Definitions of Different Types of Prevention

Primordial Prevention: Prevention of CHD risk factors

Primary Prevention: Modification of risk factors in order to prevent or delay the onset of CHD

Secondary Prevention: Initiation of therapy to reduce recurrent CHD events and decrease cardiac mortality in patients with established CHD

CHD = Coronary heart disease
Simplified Approach to Prevention
An ABC approach to prevention organizes important lifestyle changes and pharmacologic treatment

<table>
<thead>
<tr>
<th>Category</th>
<th>LIFESTYLE CHANGES</th>
<th>PHARMACOLOGICAL TREATMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Assessment of risk</td>
<td>ACE/ARB</td>
</tr>
<tr>
<td>B</td>
<td>BP control</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Cholesterol control</td>
<td>Cigarette smoking/tobacco cessation</td>
</tr>
<tr>
<td>D</td>
<td>Diet and weight management</td>
<td>DM prevention and management</td>
</tr>
<tr>
<td>E</td>
<td>Education, EF</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>Family history</td>
<td></td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; P2Y12 = platelet P2Y12 receptor antagonist.

---

Antiplatelet Therapy: Common Oral Agents

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Active Drug</th>
<th>Pro-Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Acetylsalicylic acid (ASA)</td>
<td>No</td>
</tr>
<tr>
<td>Ticlid®</td>
<td>Ticlopidine hydrochloride</td>
<td>No</td>
</tr>
<tr>
<td>Plavix®</td>
<td>Clopidogrel bisulfate</td>
<td>No</td>
</tr>
<tr>
<td>Effient®</td>
<td>Prasugrel hydrochloride</td>
<td>No</td>
</tr>
<tr>
<td>Brilinta®</td>
<td>Ticagrelor*</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Class:
- Salicylate
- Platelet P2Y12 Receptor Antagonist

Maintenance Dose:
- Acetylsalicylic acid (ASA): 75-325 mg daily
- Ticlopidine hydrochloride: 250 mg twice daily
- Clopidogrel bisulfate: 75 mg daily
- Prasugrel hydrochloride: 10 mg daily
- Ticagrelor*: 90 mg twice daily

Reversible: No

---

Aspirin Evidence: Primary Prevention in Women

Womens’ Health Study (WHS)
39,876 women randomized to aspirin (100 mg every other day) or placebo for an average of 10 years

Aspirin does not reduce CV events among women in the WHS

CV=Cardiovascular, CVA=Cerebrovascular accident, MI=Myocardial infarction

Ridker PM et al. 2005;352:1293-304
“An aspirin a day will help prevent a heart attack if you have it for lunch instead of a cheeseburger.”

Aspirin Evidence: Primary Prevention

Combined

HOT, 1998
PPP, 2001

RR of MI in Men

RR = 0.68 (0.54-0.86) P=0.001

RR = 1.13 (0.96-1.33) P=0.15

HOT, 1998
Combined

WHS, 2005
PPP, 2001

RR of MI in Women

RR = 0.99 (0.83-1.19) P=0.95

RR = 0.81 (0.69-0.96) P=0.01

Aspirin Evidence: Primary Prevention

Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) Study

2,539 diabetic patients without known coronary artery disease randomized to aspirin (81-100 mg) or placebo for a median of 4.7 years

Aspirin does not reduce the risk of adverse CV events in diabetics

Ridker P et al. NEJM 2005;352:1293-304

Ogawa H et al. JAMA 2008;300:2134-41
Aspirin Recommendations

**Primary Prevention (Women)**
1. Aspirin (81 mg daily or 100 mg every other day) in at-risk women ≥65 years of age
2. Aspirin in at-risk women <65 years of age for ischemic stroke prevention
3. Aspirin in optimal-risk women <65 years of age

CHD = Coronary heart disease

Mosca L et al. Circulation 2007;115:1481-95

Aspirin Recommendations (Continued)

**Primary Prevention (Men)**
- Aspirin (75-162 mg daily) in those at intermediate risk (10-year risk of CHD ≥10%)

*Specific guideline recommendations for men do not exist, but these guidelines are based on previous general (not gender-specific) primary prevention guidelines

CHD = Coronary heart disease


Clopidogrel Evidence: Secondary Prevention

**Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) Trial**

15,603 patients with multiple CV risk factors or known CVD randomized to aspirin (75-162 mg) or aspirin (75-162 mg) & clopidogrel (75 mg) for a mean of 30 months

