

Update on Supplements



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A brief history of medicine:

I have an earache...

2000 BC -- Here, eat this root.

1000 AD -- That root is heathen. Here, say this prayer.

1850 AD -- That prayer is superstition. Here, drink this
potion.

1940 AD -- That potion is snake oil. Here, swallow this pill.

1985 AD -- That pill is ineffective. Here, take this antibiotic.

2000 AD -- That antibiotic is artificial. Here, eat this root.

-- Anonymous



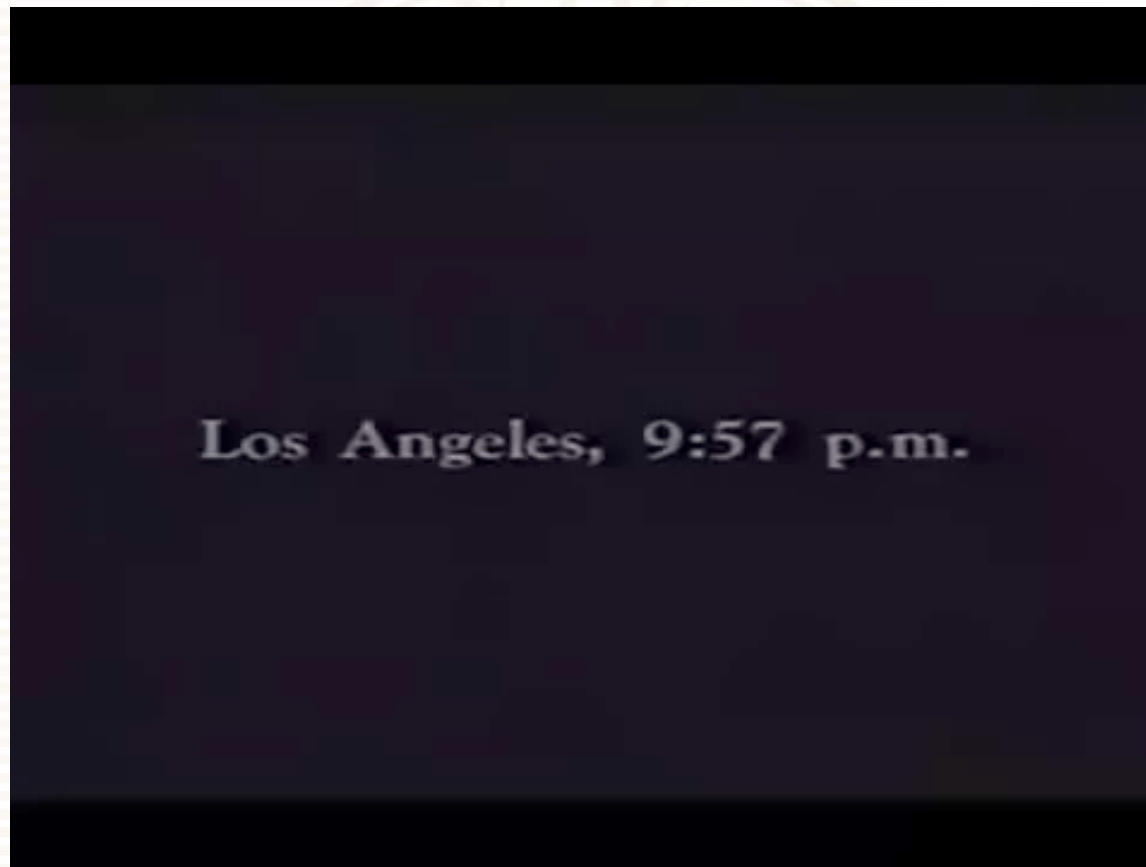
Objectives

Be able to:

- Review recent changes in supplement regulation
- Discuss the uses, mechanisms of action, and side effects of some commonly used products
- Demonstrate ability to find information on specific supplements using online resources
- Advise patients interested in supplements



Regulation



Quiz: Who was the actor in the video?

Regulatory Review

- Dietary Supplement and Health Education Act (1994).
 - No requirements for proof of safety, efficacy, quality control
- DS and Non-prescription Drug Act (2006)
 - Must report serious ADRs within 15 days
- DSHEA update (2007)



What did the DSHEA update accomplish?

- ✓ A. Required good manufacturing practice compliance
- B. Required supplements to prove safety
- C. Required supplements to prove efficacy
- D. All of the above
- E. None of the above



Independent Verification

United States Pharmacopeia



Which of the following groups also provide independent testing?



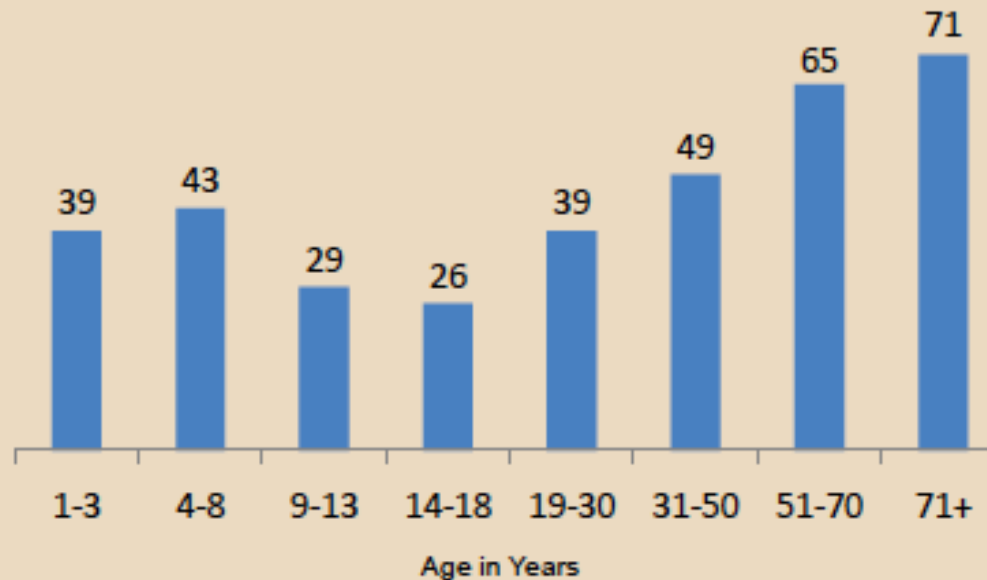
- [NNFA/Natural Products Association](#)
- [National Sanitation Foundation](#)
- [ConsumerLab](#)
- All of the above
- None of the above

Manufacturers More Likely to Produce Quality Products

- Nature's Way
- Nature's Made
- Nature's Bounty
- Costco (Kirkland)
- Walmart (Equiline)
- Phytopharmica
- Puritan's Pride



Prevalence of Use of Any Dietary Supplement (%)



Bailey et al. Journal of Nutrition, In press.

