If **further** risk stratification needed

- **Whom** to use in?
  - Borderline (5% to <7.5%) or
  - Intermediate (≥7.5% to <20%) 10-yr ASCVD risk

### Table. ASCVD risk enhancers

- Family history of premature ASCVD
- Primary hypercholesterolemia (LDL-C ≥160)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g. preeclampsia, premature menopause)
- Chronic inflammatory conditions (especially rheumatoid arthritis, psoriasis, HIV)
- High risk race/ethnicity (e.g. south Asian ancestry)

**Lipid/Biomarkers:**
- Persistently elevated triglycerides (≥175 mg/dL)

*In selected individuals if measured:*
- hsCRP ≥2 mg/L
- Lp(a) levels ≥50 mg/dL or ≥125 nmol/L
- ApoB levels ≥130 mg/dL
- Ankle-brachial index <0.9
Presence of CAC in Those With REFs From MESA

Age-Standardized Distribution of CAC by Risk Enhancing Factor Burden

- CAC=0: 17%
- CAC 1-99: 35%
- CAC ≥100: 48%

- CAC=0: 17%
- CAC 1-99: 27%
- CAC ≥100: 56%

- CAC=0: 24%
- CAC 1-99: 30%
- CAC ≥100: 46%

*Both authors contributed equally to this work.
Assessment of Cardiovascular Risk

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>4. In adults at intermediate risk (≥7.5% to &lt;20% 10-yr ASCVD risk) or selected adults at borderline risk (5% to &lt;7.5%), if risk-based decisions for preventive interventions (e.g., statin Rx) remain uncertain, it is reasonable to measure a coronary artery calcium score to guide risk discussion.</td>
</tr>
<tr>
<td>IIb</td>
<td>B-NR</td>
<td>5. For adults 20-39 y/o and for those 40-59 y/o who have &lt;7.5% 10-yr risk, estimating lifetime or 30-yr risk may be considered.</td>
</tr>
</tbody>
</table>
Risk Reclassification for Primary Prevention

PCE

+ REFs

CAC>100

#CAC>100
#SecondaryPrevention
Risk Reclassification for Primary Prevention

#ThePowerofZero
## Aspirin

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>A</td>
<td>1. <strong>Low-dose aspirin</strong> (75-100 mg orally daily) might be considered for primary prevention of ASCVD among select adults 40-70 y/o at higher ASCVD risk but <strong>not</strong> at increased bleeding risk.</td>
</tr>
<tr>
<td>III: Harm</td>
<td>B-R</td>
<td>2. <strong>Low-dose aspirin</strong> (75-100 mg orally daily) should <strong>not</strong> be administered on routine basis for primary prevention among <strong>adults &gt;70 y/o</strong>.</td>
</tr>
<tr>
<td>III: Harm</td>
<td>C-LD</td>
<td>3. <strong>Low-dose aspirin</strong> (75-100 mg orally daily) should <strong>not</strong> be administered for primary prevention among <strong>adults at increased risk of bleeding</strong>.</td>
</tr>
</tbody>
</table>
Targets for Oral Antiplatelet Rx

**ASPIRIN** – Irreversible Inhibitor of COX-1 which halts production of Thromboxane A2 and thus platelet aggregation.

Aspirin for Major CV Events (MACE): SECONDARY PREVENTION

SECONDARY PREVENTION – 27% RRR in MACE

<table>
<thead>
<tr>
<th>Category of trial</th>
<th>No of trials with data</th>
<th>MI, STROKE OR VASCULAR DEATH</th>
<th>STRATIFIED STATISTICS</th>
<th>OR and CI (Antiplatelet : Control)</th>
<th>% odds reduction (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Anti-platelet</td>
<td>Adjusted controls</td>
<td>O-E variance</td>
<td></td>
</tr>
<tr>
<td>ALL HIGH RISK**</td>
<td>142</td>
<td>4183/36,536 (14.7%)</td>
<td>5400/36,711</td>
<td>-568.8</td>
<td>1810.9</td>
</tr>
<tr>
<td>ALL LOW RISK (primary prevention)</td>
<td>3</td>
<td>652/14,608 (4.46%)</td>
<td>708/14,504 (4.85%)</td>
<td>-28.5</td>
<td>273.5</td>
</tr>
<tr>
<td>ALL TRIALS (high or low risk)</td>
<td>145</td>
<td>4835/51,144 (9.5%)</td>
<td>6108/51,315 (11.9%)</td>
<td>-597.3</td>
<td>2084.4</td>
</tr>
</tbody>
</table>

** All high risk: Prior MI, acute MI, prior stroke/TIA, other high risk

Role of aspirin in primary prevention

- Absolute risks of vascular events: lower than in secondary prevention
- Complication rates (bleeding) comparable
## Aspirin Use in Primary Prevention in U.S.