Routine DAP therapy offers little long-term benefit

CV = Cardiovascular, CVA = Cerebrovascular accident, CHD = Coronary heart disease, DAP = Dual antiplatelet, M = Myocardial infarction

Bhatt DL et al. NEJM 2006;354:1706-17
### Clopidogrel Evidence: Secondary Prevention

**Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) Trial**

<table>
<thead>
<tr>
<th>Population</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualifying CAD, CVD or PAD</td>
<td>0.88 (0.77, 0.998)</td>
<td>0.04</td>
</tr>
<tr>
<td>Multiple Risk Factors</td>
<td>1.20 (0.91, 1.60)</td>
<td>0.20</td>
</tr>
<tr>
<td>Overall Population</td>
<td>0.93 (0.83, 1.05)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*Longer term DAP may provide benefit to those with CV disease*

---

**Franklin D. Roosevelt**

- **32nd President of the United States**
- **Born**: January 30, 1882, Hyde Park, New York
- **Died**: April 12, 1945 (aged 63), Warm Springs, Georgia
- **Cause of Death**: Massive Cerebral Hemorrhage
- **CVD Risk factor**: High Blood Pressure

By the time of the Yalta conference, FDR’s BP was ~230/130.
Provides information on response to Rx. May help improve adherence to Rx and evaluate “white-coat” HTN

Ambulatory BP monitoring
Indicated for evaluation of “white-coat” HTN. Absence of 10–20% BP decrease during sleep indicates increased CVD risk

Self-measurement
Provides information on response to Rx. May help improve adherence to Rx and evaluate “white-coat” HTN

Medical Conditions
- Chronic kidney disease
- Primary hyperaldosteronism
- Renovascular disease
- Chronic steroid therapy
- Cushing’s syndrome
- Phaeochromocytoma
- Aortic coarctation
- Thyroid or parathyroid disease
- Sleep apnea

Drugs
- NSAIDS
- Oral contraceptives
- Adrenal steroids
- Sympathomimetics
- Cyclosporine or tacrolimus
- Erythropoietin
- Ephedra, mu huang, bitter orange
- Cocaine or amphetamines
- Alcohol

High Blood Pressure Evidence: Number of Medications Needed

Trial (SBP Achieved)
- UKPDS (144 mm Hg)
- ABCD (127 mm Hg)
- MDRD (132 mm Hg)
- HOT (138 mm Hg)
- AASK (127 mm Hg)

Number of Meds
1 2 3 4
## High Blood Pressure Evidence: Primary Prevention

### Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

33,357 patients with HTN and ≥1 CHD risk factor randomized to chlorthalidone, amlodipine, or lisinopril for 5 years

- **Chlorthalidone**: 0.98 (0.90-1.07) 0.65
- **Amlodipine**: 0.99 (0.91-1.08) 0.81

**Rate of MI or fatal CHD**

**BP=Blood pressure, CHD=Coronary heart disease, HTN=Hypertension, MI=Myocardial infarction**

ALLHAT investigators. *JAMA* 2002;288:2981-97

---

### Losartan intervention for Endpoint (LIFE) Reduction in Hypertension Study

9,193 high-risk hypertensive* patients with LVH randomized to losartan (100 mg) or atenolol (100 mg) for 5 years

- **Losartan**: 13% RRR, P=0.021
- **Atenolol**:

**ARB=Angiotensin receptor blocker, CV=Cardiovascular, DBP=Diastolic blood pressure, LVH=Left ventricular hypertrophy, HTN=Hypertension, SBP=Systolic blood pressure**


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### Hypertension in the Very Elderly (HYVET) Trial

3,845 patients >80 years with SBP >160 mm Hg randomized to treatment to indapamide (1.5 mg) and perindopril (2-4 mg if needed) vs. placebo for 2 years

- **Indapamide +/- perindopril**: Blood pressure control in patients >80 years of age provides benefit

**CV=Cardiovascular, CVA=Stroke**

Beckett NS et al. *NEJM* 2008;358:1887-98
High Blood Pressure Evidence: Secondary Prevention

Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) Trial

15,245 patients with untreated HTN and high CV risk randomized to a BP lowering strategy with valsartan (160 mg) or amlodipine (10 mg) for 4.2 years

Primary cardiac composite endpoint
Cardiac mortality
Cardiac morbidity
All myocardial infarction
All congestive heart failure
All stroke
All-cause death
New-onset diabetes

