Prevention of Coronary Heart Disease

(...and dementia...and even cancer...)

2017

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Co-director, UCLA Program in Preventive Cardiology
Disclosures

Research grants:: NHLBI, NIDDK, NIH BD2K

Consultant: Amarin, Amgen, Behringher Ingelheim and Quest

Speaker’s Bureau: Behringher Ingelheim
Total Deaths, United States - 2015

Heart disease
Cancer
Chronic lower respiratory disease
Accidents
Stroke
Alzheimers disease

Centers for Disease Control and Prevention, National Center for Health Statistics 2015
Dementia: The disease Americans fear the most

“What disease do you fear the most?”

Data from YouGov survey, August 2013; US respondents over 60

Graphic from 2014 Alzheimer’s Disease Facts and Figures, Alzheimer’s Association, Chicago
Dementia rates are declining

- In the Framingham Heart study, a 60 year old today has a 44% lower risk of developing dementia than 30 years ago

Dementia rates also are down in Germany

<table>
<thead>
<tr>
<th>Time period #1</th>
<th>Time period #2</th>
<th>Time period #3</th>
<th>Time period #4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at dementia onset (years)</td>
<td>80</td>
<td>82</td>
<td>84</td>
</tr>
</tbody>
</table>
Cancer rates are declining

After decades of decline, heart disease mortality rates flattened between 2011-2014 and actually **INCREASED** in 2015

Centers for Disease Control and Prevention, National Center for Health Statistics 2015
Age-period incidence rates of ischemic stroke and ST-segment elevation myocardial infarction ( STEMI) comparing four 5-year time periods for ten 5-year age groups.

Joel N. Swerdel et al. J Am Heart Assoc 2016;5:e004245
Learning Objectives

• To discuss recent increase in cardiovascular deaths and to review preventive strategies (traditional and non-traditional) for the prevention of heart disease

• To review common preventive strategies against heart disease, cancer and dementia

• To discuss controversies and complexities in prevention
CASE

• Your 61 year-old patient with hypertension and h/o gout presents for routine follow up. He’s rattled by recent high-profile cardiovascular deaths, so he’s begun drinking wine (he heard it was “good for the heart”). But he asks “What else should I be doing?”

Current medications:
Losartan 100 mg daily

Pertinent physical exam findings:
BP-149/82, BMI-34.9

Pertinent lab findings:
LDL-115  FBS – 115  HbA1c-6.5

Mr. Smith
HYPERTENSION
2014 JNC 8 Algorithm

Lifestyle Modification

Age > 60
- < 150 / 90
  - Non Black
    - Thiazide, ACE-I, ARB or CCB Alone or in combination

Age < 60
- < 140 / 90
  - Black
    - Thiazide or CCB Alone or in combination

All Ages Diabetes
- < 140 / 90
  - ACE-I or ARB Alone or in combination

All Ages CKD
- < 140 / 90

JAMA. Published online December 18, 2013. doi:10.1001/jama.2013.284427
A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group

- Randomized trial examining the effect of a SBP goal of <140 mm Hg or a goal of < 120 mm Hg
- Men and women ≥ 50 years old
- SBP 130 – 180 mm Hg (Treated or untreated)
- High Risk
  - Clinical or subclinical CVD
  - CKD (GFR 20 – 59)
  - Framingham Risk Score ≥ 15%
  - Age ≥ 75 years
- Exclusions: prior stroke, severe CKD, CHF, diabetes
SPRINT: Outcomes

Primary Outcome
(MI, Stroke, Heart failure, ACS, CV death)

- **25% RRR**
  - Standard (319 events)
  - Intensive (243 events)

Total Mortality

- **27% RRR**
  - Standard (319 events)
  - Intensive (243 events)

SPRINT. N Engl J Med 2015 November 9
## SPRINT Serious Adverse Events

<table>
<thead>
<tr>
<th>SAE reports</th>
<th>Number (%) of Participants</th>
<th>Intensive</th>
<th>Standard</th>
<th>HR (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1793 (38.3)</td>
<td>1736 (37.1)</td>
<td>1.04 (0.25)</td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
<td>110 (2.4)</td>
<td>66 (1.4)</td>
<td>1.67 (0.001)</td>
</tr>
<tr>
<td>Syncope</td>
<td></td>
<td>107 (2.3)</td>
<td>80 (1.7)</td>
<td>1.33 (0.05)</td>
</tr>
<tr>
<td>Injurious fall</td>
<td></td>
<td>105 (2.2)</td>
<td>110 (2.3)</td>
<td>0.95 (0.71)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td></td>
<td>87 (1.9)</td>
<td>73 (1.6)</td>
<td>1.19 (0.28)</td>
</tr>
<tr>
<td>Electrolyte abnormality</td>
<td></td>
<td>144 (3.1)</td>
<td>107 (2.3)</td>
<td>1.35 (0.020)</td>
</tr>
<tr>
<td>Acute kidney injury or renal failure</td>
<td></td>
<td>193 (4.1)</td>
<td>117 (2.5)</td>
<td>1.66 (&lt;0.001)</td>
</tr>
</tbody>
</table>
In general, the more intensive the pharmacologic therapy, the more side effects
Your 61 year-old patient with hypertension and h/o gout presents for routine follow up. He’s rattled by recent high-profile cardiovascular deaths, so he’s begun drinking wine (he heard it was “good for the heart”). But he asks “What else should I be doing?”

