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Nutritional Supplements in Cardiovascular Disease

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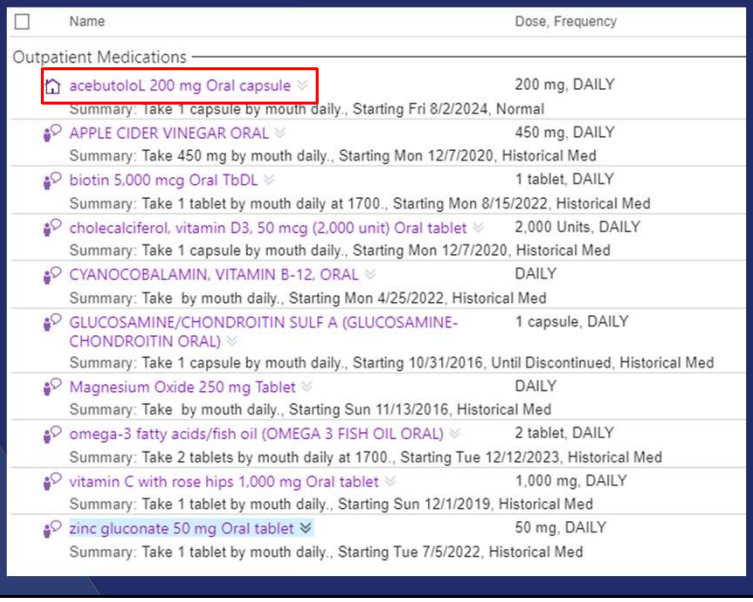
Disclosures: None

Why Discuss Supplements?



Name	Dose, Frequency
Outpatient Medications	
acebutolol 200 mg Oral capsule	200 mg, DAILY
Summary: Take 1 capsule by mouth daily., Starting Fri 8/2/2024, Normal	
APPLE CIDER VINEGAR ORAL	450 mg, DAILY
Summary: Take 450 mg by mouth daily., Starting Mon 12/7/2020, Historical Med	
biotin 5,000 mcg Oral TbDL	1 tablet, DAILY
Summary: Take 1 tablet by mouth daily at 1700., Starting Mon 8/15/2022, Historical Med	
cholecalciferol, vitamin D3, 50 mcg (2,000 unit) Oral tablet	2,000 Units, DAILY
Summary: Take 1 capsule by mouth daily., Starting Mon 12/7/2020, Historical Med	
CYANOCOBALAMIN, VITAMIN B-12, ORAL	DAILY
Summary: Take by mouth daily., Starting Mon 4/25/2022, Historical Med	
GLUCOSAMINE/CHONDROITIN SULF A (GLUCOSAMINE-CHONDROITIN ORAL)	1 capsule, DAILY
Summary: Take 1 capsule by mouth daily., Starting 10/31/2016, Until Discontinued, Historical Med	
Magnesium Oxide 250 mg Tablet	DAILY
Summary: Take by mouth daily., Starting Sun 11/13/2016, Historical Med	
omega-3 fatty acids/fish oil (OMEGA 3 FISH OIL ORAL)	2 tablet, DAILY
Summary: Take 2 tablets by mouth daily at 1700., Starting Tue 12/12/2023, Historical Med	
vitamin C with rose hips 1,000 mg Oral tablet	1,000 mg, DAILY
Summary: Take 1 tablet by mouth daily., Starting Sun 12/1/2019, Historical Med	
zinc gluconate 50 mg Oral tablet	50 mg, DAILY
Summary: Take 1 tablet by mouth daily., Starting Tue 7/5/2022, Historical Med	

Why Discuss Supplements?

- Patient medication lists with multiple supplements
- TV Ads with Doctors (Board Certified!) promoting a variety of supplements
  - Co-Q-10, Beetroot Juice, Berberine, Saw Palmetto, etc.
  - Claims of “#1 recommended” or “I wouldn’t recommend it if I didn’t believe it”, etc.