From: Prevalence of Aspirin Use for Primary Prevention of CVD in the US: 2017 National Health Interview Survey

<table>
<thead>
<tr>
<th>Aspirin Use %</th>
<th>Estimated US Population using Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
</tr>
<tr>
<td>21.8%</td>
<td>14.5 Million</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
</tr>
<tr>
<td>25.5%</td>
<td>14.5 Million</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>40-49 y</td>
<td>7.0%</td>
</tr>
<tr>
<td>2.6 Million</td>
<td></td>
</tr>
<tr>
<td>50-59 y</td>
<td>18.4%</td>
</tr>
<tr>
<td>6.7 Million</td>
<td></td>
</tr>
<tr>
<td>60-69 y</td>
<td>34.7%</td>
</tr>
<tr>
<td>10.2 Million</td>
<td></td>
</tr>
<tr>
<td>70-79 y</td>
<td>44.6%</td>
</tr>
<tr>
<td>6.5 Million</td>
<td></td>
</tr>
<tr>
<td>≥80 y</td>
<td>46.2%</td>
</tr>
<tr>
<td>3.05 Million</td>
<td></td>
</tr>
</tbody>
</table>

“An aspirin a day will help prevent a heart attack if you have it for lunch instead of a cheeseburger.”
Based on older trials, prior US guidelines had recommended low dose aspirin for primary ASCVD prevention only in setting of elevated 10-yr CVD risk.

Prior AHA/ACC Aspirin Recommendations ('97 and ‘02)

**Primary Prevention**

Aspirin (75-162 mg daily) should be used in adults at intermediate risk (10-year risk of CHD >10%)

CHD=Coronary heart disease

Aspirin for Primary Prevention of CVD

What data are the prior recommendations based on?

<table>
<thead>
<tr>
<th>Study</th>
<th>RR of MI in Men</th>
<th>RR of CVA in Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDT, 1988</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHS, 1989</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPT, 1998</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOT, 1998</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPP, 2001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>RR = 0.68 (0.54-0.86) P=0.001</td>
<td>RR = 1.13 (0.96-1.33) P=0.15</td>
</tr>
<tr>
<td>HOT, 1998</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPP, 2001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHS, 2005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>RR = 0.99 (0.83-1.19) P=0.95</td>
<td>RR = 0.81 (0.69-0.96) P=0.01</td>
</tr>
</tbody>
</table>

CVA = Cerebrovascular accident, MI = Myocardial infarction, RR = Relative risk

Aspirin for Primary Prevention of ASCVD: 2014 Meta-analysis

- **ASCVD Events** – 10% ↓
  RR 0.90 (95% CI 0.85, 0.95)

- **Major Bleeding** – 55% ↑
  RR 1.55 (1.35, 1.78)

- NNT to prevent 1 major ASCVD event over a mean f/u of 6.8 years = 284.
- NNH to cause 1 major bleeding = 299

NNT = number needed to treat; NNH = number need to harm
2014 – the Japanese Primary Prevention Project (JPPP)

Patients aged 60–85 years
- Hypertension
- Dyslipidemia
- Diabetes mellitus
  (one or more condition)

Eligible ✓

1:1 randomization

Enteric-coated aspirin 100 mg/day

No aspirin

Ongoing medications to control underlying disease(s)

Followup 6.5 years
JPPP Primary endpoint:
death from CV causes, nonfatal stroke and nonfatal MI

Ikeda et al. JAMA 2014

Aspirin
No aspirin

Proportion of patients with primary endpoint event (%)

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Aspirin</th>
<th>No aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>7220</td>
<td>7021</td>
<td>6771</td>
</tr>
<tr>
<td>6771</td>
<td>6583</td>
<td>6322</td>
</tr>
<tr>
<td>6583</td>
<td>6322</td>
<td>3639</td>
</tr>
<tr>
<td>6322</td>
<td>3639</td>
<td>169</td>
</tr>
<tr>
<td>3639</td>
<td>169</td>
<td>7244</td>
</tr>
<tr>
<td>169</td>
<td>7244</td>
<td>7073</td>
</tr>
<tr>
<td>7073</td>
<td>6861</td>
<td>6645</td>
</tr>
<tr>
<td>6861</td>
<td>6645</td>
<td>6359</td>
</tr>
<tr>
<td>6645</td>
<td>6359</td>
<td>3711</td>
</tr>
<tr>
<td>6359</td>
<td>3711</td>
<td>182</td>
</tr>
</tbody>
</table>

