Preventing Ischemic Heart Disease (IHD): Are Diet And Exercise More Powerful Than Drugs?

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NEJM Management Of Stable CAD

• Vignette: Obese hypertensive DM2 man with angina, multivessel CAD. 3 sets of experts suggest management:
  – 1: Medications, brief vague mention of diet and exercise, less than one sentence.
  – #2: PCI and medications, no mention of diet and exercise
  – #3: CABG and ‘medical therapy’, no mention of diet and exercise

• Is there a cultural problem within medicine?

NEJM 2007;357:1762-66
Secondary Prevention Outcomes: Mortality Reduction (RCT)

% IHD Mortality Reduction

Or

NNT

Mortality Reduction (%)

NNT-Mortality 3Y
Secondary Prevention Outcomes: Event Reduction (RCT)

% IHD Event Reduction

Or

NNT
References for Previous Tables


• Statin event reduction CTT Collaborators Lancet 2005;366:1267-78 Statin total mortality NNT 50 for secondary prevention, average follow up 2.6y. Fish oil NNT 108 for total mortality over 2.1y.


• For supportive analysis of diet and exercise outcomes see Iestra Circulation 2005;112:924-34,
If doctors do not put an appropriate emphasis on lifestyle when treating heart disease, does this mean that heart disease management is too important to leave to doctors?
## Statins: good drugs, but not good enough!

### Events In Major Statin Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th># Events Control</th>
<th># Events Statin</th>
<th>% Risk Reduction</th>
<th>% Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S/CARE/WOS/AFCAPS/LIPID</td>
<td>30,817</td>
<td>2,074</td>
<td>1,537</td>
<td>26</td>
<td>74</td>
</tr>
<tr>
<td>HPS</td>
<td>20,536</td>
<td>1,212</td>
<td>898</td>
<td>26</td>
<td>74</td>
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<tr>
<td>PROSPER</td>
<td>5,804</td>
<td>356</td>
<td>292</td>
<td>18</td>
<td>82</td>
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<tr>
<td>ALLHAT</td>
<td>10,355</td>
<td>421</td>
<td>380</td>
<td>9</td>
<td>91</td>
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<tr>
<td>ASCOT</td>
<td>10,305</td>
<td>154</td>
<td>100</td>
<td>36</td>
<td>64</td>
</tr>
<tr>
<td>Total</td>
<td>77,817</td>
<td>4,217</td>
<td>3,207</td>
<td>24</td>
<td>76</td>
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</tbody>
</table>

Tighter LDL control than used in these studies may reduce events a further 16% relative/4% absolute

NNT typically 30-40, often approaching 100 in high risk patients (eg ASCOT), higher for lower risk
What Advice Should You Give Your Patient If They REALLY Don’t Want Another Cardiac Event, Or A First Event?
Overview Of Diet And Exercise Interventions For IHD

• Exercise
• Diet for:
  – Event reduction independent of lipids
  – Lowering LDL and triglycerides, raising HDL
• Fish and other omega 3 fatty acids
• Targeting low HDL and high triglycerides:
  – Healthy fats, niacin, fiber, exercise, weight management
• Specific food with particular evidence for benefit: Ethanol, Chocolate
MOVE!
Exercise and Ischemic Heart Disease (IHD): Epidemiology

• Fitness associated with lower total mortality, risk of ischemic heart disease, diabetes, stroke, dementia, total cancer incidence, osteoporosis, depression

• Mechanisms:
  – Antinflammatory, antioxidant, endothelial function, neurohormonal effects…
  – Improves lipids, blood pressure, blood sugar, fat distribution…
  – Less age-dependent DNA change Arch Intern Med 2008;168:154-158

• Regular exercise associated with up to 3.7 years longer disease-free lifespan Franco Arch Intern Med 2005;165:2355-60
Exercise, Fitness and Prognosis

• <85% predicted capacity on ETT predicts, over subsequent 2.7 years
  – 2.36 x MI
  – 1.75 x revascularization
  – 2.9X all cause mortality n=9191 referred for exercise treadmill, multivariate analysis, all statistically significant, similar in all patient subgroups. Peterson, P. Arch Intern Med 2008;168:174-79