Favors valsartan
Favors amlodipine

Both blood pressure lowering regimens provide similar efficacy

ARBS=Angiotensin receptor blocker, CCB=Calcium channel blocker, CV=Cardiovascular
Julius S et al. JACC 2004;43:3032-3031

High Blood Pressure Evidence: Effect of Intensive Blood Pressure Control

Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure Trial

4,733 diabetic patients randomized to intensive BP control (target SBP <120 mm Hg) or standard BP control (target SBP <140 mm Hg) for 4.7 years

Intensive BP control in DM does not reduce a composite of adverse CV events, but does reduce the rate of stroke

BP=Blood pressure, DM=Diabetes mellitus, HR=Hazard ratio, SBP=Systolic blood pressure
ACCORD study group. NEJM 2010;Epub ahead of print

JNC VII Guidelines: Management and Treatment

SBP=SBP* SBP* SBP* SBP* SBP* DBP=Diastolic blood pressure

Drug(s) for compelling indications.
‡ Other antihypertensive drugs (as needed).
Thiazide-type diuretics for most. May consider ACE-I, ARB, BB, CCB, or combination of these.

Yes 90–99 140–159 Stage 1 Hypertension
Drug(s) for compelling indications.
‡ No antihypertensive drug indicated.

Yes 80–89 120–139 Prehypertension
Encourage <80 <120 Normal
With compelling indications
Without compelling indications

With compelling indications
Without compelling indications

Chobanian AV et al. JAMA 2003;289:2560-2572
### Lifestyle Modifications for BP Control

<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>Approximate SBP Reduction Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>Maintain normal body weight</td>
<td>5-20 mmHg/10 kg weight lost</td>
</tr>
<tr>
<td>DASH eating plan</td>
<td>Diet rich in fruits, vegetables, low fat dairy and reduced in fat</td>
<td>8-14 mmHg</td>
</tr>
<tr>
<td>Restrict sodium intake</td>
<td>&lt;2.4 grams of sodium per day</td>
<td>2-8 mmHg</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Regular aerobic exercise for at least 30 minutes most days of the week</td>
<td>4-10 mmHg</td>
</tr>
<tr>
<td>Moderate alcohol</td>
<td>&lt;2 drinks/day for men and &lt;1 drink/day for women</td>
<td>2-4 mmHg</td>
</tr>
</tbody>
</table>

BMI=Body mass index, BP=Blood pressure, SBP=Systolic blood pressure

*Chobanian AV et al. JAMA 2003;289:2560-2572

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### Statins reduce relative risk of major CVD* similarly in primary & secondary prevention

*Major CVD = first occurrence of any major coronary event (nonfatal MI, coronary death), coronary revascularization, or stroke

CTT 2010: Meta-analysis of data from 170,000 participants in 26 trials (Lancet 376:1670-81)

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### HMG-CoA Reductase Inhibitor: Chronological Order of Event Driven Trials

**Study populations:**
- Acute Coronary Syndromes (Secondary prevention)
- Chronic coronary heart disease (Secondary prevention)

<table>
<thead>
<tr>
<th>Year</th>
<th>Study Name</th>
<th>Year</th>
<th>Study Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>4S</td>
<td>2002</td>
<td>PROSPER</td>
</tr>
<tr>
<td>1995</td>
<td>WOSCOPS</td>
<td>2002</td>
<td>ALLHAT-LLA</td>
</tr>
<tr>
<td>1996</td>
<td>CARE</td>
<td>2002</td>
<td>ASCOT-LLA</td>
</tr>
<tr>
<td>1998</td>
<td>AFCAPS/TEXCAPS</td>
<td>2004</td>
<td>PROVE-IT</td>
</tr>
<tr>
<td>1998</td>
<td>LIPID</td>
<td>2004</td>
<td>A to Z</td>
</tr>
<tr>
<td>2001</td>
<td>MIRACL</td>
<td>2005</td>
<td>TNT</td>
</tr>
<tr>
<td>2002</td>
<td>HPS</td>
<td>2005</td>
<td>IDEAL</td>
</tr>
<tr>
<td>2008</td>
<td>JUPITER</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**West of Scotland Coronary Prevention Study (WOSCOPS)**

6,595 men with moderate to marked hypercholesterolemia randomized to pravastatin (40 mg) or placebo for 5 yrs.