\[ p = 0.544 \]

\[ HR \ 0.94 \ (95\% \ CI: \ 0.77–1.15) \]
ARRIVE: Aspirin in Primary Prevention

- Enrolled **12,546 patients** followed for mean of 60 months
- Adults >55 y/o (men) or >60 y/o (women) with moderate estimated CV risk (10-yr ASCVD risk 17.4%)
- However, **observed event rates were lower (<10% 10-years)**
  - Thus, population was low to moderate risk
- Excluded patients at high risk of bleeding or diabetes
- Randomized enteric-coated aspirin (100 mg) or placebo daily

Gaziano JM et al. The Lancet. 2018; 392
ARRIVE: Primary Outcome
Intention to Treat

Time to First Occurrence of CV Death, MI, UA, Stroke or TIA (Intent-to-Treat population)

Primary outcome

- Placebo
- Aspirin

Log-rank p = 0.6038
Stratified log-rank p = 0.5970

HR (95% CI)*
0.96 (0.81; 1.13)

p-Value*
0.6038

*Comparison: Aspirin vs Placebo

Gaziano JM et al. The Lancet. 2018; 392
## ARRIVE: Bleeding Intention to Treat

### Gastrointestinal Bleeding Adjudication

<table>
<thead>
<tr>
<th>Time to First GI Bleeding</th>
<th>Placebo Arm (n=6276)</th>
<th>Aspirin Arm (n=6270)</th>
<th>Hazard Ratio (95% CI)*</th>
<th>p-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with events, n (%)</td>
<td>29 (0.46%)</td>
<td>61 (0.97%)</td>
<td>2.11 [1.36;3.28]</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

### Severity of adjudicated first GI Bleeding

<table>
<thead>
<tr>
<th></th>
<th>Placebo Arm (n=6276)</th>
<th>Aspirin Arm (n=6270)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild, n (%)</td>
<td>22 (0.35%)</td>
<td>42 (0.67%)</td>
</tr>
<tr>
<td>Moderate, n (%)</td>
<td>5 (0.08%)</td>
<td>15 (0.24%)</td>
</tr>
<tr>
<td>Severe, n (%)</td>
<td>2 (0.03%)</td>
<td>4 (0.06%)</td>
</tr>
</tbody>
</table>

*Comparison: Aspirin vs Placebo; p-Value from log-rank test of time to first event
Note: Percentages based on number of subjects randomized to the indicated treatment group

Gaziano JM et al. The Lancet. 2018; 392
ASPREE: Aspirin in Primary Prevention in Older Adults

- Adults in Australia (>70 y.o) & U.S. (>65 y.o among Blacks/Hispanics)
  - 19,114 participants – excluded those with CVD, dementia, disability - followed for mean of 4.7 yrs

- Randomized to EC aspirin 100 mg daily vs. placebo

- 50% were age ≥74 years, 56% women

- primary end point was a composite of death, dementia, or persistent physical disability

ASPREE: Death, Dementia, Disability

- All Deaths
  HR 1.14 (1.01-1.29)

- Cancer Deaths
  HR 1.31 (1.01-1.29)

No benefit on Dementia or Persistent Physical Disability

### Effect of Aspirin on Cardiovascular Events in the Elderly

**Randomized, Double-Blind, Multicenter Trial**

<table>
<thead>
<tr>
<th>19,114 Patients</th>
<th>Aspirin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥70 yr of age with no known cardiovascular disease, dementia, or disability</td>
<td>N=9525</td>
<td>N=9589</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Aspirin Events (per 1000 person-yr)</th>
<th>Placebo Events (per 1000 person-yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>10.7</td>
<td>11.3</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>8.6</td>
<td>6.2</td>
</tr>
</tbody>
</table>

- **Cardiovascular disease**
  - **Aspirin**: 10.7 events per 1000 person-years (HR, 0.95; 95% CI, 0.83–1.08)
  - **Placebo**: 11.3 events per 1000 person-years

- **Major hemorrhage**
  - **Aspirin**: 8.6 events per 1000 person-years (HR, 1.38; 95% CI, 1.18–1.62, P<0.001)
  - **Placebo**: 6.2 events per 1000 person-years

*The New England Journal of Medicine*  
McNeil et al. 2018
Low dose ASA for primary prevention among pts with Type 2 diabetes: 2008 JPAD RCT

Ogawa H et al. JAMA 2008 (300) 18; 2134-2141
POPADAD: Asymptomatic “PAD” & diabetes: ASA ineffective

