# Drug Induced Nutrient Depletions: The Truth about Common Cardiovascular Medications

*By Alan C. Simon R.Ph.*

# Classes of Cardiovascular Drugs

3. Anticoagulants
40. Aspirin
44. Inotropic Agents
49. Calcium Channel Blocking Agents
53. Vasodilators
57. Diuretics
69. Antiadrenergics/Sympatholytic Agents (Beta blockers)
73. Renin Angiotensin System Antagonist (ACE Inhibitors/ Angiotensin II)
79. Antihyperlipidemic Agents

# Anticoagulants-
## WARFARIN (COUMADIN) (Vitamin K Antagonist)

- Action: Blocks the action of vitamin k (inhibits the synthesis of vitamin k-dependent clotting factors).
- Indications: Atrial fibrillation, artificial heart valves, deep venous thrombosis, pulmonary embolism, myocardial infarction.
- Dosing: **Has a narrow therapeutic index,** blood test are needed for dosing, prothrombin time and INR (international normalized ratio).
- Side Effects: Purple toes or fingers, skin changes, discoloration on the body, abdominal pain, dark urine jaundice, dark urine, blood in urine, jaundice, black, bloody, tarry stools, nose bleeds, bleeding gums, sudden headache, vasculitis, hypotension, dizziness, paresthesia, hair loss, itching, rash, nausea, vomiting, diarrhea.
- Contraindications: Pregnancy, breast feeding, blood dyscrasias, bleeding tendencies, senility, alcoholism, psychosis.
- Warnings/Precautions: Hemorrhage, necrosis, gangrene, purple toe syndrome, hepatic or renal insufficiency, severe to moderate hypertension, drug to drug interactions.

# Anticoagulants-
## WARFARIN (COUMADIN) (Vitamin K Antagonist)

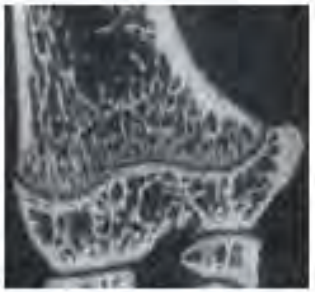
- Nutrient depletions
  - Vitamin K
  - Interferes with the enzyme responsible for the synthesis of vitamin K (Matrix Gla protein)

1. Bell RG, "Metabolism of vitamin K and prothrombin synthesis: anticoagulants and the vitamin K-epoxide cycle," Fed Proc. 1978 Oct; 37(12): 2599-604.

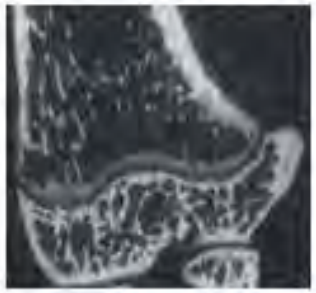
Vitamin K-deficiency may occur by either poor dietary vitamin K intake, disturbed intestinal uptake (e.g. caused by a bile duct obstruction), or by therapeutic or accidental intake of vitamin K-antagonists. As a result of the acquired vitamin K-deficiency, Gla-residues are not or incompletely formed and hence the Gla-proteins are inactive. Lack of control of the three processes mentioned above may lead to:

**1.** risk of uncontrolled and severe bleeding

2. cartilage calcification and severe malformation of developing bone



sufficient vit K



insufficient vit K

3. deposition of insoluble calcium salts in the arterial vessel wall

sufficient vit K

insufficient vit K

## The following factors, alone or in combination, may be responsible for INCREASED PT/INR response:

| ENDOGENOUS FACTORS: | | |
|---|---|---|
| blood dyscrasias — See CONTRAINDICATIONS<br>cancer<br>collagen vascular disease<br>congestive heart failure | diarrhea<br>elevated temperature<br>hepatic disorders<br>infectious hepatitis<br>jaundice | hyperthyroidism<br>poor nutritional state<br>steatorrhea<br>vitamin K deficiency |

## The following factors, alone or in combination, may be responsible for DECREASED PT/INR response:

| ENDOGENOUS FACTORS: | |
|---|---|
| edema<br>hereditary coumarin resistance<br>hyperlipemia | hypothyroidism<br>nephrotic syndrome |

# Potential drug interactions with COUMADIN

| Classes of Drugs | | |
|---|---|---|
| Adrenal Cortical Steroid Inhibitors<br>Antacids<br>Antianxiety Agents<br>Antiarrhythmics†<br>Antibiotics†<br>Anticonvulsants†<br>Antidepressants†<br>Antihistamines<br>Antineoplastics† | Antipsychotic Medications<br>Antithyroid Drugs†<br>Barbiturates<br>Diuretics†<br>Enteral Nutritional Supplements<br>Fungal Medications, Systemic†<br>Gastric Acidity and Peptic Ulcer Agents†<br>Hypnotics† | Hypolipidemics†<br>Bile Acid-Binding Resins†<br>HMG-CoA Reductase Inhibitors†<br>Immunosuppressives<br>Oral Contraceptives, Estrogen Containing<br>Selective Estrogen Receptor Modulators<br>Steroids, Adrenocortical†<br>Tuberculosis Agents†<br>Vitamins† |