<table>
<thead>
<tr>
<th>Rate of MI or CHD death (%)</th>
<th>Pravastatin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5</td>
<td>5.3</td>
<td></td>
</tr>
</tbody>
</table>

**P<0.001**

A statin provides significant benefit in those with high cholesterol levels.

**Source:** Shepherd J et al. NEJM 1995;333:1301-1307

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**Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS)**

6,605 pts with average LDL-C levels randomized to lovastatin (20-40 mg) or placebo for 5 yrs.

<table>
<thead>
<tr>
<th>Rate of MI, unstable angina, or SCD (%)</th>
<th>Lovastatin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.5</td>
<td>3.5</td>
<td></td>
</tr>
</tbody>
</table>

**P<0.001**

A statin provides benefit in those with average LDL-C levels.

**Source:** Downs JR et al. JAMA 1998;279:1615–1622

---

**Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER)**

17,802 men (>50 yrs) and women (>60) with LDL-C <130 mg/dL and hs-CRP >2 mg/L randomized to rosuvastatin (20 mg) or placebo for up to 5 yrs.

<table>
<thead>
<tr>
<th>Cumulative incidence of CV death, MI, stroke, hospitalization for unstable angina, and arterial revascularization</th>
<th>Rosuvastatin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>0.0157</td>
<td>0.025</td>
</tr>
</tbody>
</table>

**44% RRR**

**P<0.00001, NNT=25**

Statin benefits those with mean age of 66 and elevated hsCRP.

**Source:** Ridker PM et al. NEJM 2008;359:2195-2207

*The study was stopped prematurely after 1.9 years.
AIM-High: Niacin in Patients with Established Vascular Disease and Atherogenic Dyslipidemia

- DSMB stopped trial early
- "Futility" cited as reason
- 1º EP 5.6% placebo v. 5.8% niacin
- Niacin stroke (1.6% v 0.7%)
- Niacin HDL 20%, TG 25%

SHOCKING NEWS
4/25/11
- DSMB stopped trial early
- "Futility" cited as reason
- 1º EP 5.6% placebo v. 5.8% niacin
- Niacin stroke (1.6% v 0.7%)
- Niacin HDL 20%, TG 25%

Primary Endpoint
1. CHD death
2. Nonfatal MI
3. Ischemic stroke
4. ACS: hospital
5. Symptomatic Revascularization

Fibrate Evidence: Primary and Secondary Prevention
Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial

5,518 diabetic patients on statin therapy randomized to fenofibrate (160 mg) or placebo for 4.7 years

On a background of statin therapy, a fibrate does not reduce CV events in diabetics

CV=Cardiovascular, MI=Myocardial infarction, RRR=Relative risk reduction

ACCORD study group. NEJM 2010;Epub ahead of print

Recommendations for Calcium Scoring Methods

Measurement of CAC is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk (10% to 20% 10-year risk).

Measurement of CAC may be reasonable for cardiovascular risk assessment persons at low to intermediate risk (6% to 10% 10-year risk).

Persons at low risk (<6% 10-year risk) should not undergo CAC measurement for cardiovascular risk assessment.
Heart Scans from 3 Individuals
Classified at Same CHD Risk
According to FRS

Normal coronaries with little or no plaque.
Coronaries with early calcification and plaque.
Coronaries with extensive calcification and plaque.

Case: 57 year old asymptomatic male

Past History: Mild hyperlipidemia – not on Rx
TC 228; TG 112; HDL 78; LDL 128; hsCRP 1.2
Framingham Risk Score: 10%
Family History: Negative
Social: Nonsmoker

Your recommendation: (a) Therapeutic lifestyle changes only
(b) Start lipid lowering therapy
(c) Exercise treadmill testing
(d) SPECT MPI
(e) Coronary artery calcium scoring

Case: 57 year old asymptomatic male

Past History: Mild hyperlipidemia – not on Rx
TC 228; TG 112; HDL 78; LDL 128; hsCRP 1.2
Framingham Risk Score: 10%
Family History: Negative
Social: Nonsmoker

Your recommendation: (a) Therapeutic lifestyle changes only
(b) Start lipid lowering therapy
(c) Exercise treadmill testing
(d) SPECT MPI
(e) Coronary artery calcium scoring

What if hsCRP was >2?
**What do others have to say?**

- “Calcium scanning is one of the worst examples of medicine gone wild...it’s taken on a ‘cultlike’ following”.

