Preventing Cardiovascular Disease: Do Vitamins Play a Role?

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Conflict of Interest Disclosures

- Jacintha Cauffield has no conflicts of interest to disclose.
Objectives

- Identify the vitamins and nutritional supplements that are most commonly used to try to prevent heart disease.
- Discuss the data that supports or refutes the use of common vitamins and nutritional supplements to prevent cardiovascular disease.
- Determine whether a specific vitamin or nutritional supplement is appropriate for use in an individual patient.
- Counsel a patient on the use of vitamins and nutritional supplements to prevent cardiovascular disease.

Why Do Patients Use Dietary Supplements?

- Improve Overall Health
- Stay healthy
- Bone health
- To supplement diet
- To prevent health problems
- Heart health
- Boost immunity
- Arthritis
- Energy

What Dietary Supplements Do They Take?

Why the Interest Now?

CLINICAL GUIDELINE

Vitamin, Mineral, and Multivitamin Supplements for the Primary Prevention of Cardiovascular Disease and Cancer: U.S. Preventive Services Task Force Recommendation Statement

Multiple Vitamins

 Trials Using Multiple Vitamins

- Most studies performed on general population
  - Likely nutritionally “replete”
- 4 good MVI trials, 2 good cohort studies
- 1 examined antioxidants and cataracts
- 1 examined MVI and acute respiratory infections
- 1 examined vitamin A in MVI and hip fractures
- 3 trials examined CV outcomes
  - SU.VI.MAX
  - Women’s Health Initiative
  - Physicians’ Health Study II
SU.VI.MAX

- N=13,017
- Antioxidant vitamins and minerals
  - Vitamin C 120 mg daily
  - Vitamin E 30 mg daily
  - Beta-carotene 6 mg daily
  - Selenium 100 mcg daily
  - Zinc 20 mg daily
- No impact on fatal or nonfatal CVD events

Women’s Health Initiative (WHI)

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>0.96</td>
<td>0.89-1.03</td>
<td>0.27</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.99</td>
<td>0.91-1.07</td>
<td>0.75</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>1.05</td>
<td>0.85-1.29</td>
<td>0.64</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.02</td>
<td>0.97-1.07</td>
<td>0.48</td>
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</tbody>
</table>

- Observational
- N=161,808
- 41.5% used multivitamins

Physicians’ Health Study II

JAMA 2012; 308:1751.
MVI and CVD: Summary

• USPTF: “...the current evidence is insufficient to assess the benefits or harms of multivitamins for the prevention of cardiovascular disease...”

Vitamin D
**Vitamin D: Function**

- Prohormone
- Role in bone health known
- Most tissues and cells express vitamin D receptors (VDR)
- Regulates cellular functions
- Suppresses inflammation
- Cardiovascular tissues
  - Cardiac myocytes
  - Vascular smooth muscle
  - Aortic endothelial cells

**Vitamin D Metabolism**

*Circulation* 2011; 124:1808.
Vitamin D Intake: IOM

<table>
<thead>
<tr>
<th>Age</th>
<th>RDA</th>
<th>Upper Level Intake (ULI)</th>
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</thead>
<tbody>
<tr>
<td>Age 1-13</td>
<td>600 IU</td>
<td>2500-4000 IU</td>
</tr>
<tr>
<td>Ages 14-70</td>
<td>600 IU</td>
<td>4000 IU</td>
</tr>
<tr>
<td>Age &gt;70</td>
<td>800 IU</td>
<td>4000 IU</td>
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</table>

What Constitutes a Vitamin D Deficiency

<table>
<thead>
<tr>
<th></th>
<th>Vitamin D Deficiency</th>
<th>Vitamin D Insufficiency</th>
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</thead>
<tbody>
<tr>
<td>US Endocrine Society</td>
<td>&lt;20 ng/mL (SI: &lt;50 nmol/L)</td>
<td>21-29 ng/mL (SI: 52.5-72.5 nmol/L)</td>
</tr>
<tr>
<td>Institute of Medicine</td>
<td>&lt;20 ng/mL (SI: &lt;50nmol/L)</td>
<td></td>
</tr>
</tbody>
</table>