# Potential drug interactions with COUMADIN

| Classes of Drugs | | |
|---|---|---|
| alcohol† | cyclophosphamide† | phenobarbital |
| aminoglutethimide | dicloxacillin | phenytoin† |
| amobarbital | ethchlorvynol | pravastatin† |
| atorvastatin† | glutethimide | prednisone† |
| azathioprine | griseofulvin | primidone |
| butabarbital | haloperidol | propylthiouracil† |
| butalbital | meprobamate | raloxifene |
| carbamazepine | 6-mercaptopurine | ranitidine† |
| chloral hydrate† | methimazole† | rifampin |
| chlordiazepoxide | moricizine | secobarbital |
| chlorthalidone | hydrochloride† | spironolactone |
| cholestyramine† | nafcillin | sucralfate |
| clozapine | paraldehyde | trazodone |
| corticotropin | pentobarbital | vitamin C (high dose) |
| cortisone | | vitamin K |

# Botanical (Herbal) Medicines And Warfarin (package insert)

- **Botanical (Herbal) Medicines:** Caution should be exercised when botanical medicines (botanicals) are taken concomitantly with COUMADIN.

- Few adequate, well-controlled studies exist evaluating the potential for metabolic and/or pharmacologic interactions between botanicals and COUMADIN.

- Due to a lack of ***manufacturing standardization**** with botanical medicinal preparations, the amount of active ingredients may vary. This could further confound the ability to assess potential interactions and effects on anticoagulation. It is good practice to monitor the patient's response with additional PT/INR determinations when initiating or discontinuing botanicals.

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****There is manufacturing standardization in FDA Drug Registered manufacturing guidelines***.

# Botanical (Herbal) Medicines And Warfarin (package insert)

- Specific botanicals reported to affect COUMADIN therapy include the following:
  - Bromelain, danshen, dong quai (Angelica sinensis), garlic, Ginkgo biloba, ginseng, and cranberry products are associated most often with an INCREASE in the effects of COUMADIN.
  - Coenzyme Q10 and St. John's wort are associated most often with a DECREASE in the effects of COUMADIN.
- Some botanicals may cause bleeding events when taken alone (eg, garlic and Ginkgo biloba) and may have anticoagulant, antiplatelet, and/or fibrinolytic properties. These effects would be expected to be additive to the anticoagulant effects of COUMADIN. Conversely, other botanicals may have coagulant properties when taken alone or may decrease the effects of COUMADIN.

# Potential interaction of Ginkgo biloba leaf with antiplatelet or anticoagulant drugs: what is the evidence?

Mol Nutr Food Res. 2008 Jul;52(7):764-71.

- Ginkgo does not significantly impact haemostasis nor adversely affect the safety of co-administered aspirin or warfarin
  - Most of these studies were undertaken using **EGb 761**, a well-defined extract of Ginkgo biloba
- Nevertheless, the possibility of an idiosyncratic bleeding event due to Ginkgo use cannot be excluded
- PMID: 18214851

**Effect of Ginkgo biloba (EGb 761) and aspirin on platelet aggregation and platelet function analysis among older adults at risk of cardiovascular disease: a randomized clinical trial.**

Blood Coagul Fibrinolysis. 2007 Dec;18(8):787-93

- Ginkgo biloba (**EGb 761, 300 mg/day**) double-blind, placebo-controlled

- a relatively high dose of Ginkgo biloba combined with 325 mg/day daily aspirin did not have a clinically or statistically detectable impact on indices of coagulation examined over 4 weeks, compared with the effect of aspirin alone.

- PMID: 17982321
- Stanford Prevention Research Center and the Department of Medicine, Stanford University Medical School

# Common Botanicals- contraindicated with Warfarin

| Botanicals that contain coumarins with potential anticoagulant effects: | | |
|---|---|---|
| Agrimony[1] | Celery | Passion Flower |
| Alfalfa | Chamomile | Prickly Ash (Northern) |
| Angelica (Dong Quai) | (German and Roman) | Quassia |
| Aniseed | Dandelion[4] | Red Clover |
| Arnica | Fenugreek | Sweet Clover |
| Asafoetida | Horse Chestnut | Sweet Woodruff |
| Bogbean[2] | Horseradish | Tonka Beans |
| Boldo | Licorice[4] | Wild Carrot |
| Buchu | Meadowsweet[2] | Wild Lettuce |
| Capsicum[3] | Nettle | |
| Cassia[4] | Parsley | |

1 Contains coumarins, has antiplatelet properties, and may have coagulant properties due to possible vitamin K content.
2 Contains coumarins and salicylate.
3 Contains coumarins and has fibrinolytic properties.
4 Contains coumarins and has antiplatelet properties.

# Common Botanicals- contraindicated with Warfarin

| Miscellaneous botanicals with anticoagulant properties: | | |
|---|---|---|
| Bladder Wrack (Fucus) | Pau d'arco | |

| Botanicals with fibrinolytic properties: | | |
|---|---|---|
| Bromelains<br>Capsicum[3] | Garlic[5]<br>Ginseng (Panax)[5] | Inositol Nicotinate<br>Onion[5] |

| Botanicals with coagulant properties: | | |
|---|---|---|
| Agrimony[1]<br>Goldenseal | Mistletoe<br>Yarrow | |

1 Contains coumarins, has antiplatelet properties, and may have coagulant properties due to possible vitamin K content.
2 Contains coumarins and salicylate.
3 Contains coumarins and has fibrinolytic properties.
4 Contains coumarins and has antiplatelet properties.
5 Has antiplatelet and fibrinolytic properties.

