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Dietary Supplements with Cardiovascular Drugs: Helpful or Harmful?

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Conflict of Interest

- **Conflict of Interest**: None
- **Disclosure**: Clinical Lead with the Ottawa Evidence Based Practice Center (EPC)
  - Commissioned by Agency for Healthcare Research and Quality (AHRQ) to conduct SR on harms and benefits of dietary supplements in patients taking cardiovascular drugs

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Objectives

- Epidemiology of dietary supplements in cardiovascular disease
- Discuss the evidence-based benefits and harms of dietary supplements on cardiovascular disease
- Discuss the benefits and harms of co-administration of common dietary supplements with cardiovascular drugs

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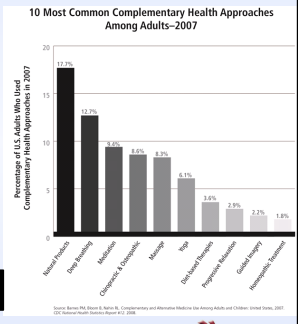
Dietary Supplements

- Complementary and Alternative Medicine (CAM)
  - Preventative or therapeutic treatments of disease not considered part of conventional medicine
    - Mind and body practices (accupuncture, yoga, massage, etc)
    - Dietary supplements (natural products)

34 Billion spent in 2007 on dietary supplements in the US



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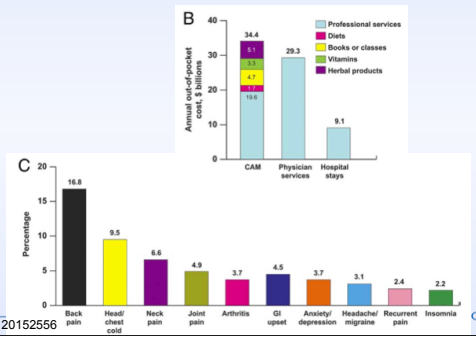
Complimentary and Alternative Medicine



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Cardiovascular Disease and Dietary Supplements

81 million Americans have cardiovascular disease

- 1/3 of all American adults
- On average 6.3 prescription drugs from 6 different drug classes daily
- 1/3 to 2/3 of all patients with CVD take some form of dietary supplements

Dietary supplements + Prescription Drugs = ?

- **Potential for benefit** (independent, additive, synergistic effects)
- **Potential for harm** (drug interactions, adverse drug events)

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How are patients informed about the risks/benefits of Dietary Supplements?

Family Doc? …Possibly
Pharmacist? …Possibly
Naturopath? …Unlikely

How are patients informed about the risks/benefits of Dietary Supplements?

Most likely…

- Friends
- Family
- Healthy looking dude from the gym
- Television

What supplements to patients with CVD take?

- 2006 Survey:
  - Omega-3 Fatty Acids, Fish oils
  - Garlic
  - Echinacea
  - Ginseng
  - Ginkgo Biloba
  - St. John's Wort
  - Ginger
  - Glucosamine

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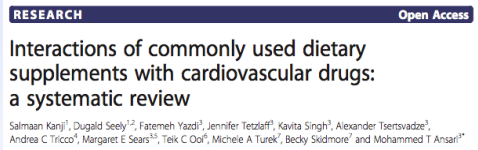
So Many Questions!

- Is it safe to take common dietary supplements with cardiovascular drugs.
- Are there combinations that provide an incremental benefit over conventional medicine alone?
- At what level have interactions been identified?
  - Pharmacokinetic level
  - Intermediate outcomes level
  - Clinical Outcomes level
- What is the quality of the evidence?
- How can we use this data to make informed decisions and advise our patients?



Research Question: What are the benefits, harms and PK interactions of dietary supplements when co-administered with cardiovascular drugs.

Study Selection: Randomized controlled trials of
Supplement + Drug vs Drug alone+/- another supplement

Supplements with evidence:

CO-ENZYME Q10	GINKGO BILOBA
GARLIC	AMERICAN GINSENG
OMEGA-3 FATTY ACIDS	VITAMIN E

Omega-3 Fatty Acids: The Claim

- At least 4 international health organizations recommend long chain marine omega-3 polyunsaturated FA (PUFA) supplementation for the primary prevention of CVD
  - Eicosapentanoic acid (EPA) and Docosahexaenoic acid (DHA)
  - 0.85 – 1.8 g/day to reduce CVD events
- Mechanism of action: Unknown
  - TG lowering?
  - Inhibition of platelet aggregation?
  - Blood pressure lowering?
  - Arrhythmia prevention?