**CASE**

Because of the SPRINT data, we add Amlodipine to treat his hypertension.

Mr. Smith mentions that he is also worried about dementia and cancer.
Rationale for Common Strategies

• Why might heart disease, dementia and cancer share common preventive strategies

• All 3 are known to have a preventive component

• All 3 are strongly age related

• All 3 involve common pathophysiology:
  1. Inflammation
  2. Oxidative stress
  3. Cellular dysfunction
All-cause and vascular dementia rates increase with increasing BP levels

**All-cause dementia**

- Normal
- PreHT
- Stage 1
- Stage 2

**Vascular dementia**

- Normal
- PreHT
- Stage 1
- Stage 2

**Alzheimer’s disease**

- Normal
- PreHT
- Stage 1
- Stage 2

Hypertension 2011. 58: 1
Treating hypertension reduces dementia

<table>
<thead>
<tr>
<th>Study</th>
<th>Active (N/n)</th>
<th>Placebo (N/n)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROGRESS RR¹²</td>
<td>3051/193</td>
<td>3054/217</td>
<td>0.89 (0.74-1.07)</td>
</tr>
<tr>
<td>Syst-Eur RR¹⁰</td>
<td>1238/11</td>
<td>1180/21</td>
<td>0.50 (0.25-1.02)</td>
</tr>
<tr>
<td>SHEP RR¹⁴</td>
<td>2365/37</td>
<td>2371/44</td>
<td>0.84 (0.55-1.30)</td>
</tr>
<tr>
<td>HYVET RR</td>
<td>1687/126</td>
<td>1649/137</td>
<td>0.90 (0.71-1.13)</td>
</tr>
<tr>
<td>Combined (random)</td>
<td></td>
<td></td>
<td>0.87 (0.76-1.00)</td>
</tr>
</tbody>
</table>

Cochran Q=2.409; p=0.491

Test for overall effect; p=0.045
Treating hypertension has no effect on cancer

**ACE inhibitors**

- No effect

**Beta blockers**

- No effect

**Calcium Channel Blockers**

- No effect

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*The Lancet Oncology 2011 12, 65-82DOI: (10.1016/S1470-2045(10)70250-6)*
COMPLEXITY

Just because an association exists between a given factor and a given outcome, doesn’t mean that modifying that factor will improve outcomes.
What do we tell our patient

• We tell him that antihypertensive therapy:
  – Will likely reduce his risk of heart disease, stroke and cardiovascular death
  – Will likely reduce his risk of dementia
  – Will likely have no effect on cancer rates
CHOLESTEROL
CASE

• A 61 year-old man with a h/o hypertension and gout presents for routine follow up. He’s rattled by recent high-profile cardiovascular deaths, so he’s begun drinking wine (he heard it was “good for the heart”). But he still wonders “What else should I be doing?”

Current medications:
Lisinopril 10 mg daily

Pertinent physical exam findings:
BP-149/82, BMI-34.9

Pertinent lab findings:
**LDL-115**  FBS – 115  HbA1c-6.5
AHA/ACC 2013 Cholesterol Treatment Guidelines


Circulation. published online November 12, 2013;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

AHA = American Heart Association; ACC = American College of Cardiology.
### ACC/AHA Statin Benefit Groups

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| **Secondary Prevention**       | - Age $\leq$ 75: High-intensity statin  
                              - Age $>$ 75: Moderate-intensity statin                                         |
| **Clinical ASCVD**             |                                                                                |
| **Primary Prevention**         | - High-intensity statin                                                          |
| **LDL-C $\geq$ 190 mg/dL**     |                                                                                |
| **Diabetes Mellitus**          | - Low risk (10-yr risk $< 7.5\%$): Moderate-intensity statin  
                              - High risk (10-yr risk $\geq 7.5\%$): High-intensity statin               |
| Age 40–75 with diabetes and LDL 70–189 mg/dL, |                                      |
| **Primary Prevention**         | - Consider moderate or high intensity statin                                     |
| Age 40–75, $> 7.5\%$ 10-yr ASCVD risk |                                      |

ASCVD Risk Estimator

- Gender
- Age
- Race
- Total Cholesterol
- HDL Cholesterol
- Systolic BP
- Treatment for BP?
- Diabetes
- Smoking

http://www.apple.com/itunes/affiliates/download/?id=808875968

Or just google: “ASCVD risk calculator”
# Intensity of Statin Therapy

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL-C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL-C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL-C on average, by &lt;30%</td>
</tr>
<tr>
<td>Atorvastatin (40†)-80 mg</td>
<td>Atorvastatin 10 (20) mg</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20 (40) mg</td>
<td>Rosuvastatin (5) 10 mg</td>
<td>Pravastatin 10-20 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20-40 mg‡</td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40 (80) mg</td>
<td>Fluvastatin 20-40 mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
<td>Pitavastatin 1 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg bid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2-4 mg</td>
<td></td>
</tr>
</tbody>
</table>
HOPE-3 Cholesterol Lowering Trial (Heart Outcomes Prevention Evaluation)