• 50% less deaths in those who do at least 30 min moderate exercise most days of week, regardless of other risk factors NIH-AARP Arch Intern Med 2007;167:2453-60
  – any regular exercise better than none
Exercise: Outcomes In RCT

• Reduces all-cause (19%) and cardiac (24%) mortality in secondary prevention

• Patients with stable CAD: Angioplasty/stent vs. exercise training: 20 min exercise bicycle/d, for 1 y
  – Equal benefits for angina relief
  – Exercise group had 60% fewer cardiac events
  Hambrecht Circulation 2004;109:1371-78
“It doesn’t much matter what exercise you take, provided it suits you in age, strength, aptitude, and experience.”

Paul Dudley White
Diet and Ischemic Heart Disease
Which Diet?

- The Mediterranean Diet pattern remains the only diet with consistent data involving substantial populations showing tolerability, fewer deaths and better clinical outcomes over a wide range of diseases:
  - Cardiovascular disease
  - Metabolic syndrome
  - Cancer…60-70% less in Lyon Heart, Greek EPIC

Recent US data and review Mitrou, P. Arch Intern Med 2007;167:2461-68
Mediterranean Diet After MI

- 202 patients with MI within 6w, Med diet vs. hospital standard AHA diet
- Med diet: up to 40% calories as fat, olive oil, avocados. Fish 3-5x week. Low in saturated fat and cholesterol.
- Event free (death, MI, stroke, cardiovascular hospitalization): 83% in Med diet group, 53% in AHA diet group. 4y, routine asa, BB, statin use. Katherine Tuttle, Providence Spokane ACC March 2007
Randomized controlled trials for secondary prevention using the Mediterranean Diet for Ischemic Heart Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Mortality reduction</th>
<th>p</th>
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<tbody>
<tr>
<td>Lyon Heart Study</td>
<td>650</td>
<td>44% at 4 y</td>
<td>Y</td>
</tr>
<tr>
<td>Circulation 1999;99:779-85</td>
<td></td>
<td></td>
<td>5 year NNT 16</td>
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<tr>
<td>Indian Heart Study</td>
<td>406</td>
<td>45% at 1 year</td>
<td>Y</td>
</tr>
<tr>
<td>BMJ 1992;304:1015-19</td>
<td></td>
<td></td>
<td>5 year NNT 2.4</td>
</tr>
<tr>
<td>GISSI-Prevenzione</td>
<td>11,324</td>
<td>40% at 6 years</td>
<td>Y</td>
</tr>
<tr>
<td>Med. Diet AHA 11/01: Marchioli</td>
<td></td>
<td>Controlled for fish oil use</td>
<td></td>
</tr>
<tr>
<td>Indo-Med Study</td>
<td>1000</td>
<td>67% at 2 years</td>
<td></td>
</tr>
<tr>
<td>Lancet 2002;360:1455-61</td>
<td></td>
<td>(cardiac deaths, p&lt;0.001). 38% less total mortality, p=.06</td>
<td></td>
</tr>
</tbody>
</table>
What Is An ‘Ideal’ Whole-Food Mediterranean Diet?

• Increased use of fruits and vegetables daily: ‘5 a day’ is a reasonable minimum
• Increased coarse whole grain, fiber, legumes/beans, nuts
• Extra-virgin olive oil typically used preference to other oils and fats.
• Increased fish, less preserved meats
• Modest reductions in saturated fat, cholesterol often occur
• Low glycemic index/glycemic load strategy amplifies benefit, treats DM2 and Metabolic Syndrome
How Does the Mediterranean Diet Work?

• No one element appears to be responsible
  – Increased antioxidants, less LDL oxidation.
  – Lower ratio of omega 6 to omega 3 dietary fatty acids.
  – Anti-inflammatory  Mitrou, P. Arch Intern Med 2007;167:2461-68
  – Improved endothelial function
  – Lower serum insulin, less metabolic syndrome.
  – Benefits on lipids; alcohol and exercise appear additive.
Extra Virgin Olive Oil