Omega-3 Fatty Acids: The Claim

- 14 Meta-Analyses evaluating cardiovascular outcomes in the last 10 years
  - 7 – Benefit
  - 6 – Mixed benefit
  - 3 – No benefit
- More than 20 RCTs, more than 70,000 patients enrolled
- 4 Most recent trials: OMEGA, Alpha OMEGA, SuFolOm3, ORIGIN

PMID: 23196817

Omega-3 Fatty Acids: The Claim

Table 1. Fish oil and cardiovascular disease (major randomized trials 2010–2012)

Study	Population	Interventions	Years	Endpoints	RR (95% CI)
OMEGA [13]	3851 patients with recent MI (≤2 weeks)	840 mg EPA + DHA vs. placebo	1	Major CV	1.21 (0.96–1.52)
				Sudden deaths	0.95 (0.56–1.60)
Alpha Omega [14]	4837 patients with history of MI (median 3.7 years)	376 mg EPA + DHA vs. placebo and ALA (1.9 g; groups combined)	3.4	Major CV	(0.87–1.17)
				CHD deaths	0.95 (0.68–1.32)
SU.FOL.OM3 [15]	2501 patients with recent coronary or cerebral ischemic event (median 101 days)	600 mg EPA + DHA vs. placebo and B vitamin groups combined	4.2	Major CV	1.08 (0.79–1.47)
				CHD deaths	Not reported
ORIGIN [12••]	12536 patients with dysglycemia	840 mg EPA + DHA vs. placebo	6.2	CVD deaths	0.98 (0.87–1.10)
				Major CV	1.01 (0.93–1.10)

ALA, alpha-linolenic acid; CHD, coronary heart disease; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MI, myocardial infarction; ORIGIN, Outcome Reduction with Initial Glargine Intervention; SU.FOL.OM3, Supplementation with Folic Acid and Omega-3.

PMID: 23196817

Omega-3 Fatty Acids: The Claim

- Newest meta-analyses suggesting no overall benefit on cardiovascular outcomes despite questionable evidence of benefit on intermediate outcomes (triglycerides, blood pressure)
- As the quality of Omega-3 FA studies improve, the signal of benefit fades
  - Selection bias?

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Interactions of commonly used dietary supplements with cardiovascular drugs: a systematic review

Clinical Outcomes: Omega-3 FA

Outcome	CV drug comparator	Number of Trials (patients)	Finding	GRADE
CV Mortality	Statins ASA warfarin fenofibrate	4 (827)	No benefit (inconclusive)	Insufficient
Myocardial Infarction	CCBs and ASA	1(58)	No benefit (inconclusive)	Insufficient
Arrhythmias	Statins	1 (256)	No benefit (inconclusive)	Insufficient

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Intermediate Outcomes: Omega-3 FA

Outcome	CV drug comparator	Number of Trials (patients)	Finding	GRADE
LDL, HDL, total CHOL	Statins	8 (441)	No benefit	Low
Triglycerides	Statins	6 (711)	Additive effect in patients with high baseline TG only	Low
Blood Pressure	ASA Beta-blockers	2 (55)	Improves SBP, not DBP	Low

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PK Outcomes and Harms: Omega-3 FA

Outcome	CV drug comparator	Number of Trials	Finding	GRADE
AUC, Cmax, Tmax	Statins	3	No interaction	Low
Adverse Events	Statins ASA Fenofibrates Beta Blockers CCBs ACE-I	22	No evidence of increased adverse events	Insufficient

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Omega-3 FA: Bottom Line

Primary Prevention
- Minimal impact, if at all on meaningful CV outcomes (mortality, MI, stroke, arrhythmia)

Co-administration with Cardiovascular drugs
- Some effect on TG (patients with high baseline TG)

Safe to take with cardiovascular drugs?
- No evidence of harm but strength of evidence is low.

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Co-Enzyme Q10: The Claims

- Slows the progression of atherosclerosis via inhibiting LDL oxidation
- Reduces blood viscosity and improves ischemia and reperfusion injury

Mechanism of action:
- Improved cellular bioenergetics
- Necessary for oxidative phosphorylation, ATP production in all cells, particularly myocytes
- Antioxidant
- Membrane stabilizer
- Improves endothelial function

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Co-Enzyme Q10: The Claims

Any evidence behind these claims?
- Very few large randomized controlled trials
- 2013 Cochrane review
  - Supplementation will increase levels
  - No effect on mortality, hospitalizations for CVD
  - One study suggesting improvement in NYHA symptoms in heart failure

PMID:24049047

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Clinical Outcomes: Co-enzyme Q10

Outcome	CV drug comparator	Number of Trials (patients)	Finding	GRADE
CV Mortality	ACE-I	1(30)	No benefit (inconclusive)	Insufficient
Myocardial Infarction	ACE-I	1(30)	No benefit (inconclusive)	Insufficient

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Intermediate, Harms and PK Outcomes: Coenzyme Q10

Outcome	CV drug comparator	Number of Trials	Finding	GRADE
HDL	Fenofibrate	1	No benefit	Low
Adverse events	Statins Fenofibrates ACE-I	5	No evidence of adverse events	Insufficient
PK interactions	-	-	-	-

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Coenzyme Q10: Bottom Line

Primary Prevention
- Really no evidence outside of large observational data suggesting symptom improvement in heart failure
- Larger RCTs needed for confirmation

Co-administration with Cardiovascular drugs
- No evidence. Unlikely

Safe to take with cardiovascular drugs?
- No evidence of harm but strength of evidence is low.