- >40% US population has 25(OH)D ≤20 ng/mL
Risk Factors for Vitamin D Deficiency

- Non-white race
- Obesity
- Low HDL
- Women
- Advanced Age
- Decreased exposure to sunlight:
  - Latitude
  - Season of the year
  - Exposed skin
  - Sunscreen

Vitamin D Deficiency and Cardiovascular Health

- Mechanistic studies
- Based upon measured 25(OH)D levels
- Endothelial dysfunction
  - Flow-mediated vasodilation (FMD)
  - Reactive hyperemia index (RHI)
- Attenuates adhesive properties of platelets
- Suppresses inflammation
  - Low 25(OH)D associated with increased levels of c-reactive protein, among other proinflammatory factors
- ?Accelerated atherosclerosis?
- Renin-angiotensin system up-regulates with 25(OH)D <15 ng/mL
**Vitamin D Deficiency and Cardiovascular Health**

- Longitudinal studies
- Low 25(OH)D serum concentrations $\uparrow$ adverse cardiovascular outcomes
  - Acute MI
  - More severe CAD
  - Coronary artery calcium
  - Coronary artery restenosis
- Several studies failed to find correlation
- Threshold effect?
  - Linear effect between 20-60 ng/mL
  - $>60$ ng/mL optimal?
  - Possible additional benefit with higher levels

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**Vitamin D Deficiency and Cardiovascular Health**

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td>1.16</td>
<td>1.012-1.334</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>1.29</td>
<td>1.019-1.633</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.31</td>
<td>2.018-2.633</td>
</tr>
<tr>
<td>HTN</td>
<td>1.40</td>
<td>1.285-1.536</td>
</tr>
<tr>
<td>All-cause death</td>
<td>2.95</td>
<td>2.135-4.073</td>
</tr>
</tbody>
</table>

- Vitamin D deficiency <30 ng/mL (mean 24 ng/mL + 13.6 ng/mL)
- Mean vitamin D dose $2254 \pm 316$ IU
- Vitamin D supplementation beneficial only in deficient patients

Vitamin D Deficiency and Cardiovascular Health

- Vitamin D deficiency associated with increased mortality
- Vitamin D supplementation beneficial only in deficient patients


Vitamin D: Does Supplementation Help?

- No trial specifically designed to address CVD risk
- Unusual dosing
  - 100,000 IU D3 q2 or 3 months
  - 50,000 IU2 weekly x 12 weeks
- Possible suboptimal dosing: 400 IU daily
- Meta-analysis: 1000 IU daily equivalent
  - CVD risk 0.90; 95% CI 0.77-1.05
### RECORD

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<tbody>
<tr>
<td>Any CVD Incidence</td>
<td>0.96</td>
<td>0.82-1.13</td>
<td>0.22</td>
</tr>
<tr>
<td>Cardiac Failure</td>
<td>0.73</td>
<td>0.55-0.96</td>
<td>0.03</td>
</tr>
<tr>
<td>MI</td>
<td>1.04</td>
<td>0.79-1.37</td>
<td>0.76</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.13</td>
<td>0.88-1.44</td>
<td>0.33</td>
</tr>
<tr>
<td>Any CVD death</td>
<td>0.91</td>
<td>0.79-1.05</td>
<td>0.175</td>
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- Vitamin D3 800 IU daily + calcium 1000 mg vs. placebo
- Major outcomes: fracture
- Serum 25(OH)D Concentrations:
  - Baseline~15 ng/mL
  - Treatment~25 ng/mL
  - Placebo~16-19 ng/mL


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### What about Calcium?

- WHI: marginal increased risk for MI
  - No correlation for stroke or composite endpoint
  - 1000 mg/day vs. placebo
  - Higher in women who were adherent
  - Progressive throughout 5 year f/u
- "Nonsignificant increases" in vascular disease mortality
- AHRQ: no effect on calcium supplementation on CV outcomes
- May confer benefit when added to vitamin D3
  - Not associated with higher risk in WHI
  - Meta-analyses suggest possible benefit

*BMJ 2008;336:262-6.*
Antioxidants: Rationale for Use

- Reactive oxygen species
- Oxidative stress → CVD
- Antioxidants:
  - Endogenous: albumin, bilirubin, glutathione
  - Exogenous (vitamins): tocopherols, carotenoids, vitamin C
  - Antioxidant enzymes
Antioxidant Vitamins