# Common Botanicals- contraindicated with Warfarin

| Botanicals that contain salicylate and/or have antiplatelet properties: | | |
|---|---|---|
| Agrimony[1] | Dandelion[4] | Meadowsweet[2] |
| Aloe Gel | Feverfew | Onion[5] |
| Aspen | Garlic[5] | Policosanol |
| Black Cohosh | German Sarsaparilla | Poplar |
| Black Haw | Ginger | Senega |
| Bogbean[2] | Ginkgo Biloba | Tamarind |
| Cassia[4] | Ginseng (Panax)[5] | Willow |
| Clove | Licorice[4] | Wintergreen |

1 Contains coumarins, has antiplatelet properties, and may have coagulant properties due to possible vitamin K content.
2 Contains coumarins and salicylate.
3 Contains coumarins and has fibrinolytic properties.
4 Contains coumarins and has antiplatelet properties.
5 Has antiplatelet and fibrinolytic properties.

# Vitamin K- Coumadin

- Package insert states:

- The amount of vitamin K in **food** may affect therapy with COUMADIN.
- Eat a normal, **balanced diet** maintaining a consistent amount of **vitamin K**.
- Avoid **drastic changes** in dietary habits, such as eating large amounts of green leafy vegetables.
- You should also avoid intake of **cranberry juice** or any other **cranberry products**.

# Vitamin K in Foods

| Beverages | Portion | Vitamin K content Micrograms |
|---|---|---|
| Coffee brewed from grounds, prepared with tap water | 6 oz | 0.2 |
| Cola with caffeine | 12 oz | 0.0 |
| Fruit punch drink with added nutrients canned | 8 oz | 0.0 |
| Milk | 1 cup | 0.5 |
| Tea brewed[†] | 6 oz | 0.0 |
| Water, tap | 8 oz | 0.0 |

| Dairy Products/Eggs | Portion | Vitamin K content Micrograms |
|---|---|---|
| Butter | 1 tbsp | 1.0 |
| Cheddar cheese | 1 oz | 0.8 |
| Eggs, cooked | 1 large | 2.6 |
| Sour cream, cultured | 1 tbsp | 0.1 |
| Yogurt plain, whole milk | 8 oz | 0.5 |
| Ice cream, vanilla | 1/2 cup | 0.2 |

# Vitamin K in Foods

| Grains | Portion | Vitamin K content Micrograms |
|---|---|---|
| Bagel, plain | 1 (4") | 1.0 |
| Bread, assorted types | 1 slice | 0.8 |
| Cereal | 1/2 cup | 2.1 |
| Flour, white, wheat, all-purpose, enriched, bleached | 1 cup | 0.4 |
| Oatmeal | 1 cup | 7.5 |
| Rice, white | 1 cup | 0.0 |
| Spaghetti, cooked, enriched | 1 cup | 0.0 |

| Fruits | Portion | Vitamin K content Micrograms |
|---|---|---|
| Apple | 1 | 3.0 |
| Banana | 1 | 0.6 |
| Blueberries, raw | 1 cup | 28.0 |
| Cantaloupe | 1/8 melon | 1.7 |
| Grapes, red or green | 10 grapes | 7.3 |
| Grapefruit | 1/2 grapefruit | 0.0 |
| Lemon | 1 | 0.0 |
| Orange | 1 | 0.0 |
| Peach | 1 | 2.5 |

# Vitamin K in Foods

| Meat | Portion | Vitamin K content Micrograms |
|---|---|---|
| Beef | 3 oz | 1.9 |
| Chicken | 1 cup | 4.3 |
| Ham | 2 slices | 0.0 |
| Salmon | 3 oz | 0.3 |
| Pork | 3 oz | 0.0 |
| Shrimp | 3 oz | 0.0 |
| Tuna, light, canned in oil | 3 oz | 37.4 |
| Tuna, light, canned in water | 3 oz | 0.2 |
| Turkey meat only, roasted | 1 cup | 5.2 |

| Fats and Dressings | Portion | Vitamin K content Micrograms |
|---|---|---|
| Margarine | 1 tbsp | 14.5 |
| Mayonnaise | 1 tbsp | 5.8 |
| Oils | | |
| Soybean | 1 tbsp | 3.4 |
| Olive | 1 tbsp | 8.1 |
| Corn | 1 tbsp | 0.3 |
| Peanut | 1 tbsp | 0.1 |
| Safflower | 1 tbsp | 1.0 |
| Sesame | 1 tbsp | 1.8 |
| Sunflower | 1 tbsp | 0.7 |