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Garlic: The Claim

- Reduces cholesterol
- Reduces blood pressure
- Inhibits platelet aggregation

Mechanism of Action:
- Allicin (active ingredient) shown to have similar effects to ACE-I
- Free radical scavenger
- Inhibits cholesterol synthesis

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Garlic: The Claim

- Is there evidence to support these claims?
  - Recent meta analyses suggest that
    - Garlic has inconsistent positive effects on total cholesterol, TG, HDL, blood pressure and platelet aggregation
    - Inconsistencies thought to be due to quantitative and qualitative variability between different formulations

PMID: 23690831

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Interactions of commonly used dietary supplements with cardiovascular drugs: a systematic review

Clinical and Intermediate Outcomes: Garlic

Outcome	CV drug comparator	Number of Trials (patients)	Finding	GRADE
Clinical Outcomes	-	-	-	-
Total Cholesterol, LDL, TG	ASA Statins warfarin Nitrates	3 (131)	No benefit	insufficient
HDL	Nitrates	1(50)	Combination better than nitrates alone	insufficient

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Interactions of commonly used dietary supplements with cardiovascular drugs: a systematic review

Harms and PK Outcomes: Garlic

Outcome	CV drug comparator	Number of Trials	Finding	GRADE
Adverse events	Warfarin Nitrates Statins	3	No evidence of adverse events	Insufficient
AUC, Half-life, clearance	Warfarin	2	No evidence of interaction	low

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Garlic: Bottom Line

Primary Prevention
- Probably has some effect on lipid profiles and perhaps blood pressure in patients not taking lipid lowering or blood pressure meds.
- Future trials need to standardize their interventions

Co-administration with Cardiovascular drugs
- Some effect on TG (patients with high baseline TG)

Safe to take with cardiovascular drugs?
- No evidence of harm but strength of evidence is low.

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Ginkgo biloba: The claims

- Most claims related to memory, alzheimers, dementia
- Peripheral vascular disease, intermittent claudication
- Inhibition of platelet aggregation
- Reduction in coronary artery disease

Mechanism of action:

- Small studies suggest:
  - Flavonoids are a big component of ginkgo
    - Antioxidant, platelet inhibition
    - Vasodilatory effect via release of nitric oxide

PMID: 20123670

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Ginkgo biloba: The Claims

- Is there evidence to support these claims?
  - Intermittent Claudication:
    - 11 conflicting RCTs (477 patients) as of 2013
    - suggest improved pain free walking distance (65m, p=0.06) when compared to placeb
  - Primary prevention of CAD:
    - Largest placebo controlled RCT of >3500 patients over the age of 75 showed no difference in stroke, MI or angina
    - Non-statistically significant increase in hemorrhagic stroke (16 vs 8, p=0.12)

PMID 11014719, 20123670, 20464671

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Interactions of commonly used dietary supplements with cardiovascular drugs: a systematic review

Clinical and Intermediate Outcomes: Ginkgo Biloba

Outcome	CV drug comparator	Number of Trials (patients)	Finding	GRADE
All cause mortality	ASA +/- pentoxyfylline	1 (62)	No evidence benefit	insufficient
Cholesterol, blood pressure, INR	ASA, clopidogrel, ticlopidine, warfarin, cilostazol	5 (156)	No evidence of benefit	insufficient

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Interactions of commonly used dietary supplements with cardiovascular drugs: a systematic review

Harms and PK Outcomes: Ginkgo Biloba

Outcome	CV drug comparator	Number of Trials	Finding	GRADE
Adverse events	Warfarin, digoxin, ASA, nitrates, clopidogrel, ticlopidine, cilostazol	7	No evidence of adverse events	Insufficient
AUC, Half-life, Cmax	Warfarin, digoxin, ticlopidine	3	No evidence of interaction	insufficient

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Ginkgo biloba: Bottom Line

Primary Prevention

- Supportive evidence in alzheimers is weakening as larger more robust studies are conducted
- Supportive evidence in CAD prevention was never there to begin with
- May play a role in symptom/function management in intermittent claudication

Co-administration with Cardiovascular drugs

- No effect obseved

Safe to take with cardiovascular drugs?

- Despite reports of increased bleeding, no consistent evidence from clinical trials, PK studies.