- 12,705 intermediate risk patients (average ASCVD risk ~ 10%) randomized to receive either rosvuavatatin 10 mg daily (moderate intensity statin) or placebo
- No entry lipid criteria
- No routine monitoring
- No dose titration

HOPE 3: CV Death, MI, Stroke, Cardiac Arrest, Revascularization, Heart Failure

HR (95% CI) = 0.75 (0.64-0.88)

CASE

• A 61 year-old man with a h/o hypertension and gout presents for routine follow up. He’s rattled by recent high-profile cardiovascular deaths, so he’s begun drinking wine (he heard it was “good for the heart”). But he still wonders “What else should I be doing?”

Because of compelling clinical trial data and elevated ASCVD risk, we add atorvastatin to his regimen.

Current medications:
Lisinopril 10 mg daily

Pertinent physical exam findings:
BP-149/82, BMI-34.9

Pertinent lab findings:
LDL-115, FBS – 115, HbA1c-6.5
Statin use is associated with reduced dementia risk in observational studies

Results of 7 observational studies

Rockwood K et al. Arch Neurol. 2002;59:223-227
Yaffe K et al. Arch Neurol. 2002;59:378-384

ALL COHORT STUDIES

0.43 (0.31-0.62)

Etminan et al. Pharmacotherapy. 2003;23:726-730
Statin use had no effect on cognitive function in the PROSPER trial (RCT)

5,804 patient > 70 y.o. Randomized to pravastatin 40 mg daily or placebo. Formal cognitive testing performed.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Pravastatin - Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of correct letter digits recalled</td>
<td>-0.01 (-0.24-0.23)</td>
<td>0.95</td>
</tr>
<tr>
<td>Number of words Remembered</td>
<td>+0.02 (-0.12-0.16)</td>
<td>0.80</td>
</tr>
<tr>
<td>Time needed to complete Stroop test</td>
<td>+0.8 s (-0.4-2.0)</td>
<td>0.19</td>
</tr>
<tr>
<td>MMSE score</td>
<td>+0.06 (-0.04-0.16)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Even if observational studies suggest benefit of a given therapy, we don’t truly know if the therapy works until we test it by randomized controlled trial.
Low cholesterol levels are associated with increased cancer rates in observational studies.

70,179 Copenhagen cardiovascular study participants

Genetically decreased LDL cholesterol levels are not associated with cancer rates. “This finding suggests that low LDL cholesterol levels per se do not cause cancer.”

Marianne Benn et al. JNCI J Natl Cancer Inst 2011;jnci.djr008
### Statin therapy has no effect on cancer rates

<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment</th>
<th>Control</th>
<th>Rate Ratio (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 year</td>
<td>412 (1.0)</td>
<td>441 (1.1)</td>
<td>0.95 (0.81 – 1.12)</td>
</tr>
<tr>
<td>1-2 years</td>
<td>532 (1.4)</td>
<td>513 (1.3)</td>
<td>1.03 (0.89 – 1.20)</td>
</tr>
<tr>
<td>2-3 years</td>
<td>512 (1.4)</td>
<td>514 (1.4)</td>
<td>0.99 (0.85 – 1.15)</td>
</tr>
<tr>
<td>3-4 years</td>
<td>494 (1.4)</td>
<td>476 (1.4)</td>
<td>1.00 (0.86 – 1.16)</td>
</tr>
<tr>
<td>4-5 years</td>
<td>384 (1.3)</td>
<td>374 (1.3)</td>
<td>1.02 (0.86 – 1.21)</td>
</tr>
<tr>
<td>5+ years</td>
<td>233 (1.3)</td>
<td>218 (1.2)</td>
<td>1.05 (0.84 – 1.32)</td>
</tr>
<tr>
<td>All times</td>
<td>2567 (6.4)</td>
<td>2536 (6.4)</td>
<td>1·00 (0·95 – 1·06)</td>
</tr>
</tbody>
</table>

Effect p = 0.9

---

COMPLEXITY

Reverse causality (chicken vs. egg) can lead us astray when assessing associations.
What do we tell our patient

• We tell him that statin therapy:
  – Will likely reduce his risk of heart disease, stroke and cardiovascular death
  – Will likely have **no** effect on cognitive function
  – Will likely have **no** effect on cancer rates
OBESITY
CASE

• A 61 year-old man with a h/o hypertension and gout presents for routine follow up. He’s rattled by recent high-profile cardiovascular deaths, so he’s begun drinking wine (he heard it was “good for the heart”). But he still wonders “What else should I be doing?”

Current medications:
Lisinopril 10 mg daily

Pertinent physical exam findings:
BP-149/82  BMI-34.9

Pertinent lab findings:
LDL-115, FBS – 115  HbA1c-6.5
Swedish Obese Subjects (SOS) Study

Nonrandomized prospective study of obese patients. 2,010 had surgery compared with 2,037 contemporaneously matched controls.