- Associated with the Med diet model, and:
  - Reduces post-prandial activation of Factor VII
  - Reduces postprandial inflammation, increases pp antioxidants  Bogani, P. Atherosclerosis 2007;190:181-6
  - Modest lipid benefits
- Many of the benefits appear to be phenol-mediated, so watch out for extra food processing, microwave
Fish, Fish Oil and Ischemic Heart Disease
Fish Oil and IHD: Epidemiology

- Frequent fish consumption historically related to less IHD and sudden death:
  - 40-60% lower risk IHD with high (8 servings/week) vs low intake of fish in Japan
    Iso. Circulation 2006;113:195-202
  - 38% lower IHD mortality with 5 fish servings/week Metaanalysis He Circulation 2004;109:2705-11

- Only nutritional supplement recommended by AHA
  Circulation 2002;106:2747-57

- Vegetable source omega-3 fatty acids (alpha linolenic) probably beneficial Albert. Circulation 2005;112:3232-38
Fish Oil (EPA, DHA) Mortality in RCT

- Secondary prevention, fish oil lowers
  - Overall mortality 23%
  - Cardiac mortality 32%  
  - Typical dose 1gm EPA + DHA
  - Additive to statin: 1.8g EPA Additional 19% reduction in major cardiac events beyond statin alone. 
  JELIS Yokoyama Lancet 2007;369:1090-98
Fish Oil: Possible Mechanisms

  – But maybe not in patients with AICD
- Antithrombotic and anti-inflammatory effects on platelet and neutrophil function. Zampelas JACC 2005;46:120-4
- Lowers TG, and probably Lp(a), at high doses, modestly increases on HDL
- Lowers post-prandial lipemia, mild reduction BP
- Improves endothelial function. Circulation 1997;96:2802-7
Using Fish and Fish Oil

• Primary prevention:
  – 0.5 gm/day of EPA + DHA, e.g. 1 Lovaza every day or two, ½ tsp fish oil, 2x 1000mg fish oil capsules

• Secondary prevention:
  – Aim for about 1 g or more EPA + DHA, e.g.
  – E.g. One capsule (1,000mg) Lovaza, 3 or 4 x 1g nutritional supplement fish oil capsules, 1 tsp fish oil.

Lovaza is Rx, more reliable composition

Fish As A Source Of EPA + DHA
It Doesn’t Take Much. Look At Total Intake, Not Daily Intake

• To get 500mg of EPA + DHA (aprox):
  – 200g light tuna in water
  – 60g albacore tuna in water
  – 25-50 g salmon, farmed or wild
  – 25 g herring
  – 50 g trout, farmed or wild
  – 100g halibut
  – 150g shrimp

• USDA www.ars.usda.gov/nutrientdata
Using Higher Dose Fish Oil

• For high triglycerides, some inflammatory disorders:
  – Aim for 3.6 g or more EPA + DHA: 45% reduction
  – E.g. 4x1000mg Lovaza, 12x 1000mg typical nutritional supplement caps, or 1 TBSP fish oil (e.g. Carlson Lemon Flavored, others)

• Take before largest meal. Cold oil burps less, OK to freeze capsules. Split doses OK. Need not be daily.

• Possible higher compliance, outcomes data for Lovaza (less fishy), but $$
Lowering Triglycerides: These Are Good Rules For All Of Us.

- Treat to maximize HDL
- Demonize: white flour, processed sugars, high fructose corn syrup, sweet drinks, cold breakfast cereals, hydrogenated oils,
- Encourage good fats
- The coarser the whole grain, the better
- Max 1 alcoholic drink/day
- Daily exercise 30-60 min
- Portion control, weight control, glucose control
- Fish oil/Lovaza, Niacin/Niaspan, Statin. Fibrate?
High Density Lipoproteins (HDL) and Ischemic Heart Disease
Potential Antiatherogenic Mechanisms of HDL

• Reverse cholesterol transport, aids efflux of lipid from artery wall.