Supplements through History

- "Iceman" – 5300 yrs ago, frozen, well-preserved remains.
- Eggs of Trichuris trichiura (Whipworm) found in his rectum
- Also found with him were two lumps of the woody fruit of Fomitopsis Betulina fungus that contain toxic resins and Agaric Acid
  - Powerful Purgatives with Antiparasitic properties

THE LANCET • Vol 352 • December 5, 1998

Supplements through History

- Hippocrates and Galen promoted herbal remedies
- Chinese herbal medicine well entrenched
- European immigrants brought herbal remedies to USA
- First Edition of the USP 1820
  - Two thirds of entries were botanical

Use of Herbal and nonbotanical Supplements

- 1990 – 2.5% of adults used herbal medicines
- 1997 – 12.1 % respondents reported use
- 2012 – 17.7% adults used in the preceding year
- 2018 – 56% adults used Vitamins/Minerals and Non-Vitamin/Non-Mineral Supplements
- 25% of adults >60 y/o take 4 or more daily supplements
- 2022 – total sales of herbal and dietary supplements estimated to be $12.1 Billion

Regulation

- Herbal medicines assigned to category of food supplements
- Required to state “this product is not intended to diagnose, treat, cure or prevent any disease”
- Allowed to make health claims such as “supports the circulatory system”.
- Not required to report post-marketing adverse events to the FDA

Efficacy/Safety

- Highly variable Quality/Efficacy
  - Claims of efficacy often not proven in rigorous clinical trials, e.g., St. John's Wort, Gingko, Saw Palmetto, Echinacea
- Lack of Standardization
- Variable labeling (one study 32% of products did not contain ANY of the labeled ingredient)
- Purity and Efficacy – examples of supplements:
  - Adrenal support- contained T4 and steroids
  - Sexual enhancement – contain sildenafil
  - Weight loss – laxatives
  - Muscle building – anabolic steroids

Safety/Adverse Effects

- Reports of fatal AE's such as HTN, MI, CVA, Sz with ephedra
- Reports of hepatic & renal toxicity, carcinogenicity, heavy metal toxicity
- Drug interactions – e.g.,
  - CYP 3A4 (St. John's Wort)
  - Antiplatelet/anticoagulant effect (Gingko)
  - Others

10 Most Common Supplements (2012 NHIS Survey)

1. Fish oil
2. Glucosamine or Chondroitin
3. Probiotics or prebiotics
4. Melatonin
5. Coenzyme Q10
6. Echinaceae
7. Cranberry
8. Garlic
9. Ginseng
10. Ginkgo biloba

Cardiovascular Supplements

- Treatment
  - Lipid Management
  - Vascular health
  - BP control
  - Rx side effects (Co-Q-10)
- Prevention (Primary and Secondary)
  - Inflammation and Oxidative Stress
  - Reduction in CV risk

Cardiovascular Dietary Supplements (Effective/Possibly Effective)

- Omega 3 FA's
- Red Yeast Rice Extract
- Berberine
- Phytosterols
- EVOO
- Beet Root Extract
- Probiotics

Omega 3 FA's

- Lower TG's, may Increase TC/LDL
- Meta-analysis of 55 trials, 1 g/d lowered TG's by 5.9 mg/dl (J Am Coll Cardiol. 2011 Nov;58(20):2047-67)
- Meta-analysis of 7 Trials, 4 g/d Krill Oil:
  - Lowered LDL 15.5 mg/dl
  - Lowered TG's 14 mg/dl
  - Raised HDL 6.6 mg/dl

(Nutr Rev. 2017;75(5):361)

Red Yeast Rice Extract

- Contains monacolin K (HMG Co-A Reductase inhibitor - active ingredient in lovastatin)
- Also includes Sterols, isoflavones and mono-unsaturated fatty acids
- Issues with variable potency, bioavailability and lack of standardization
  - 12 different preparations evaluated
  - Monocolin K content ranged from 0.10 to 10.09 mg/capsule
  - 4/12 preparations had potentially nephrotoxic contaminants