# Vitamin K in Foods

| Vegetables | Portion | Vitamin K content (mcg) |
|---|---|---|
| Asparagus, *frozen, cooked* | 1 cup | 144.0 |
| Avocado | 1 oz | 6.0 |
| Beans, *green* | 1 cup | 20.0 |
| Broccoli, *cooked* | 1 cup | 220.1 |
| Brussels sprouts, *cooked* | 1 cup | 218.9 |
| Cabbage, *raw* | 1 cup | 53.2 |
| Carrots | 1 cup | 21.4 |
| Cauliflower, *boiled* | 1 cup | 17.1 |
| Celery | 1 cup | 56.7 |
| Collard greens | 1 cup | 1059.4 |
| Corn | 1 cup | 0.5 |
| Cucumber, *peel removed* | 1 cup | 8.6 |
| Eggplant, *cooked* | 1 cup | 2.9 |
| Endive, *raw* | 1 cup | 115.5 |
| Kale, *cooked* | 1 cup | 1146.6 |
| Lettuce, romaine or green leaf, *raw* | 1 cup | 97.2 |
| Lettuce, iceberg, *raw* | 1 cup | 13.3 |
| Mushrooms | 1 cup | 0.2 |
| Mustard greens, *cooked* | 1 cup | 419.3 |
| Parsley | 10 sprigs | 164.0 |
| Peas, *cooked* | 1 cup | 48.3 |
| Pepper, green, *raw* | 1 cup | 11.0 |
| Potato, *baked* | 1 | 4.0 |
| Pumpkin, *boiled, drained, no salt* | 1 cup | 2.0 |
| Sauerkraut, *canned* | 1 cup | 30.7 |
| Spinach, *cooked* | 1 cup | 1027.3 |
| Spinach, *raw leaf* | 1 cup | 144.9 |
| Spring onion or scallion, *raw* | 1 cup | 207.0 |
| Tomato | 1 | 9.7 |
| Turnip greens, *boiled, drained, no salt* | 1 cup | 529.3 |
| Watercress, *raw* | 1 cup | 85.0 |

# Vitamin K in Foods

| Condiments and Sweeteners | Portion | Vitamin K content (mcg) |
|---|---|---|
| Gelatin | 1/2 cup | 0.0 |
| Honey | 1 tbsp | 0.0 |
| Peanut butter | 2 tbsp | 0.2 |
| Pickle, dill | 1 pickle | 25.4 |
| Sugar, white, granulated | 1 tsp | 0.0 |

# Warfarin use and the risk of valvular calcification.

Thromb Haemost. 2009 Dec;7(12):2023-7.

- Warfarin affects the synthesis and function of the **matrix Gla-protein**, a vitamin K-dependent protein, which is a **potent inhibitor of tissue calcification**.

- RESULTS: **significant association between the use of warfarin and the risk of calcification**
  - 473 of 725 patients (**65%**) on warfarin vs. 225 of 430 patients (**52%**) not on warfarin.

- CONCLUSIONS: Use of warfarin in patients with AF is associated with an increased prevalence **of mitral or aortic valve calcium.**

- PMID: 19793187

# Relation of circulating Matrix Gla-Protein and anticoagulation status in patients with aortic valve calcification.

Thromb Haemost. 2009 Apr;101(4):706-13

- Matrix-Gla Protein (MGP) is a vitamin K-dependent protein acting as a local inhibitor of vascular calcification.
- Vitamin K-antagonists (oral anticoagulant; OAC) inhibit the activation of MGP by **blocking vitamin K-metabolism**.
- Our data suggest that OAC treatment may decrease local expression of MGP, resulting in decreased circulating MGP levels and subsequently **increased aortic valve calcifications as an adverse side effect**.
- PMID: 19350115

**Relation of oral anticoagulation to cardiac valvular and coronary calcium assessed by multislice spiral computed tomography.**

- Am J Cardiol. 2005 Sep 15;96(6):747-9.

- Patients with long-term oral anticoagulation therapy (mean duration 88 +/- 113 months) were compared with those without anticoagulation .

- The results of our study have demonstrated that oral anticoagulation may be associated with **increased valvular and coronary calcium in patients with aortic valve disease**, presumably due to decreased activation of the matrix Gla protein.

- PMID: 16169351

**Long-term oral anticoagulation reduces bone mass in patients with previous hemispheric infarction and nonrheumatic atrial fibrillation.**

Stroke. 1997 Dec;28(12):2390-4

- CONCLUSIONS: **Bone mineral density was significantly lower in stroke patients** with long-term warfarin treatment than in untreated patients.

- Both warfarin-induced reduction in vitamin K function and **lowered vitamin K1 concentrations are probable causes of this osteopenia**.

- PMID: 9412619

# A high menaquinone intake reduces the incidence of coronary heart disease.

Nutr Metab Cardiovasc Dis. 2009 Sep;19(7):504-10

- To examine the relationship between dietary vitamins K(1) and K(2) intake, and its subtypes (MK-7, MK-8, MK-9), and the incidence of CHD.
  - We used data from the Prospect-EPIC cohort consisting of 16,057 women, enrolled between 1993 and 1997 and aged 49-70 years, who were free of cardiovascular diseases at baseline.
- we observed **an inverse association between vitamin K(2) and risk of CHD**
- Vitamin K(1) intake was not significantly related to CHD
- CONCLUSIONS: A high intake of **menoquinones, especially MK-7**, MK-8 and MK-9, **could protect against CHD**.
- PMID: 19179058

## Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: the Rotterdam Study.

J Nutr. 2004 Nov;134(11):3100-5.

- 4807 subjects (over 10 year period) with dietary data and no history of myocardial infarction at baseline (1990-1993)
  - Examined dietary intake of phylloquinone (vitamin K-1) and menaquinone (vitamin K-2)

- Dietary intake of **menaquinone was inversely related to CHD and all-cause mortality** (50% reduction). Phylloquinone intake was not.

- These findings suggest that an adequate intake of menaquinone could be important for CHD prevention.