• Antioxidant, antithrombotic, vasoprotective, and anti-inflammatory:
  – Carrier for antioxidant enzymes paraoxonase, PAF acetylhydrolase. Oxidized lipoproteins accumulate in plaque, stimulate inflammation

• Induce TGF-B2, stabilizing plaque

Recent Review: Singh, I. JAMA 2007;298:786-98
Combination Therapy vs. Monotherapy

Reduction in CV Events

- WOSCOPS Prava
- 4S Simva
- CARE Prava
- HPS Simva
- PostCABG Lova
- AFCAPS Lova
- ASCOT Atorva
- FATS
- HATS
- FATS 10 YR F/U

Brown BG et al. NEJM 2001;345(22):1583-92 Also see Superko, R. Circulation 2008;117:560-568
Raising HDL AND Improving Outcomes: Drugs, Diet, Lifestyle

**Pharmaceutical:**
- Niacin 15-30%
- Fibrates 5-15%
- Statins 0-17%
- (Bile acid binders 3-5%)
- (Pioglitazone 14%)
- (Estrogen, alpha blockers, phenytoin.)

**Non-Pharmaceutical**
- Dietary fat
- Omega 3 fats 4-9%
- Reduce sugars
- Exercise & weight loss 10-25%
- Alcohol 10-15%
- Smoking cessation 12%

**Recent Review:** Singh, I. JAMA 2007:298:786-98
Niacin: Lipid Effects

Niaspan data

Niacin also favorably alters LDL subclass, tending to convert small dense ‘B’ to large buoyant ‘A’.

Percent Change From Baseline

Data on file KOS
How to Use Niacin

Patient education by a trained clinician is critical.

- Review contraindications

- Use ER Niacin (e.g. Niaspan, Advicor) at bedtime, or crystalline immediate release niacin tid. Start low, titrate slowly 500mg/month for ER Niacin

- Tell the patient about itching, flushing, sleep disturbance, but that it will usually go away...and explain that it might save their life
  - Make the side effects sound BAAAAD! They’ll be pleasantly surprised
  - 30% don’t experience flushing
More About How To Use Niacin

• Take with high fiber snack, applesauce or Metamucil, use aspirin with or prior to niacin, and avoid hot drinks, spices, hot showers close to dose. Use aspirin or ibuprofen for acute flushing.

• Stop antioxidant supplements: Combination of Vit E 800IU/d, C 1000mg, B carotene 30mg, selenium 100mcg blocked response of HDL, to statin/niacin treatment. Cheung. Arterioscler Thromb Vasc Biol 2001;21:1320-26
Fixed Combination Statin + Niacin

- **Advicor**: ER Niacin + Lovastatin
  - 500/20, 750/20, 1000/20, 1000/40

- **Simcor**: ER Niacin + Simvastatin
  - 500/20, 750/20, 1000/20, 1000/40
  - Simvastatin 80mg compared to ER Niacin 2000 plus Simvastatin 40 (Simcor):
    - Lowered non-HDL 17%, LDL 12%, TG 32%
    - Improved HDL 22%, TC:HDL 25%  
      Ballantyne, C. SEACOAST AHA 2008
HDL, Food, and Exercise

- Think ‘healthy fats’, not low fat: HDL up 10-15%
  - Olive Oil
  - Nuts
  - Omega 3 fatty acids: fish, flax, avocado, nuts

- Think **minimally processed** whole foods:
  Vegetables, whole fruit, beans, whole grains

- Think daily exercise

- Think healthier patients, not just better numbers
Nuts, HDL, and CAD

• Raw Almonds: 2 handfuls/day (73g) lowered Lp(a), oxidized LDL, LDL 9.4% and TC:HDL 9%  
  Jenkins. Circulation 2002;106:1327-32

• Similar results with walnuts

• Nuts associated with less CAD:  
  – 5oz/week associated with 35% less IHD risk.  

  – 2 or more servings/week: 47% less sudden death  
    Arch Int Med 2002;162:1382-87
Treating Low HDL, High TG

- R.I. 44 yo male, recent history of angina and 2 vessel disease

- On low-fat diet and Lipitor 10 mg
  - TC 114  TG 292  HDL 27  LDL 29  TC:HDL 4.2

- Changed to lower refined carb diet, good fats, improved exercise, simvastatin 5 mg, ER Niacin 2000 mg, Fish oil 4g (and off PPI for GERD); no weight loss
  - TC 135  TG 88  HDL 50  LDL 67  TC:HDL 2.7
Combine Foods To Lower LDL 30%

• Psyllium (e.g. Metamucil)
  – 15 gm + 10mg simvastatin= 20mg simva
    Moreyra Arch Int Med 2005;165:1161-1166