- Vitamin E:
  - “Chain breaker”
  - Circulates in LDL-protects against oxidative damage
- Carotenoids:
  - Lipid-soluble
  - Decreases lipid peroxidation
- Complementary antioxidant for carotenoids and tocopherols
  - Co-nutrient of vitamin E

Vitamin E

- 4 stereoisomer classes:
  - Alpha-tocopherol (supplemental “Vitamin E”)
  - Beta-tocopherol
  - Gamma-tocopherol: major dietary form of Vitamin E
  - Delta-tocopherol
- Alpha-tocopherol has highest circulating levels
- Exists in LDL
- ↑Increased dietary intake=↓ CVD risk
  - Nurses’ Health Study
  - Health Professionals Follow-Up Study
- 400 IU daily RRR-alpha-tocopherol ("all-rac" alpha-tocopherol)
Vitamin E: HOPE-TOO

Vitamin E: Adverse Outcomes

- PHS-II: increased hemorrhagic stroke by 74%
  - [RR: 1.74, 95% CI: 1.04, 2.91]
- ATBC: hemorrhagic stroke
- HOPE TOO: ?increased risk of heart failure?
  - [RR 1.13, 95% CI: 1.01-1.24, P=0.03]
- Cache County Study:
  - "Null relationship" between vitamin E and CV mortality
  - Increased mortality with:
    - CVA
    - CABG
    - MI
    - Nitrates, warfarin, diuretics
  - Decreased mortality in absence of these factors
  - Vitamin C had no effect
Vitamin C

- PHS-II (500 mg daily: no difference in
  - MI (p=0.65)
  - Stroke (p=0.21)
  - Death from any CVD event (p=0.86)
- WAC: no effect on combined cardiovascular events

Vitamin A

- “Retinols”
- No benefit
- Daily Upper Tolerable Limit=3,000 mcg (10,000 units)
- Vitamin A supplementation above this is toxic
  - Hepatotoxicity
  - Increased mortality
**Beta Carotene**

- Beta-carotene is a vitamin A precursor
- Conversion dependent on vitamin A levels in body
- Carotenoids provide 50% of dietary vitamin A
- High carotenoid intake correlated to lower CVD risk
- Beta-carotene supplementation not beneficial
- Serum concentrations
  - Relationship less clear
- High levels=pro-oxidant?
- ATBC and CARET:
  - Increased lung cancer
  - Smokers or h/o exposure to asbestos

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**Selenium**

- Given with other antioxidants (vitamin C, vitamin E, beta-carotene)
- Balance deficiency with toxicity
- UL=400 mcg daily
- Intake dependent on soil levels
- Plant intake (broccoli, garlic, onions)
- Slight decrease in non-HDL cholesterol
- NO benefit against cardiovascular disease
- May lower HDL-2
Miscellaneous

Folic Acid/B vitamins

- Lowers homocysteine (Hcy) concentrations
- Often given with vitamin B12 and pyridoxine
- Pyridoxine needs physiologic levels of B12 and folate to be effective
Folic Acid/B vitamins

• ↓HCY ≠ decreased CVD risk
• Randomized trials failed to show improvement in cardiovascular outcomes
  o Patients with pre-existing CVD
  o Recurrent stroke
  o Restenosis s/p PCI
• No effect regardless of homocysteine status
• Dependent upon nutritional state?
• May benefit patients with end stage renal disease
• L-methylfolate

Fish Oil (Omega-3 Fatty Acids)

http://acsh.org/2013/10/prescription-fish-oil-remains-approved-triglycerides-cholesterol/
Fish Oil (Omega-3 Fatty Acids)

Omega-3 Fatty Acids

Fish Oil

- Beneficial effects on lipid profile
- Eating fatty fish 2-3 times weekly
- Decreases risks from cardiovascular disease
  - Primary prevention
  - Secondary prevention
- Fish oil benefits mixed
  - Beneficial for overall mortality
  - CVD mortality more inconsistent

Overall Impressions
Conclusions: USPTF

- Evidence sufficient to discourage research in the general population for:
  - Vitamin A
  - Beta-carotene
  - Vitamin C
  - Vitamin E
  - Folic acid
- Selenium: differentiate between low and adequate selenium levels
- Calcium may have harmful effects on CVD
- Study vitamin D and calcium separately

Eat Healthy!