- PMID: 15514282

**High dietary menaquinone intake is associated with reduced coronary calcification.**

- Atherosclerosis. 2009 Apr;203(2):489-93.
- Cross-sectional study among 564 post-menopausal women (62% had coronary calcification)
- CONCLUSION: This study shows that high dietary **menaquinone intake, but probably not phylloquinone, is associated with reduced coronary calcification**. Adequate menaquinone intakes could therefore be important to prevent cardiovascular disease.
- PMID: 18722618

**Vitamin K supplementation can improve stability of anticoagulation for patients with unexplained variability in response to warfarin.**

- Blood. 2007 Mar 15;109(6):2419-23.

- Patients receiving warfarin who have unstable control of anticoagulation have a significantly lower intake of dietary vitamin K compared with their stable counterparts.
- 70 warfarin-treated patients with **unstable anticoagulation control**
- randomly assigned **double-blinded 150 mcg oral vitamin K** or placebo orally for 6 months
- Anticoagulation **control improved in 33 of 35 patients** receiving vitamin K supplementation
- Concomitant supplementation of vitamin K, perhaps through **reducing the relative day-to-day variability in dietary vitamin K intake, can significantly improve anticoagulation control** in patients with unexplained instability of response to warfarin.

- PMID: 17110451

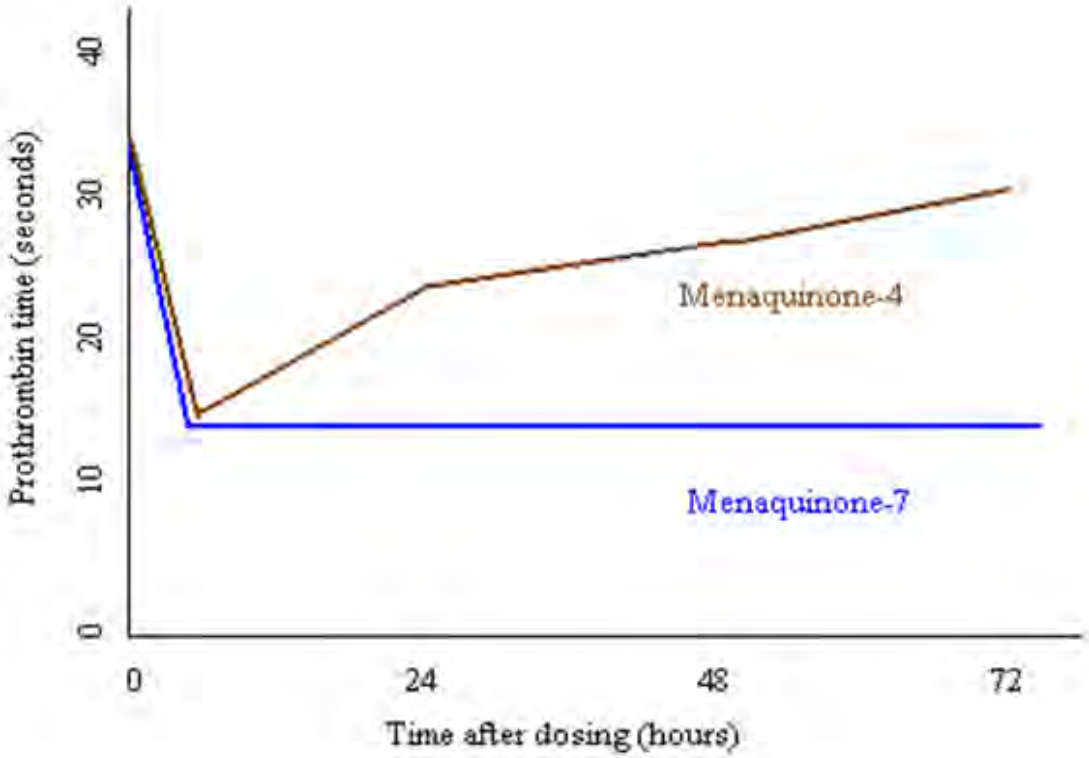
## Vitamin K–containing dietary supplements: comparison of synthetic vitamin K 1 and natto-derived menaquinone-7

- we propose to use an **upper safety limit for intake of 50 mcg/d for long-chain menaquinones** (including MK-7) in patients on oral anticoagulant treatment.
- This dose is **comparable with the menaquinone content** of **75 to 100 g of cheese**; such amount would lead to a disturbance of the INR value of no more than 10%, which may be regarded as tolerable in the management of oral anticoagulant therapy.
- On the other hand, its **long half-life** time suggests that regular intake of MK-7 in combination with properly adapted coumarin doses may **result in more stable INR values**.

blood

- **Blood. 2007;109:3279-3283**

# Pharmacokinetics of MK-4 and MK-7




Prothrombin time in vitamin K-deficient rats after an oral dose of MK-4 or MK-7 (50 nmol/kg; approximately 2 mg/70 kg of body weight).

*Br J Nutr* 2002;87:307-314.