- 1276 adults age >40 with diabetes and ABI <0.99, but no clinical CVD

- RCT of ASA 100 mg/d vs. placebo ± antioxidant in 2 x 2 factorial design

- Median follow-up 6.7 yrs
ASCEND: Aspirin in Primary Prevention in DM

- Adults with diabetes, but no CVD
  - 15,480 participants followed for mean of 7.4 yrs
- Randomized to aspirin 100 mg daily vs. placebo
- Mean age 63 years, 38% women
- Primary outcome – major vascular event (MI, stroke/TIA, vascular death)

ASCEND
Primary Outcome

BENEFIT: Vascular Events
- Aspirin group [8.5%] vs. Placebo group [9.6%]

HR 0.88 (0.79-0.97)
12% RRR
ASCEND:
Effect of aspirin on major BLEED

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Aspirin (N=7740)</th>
<th>Placebo (N=7740)</th>
<th>Rate Ratio (95% CI)</th>
<th>Absolute Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>55 (0.7)</td>
<td>45 (0.6)</td>
<td>1.29 (1.09–1.52)</td>
<td>0.1</td>
</tr>
<tr>
<td>Sight threatening eye bleed</td>
<td>57 (0.7)</td>
<td>64 (0.8)</td>
<td></td>
<td>-0.1</td>
</tr>
<tr>
<td>Serious gastrointestinal hemorrhage</td>
<td>137 (1.8)</td>
<td>101 (1.3)</td>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>Other major bleed</td>
<td>74 (1.0)</td>
<td>43 (0.6)</td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>Any major bleed</td>
<td>314 (4.1)</td>
<td>245 (3.2)</td>
<td>1.29 (1.09–1.52)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Rate Ratio 1.29 (1.09-1.52)

In recent cohort studies/trials, estimated ASCVD risk has exceeded actual risk observed during follow-up.

In addition, ASCVD risk generally tracks with bleeding risk.

The committee felt there was insufficient evidence to recommend a specific PCE risk threshold as an inclusion criterion for aspirin.

Instead clinicians should consider the totality of evidence for ASCVD risk [inclusive, where appropriate, of risk-enhancing factors, such as strong family history of premature MI, inability to achieve lipid or BP or glucose targets, or significant elevation in coronary artery calcium score] & to also tailor decisions about prophylactic aspirin to patient and clinician preferences.

Arnett DK, Blumenthal RS,....Michos ED...et al. Circulation 2019
A non-exhaustive list of scenarios associated with increased risk of bleeding includes:

- a history of previous GI bleeding or peptic ulcer disease or bleeding from other sites,
- age >70 years,
- thrombocytopenia, coagulopathy,
- chronic kidney disease,
- or concurrent use of other medications that increase bleeding risk such as NSAIDs, steroids, DOACs, or warfarin.
Role of Aspirin in Primary Prevention in Modern Era:

• Three recent large-scale primary prevention trials suggest aspirin may do more harm than good. Why?

• Compared to prior decades, in modern preventive practice:
  – Less smoking
  – Increased utilization of statins/aggressive lipid lowering
  – Better BP control

• Percent taking statin Rx in ASPREE, ARRIVE, & ASCEND was 34%, 43%, and 75%, respectively.

• Aspirin may reduce incidence of colorectal cancers (but cancer reduction not seen in ASCEND or ASPREE)
### Figure 3. Exploratory Cancer Outcomes