Bariatric Surgery and Prevention of Type 2 Diabetes in Swedish Obese Subjects

Lena M.S. Carlsson, M.D., Ph.D., Markku Peltonen, Ph.D., Sofie Ahlin, M.D., Åsa Anveden, M.D., Claude Bouchard, Ph.D., Björn Carlsson, M.D., Ph.D., Peter Jacobson, M.D., Ph.D., Hans Lönnroth, M.D., Ph.D., Cristina Maglio, M.D., Ingmar Näslund, M.D., Ph.D., Carlo Pirazzi, M.D., Stefano Romeo, M.D., Ph.D., Kajsa Sjöholm, Ph.D., Elisabeth Sjöström, M.D, Hans Wedel, Ph.D., Per-Arne Svensson, Ph.D., and Lars Sjöström, M.D., Ph.D.

ABSTRACT

BACKGROUND

Weight loss protects against type 2 diabetes but is hard to maintain with behavioral...
Bariatric Surgery is Associated with Reduced Mortality: SOS Study 15 year f/u

30% lower mortality risk
41% lower CAD risk

Sjostrom L NEJM 2007: 357-741-752
Effect of bariatric surgery on cancer incidence – SOS study

Men: No effect

Women: 42% lower cancer risk

Figure 3: The unadjusted cumulative fatal plus non-fatal cancer incidence from the start of the intervention by sex in surgically treated obese individuals and in obese control individuals

What about dementia?

Obesity is associated with lower brain volumes

- Obesity is associated with:
  - Lower brain volumes  
    *Ward, et al., 2005*
  - Worse cognitive function  
    *Debette, et al., 2011*
  - Brains of overweight / obese people appear 8 and 16 years older, respectively  
    *Raji, et al., 2010*
CASE

We recommend 30 minutes of brisk walking daily and a calorie reduced diet for weight reduction.

Current medications:
Lisinopril 10 mg daily

Pertinent physical exam findings:
BP-149/82, BMI-34.9

Pertinent lab findings:
LDL-115, FBS – 115  HbA1c-6.5

Mr. Smith
What do we tell our patient

• We tell him that weight loss:
  – Will likely reduce his risk of heart disease, stroke and cardiovascular death
  – May reduce his risk of cancer
  – May improve his cognitive function
CASE

• A 61 year-old man with a h/o hypertension and gout presents for routine follow up. He’s rattled by recent high-profile cardiovascular deaths, so he’s begun drinking wine (he heard it was “good for the heart”). But he still wonders “What else should I be doing?”

Current medications:
Lisinopril 10 mg daily

Pertinent physical exam findings:
BP-149/82, BMI-34.9

Pertinent lab findings:
LDL-115  FBS – 115  HbA1c-6.5
Criteria for the Diagnosis of Diabetes

A1C ≥6.5%

or

Fasting plasma glucose ≥126 mg/dL

or

2-h plasma glucose ≥200 mg/dL

or

Random plasma glucose ≥200 mg/dL

ADA. 2. Classification and Diagnosis. Diabetes Care 2015;38(suppl 1):S9; Table 2.1
UKPDS Glucose Interventional Trial

Randomisation
1977-1991

- 2,729 Intensive
  with sulfonylurea/insulin

- 1,138 (411 overweight) Conventional
  with diet

Trial end 1997

- Intensive

- Conventional

5,102 Newly-diagnosed type 2 diabetes

4209

- 342 (all overweight) Intensive
  with metformin
# Effect of Metformin Therapy

*After median 8.8 years post-trial follow-up*

<table>
<thead>
<tr>
<th>Aggregate Endpoint</th>
<th>1997</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes related endpoint</td>
<td>RRR: 32%</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>(p: 0.0023)</td>
<td>(0.013)</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>RRR: 29%</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>(p: 0.19)</td>
<td>(0.31)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>RRR: 39%</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>(p: 0.010)</td>
<td>(0.005)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>RRR: 36%</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td>(p: 0.011)</td>
<td>(0.002)</td>
</tr>
</tbody>
</table>

RRR = Relative Risk Reduction, \(P = \text{Log Rank}\)

NEJM 2008 : 359
CASE

- A 61 year-old man with a h/o hypertension and gout presents for routine follow up evaluation.