**Table 2.** Mean of K vitamins (µg/100 g or µg/100 ml) in various foods

| Type of food | n | $K_1$ | MK-4 | MK-5 | MK-6 | MK-7 | MK-8 | MK-9 |
|---|---|---|---|---|---|---|---|---|
| *Meat* | | | | | | | | |
| Beef | 7 | 0.6 (0.6–0.7) | 1.1 (0.7–1.3) | – | – | – | – | – |
| Chicken breast | 7 | – | 8.9 (6.4–11.3) | – | – | – | – | – |
| Chicken leg | 7 | – | 8.5 (5.8–10.5) | – | – | – | – | – |
| Pork steak | 7 | 0.3 (0.2–0.4) | 2.1 (1.7–2.4) | – | – | 0.5 (0.4–0.7) | 1.1 (0.9–1.2) | – |
| Pork liver | 7 | 0.2 (0.1–0.3) | 0.3 (0.3–0.4) | – | – | – | – | – |
| Minced meat | 7 | 2.4 (2.2–2.5) | 6.7 (6.5–6.7) | – | – | – | – | – |
| Salami | 7 | 2.3 (2.1–2.5) | 9.0 (8.2–10.1) | – | – | – | – | – |
| Luncheon meat | 7 | 3.9 (3.8–4.2) | 7.7 (7.4–9.1) | – | – | – | – | – |
| Hare leg | 7 | 4.8 (4.5–5.3) | 0.1 (0.0–0.2) | – | – | – | – | – |
| Deer back | 7 | 2.0 (1.9–2.2) | 0.7 (0.6–0.7) | – | – | – | – | – |
| Goose leg | 5 | 4.1 (3.5–4.8) | 31.0 (28.2–33.1) | – | – | – | – | – |
| Goose liver paste | 5 | 10.9 (9.3–12.1) | 369 (317–419 ) | – | – | – | – | – |
| Duck breast | 7 | 1.9 (1.7–2.2) | 3.6 (3.3–3.9) | | | | | |
| *Fish* | | | | | | | | |
| Prawn | 7 | 0.1 (0.0–0.1) | – | – | – | – | – | – |
| Mackerel | 7 | 2.2 (1.8–2.6) | 0.4 (0.3–0.5) | – | – | – | – | – |
| Herring | 7 | 0.1 (0.0–0.2) | – | – | – | – | – | – |
| Plaice | 7 | – | 0.2 (0.1–0.3) | – | 0.3 (0.2–0.3) | 0.1 (0.0–0.1) | 1.6 (1.3–1.8) | – |
| Eel | 7 | 0.3 (0.2–0.5) | 1.7 (1.4–2.1) | – | 0.1 (0.0–0.2) | 0.4 (0.2–0.6) | – | – |
| Salmon | 7 | 0.1 (0.1–0.2) | 0.5 (0.4–0.6) | – | – | – | – | – |
| *Fruits and vegetables* | | | | | | | | |
| Kale | 4 | 817 (752–881) | – | – | – | – | – | – |
| Spinach | 6 | 387 (299–429) | – | – | – | – | – | – |
| Broccoli | 5 | 156 (139–189) | – | – | – | – | – | – |
| Green peas | 4 | 36.0 (31.2–39.4) | – | – | – | – | – | – |
| Sauerkraut | 7 | 25.1 (23.8–27.5) | 0.4 (0.3–0.5) | 0.8 (0.6–1.0) | 1.5 (1.4–1.6) | 0.2 (0.1–0.3) | 0.8 (0.6–0.9) | 1.1 (0.9–1.3) |
| Natto | 5 | 34.7 (31.2–36.7) | – | 7.5 (7.1–7.8) | 13.8 (12.7–14.8) | 998 (882–1,034) | 84.1 (78.3–89.8) | – |
| Banana | 4 | 0.3 (0.2–0.4) | – | – | – | – | – | – |
| Apple | 4 | 3.0 (2.7–3.4) | – | – | – | – | – | – |
| Orange | 4 | 0.1 (0.1–0.2) | – | | | | | |

**Table 2** (continued)

| Type of food | n | $K_1$ | MK-4 | MK-5 | MK-6 | MK-7 | MK-8 | MK-9 |
|---|---|---|---|---|---|---|---|---|
| *Dairy produce* | | | | | | | | |
| Whole milk | 6 | 0.5 (0.4–0.6) | 0.8 (0.7–0.9) | 0.1 (0.0–0.1) | – | – | – | – |
| Skimmed milk | 6 | – | – | – | – | – | – | – |
| Buttermilk | 6 | – | 0.2 (0.2–0.3) | 0.1 (0.1–0.2) | 0.1 (0.0–0.2) | 0.1 (0.1–0.3) | 0.6 (0.5–0.6) | 1.4 (1.2–1.6) |
| Whole yoghurt | 6 | 0.4 (0.3–0.5) | 0.6 (0.5–0.7) | 0.1 (0.0–0.2) | – | – | 0.2 (0.2–0.3) | – |
| Skimmed yoghurt | 6 | – | – | – | – | – | 0.1 (0.0–0.2) | – |
| Whipping cream | 6 | 5.1 (4.9–5.5) | 5.4 (5.2–5.6) | – | – | – | – | – |
| Chocolate | 6 | 6.6 (6.4–6.7) | 1.5 (1.4–1.6) | – | – | – | – | – |
| Hard cheeses | 15 | 10.4 (9.4–12.1) | 4.7 (4.2–6.6) | 1.5 (1.3–1.7) | 0.8 (0.6–1.0) | 1.3 (1.1–1.5) | 16.9 (14.9–18.2) | 51.1 (45.3–54.9) |
| Soft cheeses | 15 | 2.6 (2.4–2.9) | 3.7 (3.3–3.9) | 0.3 (0.2–0.4) | 0.5 (0.6–0.7) | 1.0 (0.9–1.1) | 11.4 (10.7–12.2) | 39.6 (35.1–42.7) |
| Curd cheese | 12 | 0.3 (0.2–0.4) | 0.4 (0.3–0.6) | 0.1 (0.0–0.2) | 0.2 (0.1–0.3) | 0.3 (0.2–0.5) | 5.1 (4.8–5.4) | 18.7 (18.1–19.2) |
| Egg yolk | 8 | 2.1 (1.9–2.3) | 31.4 (29.1–33.5) | – | 0.7 (0.6–0.8) | – | – | – |
| Egg albumen | 8 | – | 0.9 (0.8–1.0) | – | – | – | – | – |
| *Oils and margarines* | | | | | | | | |
| Margarine | 6 | 93.2 (85.6–98.3) | – | – | – | – | – | – |
| Butter | 6 | 14.9 (13.2–15.9) | 15.0 (13.5–15.9) | – | – | – | – | – |
| Corn oil | 6 | 2.9 (2.7–3.1) | – | – | – | – | – | – |
| Sunflower oil | 6 | 5.7 (5.5–5.9) | – | – | – | – | – | – |
| Olive oil | 6 | 53.7 (49.9–57.2) | – | – | – | – | – | – |
| *Bread* | | | | | | | | |
| Rue bread | 6 | 0.7 (0.5–0.9) | – | – | – | – | – | – |
| Wheaten bread | 6 | 1.1 (1.0–1.2) | – | – | – | – | – | – |
| Sourdough bread | 6 | 1.0 (0.9–1.1) | – | – | – | – | – | – |
| Buckwheat bread | 6 | 3.0 (2.8–3.4) | – | – | – | 1.1 (1.0–1.2) | – | – |
| *Beverages* | | | | | | | | |
| Tea | 4 | 0.3 (0.2–0.4) | – | – | – | – | – | – |
| Coffee | 4 | – | – | – | – | – | – | – |
| Orange juice | 4 | – | – | – | – | – | – | – |