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>No. of Studies</th>
<th>No. of Aspirin Events</th>
<th>No. of Aspirin Participants</th>
<th>No. of No Aspirin Events</th>
<th>No. of No Aspirin Participants</th>
<th>Absolute Risk Difference, % (95% CI)</th>
<th>HR (95% CI)</th>
<th>Favors Aspirin</th>
<th>Favors No Aspirin</th>
<th>$\hat{p}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incident cancer</td>
<td>10</td>
<td>4507</td>
<td>63048</td>
<td>4409</td>
<td>61475</td>
<td>0.03 (-0.37 to 0.46)</td>
<td>1.01 (0.93-1.08)</td>
<td></td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Cancer mortality</td>
<td>12</td>
<td>1530</td>
<td>75353</td>
<td>1447</td>
<td>73781</td>
<td>0.05 (-0.11 to 0.23)</td>
<td>1.03 (0.96-1.11)</td>
<td></td>
<td></td>
<td>17</td>
</tr>
<tr>
<td>Low CV risk participants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incident cancer</td>
<td>4</td>
<td>2837</td>
<td>38905</td>
<td>2730</td>
<td>39044</td>
<td>0.41 (-0.13 to 1.01)</td>
<td>1.06 (0.95-1.24)</td>
<td></td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>Cancer mortality</td>
<td>5</td>
<td>823</td>
<td>49942</td>
<td>748</td>
<td>50078</td>
<td>0.16 (-0.06 to 0.42)</td>
<td>1.11 (0.93-1.33)</td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>High CV risk participants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incident cancer</td>
<td>6</td>
<td>1670</td>
<td>24143</td>
<td>1679</td>
<td>22431</td>
<td>-0.30 (-0.76 to 0.19)</td>
<td>0.96 (0.90-1.03)</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Cancer mortality</td>
<td>7</td>
<td>707</td>
<td>25411</td>
<td>699</td>
<td>23703</td>
<td>-0.13 (-0.41 to 0.17)</td>
<td>0.96 (0.86-1.06)</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Participants with diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incident cancer</td>
<td>3</td>
<td>1091</td>
<td>9640</td>
<td>1116</td>
<td>9655</td>
<td>-0.68 (-2.09 to 0.95)</td>
<td>0.95 (0.74-1.14)</td>
<td></td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>Cancer mortality</td>
<td>4</td>
<td>445</td>
<td>10667</td>
<td>438</td>
<td>10685</td>
<td>0.16 (-0.56 to 1.02)</td>
<td>1.05 (0.80-1.43)</td>
<td></td>
<td></td>
<td>25</td>
</tr>
</tbody>
</table>

**2019 Meta-Analysis: Aspirin Use for Primary Prevention with CVD & Bleeding Events**

**CVD prevention:** Number Needed to Treat: **265**

**Major Bleeding:** Number Needed to Harm: **210**

2.5% of women & 2% of men likely to have net benefit if 1 CVD event = 1 major bleed,
21.4% of women & 41% of men likely to have net benefit if 1 CVD event = 2 major bleeds.

• For some persons without CVD, aspirin is likely to result in net benefit.

• Net benefit subgroups had higher baseline CVD risk, higher levels of most established CVD risk factors, & lower levels of bleeding-specific risk factors than net harm subgroups.

• No matter which weighting is used (1:1 or 1:2), fewer than half of all patients ages 30-79 years without known CVD likely derive benefit from aspirin therapy for primary CVD prevention.

• (Prevention of cancer was not included in the analysis).

So who might benefit from aspirin for primary ASCVD prevention?

- Those with subclinical atherosclerosis (CAC)?
Assessment of ASCVD: Use of CAC
Coronary Artery Calcium (CAC) obtained by non-contrast cardiac CT

~1 mSv
Can CAC inform Aspirin Decision? (modeling from MESA)

NNH = Bleeds

So who else might benefit from aspirin for primary ASCVD prevention?
Remaining questions: Other subgroups that might benefit?

- **HIV**
  - Increased platelet dysfunction & immune activation in HIV, which is decreased with aspirin
  - Do we need a “REPRIEVE”-like trial for aspirin?

- **Auto-immune Disease**
  - RA, SLE, & psoriatic arthritis are inflammatory disorders with increased burden of subclinical CAD & clinical CVD risk
What about aspirin in those age >70 for primary prevention?

- Avoid initiating in “healthy” older adults age >70
  - Taking it preventively will not increase survival.
  - Given higher bleeding risk, difficult to justify routine use.
  - Don't take it to prevent cancer, as we do not know whether it helps or hurts

- What if already on therapy & doing well, should we de-prescribe?
  - We say say Yes
  - But engage patient in a shared discussion making discussion about stopping vs continuing
Making sense of Aspirin for CV Prevention: Our thoughts

• Aspirin still strongly indicated for secondary prevention

• Most healthy people should not take daily aspirin

• These recommendations differ from prior AHA guidelines recommending that aspirin is considered for patients with 10-yr ASCVD risk ≥10%.

• There may be select patients age 40 to 70 who have a very high risk of ASCVD, who may benefit if low risk for bleeding.
Making sense of Aspirin for CV Prevention: Our thoughts

- Consider low-dose aspirin (75-100 mg/day) in:
  - current smoking
  - strong family history of premature heart attacks
  - very elevated cholesterol with intolerance to statins
  - Subclinical atherosclerosis, $\text{CAC} > 100$
  - Select patients with diabetes with ASCVD $> 10\%$?
Making Sense of Aspirin for CV Prevention

- Consider low-dose aspirin (75-100 mg/day) in:
  - Current smoking
  - Strong family history of early heart attacks
  - Very elevated cholesterol with statin intolerance
  - Subclinical atherosclerosis, CAC >100
  - Select patients with ASCVD >20%?
- Thoughtful decisions needed in context of risk discussion
“Thus, beyond diet maintenance, exercise, and smoking cessation, the best strategy for the use of aspirin in the primary prevention of cardiovascular disease may simply be to prescribe a statin instead.”