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Ginseng: The claims

- Ginseng (panax, american, siberian)
- Used as a medicine for >2000 years
- 6 million Americans take Ginseng regularly
- Health claims from depression to cystic fibrosis
- CV claims: lowers blood pressure, protects from CAD, slows the progression of heart failure

Mechanism of action:

- Active ingredients are a variety of different ginsenosides (Rb1, Rg1, Rg3, Rh1, Re, Rd)
- Free radical scavenger, reduces apoptosis in reperfusion injury
- Reduced platelet aggregation
- Vasodilation via nitric oxide release
- Anti-inflammatory

PMID: 23717100, 21985167

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Ginseng: The Claims

- Evidence to support these claims?
  - Hypertension
    - Human studies conflicting: More recent studies suggesting no clinically significant effect in hypertensive patients
  - Hyperlipidemia
    - Mostly animal studies suggesting beneficial effect on total cholesterol and TG

PMID: 23717100, 21985167

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Interactions of commonly used dietary supplements with cardiovascular drugs: a systematic review

Clinical and Intermediate Outcomes: Ginseng

Outcome	CV drug comparator	Number of Trials (patients)	Finding	GRADE
Clinical Outcomes	-	-	-	-
INR	Warfarin	3(78)	No evidence of benefit	insufficient

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Harms and PK Outcomes: Ginseng

Outcome	CV drug comparator	Number of Trials	Finding	GRADE
Adverse events	Warfarin	3	No evidence of adverse events	Insufficient
AUC	Warfarin	1	Reduction in warfarin AUC	insufficient

Upregulation of CYP450-2C9?

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Ginseng: Bottom Line

Primary Prevention
- Very little evidence

Co-administration with Cardiovascular drugs
- No clinical advantage with respect to blood pressure, CAD

Safe to take with cardiovascular drugs?
- Some ginsenosides do inhibit 2C9
- This inhibition probably varies from formulation to formulation
- Can influence warfarin PK. Insufficient evidence to determine clinical significance.
- Awareness of this interaction important for pharmacists

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Vitamin E: The Claims

- Primary prevention of coronary heart disease
- Reduced mortality in patients with coronary heart disease
- Reduce cholesterol

Mechanism of action
- Vit E is a collective of 8 different fat-soluble chemicals
- Only alpha-tocopherol is recognized as a nutritional requirement
- Anti-oxidant (inhibits reactive oxygen species formation during lipid oxidation
- Anti-inflammatory (suppresses arachadonic acid metabolism)

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Vitamin E: The Claims

- Is there evidence to support these claims?
- Early observational studies suggest primary and secondary prevention of coronary heart disease including cardiovascular mortality
- RCT evidence:
  - HOPE and HOPE-TOO (n=10,000 secondary prevention, 400IU/day vs placebo, 4.5-7y)
    - No benefit after 4.5 years
    - After 7 years, 13% more likely to be hospitalized for heart failure
  - Women's Health Study (n=40,000 primary prevention, 600 IU every other day vs placebo, 10 years)
    - No benefit, no harm

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Vitamin E: The Claims

- Systematic Reviews:
  - 46 RCTs (n=171,000)
  - At doses below the RDA (15mg or 22.4 IU) no benefit, no harm
  - At doses above the RDA (alone or in combination with other antioxidants) there is evidence of increased mortality (RR 1.03, 95% CI 1.00 to 1.05)

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Interactions of commonly used dietary supplements with cardiovascular drugs: a systematic review

Clinical and Intermediate Outcomes: Vitamin E

Outcome	CV drug comparator	Number of Trials (patients)	Finding	GRADE
Stroke	ASA	1(100)	No evidence of benefit	insufficient
Stroke, MI or vascular death	ASA	1 (19,934)	No evidence of benefit	
Total Cholesterol, LDL, TG	Nifedipine	1(30)	Combination better than nifedipine alone	low
Blood pressure	Nifedipine	1(30)	Combination better than nifedipine alone	insufficient

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Interactions of commonly used dietary supplements with cardiovascular drugs: a systematic review

Harms and PK Outcomes: Vitamin E

Outcome	CV drug comparator	Number of Trials	Finding	GRADE
Adverse events	ASA, nifedipine, furosemide, statins	10	No evidence of adverse events	Insufficient
PK outcomes	-	-	-	-

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Vitamin E: Bottom Line

Primary Prevention and Secondary Prevention
- Lack of effect is convincing
- Risk of harm (increased mortality, hospitalization) appears small but evident in high doses
- No role above RDI (15mg or 22.4 IU)

Co-administration with Cardiovascular drugs
- No clinical advantage with respect to clinical outcomes, cholesterol, blood pressure

Safe to take with cardiovascular drugs?
- Given the lack of proven benefit and paucity of safety data with other drugs would suggest to avoid in doses above 15 mg

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