As guidelines recommend we begin Metformin therapy for his Type 2 DM

Current medications:
Lisinopril 10 mg daily

Pertinent physical exam findings:
BP-149/82, BMI-34.9

Pertinent lab findings:
LDL-115  FBS – 115  HbA1c-6.5
Diabetes is associated with increased risk of cancers

- **Pancreas** Huxley, Br. J Cancer 2005
- **Colorectal** Larsson, J Ntl Cancer Insti 2005
- **Bladder** Larsson, Diabetologia 2005
- **Prostate** Kasper, Cancer Epi 2006
- **Liver** El-Sarag, Clin GE Hepat 2006
- **Breast** Larsson, Int J Cancer 2007
- **Endometrial** Friberg, Diabetologia 2007
- **NH Lymphoma** Mitri, Diabetes Care 2005
- **Bladder** Larsson, Diabetologia 2005

Decreased Risk

<table>
<thead>
<tr>
<th>Decreased Risk</th>
<th>Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6</td>
<td>1.3</td>
</tr>
<tr>
<td>0.9</td>
<td>1.43</td>
</tr>
<tr>
<td>1.0</td>
<td>1.82</td>
</tr>
<tr>
<td>1.3</td>
<td>2.5</td>
</tr>
<tr>
<td>1.6</td>
<td>2.1</td>
</tr>
<tr>
<td>1.9</td>
<td>2.1</td>
</tr>
<tr>
<td>2.1</td>
<td>2.5</td>
</tr>
<tr>
<td>3.0</td>
<td></td>
</tr>
</tbody>
</table>
Diabetes is associated with increased risk of dementia

**ALL DEMENTIA**

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>English and Scottish Health surveys</td>
<td>1.15 (0.88, 1.92)</td>
<td>0.15</td>
</tr>
<tr>
<td>ACT Study</td>
<td>1.23 (0.86, 1.76)</td>
<td>0.32</td>
</tr>
<tr>
<td>Hisayama Study</td>
<td>1.51 (0.87, 2.63)</td>
<td>0.21</td>
</tr>
<tr>
<td>Kundsholmen Project</td>
<td>1.57 (1.06, 2.35)</td>
<td>0.25</td>
</tr>
<tr>
<td>NHIC Korea</td>
<td>1.60 (1.40, 1.89)</td>
<td>1.78</td>
</tr>
<tr>
<td>MHAS</td>
<td>1.63 (1.33, 2.91)</td>
<td>0.21</td>
</tr>
<tr>
<td>OCTO-Twin Study</td>
<td>1.66 (1.14, 2.43)</td>
<td>0.29</td>
</tr>
<tr>
<td>NHI, Taiwan</td>
<td>1.66 (1.65, 1.72)</td>
<td>95.98</td>
</tr>
<tr>
<td>Kame project</td>
<td>1.77 (0.93, 3.38)</td>
<td>0.10</td>
</tr>
<tr>
<td>SALSA Study</td>
<td>1.98 (1.24, 3.15)</td>
<td>0.19</td>
</tr>
<tr>
<td>Framingham Study</td>
<td>2.11 (1.29, 3.38)</td>
<td>0.17</td>
</tr>
<tr>
<td>CCMS</td>
<td>2.24 (1.28, 3.37)</td>
<td>0.16</td>
</tr>
<tr>
<td>Norwegian Counties Study</td>
<td>2.25 (0.84, 6.07)</td>
<td>0.04</td>
</tr>
<tr>
<td>ARIC</td>
<td>2.28 (1.49, 3.49)</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>1.68 (1.64, 1.71)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

*P = 0.0%*, *p = 0.650*

**VASCULAR DEMENTIA**

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>MNAS</td>
<td>1.12 (0.33, 3.76)</td>
<td>3.26</td>
</tr>
<tr>
<td>ACT Study</td>
<td>1.19 (0.47, 3.47)</td>
<td>4.21</td>
</tr>
<tr>
<td>NHIC, Taiwan</td>
<td>1.47 (1.87, 2.25)</td>
<td>37.62</td>
</tr>
<tr>
<td>Hisayama Study</td>
<td>2.01 (0.96, 3.16)</td>
<td>6.04</td>
</tr>
<tr>
<td>NHIC Korea</td>
<td>2.30 (2.00, 2.90)</td>
<td>21.37</td>
</tr>
<tr>
<td>Kundsholmen Project</td>
<td>2.86 (1.08, 7.60)</td>
<td>4.84</td>
</tr>
<tr>
<td></td>
<td>2.26 (1.56, 3.24)</td>
<td>7.96</td>
</tr>
<tr>
<td></td>
<td>2.15 (1.80, 2.59)</td>
<td>4.01</td>
</tr>
</tbody>
</table>

*P = 0.0%*, *p = 0.137*

**NON-VASCULAR DEMENTIA**

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-vascular dementia</td>
<td>5.75 (2.11, 14.41)</td>
<td>4.98</td>
</tr>
<tr>
<td>MNAS</td>
<td>2.34 (1.86, 2.94)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

*P = 29.9%, *p = 0.161*

**DIABETES LESS RISKY**

**DIABETES MORE RISKY**

Saion Chatterjee et al. Dia Care 2016;39:300-307
Total Recall: Metformin vs. Placebo

80 men and women (55 to 90 years old) with minor cognitive impairment + overweight or obesity; randomized to metformin 1000 mg twice a day or matching placebo for 12 months.
Proposed mechanism of action of metformin in cancer.