-Dr. Paul Ridker, NEJM 2018
ASPIRIN
Healthy lifestyle is anti-inflammatory

“To prevent a heart attack, take one aspirin a day. Take it out for a jog, then take it to the gym, then take it for a bike ride…”
## Blood Pressure

<table>
<thead>
<tr>
<th>Blood Pressure Category</th>
<th>Systolic mm Hg (upper number)</th>
<th>Diastolic mm Hg (lower number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Less than 120</td>
<td>Less than 80</td>
</tr>
<tr>
<td>Elevated</td>
<td>120 – 129</td>
<td>Less than 80</td>
</tr>
<tr>
<td>High Blood Pressure (Hypertension) Stage 1</td>
<td>130 – 139</td>
<td>80 – 89</td>
</tr>
<tr>
<td>High Blood Pressure (Hypertension) Stage 2</td>
<td>140 or higher</td>
<td>90 or higher</td>
</tr>
<tr>
<td>Hypertensive Crisis (consult your doctor immediately)</td>
<td>Higher than 180</td>
<td>Higher than 120</td>
</tr>
</tbody>
</table>
**BLOOD PRESSURE**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>1. In adults with elevated blood pressure (BP) including those requiring antihypertensive medications nonpharmacological interventions are recommended:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• weight loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• heart-healthy dietary pattern</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• sodium reduction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• dietary potassium supplementation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• increased physical activity with a structured exercise program</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• limited alcohol</td>
</tr>
</tbody>
</table>
Adults With High Blood Pressure

10-yr risk <10%

Heart Healthy lifestyle

10-yr risk ≥10%

Diabetes

CKD

Heart Healthy lifestyle

Pharmacotherapy

Intensive lifestyle modification

Pharmacotherapy

Intensive lifestyle modification

Goal BP

130/80

140/90
Cholesterol Take Home Message

• **STATIN** Rx is 1st-line for primary prevention of ASCVD in patients:
  • Elevated LDL-C levels (≥190 mg/dl)
  • Those with diabetes mellitus who are age 40–75
  • Those determined to be at sufficient ASCVD risk after risk discussion
2. If clinical ASCVD, reduce LDL-C with high-intensity statin or max. tolerated statin

The more LDL-C is reduced → the greater the risk reduction

Use max. tolerated statin to lower LDL-C by ≥50%
3. **Very high-risk ASCVD**: use LDL-C threshold of 70 mg/dL to consider nonstatin

- **Very high-risk**: multiple major events or 1 major event + high-risk conditions
- Reasonable to add **ezetimibe** to max. tolerated statin if LDL-C remains ≥70
- If LDL-C ≥70 on max. statin + ezetimibe → adding **PCSK9i** is reasonable
  * long-term (>3 yrs) cost-effectiveness less certain
4. Severe primary hypercholesterolemia (LDL-C ≥190) → begin high-intensity statin

• If LDL-C ≥100 → ezetimibe reasonable

• If LDL-C on statin + ezetimibe remains ≥100 & other risk factors → consider PCSK9i, though long-term (>3 yrs) economic value less clear
B. Treatment goal for LDL-C

- Low
  - 3.0 mmol/L (116 mg/dL)
  - Score <1%
  - Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years without other risk factors

- Moderate
  - 2.6 mmol/L (100 mg/dL)
  - Score ≥1% and <5%
  - Markedly elevated single risk factors, in particular TC >8 mmol/L (310 mg/dL) or LDL-C >4.9 mmol/L (190 mg/dL) or BP ≥180/110 mmHg
  - FH without other major risk factors
  - Moderate CKD (eGFR 30–59 mL/min)
  - DM w/o target organ damage, with DM duration ≥10 years or other additional risk factor

& ≥50% reduction from baseline

- High
  - 1.8 mmol/L (70 mg/dL)
  - ASCVD (clinical/imaging)
  - Score ≥10%
  - FH with ASCVD or with another major risk factor
  - Severe CKD (eGFR <30 mL/min)

- Very High
  - 1.4 mmol/L (55 mg/dL)
  - DM & target organ damage: ≥3 major risk factors; or early onset of T1DM of long duration (>20 years)
Key Inclusion Criteria – REDUCE-IT

1. Age ≥45 years with established CVD (Secondary Prevention Cohort) or ≥50 years with DM with ≥1 additional risk factor for CVD (Primary Prevention Cohort)

2. Fasting TG levels ≥150 mg/dL & <500 mg/dL*

3. LDL-C >40 & ≤100 mg/dL and on stable statin Rx (± ezetimibe) for ≥4 weeks prior to qualifying measurements for randomization

*Due to the variability of triglycerides, a 10% allowance existing in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL. Protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL, with no variability allowance.