Red Yeast Rice Extract (Clinical Trials)

- 83 patients, 2.4 gm/d vs Placebo for 8 weeks
  (Am J Clin Nutr. 1999;69(2):231)

Lipid	RYRE	PLACEBO
TC	208	251
LDL	135	175

- 62 patients, 1800 mg BID x 24 weeks
  (Ann Intern Med. 2009;150(12):830)

Lipid	RYRE	PLACEBO
TC	-15%	-5%
LDL	-21%	-9%

Berberine

- Alkaloid found in a number of plants
- Lowers Cholesterol by
  - Decreased absorption/Increased fecal excretion
  - Downregulation of PCSK9 Expression by suppression of transcription
  - Upregulation of LDL Receptor Expression
- Meta-analysis of 6 trials (229 patients) using 900-1500 mg/d vs. Placebo (J Ethnopharmacol. 2015;161:69):
  - Total Cholesterol reduced 25 mg/dl
  - LDL Cholesterol reduced 25 mg/dl
  - Triglycerides reduced 34 mg/dl

Phytolsterols/Phytostanols

- Plant-derived substances found in nuts, legumes, fruits, grains and plant oils
- Similar in structure to cholesterol
- Inhibit cholesterol absorption
- Major components Sitostanol and Campestanol
- Available as pills, capsules and in Fortified Margarines (e.g., Benecol)

Phytolsterols/Phytostanols

- 22 postmenopausal women with CHD
  - sitostanol fortified margarine lowered TC 13% and LDL 20% [Circulation 1997; 96:4226.]
- Patients already taking a statin:
  - Patients on a statin for 3 month with LDL cholesterol ≥130 mg/dL, adding 5.1 g/day of plant stanol ester lowered TC 12% and LDL 17% [Am J Cardiol 2000; 86:46].
  - Women with CAD on simvastatin, adding sitostanol fortified margarine lowered TC 11% and LDL 16% [Circulation 1997; 96:4226.]

REDUCTION OF SERUM CHOLESTEROL WITH SITOSTANOL-ESTER MARGARINE IN A MILDLY HYPERCHOLESTEROLEMIC POPULATION

N Engl J Med 1995;333:1308-1312

- 153 pts randomized to 8 g margarine fortified with sitostanol ester TID vs margarine without sitostanol ester for 1 year
- TC 10% lower (24 mg/dl)
- LDL 14% lower (21 mg/dl)
- HDL/TG – no change

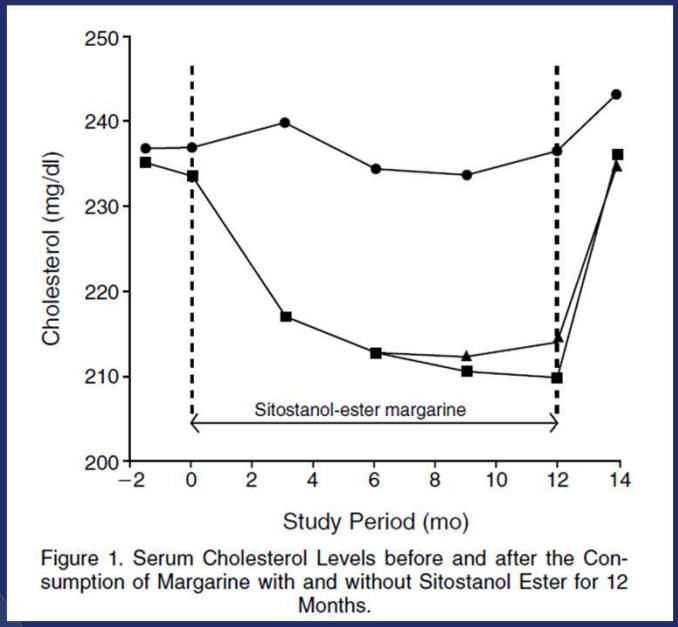


Figure 1. Serum Cholesterol Levels before and after the Consumption of Margarine with and without Sitostanol Ester for 12 Months.