ELEVATED INSULIN LEVELS

INDIRECT

DIRECT

Proposed Mechanism of Metformin Action Against Cancers
Meta-analysis: metformin use and cancer

A. Cancer Incidence

- Schernthaner, 2004 (QUARTET-M)
- Hanefeld, 2004 (QUARTET-C)
- Kahn, 2006 (ADOPT-G)
- Kahn, 2006 (ADOPT-R)
- Morgan, 2009
- Currie, 2009
- Libby, 2009
- Hense, 2011
- Ngwana, 2012
  - SRR adjusted for BMI: 0.82 (0.70-0.96)
  - Summary RR: 0.69 (0.52-0.90)
  - $\hat{I}^2=88$

B. Cancer Mortality

- UKPDS, 1998
- Landman, 2009
- Libby, 2009
- Bo, 2011
- Baur, 2011
  - SRR adjusted for BMI: 0.60 (0.45-0.80)
  - Summary RR: 0.66 (0.54-0.81)
  - $\hat{I}^2=66$

What do we tell our patient

• We tell him that metformin therapy:
  – May reduce his risk of heart disease, stroke and cardiovascular death
  – May reduce his risk of cancer
  – May improve his cognitive function
Should he take daily Aspirin to lower his cardiovascular risk?
People 50 - 69 years old who have a 10% or greater 10-year risk for CVD and who do not have a higher risk of bleeding should consider taking low-dose aspirin to help prevent CVD and colorectal cancer.
How can we determine who should get aspirin?

• The **ASPIRIN GUIDE**: an app developed by physicians at Brigham & Women’s Hospital (Harvard)

• The app calculates potential vascular benefit (from ASCVD risk score) and also potential bleeding risk

• From this, an aspirin recommendation is made
How can we determine who should get aspirin?

Guidance: Advise low-dose aspirin (75-81 mg/d)

ASCVD Risk Score: 15.3% over 10 years without aspirin use.

Bleeding Risk Score: 2.1% over 10 years without aspirin use.
2 risk factors for increased risk of bleeding
- Age > 60
- Male
COMPLEXITY

When trying to prevent one disease, it is important to beware of causing another disease.
Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials

A

Incidence

Mortality

Risk (%)

p=0.04

p=0.006

Control

Aspirin
Risk of Colorectal cancer in patients using aspirin in 15 year period prior to diagnosis

Adjusted odds ratios and 95% confidence intervals

Reduced esophageal, pancreatic, lung, brain, stomach and prostate cancers are also associated with regular ASA use

<table>
<thead>
<tr>
<th>Duration</th>
<th>N of cases</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 to 6 years</td>
<td>378</td>
<td>0.96 (0.84 to 1.10)</td>
</tr>
<tr>
<td>7 to 9 years</td>
<td>233</td>
<td>0.87 (0.73 to 1.02)</td>
</tr>
<tr>
<td>10 to 14 years</td>
<td>164</td>
<td>0.81 (0.66 to 0.98)</td>
</tr>
</tbody>
</table>

Lancet Volume 376, No. 9754, p1741–1750, 20 November 2010
Low-Dose Aspirin and Dementia in Older Women

- Observational study of 681 Swedish women (70 - 92 years)
- Women taking regular aspirin had less cognitive decline
- Equivalent data in men are lacking
- ASPREE RCT is underway

What do we tell our patient

• We tell him that regular aspirin use:
  – Will likely reduce his risk of heart disease, and cardiovascular death.
  – Will likely reduce his risk of cancer (after ~10 years of use)
  – May improve his cognitive function
Nonsteroidal Anti-inflammatory Drugs increase Cardiovascular Risk

Meta-analysis of 121 randomized trials evaluating the CV effects of COX-2 inhibitors

<table>
<thead>
<tr>
<th>COX 2 inhibitor</th>
<th>No of trials</th>
<th>Events/person years</th>
<th>Rate ratio</th>
<th>COX 2 inhibitor: placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Allocated COX 2 inhibitor</td>
<td>Allocated placebo</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>37</td>
<td>54/6638</td>
<td>30/6415</td>
<td>1.86 (1.33 to 2.59) P=0.0003</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>41</td>
<td>44/8976</td>
<td>9/4953</td>
<td></td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>17</td>
<td>2/753</td>
<td>0/414</td>
<td></td>
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<tr>
<td>Lumiracoxib</td>
<td>12</td>
<td>5/1375</td>
<td>2/584</td>
<td></td>
</tr>
<tr>
<td>Valdecoxib</td>
<td>14</td>
<td>8/748</td>
<td>1/273</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>121</td>
<td>113/18 490</td>
<td>42/12 639</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.6%/year)</td>
<td>(0.3%/year)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity between five drugs: $\chi^2=1.0$, df=4, P=0.9

COX-2 NSAIDs increase the risk of adverse CV events

Kearney PM et al. BMJ 2006;332:1302-1306
COMPLEXITY

If a little is good...a lot is not always better
What should he eat?
Reduced cardiovascular mortality with increased adherence to Mediterranean diet