• Oat Bran 4-8TBSP/day. 10-26% LDL reduction.
  JACN 1998;17:601-608 2.6g soluble fiber

• Soy, e.g soybeans, edamame or soynuts, providing
  25g protein 11% lower LDL  Welty, F. Arch Intern Med 2007;167:1060-7

• Raw almonds (73gm=2 handfuls): LDL down 9%
  less oxidized LDL and Lp(a).  Circulation 2002;106:1327-32

• Eggplant 200g qod (or okra 100g)
Plant Stanols And Sterols Might Not Be Such A Great Idea

- Plant sterols and stanols:
  - Naturally present in whole foods
  - At 2 gm/day lower LDL by 10% or more
  - Often packaged with hydrogenated (trans fats?) oils
  - In purified form, raise plasma sterol levels, which appears to be a IHD risk factor
    - Fransen, H. J Nutr 2007;137:1301-6
  - Lower blood carotenes
Patients Who Can’t Take Statins

• Consider CoQ10 200 mg/day: 40% less myalgia..is it worth it? Caso, G. Am J Cardiol 2007;99:1409-12

• 56% less events: Niacin/Gemfribrozil/Chole

• Remember the power of a prescribed lifestyle program
  – RH 46 yo with HTN, Dyslipid, FH
    • TC 205 TG 131 HDL 38 LDL 141 TC:HDL 5.4
  – Stopped smoking, diet rx, no meds
    • TC 205 TG 76 HDL 62 LDL 128 TC:HDL 3.3
Vitamin D and Heart Disease

• Low vitamin D associated with hypertension, triglycerides, diabetes, obesity
  – more IHD in those with HTN

• Almost everyone in the NW of the US is low in Vit D

• Vit D supplements associated with lower mortality in RCT
  Autier, P. Arch Intern Med 2007;167:1730-37

• Consider supplementing with 1000-2000 IU Vit D3 daily, or Cod liver oil 1 TBSP might be perfect for those with heart disease!
Soft Drinks, Sugar-Sweetened Or Diet, Do Many Bad Things!

• One or more soft drinks daily:
  – 44% more metabolic syndrome
  – 31% more increase in waist circumference and obesity
  – 25-32% more abnormal HDL (‘Good Cholesterol’) and high triglycerides
  – 18-25% more high blood pressure and high blood glucose

Framingham, 4 yrs, n=6039, Dhingra Circulation 2007;116:480-88
What To Avoid

• Avoid:
  – Partially hydrogenated oils
  – White flour (including most bagels and pasta), sweets
  – Preserved meats e.g. bacon, lunch meats, commercially fried foods.
  – Sweet drinks and juices
  – Artificial sweeteners
  – Elevators, television
• Read Ingredient labels!
• Every food processing step destroys nutrients
Making Simultaneous vs. Sequential Lifestyle Changes

• Hypertensive patients randomized to lower salt intake, stop smoking, and increase activity either (a) simultaneously, or (b) adding them at 6 monthly intervals

• At 18 months, significantly greater success in change seen in those given simultaneous advice
  
  n=289, hypertensive African-Americans, initially nonadherent Hyman Arch Intern Med 2007;167:1152-58

• Do you have too low of expectations for your patients?
Thoughts for Health Professionals

• **Vigorously** present the diet and activity aspects of prevention and treatment as being at least as important as medications

• Have specific guidelines, information and follow-up for your lifestyle prescription, just as you would for any other prescription

• Daily exercise prescription

• Consider fish oil and niacin in every patient

• Be an example
Some Resources

• ‘The Omega Diet’, Simopoulos and Robinson
• ‘The Mediterranean Diet Cookbook,’ Nancy Harmon Jenkins
• ‘Eat Drink and Be Healthy.’ Walter Willett
• ‘The Schwarzbein Principle.’ Schwarzbein
• Good Food, Great Medicine (Hassell & Hassell)
  – Soon, handy handouts on our website:
    www.goodfoodgreatmedicine.com
• “Whole Foods Weight Loss Eating Plan” from Texas Tech:
  www.ttuhsc.edu/SOM/FamMed/wholefoods.html