N Engl J Med 1995;333:1308-1312

Olive Oil

- Olive oil is high in monounsaturated fat (MUFA), especially oleic acid, vitamin E, polyphenols, and lipid molecules that may contribute to its anti-inflammatory and antioxidant properties.
- Consumption of olive oil improves CV risk factors, including inflammatory and lipid biomarkers.
- Observational studies have found that olive oil intake is inversely associated with CVD and all-cause death. (J Am Coll Cardiol 2020;75:1729–39)
- A Mediterranean diet supplemented with extra-virgin olive oil, compared with a control diet, has been shown to reduce the risk of a composite of CVD events by 31% (N Engl J Med 2018;378)
- "I have a jigger every morning".

Olive Oil Consumption and Cardiovascular Risk in U.S. Adults

(J Am Coll Cardiol 2020;75:1729–39)

- 61,181 women from the Nurses' Health Study and 31,797 men from the Health Professionals Follow-up Study who were free of cancer, heart disease, and stroke
- Diet was assessed using food frequency questionnaires at baseline and then every 4 years at baseline.
- Compared with nonconsumers, those with higher olive oil intake (>0.5 tablespoon/day or >7 g/day) had **14% lower risk of CVD and 18% lower risk of CHD**
- Each **5-g/day increase** in olive oil consumption was associated with an **8% lower risk of fatal CVD**

Olive Oil Consumption and Cardiovascular Risk in U.S. Adults

(J Am Coll Cardiol 2020;75:1729–39)

TABLE 2 Risk of Cardiovascular Events According to Categories of Total Olive Oil Intake

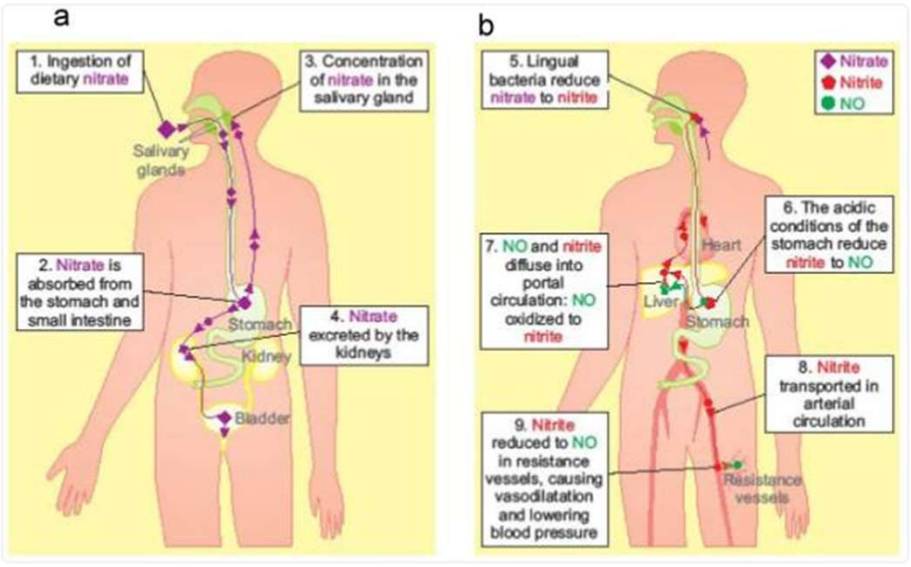
		RR (95% CI)				
	Never or <1 per Month	>0 to ≤4.5 g/day (>0 to ≤1 Teaspoon)	>4.5 to ≤7 g/day (>1 Teaspoon to ≤0.5 TBS)	>7 g/day (>0.5 TBS)	p Value for Trend	HR (95% CI) for 5-g Increase in Olive Oil Intake
Total CVD: fatal and nonfatal myocardial infarction + fatal and nonfatal stroke						
NHS olive oil						
Mean total	0	1.5 ± 1.2	5.6 ± 0.7	11.7 ± 5.7		
No. of cases/person-yrs	1,971/399,686	2,658/638,583	367/106,313	491/150,743		
Incidence rate, %	0.49	0.41	0.34	0.32		
Age-adjusted model 1	1.00 (Ref.)	0.81 (0.77-0.86)	0.72 (0.64-0.81)	0.69 (0.62-0.76)	<0.001	0.87 (0.84-0.90)
Multivariable model 2	1.00 (Ref.)	0.90 (0.85-0.96)	0.86 (0.76-0.96)	0.86 (0.77-0.95)	0.01	0.94 (0.90-0.97)
Multivariable model 3	1.00 (Ref.)	0.92 (0.86-0.97)	0.88 (0.78-0.98)	0.88 (0.79-0.98)	0.05	0.95 (0.91-0.99)
HPFS olive oil						
Mean total	0	1.5 ± 1.2	5.6 ± 0.7	11.2 ± 5.4		
No. of cases/person-yrs	1,696/191,480	2,041/308,406	258/45,995	315/55,468		
Incidence rate, %	0.88	0.66	0.56	0.56		
Age-adjusted model 1	1.00 (Ref.)	0.79 (0.74-0.85)	0.69 (0.60-0.78)	0.72 (0.64-0.82)	<0.001	0.88 (0.84,-0.93)
Multivariable model 2	1.00 (Ref.)	0.85 (0.80-0.91)	0.77 (0.67-0.88)	0.82 (0.72-0.93)	0.001	0.93 (0.88-0.97)
Multivariable model 3	1.00 (Ref.)	0.86 (0.80-0.92)	0.77 (0.68-0.89)	0.83 (0.73-0.94)	0.004	0.93 (0.89-0.98)
Pooled model 3	1.00 (Ref.)	0.89 (0.85-0.93)	0.83 (0.76-0.91)	0.86 (0.79-0.94)	<0.001	0.94 (0.92-0.97)