NHANES 2007-2008 data

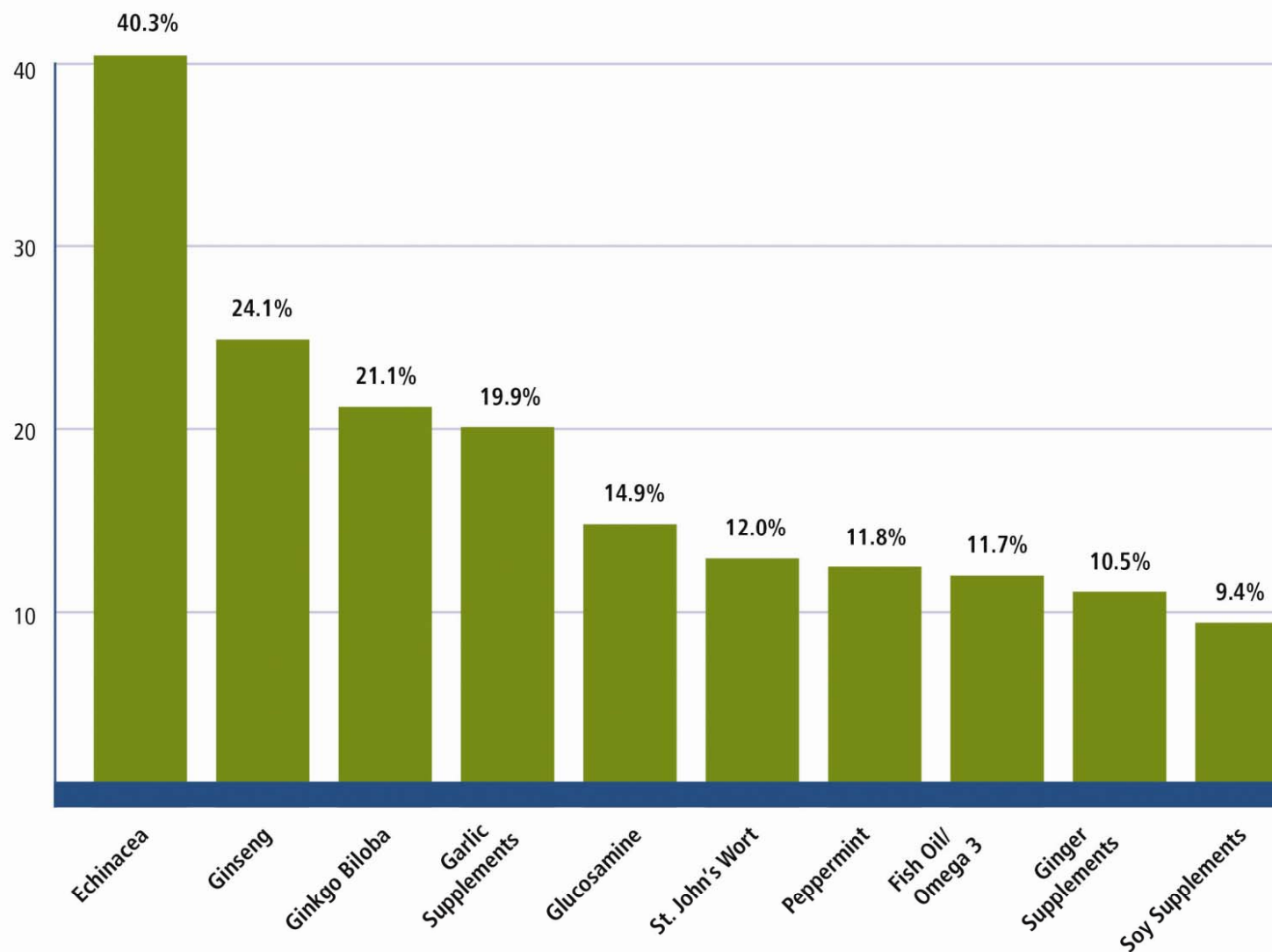
“Have you used a supplement in the last 30 days?”



Top Supplements!



10 Most Common Natural Products Among Adults* - 2002



*Percentages among adults who used natural products in the last 12 months.

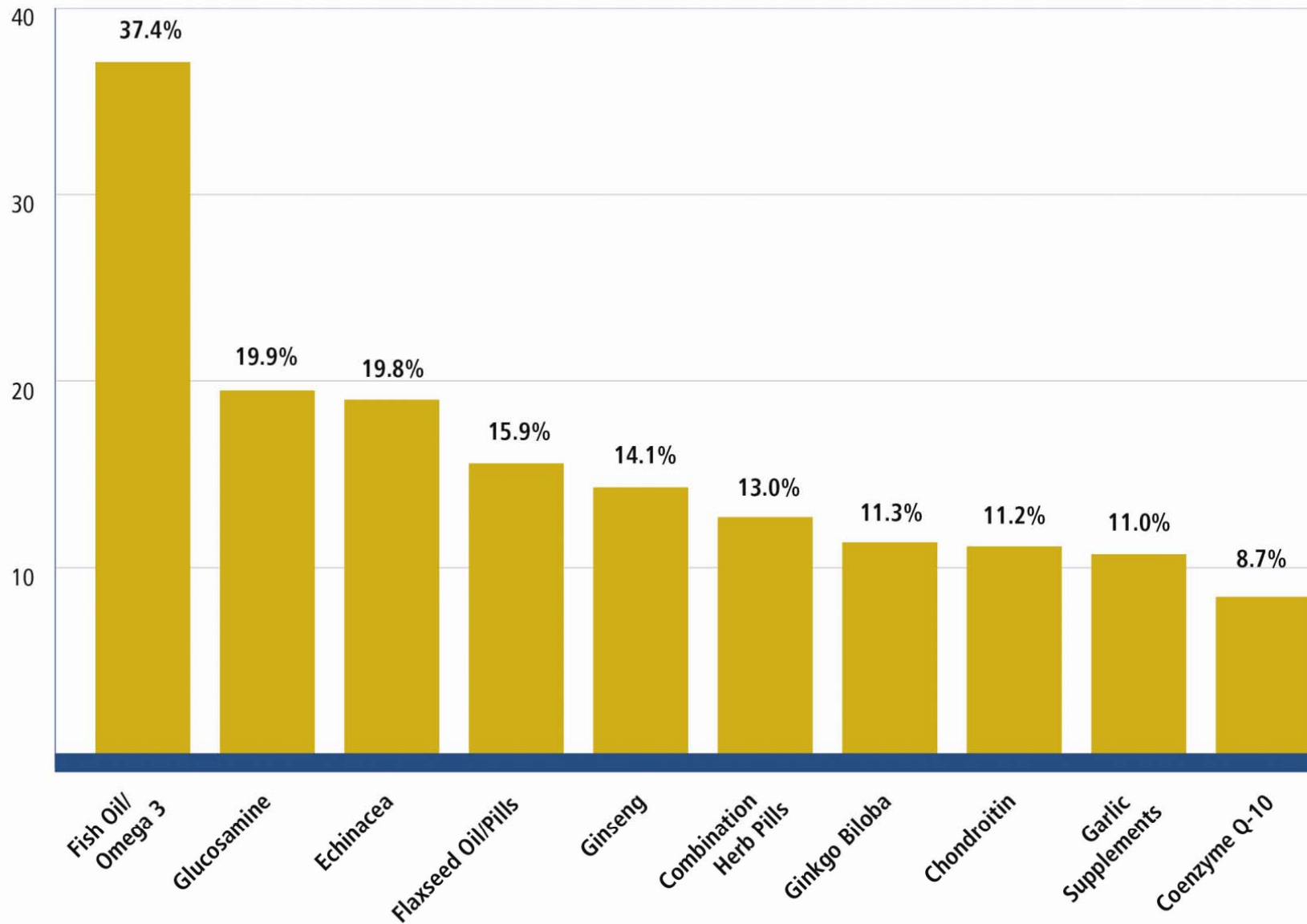
Source: Barnes P, Powell-Griner E, McFann K, Nahin R. *CDC Advance Data Report #343*. Complementary and Alternative Medicine Use Among Adults: United States, 2002. May 2004.

Which supplement was #1 in 2007?

- A. Echinacea
- B. Glucosamine
- ✓ C. Fish oil
- D. Soy



10 Most Common Natural Products Among Adults* - 2007



*Percentages among adults who used natural products in the last 30 days.