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative risk (95% CI)</th>
<th>Weight (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trichopoulou et al 2003&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0.82 (0.69 to 0.97)</td>
<td>5.90</td>
<td></td>
</tr>
<tr>
<td>Knoops et al 2004&lt;sup&gt;5&lt;/sup&gt;</td>
<td>0.84 (0.76 to 0.94)</td>
<td>14.34</td>
<td></td>
</tr>
<tr>
<td>Mitrou et al 2007 (men)&lt;sup&gt;11&lt;/sup&gt;</td>
<td>0.92 (0.89 to 0.96)</td>
<td>47.83</td>
<td></td>
</tr>
<tr>
<td>Mitrou et al 2007 (women)&lt;sup&gt;11&lt;/sup&gt;</td>
<td>0.93 (0.88 to 0.99)</td>
<td>31.93</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.91 (0.87 to 0.95)</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>
Reduced cancer with increased adherence to Mediterranean diet

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative risk (95% CI)</th>
<th>Weight (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knoops et al 2004</td>
<td>0.95 (0.90 to 1.00)</td>
<td>17.20</td>
<td>0.95 (0.90 to 1.00)</td>
</tr>
<tr>
<td>Lagnou et al 2006</td>
<td>0.89 (0.77 to 1.03)</td>
<td>1.89</td>
<td>0.89 (0.77 to 1.03)</td>
</tr>
<tr>
<td>Fung et al 2006</td>
<td>0.91 (0.82 to 1.01)</td>
<td>3.64</td>
<td>0.91 (0.82 to 1.01)</td>
</tr>
<tr>
<td>Mitrou et al 2007 (men)</td>
<td>0.94 (0.91 to 0.97)</td>
<td>46.79</td>
<td>0.94 (0.91 to 0.97)</td>
</tr>
<tr>
<td>Mitrou et al 2007 (women)</td>
<td>0.96 (0.92 to 1.00)</td>
<td>24.69</td>
<td>0.96 (0.92 to 1.00)</td>
</tr>
<tr>
<td>Benetou et al 2008</td>
<td>0.88 (0.81 to 0.96)</td>
<td>5.78</td>
<td>0.88 (0.81 to 0.96)</td>
</tr>
<tr>
<td>Total</td>
<td>0.94 (0.92 to 0.96)</td>
<td>100.00</td>
<td>0.94 (0.92 to 0.96)</td>
</tr>
</tbody>
</table>
Reduced dementia with increased adherence to Mediterranean diet

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative risk (95% CI)</th>
<th>Weight (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scarmeas et al 2006 (^9)</td>
<td>0.83 (0.70 to 0.98)</td>
<td>31.06</td>
<td></td>
</tr>
<tr>
<td>Gao et al 2007 (men) (^10)</td>
<td>0.93 (0.80 to 1.08)</td>
<td>38.88</td>
<td></td>
</tr>
<tr>
<td>Gao et al 2007 (women) (^10)</td>
<td>0.85 (0.72 to 1.00)</td>
<td>30.06</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.87 (0.80 to 0.96)</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>
Increased Sugar intake increases Cardiovascular Mortality (NHANES-31,147 people)

The average American consumes about 15% of total calories as added sugar

For a 2,000 calorie diet that’s the amount of sugar in a 16 oz. soda

A prudent upper limit of intake...for most American women is no more than 100 calories per day and for most American men is no more than 150 calories per day from added sugars.
Association between sugar consumption and cognitive function

737 people without diabetes

Cognitive impairment

- lowest intake
- highest intake

Br J Nutr. 2011 Nov;106(9):1423-32
Sugar intake and cancer

• Sugar, itself, is not carcinogenic
• However, cancer cells do thrive on sugar
• The preferred energy source for cancer cells is sugar, and cancer cells will utilize more sugar than normal cells
• Studies assessing the association between sugar intake and cancer incidence are largely negative
• When looking at cancer mortality, however, most studies show that increased sugar intake increases cancer mortality
Sugar-sweetened beverage intake associated with increased mortality in cancer patients

1,011 stage III colon cancer patients

What about alcohol?
There is a J-shaped relationship between alcohol intake and mortality

Meta-analysis of 34 studies (1,015,835 people)

Most of the mortality reduction is due to reduction in cardiovascular death

Di Castelnuovo et al, Arch Intern Med. 2006;166:2437-2445
Moderate alcohol intake is associated with reduced Alzheimer’s disease incidence

OR (3-4 glasses/day) AD[32] 10.70 (2.00, 56.00)
OR (Wine-weekly) AD[38] 0.49 (0.28, 0.88)
OR (Beer-weekly) AD [38] 0.84 (0.51, 1.41)
OR (Spirits-weekly) AD[38] 0.78 (0.22, 1.19)
RR (1-21 units/wk(m) 1-14u/wk(f) AD[43] 0.40 (0.20, 0.60)
RR (250-500ml/day) AD[235] 0.53 (0.30, 0.95)
RR (<=250ml/day) AD[29] 0.55 (0.31, 0.99)
RR (250-500ml/day) AD[29] 0.28 (0.08, 0.99)
RR (>=500ml/day) AD[29] 0.48 (0.06, 3.92)
OR (Women 7-13 drinks/week) AD[25] 0.27 (0.10, 0.72)
OR (Men 1-6 drinks/week) AD[25] 0.36 (0.17, 0.80)
RR (Wine 1-21 drinks/week) AD[31] 0.69 (0.45, 1.09)
OR (Alcohol consumed) AD[45] 0.63 (0.35, 1.14)
combined 0.57 (0.44, 0.74)
Even moderate alcohol intake is associated with increased incidence of many cancers