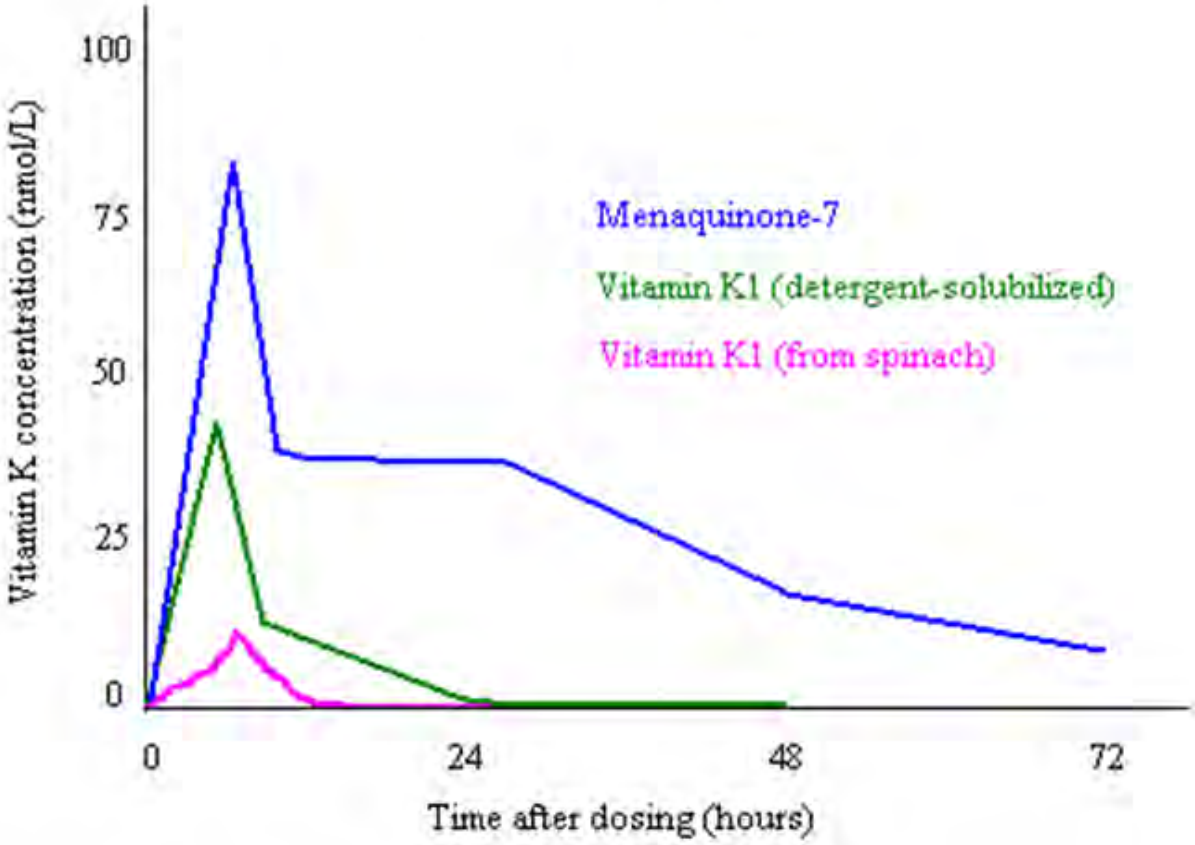
All samples were assessed in duplicate. Values are mean values. Highest and lowest values are given in parentheses. Foods were bought from shops in and around Maastricht. MK-10 was not detectable in any of the foods. N = Number of different samples tested; – = not detectable.