[NCCAM "Use of CAM" survey](#)

Which supplements were #1 with GIM faculty?

Coenzyme Q10

Echinacea

Fish oil

Flaxseed

Ginseng

Ginkgo

Glucosamine

Garlic

Probiotics

SAM-e

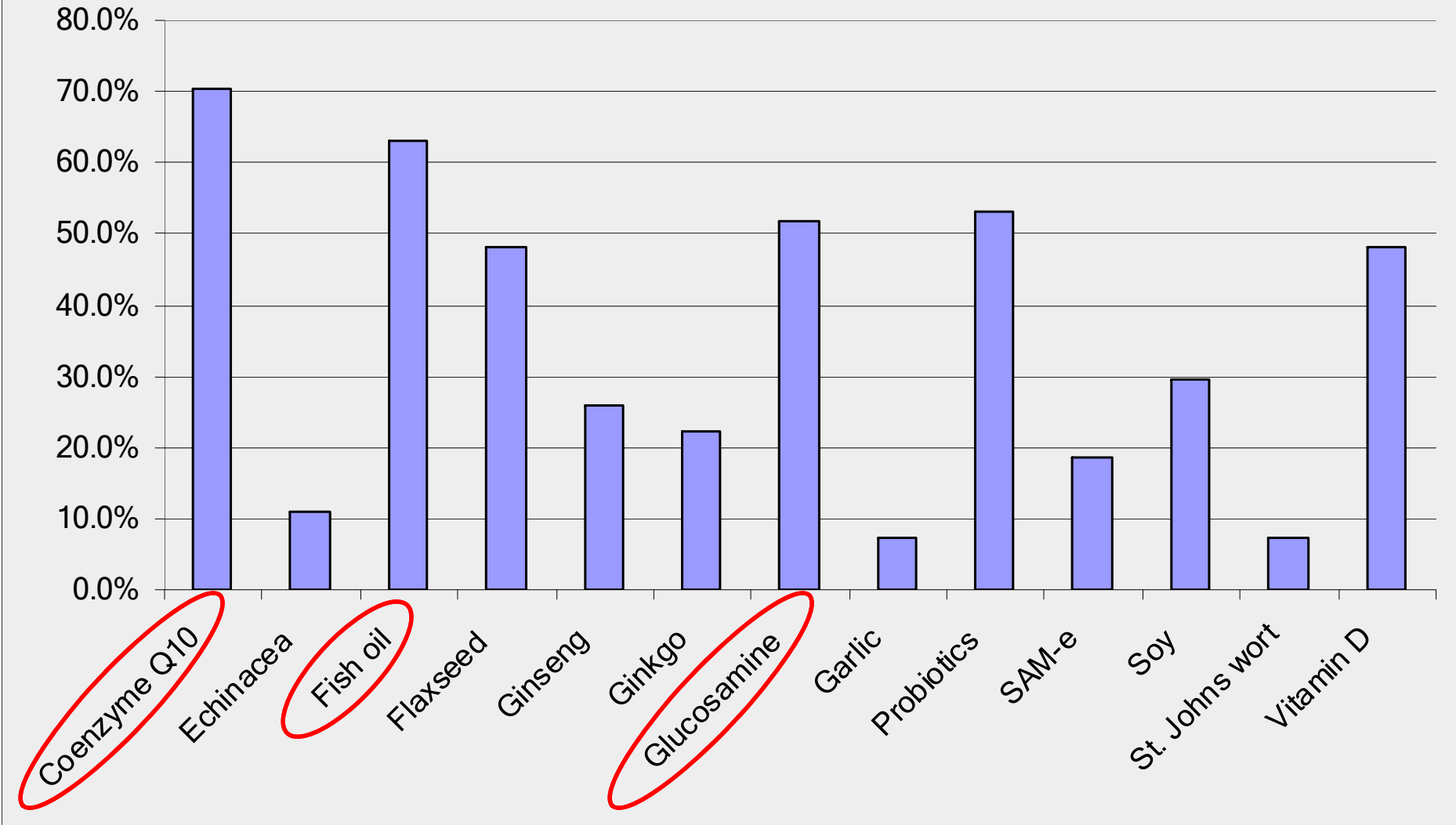
Soy

St. Johns wort

Vitamin D



GIM Faculty Interest Survey, N=29



Information on Supplements

- UpToDate
- Ovid / PubMed
- Cochrane Collaboration
- Epocrates (\$ for CAM content)
- Micromedex
- [Natural Medicines Comprehensive Database](#)
- [National Center for Complementary / Alternative Medicine](#)
- [Office of Dietary Supplements](#)
- [FDA](#)

NATURAL MEDICINES
COMPREHENSIVE DATABASE



NMCD

Safety ratings

- Likely safe
- Possibly safe
- Possibly unsafe
- Likely unsafe
- Unsafe
- Insufficient evidence

- Effective
- Likely effective
- Possibly effective
- Possibly ineffective
- Likely ineffective
- Ineffective
- Insufficient evidence

Efficacy ratings



What is this natural product?



A. Cranberry

✓ B. Coffee

C. Grapes (grapeseed extract)



GIM Grand Rounds

True Top Natural Product



Coenzyme Q-10 Quiz

- Is coenzyme Q-10 a vitamin?
 - Yes
 - ✓ – No
- How much is a 30 tab bottle of 400 mg coenzyme Q-10 at Target.com?
 - \$20.99
 - \$46.99
 - ✓ – \$52.99



Coenzyme Q-10 NMCD

- Effective
 - No ratings
- Likely effective
 - Coenzyme Q10 deficiency
 - Mitochondrial encephalomyopathies
- Possibly effective
 - CHF
 - HTN
 - HIV
 - Migraines
 - Secondary MI prevention
 - Parkinsons
- Insufficient evidence
 - Prevention of statin myopathy



Top 4 CoQ10 Supplements Reviewed

For: Energy, Cardiac Strength, Stamina, Antioxidants, and More!

Omega Q Plus: our top rated product with five stars.



CoQ10 for secondary prevention of myocardial infarction

- N = 144, MI within 72 hours; well stratified
- All received usual care, though study done in 1996 (prior to routine ACE-I / BB)
- Double blind, placebo controlled, randomized
- 120 mg CoQ10 / day vs 32 mg vitamin B