Alcohol and Oral Cancer

Alcohol and Esophgaeal Cancer

Alcohol and Liver Cancer

Alcohol and Breast Cancer

Bagnardi et al, British Journal of Cancer 2001
What about Coffee?
Moderate coffee intake is associated with reduced CVD

- A meta analysis of 36 prospective studies (1,279,804 people)
- Found a J-shaped relationship between coffee consumption and CVD, CHD and stroke
- Consumption of up to ~3-4 cups of coffee per day was associated with decreased risk
- Consumption of more than ~ 5 cups of coffee per day was associated with increased risk

Ming Ding et al. Circulation. 2014;129:643-659
Cognitive function is associated with increased lifetime coffee consumption


Improved cognitive function

Increasing coffee consumption

Coffee consumption and cancer mortality

Data from 21 prospective studies, with 997,464 participants

No significant effect
Exercise
Physical activity is associated with reduced cardiovascular risk
Physical activity improves cognition

Meta-analysis of 18 intervention Studies

Effect Size (g)

Task Type

Executive
Control
Exercise

Physical activity is associated with reduced cancer risk

- Pooled data from 1.44 million adults (US and Europe)
- 11 year of follow up
- The most active people had a 20% lower risk of developing cancer

The most active people did the equivalent of 7 hours of brisk walking per week
How much exercise for health **HARMS?**

Observational studies of the dose-response relationship between physical activity and mortality

**A. Williams et al.**

**B. Wannamethee et al.**

**C. Mons et al.**

**D. Moholdt et al.**

- **CVD mortality**
- **Total mortality**

Can too much exercise harm the heart?

• The book the Haywire Heart argues that too much exercise can kill you.
• “...going too hard or too long can damage your heart forever.”
• According to the publisher: This book is intended for anyone who competes in endurance sports like cycling, triathlon, running races of all distances, and cross-country skiing,
<table>
<thead>
<tr>
<th></th>
<th>CVD</th>
<th>Dementia</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of hypertension</td>
<td>😊</td>
<td>😊</td>
<td>😐</td>
</tr>
<tr>
<td>Statin therapy</td>
<td>😊</td>
<td>😐</td>
<td>😐</td>
</tr>
<tr>
<td>Treatment of obesity</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
</tr>
<tr>
<td>Primary prevention aspirin</td>
<td>😊</td>
<td>😐</td>
<td>😊</td>
</tr>
<tr>
<td>Mediterranean diet</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
</tr>
<tr>
<td>Coffee intake &lt;3-4 cups/day*</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
</tr>
<tr>
<td>Moderate wine intake*</td>
<td>😊</td>
<td>😊</td>
<td>😐</td>
</tr>
<tr>
<td>MODERATE exercise*</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
</tr>
</tbody>
</table>

* Evidence is from observational studies only
<table>
<thead>
<tr>
<th>Treatment of hypertension</th>
<th>Statin therapy</th>
<th>Treatment of obesity</th>
<th>Primary prevention aspirin</th>
<th>Metformin therapy</th>
<th>Mediterranean diet</th>
<th>Coffee intake (&lt;3-4 cups/day)*</th>
<th>Moderate wine intake*</th>
<th>MODERATE exercise*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beneficial</strong></td>
<td><strong>Beneficial</strong></td>
<td><strong>Beneficial</strong></td>
<td><strong>Neutral</strong></td>
<td><strong>Beneficial</strong></td>
<td><strong>Beneficial</strong></td>
<td><strong>Beneficial</strong></td>
<td><strong>Beneficial</strong></td>
<td><strong>Beneficial</strong></td>
</tr>
<tr>
<td><strong>Not sure</strong></td>
<td><strong>Neutral</strong></td>
<td><strong>Beneficial</strong></td>
<td><strong>Neutral</strong></td>
<td><strong>Neutral</strong></td>
<td><strong>Beneficial</strong></td>
<td><strong>Beneficial</strong></td>
<td><strong>Neutral</strong></td>
<td><strong>Beneficial</strong></td>
</tr>
<tr>
<td><strong>Harmful</strong></td>
<td><strong>Neutral</strong></td>
<td><strong>Neutral</strong></td>
<td><strong>Neutral</strong></td>
<td><strong>Neutral</strong></td>
<td><strong>Beneficial</strong></td>
<td><strong>Beneficial</strong></td>
<td><strong>Beneficial</strong></td>
<td><strong>Neutral</strong></td>
</tr>
</tbody>
</table>
Prevention

• Prevention is where medicine gets hard
• To prevent something that may or may not happen in the future is difficult.
• Preventive medicine also requires us to treat people who are not sick, so the most important principle is "do no harm."
• But the good news is that many preventive therapies reduce risks for heart disease, dementia...and even cancer
Why we need to \textit{PREVENT} chronic diseases

If we keep on doing what we've always done...we'll keep on getting what we've always gotten...
Questions?