Beet Root Extract

- Beta vulgaris rubra
- Source of nitrate providing a means of increasing *in vivo* Nitric Oxide via the Nitrate-Nitrite-Nitric oxide (NO) pathway
- Also contains phytochemical compounds that include ascorbic acid, carotenoids, phenolic acids, flavonoids and betalains that
  - Possess *in vitro* and *in vivo* Antioxidant/Anti-inflammatory properties
  - Inhibit platelet aggregation

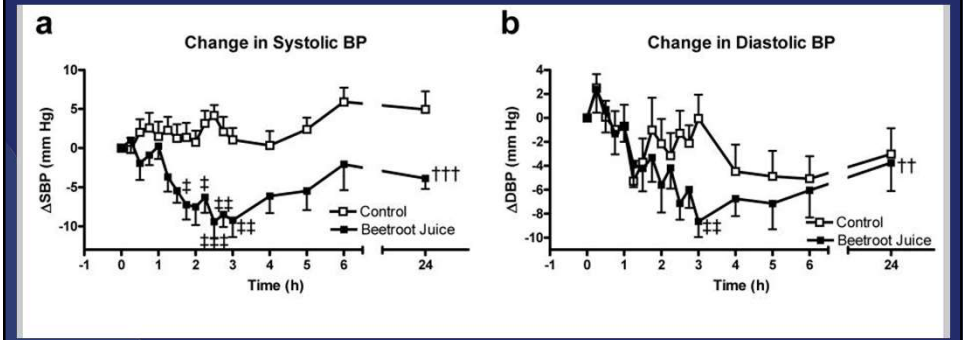
Nitrate-Nitrite-Nitric Oxide Pathway

Webb, et al. Hypertension Volume 51, Number 3



The effect of beetroot juice on the change from baseline of systolic and diastolic BP