CoQ10 for secondary prevention of myocardial infarction

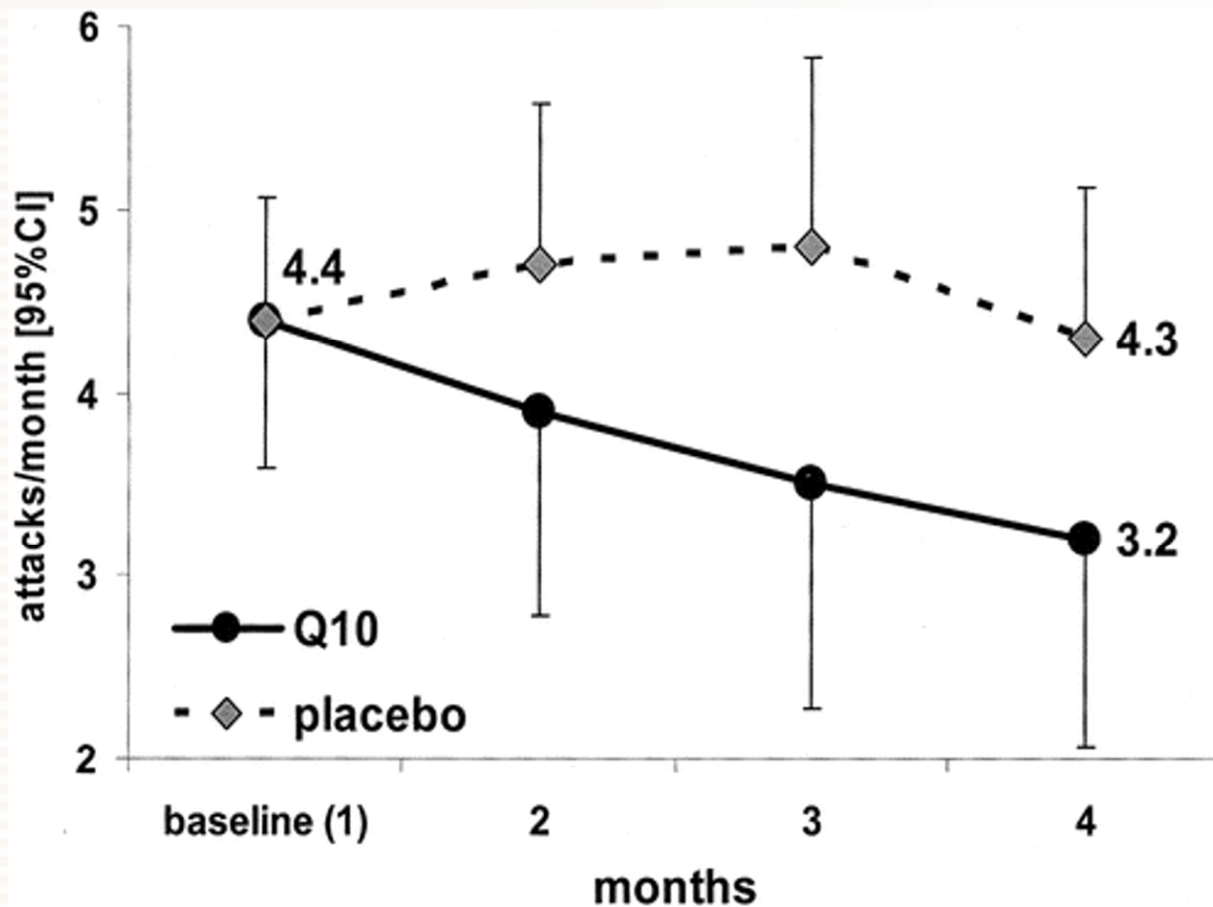
Cardiac events	Coenzyme Q10 (n = 73)	B vitamins (n = 71)	Relative risk (95%) confidence interval
Sudden cardiac death (< 1 h)	3 (4.1)	5 (7.0)	0.58
Fatal myocardial infarctions	5 (6.8)	9 (12.7)	0.53
Non-fatal myocardial infarction	10 (13.7)*	18 (25.3)	0.54
Total cardiac deaths	8 (10.9)	14 (19.7)	0.55
Stroke	–	2 (2.8)	0.46
Angioplasty or CABG	1 (1.3)	3 (4.2)	0.31
Total cardiac events	18 (24.6)**	32 (45.0)	0.54
Total cardiovascular events	18 (24.6)**	34 (47.8)	0.51
Total cardiac end points	19 (25.9)**	37 (52.0)	0.49



CoQ10 for prevention of migraines

- N = 43, 2-8 migraines/month, on no prophylactic meds
- Placebo x 1 month; randomized if had a migraine
- Double blind, placebo controlled, randomized
- 100 mg CoQ10 TID vs placebo





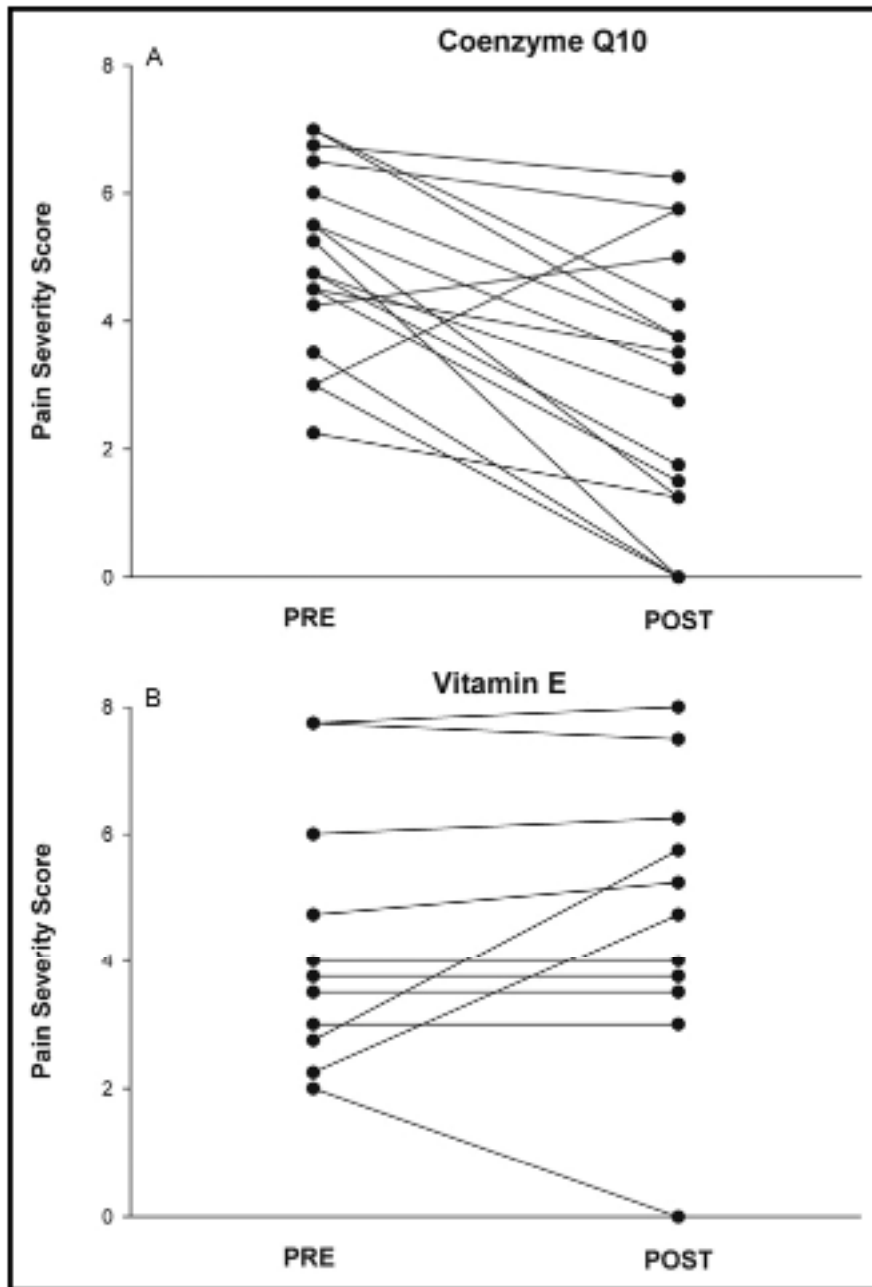
- Placebo: 8 increase, 8 decrease, 5 no change
- CoQ10: 1 increase, 15 decrease, 1 no change



CoQ10 for prevention of statin myopathy

- N = 32, on a statin reporting muscle pain
- Double blind, placebo controlled, randomized
- 100 mg CoQ10 daily vs 400 IU vitamin E





Pain decreased 40% in treatment group, none in vitamin E group, $p < 0.0001$

Caso G. Am J Cardiol 2007.