Together with
Primary End Point:
USA Subgroup CV Death, MI, CVA, Revasc, UAP

Hazard Ratio, 0.69
(95% CI, 0.59–0.80)
RRR = 31%
ARR = 6.5%
NNT = 15 (95% CI, 11–27)
P = 0.000001


*Estimated Kaplan-Meier event rate at approximately 5.7 years. The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses.
Cigarettes: Rx Options for Cessation

Nicotine replacement therapy:

- **Patch**
  - If >10 cigarettes/day use 21 mg
  - If <10 cigarettes/day use 14 mg or 7 mg

- **Gum**
  - 2 mg or 4 mg (start with 4mg if first tobacco is ≤30 min from waking); max is 20 lozenges or 24 pieces of gum per day

- **Lozenge**

- **Nasal spray**
  - 10 mg/mL

- **Oral inhaler**
  - 10 10-mg cartridge (max 6-16 cartridges/day)

Other pharmacotherapies:

- **Bupropion**
  - 150 mg SR daily (up to twice daily)

- **Varenicline**
  - 0.5 mg daily titrated to 1 mg twice daily
Cigarette/Tobacco Cessation

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>To facilitate tobacco cessation, it is reasonable to dedicate trained staff to tobacco treatment in every healthcare system.</td>
</tr>
<tr>
<td>III: Harm</td>
<td>B-NR</td>
<td>All adults &amp; adolescents should avoid secondhand smoke exposure to reduce risk.</td>
</tr>
</tbody>
</table>
Diet/Nutrition

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-R</td>
<td>1. Diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, &amp; fish is recommended to decrease risk factors.</td>
</tr>
<tr>
<td>IIA</td>
<td>B-NR</td>
<td>2. Replacement of saturated fat with dietary monounsaturated &amp; polyunsaturated fats can be beneficial.</td>
</tr>
<tr>
<td>IIA</td>
<td>B-NR</td>
<td>3. Diet containing reduced amounts of cholesterol &amp; sodium can be beneficial.</td>
</tr>
</tbody>
</table>
### DIET

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>4. As part of a healthy diet, it is reasonable to minimize intake of processed meats, refined carbohydrates, &amp; sweetened beverages.</td>
</tr>
<tr>
<td>III-Harm</td>
<td>B-NR</td>
<td>5. As part of a healthy diet, the intake of trans fats should be avoided to reduce risk.</td>
</tr>
</tbody>
</table>
Achieving Healthy Weight

Comprehensive lifestyle program ≥ 6 months
- Face-to-face or telephone-delivered weight loss program

Reduce caloric intake 500+ kcal/day
- Start by reducing intake > 300 kcal/day

Increase physical activity to > 150 min of brisk activity weekly
- Engage in >200 min/week of brisk activity

Monitor weight, BMI & WC
- Measure weight weekly
- Aim for > 5% of body weight.
### Diabetes: Non-pharmacologic Recommendations for T2DM

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tailored Comprehensive Nutritional Plan</strong></td>
</tr>
<tr>
<td>- Mediterranean, DASH, vegetarian/vegan</td>
</tr>
<tr>
<td>- Team based approach: registered dietitian-nutritionist or DM education program.</td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
</tr>
<tr>
<td>- A combination of aerobic and resistance is better than either alone.</td>
</tr>
<tr>
<td><strong>Set A GOAL</strong></td>
</tr>
<tr>
<td>- Better glycemic control + improve weight</td>
</tr>
</tbody>
</table>
### Diabetes Mellitus – Type 2

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>3. For adults with T2DM, it is reasonable to initiate <strong>metformin</strong> as 1st-line Rx along with lifestyle therapies at time of diagnosis to improve glycemic control &amp; reduce risk.</td>
</tr>
<tr>
<td>COR</td>
<td>LOE</td>
<td>Recommendations</td>
</tr>
<tr>
<td>-----</td>
<td>-----</td>
<td>-----------------</td>
</tr>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>4. For adults with T2DM &amp; additional ASCVD risk factors who require glucose-lowering Rx despite initial lifestyle modifications &amp; metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control &amp; reduce risk.</td>
</tr>
</tbody>
</table>
## CV risk categories in patients with DM