  ~Dr. Steve Nissen, Cleveland Clinic

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**Mike “David Koresh” Blaha**

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13
2012 – A Year Of Controversy: What To Do About Statins?

Makers of the case for widespread use of statins in the primary prevention of cardiovascular disease are in a bind. The latest scientific evidence is conflicting, and many doctors are concerned that the benefits may be overstated. The question of whether statins are effective in preventing heart disease is a complex one, and there is no easy answer.

September 2011: Archives of Internal Medicine


May 2012: The American Journal of Medicine


Wall Street Journal 1/23/2012

Should Healthy People Take Cholesterol Drugs to Prevent Heart Disease?
Statins should not be given to any primary prevention patients. • Side effects • No improvement in Mortality • Costs • “Moral Hazard”—excuse to not improve lifestyle

2012 - A Year Of Controversy: What To Do About Statins?

The Debut of Dueling Viewpoints

June 2012: JAMA

Statin Therapy for Healthy Men Identified as “Increased Risk”

Healthy Men Should Not Take Statins


June 2012: JAMA

Statin Primary Prevention: Reviewing the Data

Table 1: Characteristics and Results of the Four Randomized Trials Included in the Meta-analysis for Statin and Primary Prevention

Quality of data limited by duration of long term follow-up

15
Statin Primary Prevention: Morbidity & Mortality

| Table 1: Characteristics and Results of the Three Most Recently Published Meta-analyses for Statin Primary Prevention
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Year Published</td>
</tr>
<tr>
<td>2009</td>
</tr>
<tr>
<td>2010</td>
</tr>
<tr>
<td>2011</td>
</tr>
</tbody>
</table>

---

When To Start Treatment?

"We agree that statins are not likely to benefit patients with low CVD risk but emphasize that it is paramount to make the distinction between low-risk patients and patients with risk factors resulting in intermediate to high lifetime risk of developing coronary heart disease...existing risk-based treatment algorithms...suggest a benefit for statin use in those considered at intermediate (Framingham risk score 5%-20%) risk..."

Table from JUPITER:

“All I've got to say is don’t be faultless to a fault, fellas”

Robert Browning

Costs of Diet & Exercise

• Fundamentally free

• Some considerations:
  - Nutritionist fees
  - Exercise equipment fees
  - Gym fees

Exercise

• Simple message that can work for many patients:
  - Wear pedometer & aim for ≥10,000 steps/day.
  • Can quantify the activity level across a broad range of activities, including walking, jogging, running, and tennis.
Statins in Low Risk Patients: 2012 CTT Mortality Data

Reduction in total mortality includes high risk pts with known vascular disease AND those without disease but 5-10% 5-year risk of MVE

How 99.9% of us think about prescribing a generic statin to adults at increased risk

• It’s like one of the certainties of life -- like Billy Joel selling out the Garden in less than an hour.

Five P's to Consider when Discussing Personalized Statin Initiation in a High Lifetime Risk Patient

• Preference: What does the patient prefer?
• Precision: Is further testing for more precise risk stratification warranted?
• Participation: How motivated is the patient to improve lifestyle habits?
• Potency: What statin potency will likely be required to attain therapeutic targets?
• Price: Can the patient afford the drug and do the benefits likely outweigh the risks?
How Long Will It Take Us to Evolve?

Risk Factors: Guess & Treat
Paradigm Shift
Directly Measure & Rx Accordingly

„I’m prescribing a patch to help you quit smoking. Wear it over your mouth.„

Tobacco Cessation Recommendations

<table>
<thead>
<tr>
<th>Goals</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete cessation</td>
<td>Ask about tobacco use at every visit</td>
</tr>
<tr>
<td></td>
<td>In a clear, strong, and personalized manner, advise the patient to stop smoking</td>
</tr>
<tr>
<td>No environmental tobacco smoke exposure</td>
<td>Urge avoidance of exposure to second-hand smoke at work and home</td>
</tr>
<tr>
<td>J  B  I  II  III</td>
<td>Assess patient’s willingness to quit smoking</td>
</tr>
<tr>
<td></td>
<td>Develop a plan for smoking cessation and arrange follow-up</td>
</tr>
<tr>
<td></td>
<td>Provide counseling, pharmacologic therapy, and referral to a formal cessation program</td>
</tr>
</tbody>
</table>

Smith SC Jr. et al. JACC 2006;47:2130-9