CoQ10 for prevention of statin myopathy

- N = 33, h/o statin related muscle pain
- Double blind, placebo controlled, randomized
- 200 mg CoQ10 daily vs placebo
- Began with 10 mg simvastatin / day, increased to max of 40 mg/day as tolerated



Table 2
Simvastatin dose tolerated at 12 weeks

Tolerated Dose (mg/day)	Coenzyme Q ₁₀ and Simvastatin Therapy (n = 22)	Simvastatin Alone (n = 22)
40	16 (73%)	13 (59%)
20	0	3 (14%)
10	0	2 (9%)
0	6 (27%)	4 (18%)

Data are expressed as number (percentage) of patients.

$p = 0.34$ for comparison of the number of patients who tolerated simvastatin 40 mg/day (chi-square test); $p = 0.47$ for comparison of the number of patients remaining on simvastatin (chi-square test).

No difference in number of patients able to tolerate 40 mg simvastatin



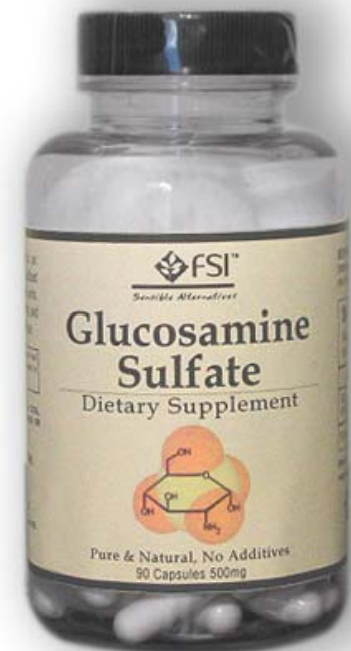
CoQ-10 Safety

- Used safely in studies up to 30 months
- GI side effects in <1%; minimized by dividing doses over 100 mg
- Allergic rash in one study
- Drug interactions (theoretical) – warfarin (vitamin K-like), chemotherapy (antioxidant), antihypertensives (additive effect)

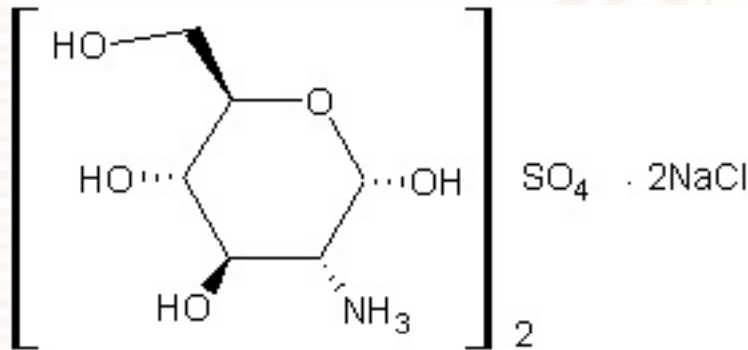


Glucosamine Quiz

- Does glucosamine raise glucose levels?
 - Yes
 - ✓ – No
- Which of the following is also marketed for osteoarthritis?
 - Lactobacillus
 - Feverfew
 - ✓ – S-adenosyl methionine (SAME)



Glucosamine



- Glucosamine hydrochloride, glucosamine sulfate, N-acetyl glucosamine all likely active
- Required for production of glycosaminoglycans
- Derived from marine exoskeletons or synthesized
- Stimulates chondrocytes, synovial cells



Glucosamine - NMCD

- Insufficient evidence to rate
 - Osteoarthritis
 - Knee
 - Low back
 - Hip
 - Rheumatoid arthritis



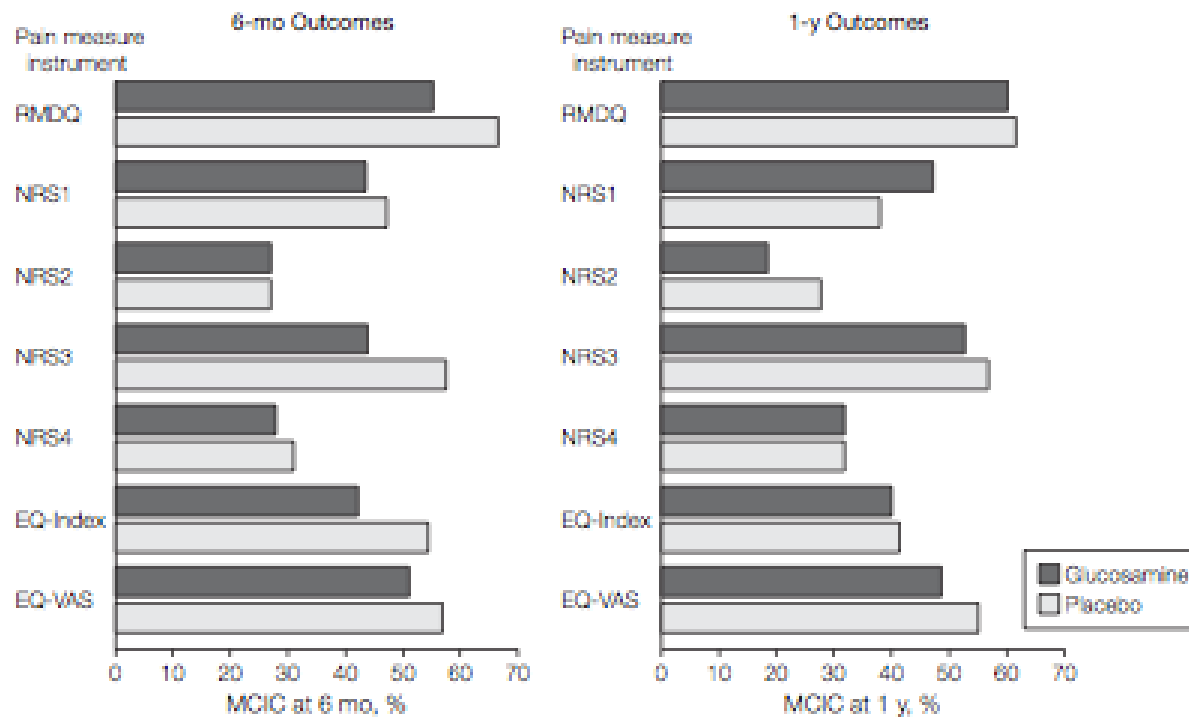
Glucosamine for chronic LBP

- N = 250, adults over age 25, chronic low back pain and degenerative lumbar osteoarthritis
- Double blind, placebo controlled, randomized
- 1500 mg glucosamine / day vs placebo x 6 months



Glucosamine for LBP

Figure 2. Percentage of Participants With Minimal Clinically Important Change for Main Primary and Secondary Outcomes at 6 Months and 1 Year



Glucosamine +/- Chondroitin for Knee Pain

- N=1583
- Randomized; stratified by severity
- 1500 mg glucosamine, 1200 mg chondroitin, both, 200 mg celecoxib, or placebo x 24 weeks
- Primary outcome – 20% decrease in knee pain



GAIT trial – Endpoint Reached

All patients

- Placebo: 60%
- Glucosamine: 64%
- Chondroitin: 65%
- Combo: 67%
- Celecoxib: 70%*