Webb, et al. **Hypertension** Volume 51, Number 3



Effect of Beet Root on Blood Pressure

Br J Clin Pharmacol 2013 Feb 5;75(3):677–696

Study	Source	Nitrate (mmol)	Peak ΔSBP (mmHg) (time)	Peak ΔDBP (mmHg) (time)
Larsen *et al.* (2006) [78]	Sodium nitrate 3 days	~7*	–	−3.7
Webb *et al.* (2008) [79]	Beetroot juice 500 ml × 1	22.5	−10.4 (2.5–3 h)	−8
Kapil *et al.* (2010) [82]	Potassium nitrate × 1	24	−9.4 (6 h)	−6.0 (2.75 h)
		12	−6 (2.25 h)	−4.5 (3 h)
		4	−2.5 (1.75 h)	−4.5 (2.25 h)
Kapil *et al.* (2010) [82]	Beetroot juice 250 ml × 1	5.5	−5.4	–
Sobko *et al.* (2010) [9]	Japanese Traditional Diet 10 days	~18	–	−4.5
Vanhatalo *et al.* (2010) [88]	Beetroot juice (500 ml) 15 days	5.2	−7	−5
Bahra *et al.* (2012) [148]	Potassium nitrate × 1	8	−5	–
Bondonno *et al.* (2012) [89]	Spinach (200 g) × 1	3	−2.7	–
Hobbs *et al.* (2012) [90]	Beetroot juice (100, 250, 500 g)	2.3	−13.1 (2–3 h)	−16.6 (2–3 h)
		5.7	−20.5 (2–3 h)	−14.6 (2–3 h)
		11.4	−22.2 (2–3 h)	−18.3 (2–3 h)
Hobbs *et al.* (2012) [90]	Beetroot-enriched bread (100 g) with white beetroot	1.8	−16.5 (2–3 h)	−23.2 (2–3 h)
		1.6	−19.3 (2–3 h)	−23.6 (2–3 h)

Effect of Beet Root Juice on Platelet Aggregation and Endothelial Function

Hypertension. 2008 Feb 4;51(3):784–790

- Consuming 500 ml Beet Root Juice
- Inhibited platelet aggregation to ADP and collagen 2.5h after beetroot ingestion (both $P<0.001$)
- Completely prevented ischemia-induced endothelial dysfunction (measured by flow-mediated dilatation, FMD, $P<0.05$)

Probiotics

- Living micro-organisms found in fermented foods
- Meta-analysis of 30 RCTs, >1600 patients treated for 3-12 weeks
  - TC and LDL both reduced ~7 mg/d
- Meta-analysis of 11 RCTs, ~600 patients treated for 2-10 weeks
  - TC reduced 6.6 mg/dl
  - LDL reduced 8.5 mg/dl

Cardiovascular Supplements Vitamins/Anti-Oxidants

- Vitamins A, C, E and D
- B vitamins/Homocysteine/Folic Acid (B9)
- Multivitamins
- β-Carotene
- Coenzyme Q- 10

Cardiovascular Supplements Vitamins/Anti-Oxidants

- The value of vitamin supplementation in the prevention or reversal of cardiovascular disease has been disproven in most cases
- **Vitamin A,C and E**
  - Purported to have anti-oxidant properties
  - RCTs have shown NO benefit with supplementation
- **Vitamin D**
  - Low vitamin D levels associated with CVD
  - RCTs have shown NO benefit with supplementation
- **B Vitamins**
  - Hyperhomocysteinemia is associated with increased CV risk
  - B vitamins (B6, B9 and B12) can decrease homocysteine levels
  - RCTs have shown NO benefit with supplementation
- **Multivitamins**
  - 2022 Review of 84 trials showed NO benefit in preventing CV disease

Cardiovascular Supplements Vitamins/Anti-Oxidants

- **Beta-carotene**
  - RCTs have shown NO benefit for Primary or Secondary Prevention
  - Reviews of trials suggest potential harm/increased CV mortality
  - A Review of RCTs of Beta-carotene +/-vitamin A
    (JAMA. 2022;327(23):2334.)
    - Increased Cardiovascular Mortality (5 RCTs, OR, 1.10).
    - Increased risk of lung cancer (4 RCTs, OR, 1.20)
  - A Meta-analysis of 8 Beta carotene trials showed an
    - Increased All-cause Mortality (7.4 vs 7.0%, p=0.003)
    - Increased Cardiovascular Death (3.4 vs 3.1%, p=0.003)

    (Lancet. 2003;361(9374):2017.)