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very high-risk</strong></td>
<td>Patients with DM and established CVD or other target organ damage(^a) or three or more major risk factors(^b) or early onset T1DM of long duration (&gt;20 years)</td>
</tr>
<tr>
<td><strong>High-risk</strong></td>
<td>Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor</td>
</tr>
<tr>
<td><strong>Moderate-risk</strong></td>
<td>Young patients (T1DM &lt;35 years; T2DM &lt;50 years) with DM duration &lt;10 years, without other risk factors</td>
</tr>
</tbody>
</table>

\(^a\)Proteinuria, renal impairment defined as eGFR < 30mL/min/1.73m², left ventricular hypertrophy, or retinopathy.

\(^b\)Age, hypertension, dyslipidaemia, smoking, obesity
Spectrum of Physical Activity

Less Sedentary Time/
More Physical Activity
NO LOWER LIMIT

300 min of Moderate-intensity/week
150 min of vigorous-intensity/week

Higher better

? Diminished additive benefit

CV benefit
Cumulative Impact of Evidence-Based Heart Failure with Reduced EF Medical Therapies

<table>
<thead>
<tr>
<th></th>
<th>Relative-risk</th>
<th>2 yr Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>- -</td>
<td>35%</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>↓ 23%</td>
<td>27%</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>↓ 35%</td>
<td>18%</td>
</tr>
<tr>
<td>Aldosterone Ant</td>
<td>↓ 30%</td>
<td>13%</td>
</tr>
<tr>
<td>ARNI (replacing ACEI/ARB)</td>
<td>↓ 16%</td>
<td>11%</td>
</tr>
<tr>
<td>SGLT2 inhibitor</td>
<td>↓ 17%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Cumulative risk reduction if all evidence-based medical therapies are used: Relative risk reduction 74.0%, Absolute risk reduction: 25.9%, NNT = 3.9

**Assess Risk:** #PCE 1st → Personalized assessment (Low risk: <5%, Borderline/Intermediate risk: 5-%<20% & high risk: >20%) → Refine by CAC; CHA2DS2-VASc for CVA risk in case of Afib

**Antiplatelet Therapy:** #Rethink aspirin – Smoking, FamHx early MI, HeFH, CAC >100? ASCVD >20%?; P2Y12 inhibitor if recent PCI; Anticoagulate with NOAC or warfarin

**Blood Pressure:** #120 is new 140, Lifestyle 1st, If high risk → meds @ 130/80, If low risk → meds @ 140/90

**Cholesterol:** #PCE + REF; Shared decision making; Discuss statin if intermediate risk; Refine by CAC: Power of Zero!; If high-risk → target LDL-C <70mg/dl; Maximize statin → ezetimibe → PCSK9i

**Cigarette:** #Never too late to quit; 1st motivational interviewing → PharmacoRx next; Individualized and/or group social support counseling.
**Diabetes:** Screen for high risk (long duration, albuminuria, eGFR<60, retinopathy, neuropathy, ABI<0.9); Rx: Lifestyle → Metformin → SGLT2i/GLP1-RA; ACEI/ARB for BP.

**Diet:** Calculate BMI; Eat vegetables, fruits, nuts, legumes, whole grains, fish; Counseling & caloric restriction for maintaining weight loss

**Exercise:** Target >150 min./week of moderate or >75 min./week of vigorous-intensity activity; Any moderate-intensity physical activity is beneficial; Consider mHealth!

**Heart Failure:** ACEI/ARB/Aldosterone antagonist/ARNI/Beta Blocker should be considered; Consider ICD for those with low EF
‘ABCDEF’ of Cardiovascular Disease Management

A
- Antiplatelet therapy (SAP or DAP)
- Anticoagulant therapy (NOAC or warfarin)

B
- Beta-Blocker
- Blood Pressure: goal < 130/80

C
- Cholesterol
- Cigarette Cessation

D
- Diet & Weight Guidance
- Diabetes Prevention/Management (Metformin, SGLT2i, GLP1-RA)

E
- Exercise: >150 min of moderate or > 75 min of vigorous activity per week

F
- Heart Failure
  - ACE-I or ARB
  - ARNI
  - Aldosterone Antagonist
  - Beta blocker
  - SGLT2-i
Thank you!

Life’s Simple 7™

- Healthy Blood Pressures
- Be active
- Healthy Blood Cholesterol
- Healthy Diet
- Maintain normal weight
- Don’t smoke
- Normal blood sugar