Mod / severe OA

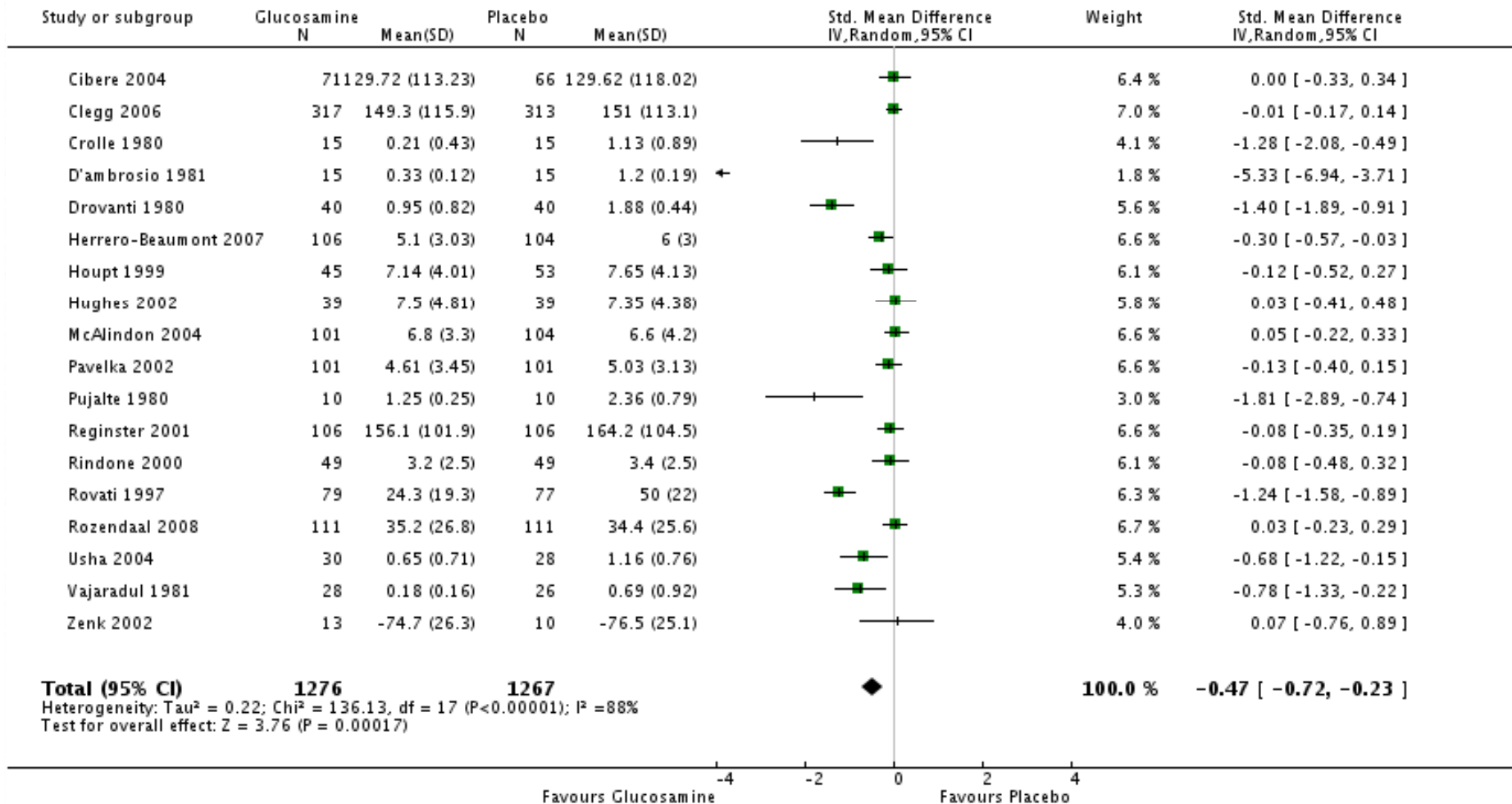
- Placebo: 54%
- Glucosamine: 66%
- Chondroitin: 61%
- Combo: 79%**
- Celecoxib: 69%

*p=0.008 **p < 0.002



Glucosamine for OA – Cochrane 2009

Review: Glucosamine therapy for treating osteoarthritis
 Comparison: 1 Glucosamine versus placebo
 Outcome: 1 Pain



Glucosamine Safety

- Side effects
 - Mild GI upset
- Theoretical drug interactions
 - Warfarin (heparin-like; antiplatelet activity)
- Glucose control in DM – no change



Fish Oil Quiz

- Why is fish oil preferred over cod liver oil?
- Why is fish oil preferred over plant sources of omega 3 fatty acids?



Fish Oil Quiz



- Why is fish oil preferred over cod liver oil?
 - Too much vitamin A in cod liver oil
- Why is fish oil preferred over plant sources of omega 3 fatty acids?
 - Body must process alpha-linoleic acids in plants to the DHA / EPA omega 3 fatty acids