Cardiovascular Supplements Vitamins/Anti-Oxidants

- Coenzyme Q10 (CoQ10, ubiquinone)
  - Important role in muscle cell energy production
  - Speculated that a reduction in ubiquinone in skeletal muscle may contribute to statin-induced muscle injury
  - Some studies have found that statins decrease skeletal muscle and plasma concentrations of ubiquinone; however, other studies have not
  - Proposed that CoQ10 can reduce Statin Associated Muscle Symptoms (SAMS)

CoQ10 - Conflicting information

- **PRO**
  - In a meta-analysis of 12 RCTs, CoQ10 supplementation ameliorated SAMS such as myalgias but there was no difference in plasma CK levels
    - Although symptoms were reduced, there was substantial heterogeneity among trials and most did not identify whether patients had TRUE statin myalgia
- **CON**
  - Little published evidence showing benefit of CoQ10 for the **treatment** of myalgia or myopathy. J Clin Lipidol. 2014 May;8(3 Suppl):S58-71.
  - Randomized double-blind, placebo, crossover trial found no benefit of CoQ10 in patients with simvastatin-induced myalgia (Atherosclerosis. 2015;238(2):329.)
  - American Heart Association (AHA) statement on statin safety concluded that CoQ10 is not helpful in SAMS (Arterioscler Thromb Vasc Biol. 2019;39(2).
  - Randomized, double-blind placebo-controlled crossover trial showed no benefit of CoQ10 for the **prevention** of statin-induced muscle (J Am Coll Cardiol. 2007;49(23):2231)
- **RECOMMENDATIONS:**
  - **Grade 2C Recommendation** not to administer CoQ10 for **treatment or prevention** of statin myopathy. However, there may be a subset of patients who may derive benefit with little to no risk.

High Risk Supplements

- May contain alduterants
- Lack of FDA regulation
- Untested health claims
- Inadequate labeling
- Quantity and adverse effects are not required
- Drug interactions not required

Cardiovascular Dietary Supplements (Ineffective/Not Recommended)

- **Tea & Tea Extracts**
  - May lower TC and LDL but reports of severe hepatotoxicity
- **Selenium** – No Benefit
- **Calcium** – No Benefit
- **Garlic** – No Benefit in large scale trial
- **Coconut Oil/Water** – No Benefit
- **Bergamot** – Suggested benefit in metabolic syndrome but high quality data lacking
- **Resveratrol** – Meta-analysis of 7 RCTs showed No effect on any lipid paramaters
- **Soy Isoflavones** – No Benefit

SUMMARY

- Nutritional and Dietary Supplements are commonly used by patients for the prevention and treatment of Cardiovascular Diseases
- Some supplements have documented efficacy/safety; some do not
- Uncertain bioavailability/purity/contamination
- Patients should be asked about the use of dietary supplements
- PCPs should advise patients on the use of supplements
  - Definitely/Possibly Effective
  - Ineffective/Unsafe
  - Review prescription drugs for potential interactions

Schema for advising patients about herbal products

Herbal product					Clinical Advice
Quality		Efficacy		Safety	
Present	AND	Present	AND	Present	Recommend
Uncertain	OR	Uncertain	OR	Uncertain	Counsel and caution
Absent	OR	Ineffective	OR	Unsafe	Discourage

Adapted from: Saper, RB, Eisenberg, D, Phillips, R. Common dietary supplements for weight loss. Am Fam Physician 2004; 70:1731 and Weiger, WA, Smith, M, Boon, H, et al. Advising patients who seek complementary and alternative medical therapies for cancer. Ann Intern Med 2002; 137:889.

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