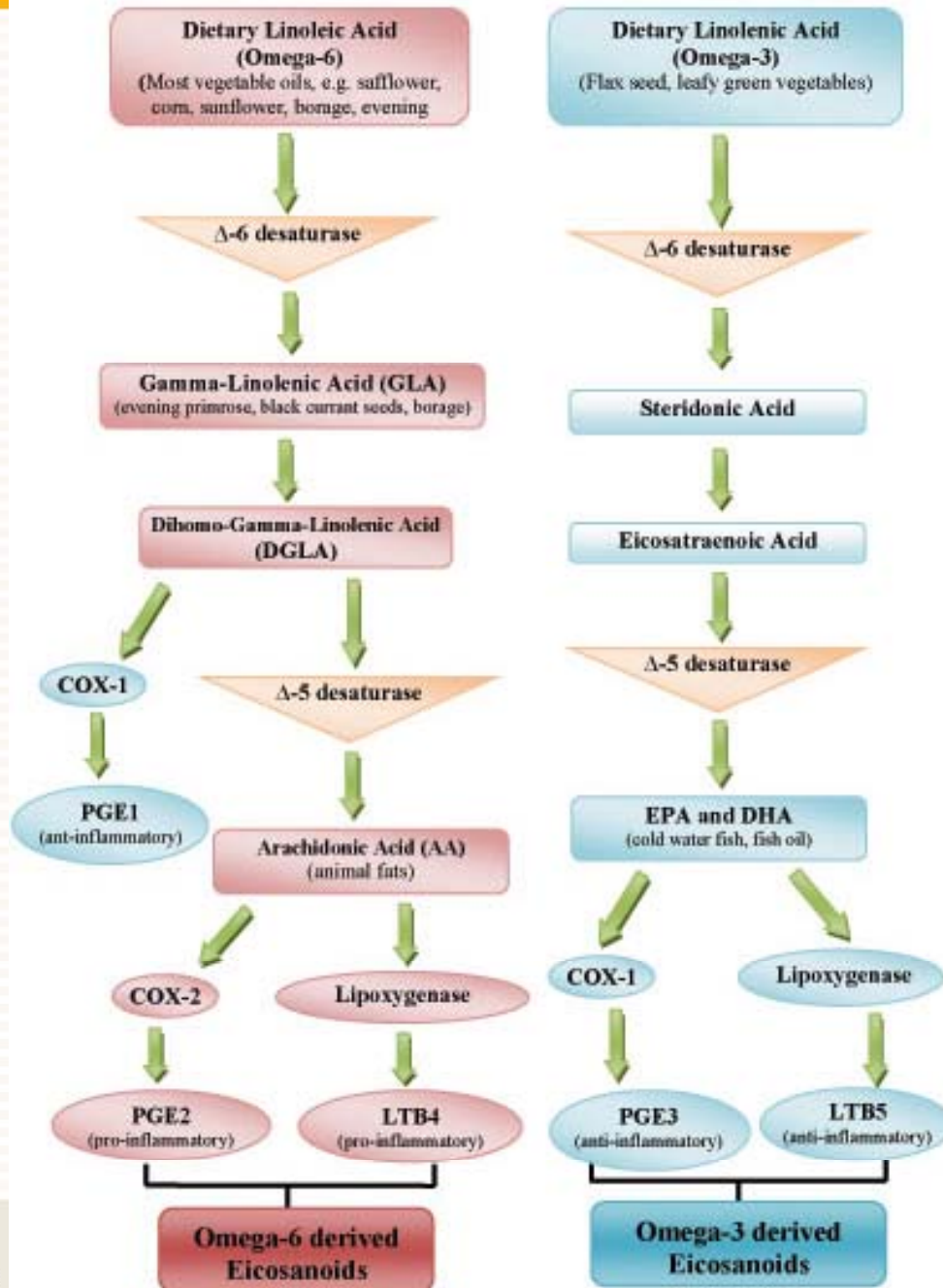


Fish Oil



- Omega 3 fatty acids
(Eicosapentaenoic acid (EPA), Docosahexaenoic acid (DHA))
 - Long chain, polyunsaturated fats
 - Cannot be made by the body
 - Antiinflammatory, vasodilatory, antiplatelet
 - Inhibit growth factors, angiogenesis
- Which fish?
Herring, kipper, mackerel, menhaden, pilchard, salmon, sardine, trout
- Plants?
Alpha-linoleic acid, *precursor* for DHA/EPA – some similar clinical effects
but not on cholesterol





Fish Oil - NMCD

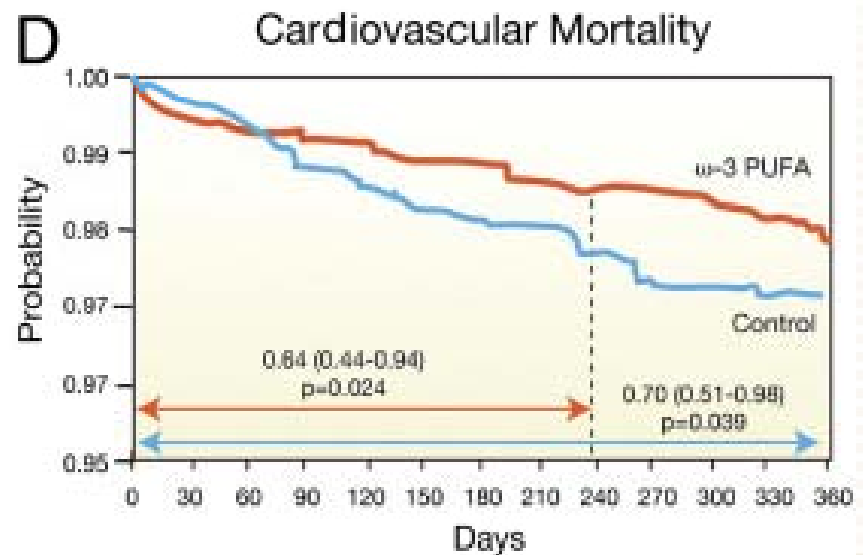
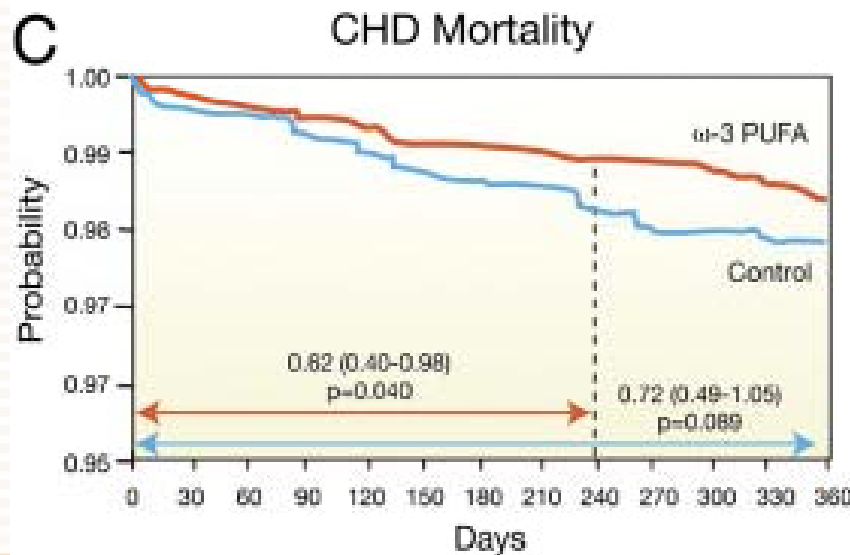
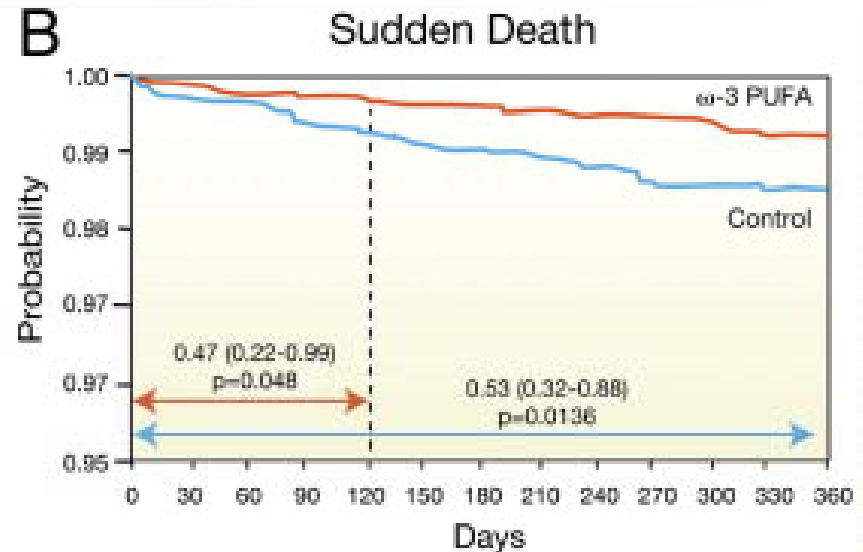
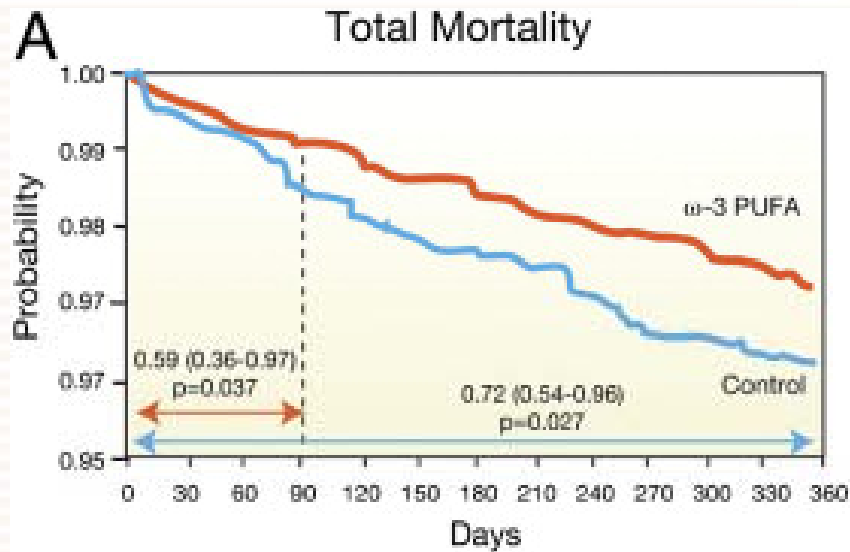
- Effective
 - Hypertriglyceridemia
- Likely effective
 - Cardiovascular disease
(primary and secondary prevention)
- Possibly effective
 - 29 listings
- Possibly / likely ineffective
 - 9 listings
- Insufficient evidence
 - 22 listings



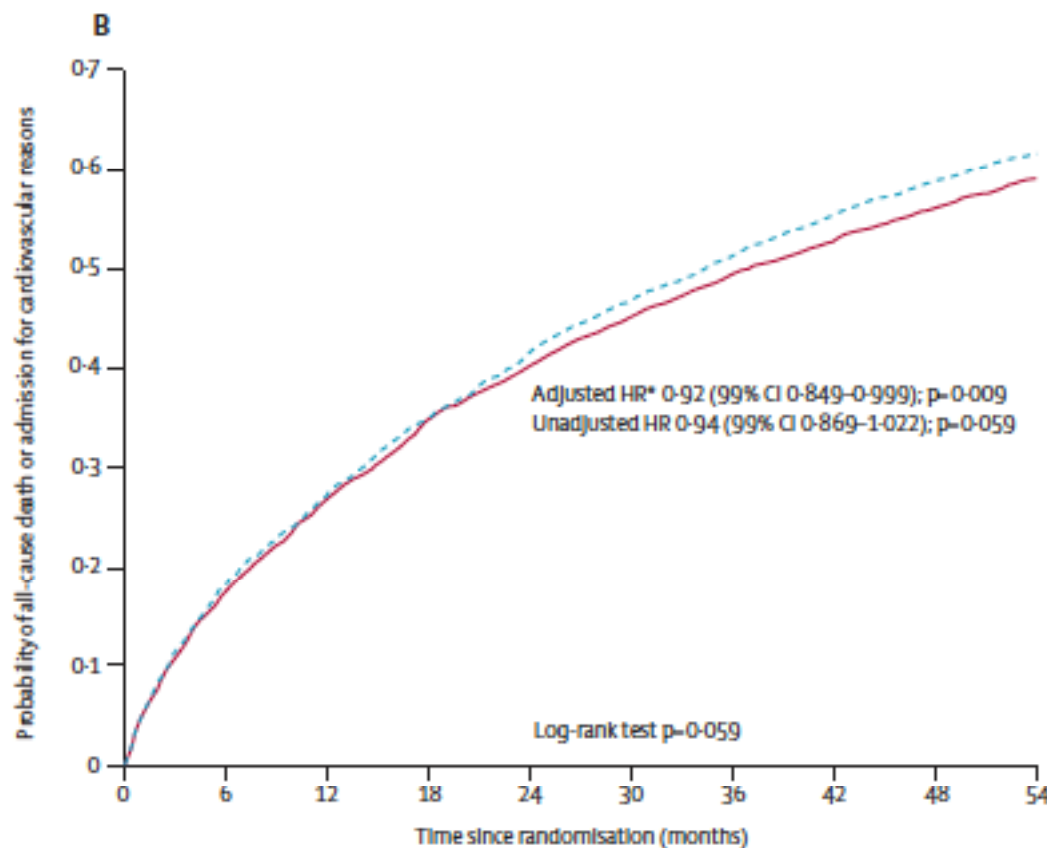
Omega 3 FA for Secondary Prevention

- N=11323 with MI within 3 months
- N-3 PUFAs (1 gm), vitamin E (300 mg), both, neither
- All received optimal med and lifestyle tx
- Reduced many endpoints





Omega 3 for CHF



- 7046 patients with class II-IV CHF
- 1 gm n-3 PUFA vs placebo
- NNT to prevent 1 death in 4 years = 56

Patients at risk

n-3 PUFA	3494	2876	2543	2261	2066	1896	1718	1342	949	502
Placebo	3481	2846	2518	2251	1826	1826	1640	1254	876	446





Fish Oil Safety

- Inhibition of coagulation / bleeding
- Fishy taste, GI effects
 - Minimize with food or freezer
- Immunosuppression at high doses
- Mercury concern likely negligible; concentrates in meat > oils
- May lower blood pressure
- May decrease pulmonary function if aspirin sensitive



Advising patients

- “Natural” \neq safe, “test-of-time” \neq safe
- Tradition or anecdotal successes are not proof of safety or efficacy
- Supplements used for health purposes should be treated with the same cautions as other medications
- Supplements are not required to be shown safe or effective before marketing



Advising Patients

- Maximize benefits and minimize risks by:
 - Discussing with your health care provider
 - Stop taking the product if you notice side effects, and report them to your provider
 - Avoid combination and MLM products
 - Look for well-labeled products (scientific name of the plant, information about the manufacturer, dosing guidelines, expiration, and possible side effects)
 - Look for USP or other quality designation



**“What we know for sure is
the United States secretes
the richest urine in the world”**

--Victor Herbert, MD



Resources – General Information

- [FDA Dietary Supplements 101](http://www.fda.gov/food/dietarysupplements/default.htm)
(www.fda.gov/food/dietarysupplements/default.htm)
- [Medline Plus –supplements](http://www.nlm.nih.gov/medlineplus/druginfo/herb_All.html)
(www.nlm.nih.gov/medlineplus/druginfo/herb_All.html)
- [UpToDate](http://www.uptodate.com) (www.uptodate.com)
- [PubMed](http://www.ncbi.nlm.nih.gov/pubmed/) (www.ncbi.nlm.nih.gov/pubmed/)
- [Cochrane Collaboration](http://www.cochrane.org) (www.cochrane.org)
- [Epocrates](http://www.epocrates.com) (www.epocrates.com)
- [Micromedex](http://www.micromedex.com/) (www.micromedex.com/)
- [Natural Medicines Comprehensive Database](http://naturaldatabase.therapeuticresearch.com/home.aspx?cs=475965)
(naturaldatabase.therapeuticresearch.com/home.aspx?cs=475965)
- [National Center for Complementary / Alternative Medicine](http://nccam.nih.gov/health/supplements/)
(nccam.nih.gov/health/supplements/)
- [Office of Dietary Supplements](http://ods.od.nih.gov/) (ods.od.nih.gov/)



Resources – Safety / Standardization

- [Adverse event reporting](http://www.fda.gov/Food/DietarySupplements/Alerts/ucm111110.htm)
(www.fda.gov/Food/DietarySupplements/Alerts/ucm111110.htm)
- [United States Pharmacopeia](http://www.usp.org/USPVerified/dietarySupplements/)
(www.usp.org/USPVerified/dietarySupplements/)
- [NNFA/Natural Products Association](http://www.npainfo.org/)
(www.npainfo.org/)
- [National Sanitation Foundation](http://www.nsf.org/business/dietary_supplements/index.asp?program=DietarySupps)
(www.nsf.org/business/dietary_supplements/index.asp?program=DietarySupps)
- [ConsumerLab](http://www.consumerlab.com/)
(www.consumerlab.com/)



Getting familiar with NMCD

- The following slides are for you to practice finding information using the NMCD
1. Begin on the Health Sciences Library home page: <http://hslibrary.ucdenver.edu/>
 2. Select “Natural Medicines” on left under “Top Resources”



Getting familiar with NMCD

- Questions to answer
 1. Which product(s) are “likely effective” for osteoarthritis?
 2. What dose of SAME is suggested for osteoarthritis?
 3. Are there any USP grade SAME products?
 4. Which of the following medications may have interactions with SAME: fluoxetine, levodopa, digoxin, MAO inhibitors, coumadin?
 5. For which conditions has marijuana been shown “possibly effective”?

Answers on last slide



Getting familiar with NMCD

- Answers
 1. SAME, glucosamine
 2. 200 mg TID
 3. No
 4. fluoxetine, levodopa,, MAO inhibitors
 5. Glaucoma, spasticity / tremor in MS, HIV-related weight loss

Answers on last slide