# K2 vs. K1

- Human studies show that **vitamin K2 is up to ten times more bioavailable than is K1**.
- Vitamin K2 remains biologically active in the body far longer than K1.
  - For instance, **K1** is rapidly cleared by the liver within **eight hours**, whereas measurable levels of **K2** have been detected **72 hours** after ingestion.
- Animal studies suggest vitamin K intake not only blocks the progress of further calcium accumulation but also induces 37% regression of preformed arterial calcification.[1,2]
- Low-Dose Vitamin K2 contains the menaquinone-7 form of vitamin K2, which is not metabolized quickly by the liver, thereby making it available to provide a more consistent supply of vitamin K to the body.


1. *Spronk et al. J Vasc Res* 2003;40:531
2. *Schurgers et al. Blood* 2007;109:2823

# Bioavailability of different forms of vitamin K




Pharmacokinetics of oral vitamin $K_1$ and MK-7 (approximately 2 mg) in healthy volunteers.

*Haemostasis* 2000;30:298-307.

# 45 mcg K2

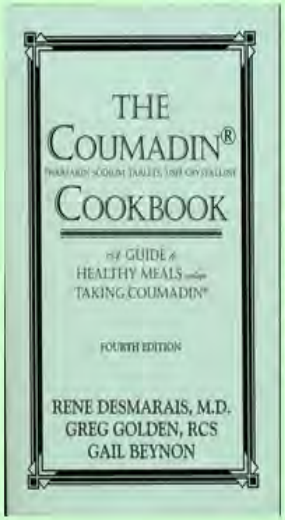

To obtain 45 mcg of vitamin K2 one should consume:
OR
OR
OR
OR
OR
beef
4 kg = 8.8 lbs
milk
5 liters = 1.32 gallons
whole yoghurt
5 liters = 1.32 gallons
soft cheese
80 g = 0.175 lbs
hard cheese
59 g = 0.129 lbs
egg yolk
140 g = 8 yolks
OR

# Best Support

- Counsel patient on importance of consistent dosing of vitamin k.
- Consider use of K2 Menaquinone 7
- 45 mcg/d
- Monitor therapy if adding or removing any dietary supplements

# THE COUMADIN® COOKBOOK

## A complete guide to healthy meals when taking Coumadin®




466 pages written by Rene Desmarais, MD, Greg Golden, RCS and Gail Beynon

In addition, Gail Beynon offers numerous tips concerning food preparation and storage that are sure to be helpful in any kitchen.

Patients on COUMADIN® have always had to pay attention to the Vitamin K content in their foods. "The COUMADIN® Cookbook" provides guidelines for stabilizing daily Vitamin K intake to patients on COUMADIN®.

In addition to clear directions for preparing a variety of tasty dishes, each recipe in the book gives the number of micrograms of Vitamin K contained per serving. This cookbook is written with the viewpoint of the patient in mind. With the use of the cookbook, it should be easier for the patient to eat a wide variety of healthy foods AND consume roughly the same amount of vitamin K each day.

The "INTRODUCTION" reviews several important facts regarding COUMADIN® and vitamin K.

In the section "USEFUL DIETARY TIPS", the patient is provided with general information on how to make their intake of Vitamin K more constant.

The Coumadin® Cook Book lists around 200 foods low in Vitamin K per serving.

Over 300 tasty recipes with known Vitamin K content per serving are provided. These include SALADS and VEGETABLES. Every food group is represented in the recipes.

# Aspirin

- Nutrient Depletions
  - Vitamin C: most likely to deplete in normal individuals
  - Iron: due to blood loss in GI tract
  - Folic acid: displaces bound serum folate
  - Potassium: increased urinary loss
  - Zinc: increased urinary loss


1. Loh HS, et al, "The effects of aspirin on the metabolic availability of ascorbic acid in human beings," J Clin Pharmacol. 1973; 13(11): 480-6.
2. Lawrence VA, et al, "Aspirin and folate binding in vivo and in vitro studies of serum binding and urinary excretion of endogenous folate," J Lab Clin Med. 1984; 103(6): 944-8.
3. Nain, et al. "Acetylsalicylic acid-induced biochemical changes in gastric juice," Indian J Gastroenterol. 1996; 56: 421-29.
4. Ambanelli U, Ferraccioli GF, Serventi G, Vaona GL. Changes in serum and urinary zinc induced by ASA and indomethacin. *Scand J Rheumatol* 1982;11:63–4

## *The protective effect of liquorice components and their derivatives against gastric ulcer induced by aspirin in rats.*

- Aspirin coated with liquorice **reduced the number and size of ulcers** reducing the ulcer index from 1.5 +/- 0.12 to 0.5 +/- 0.12 and the incidence from 96% to 46%.

- Coating with derivatives was less effective (ulcer index, 0.70-0.94; incidence 62-76%).

Dehpour AR, Zolfaghari ME, Samadian T, Vahedi Y. *J Pharm Pharmacol*. 1994 Feb;46(2):148-9.

# Effect of deglycyrrhizinated liquorice on gastric mucosal damage by aspirin.

- Gastric mucosal damage induced by giving 60 mg aspirin orally to rats was reduced by simultaneous administration of 100-500 mg deglycyrrhizinated liquorice.

- **Human faecal blood** loss induced by 975 mg aspirin orally three times a day **was less** when **350 mg** deglycyrrhizinated liquorice was given **with each dose of aspirin.**

Rees WD, Rhodes J, Wright JE, Stamford LF, Bennett A. *Scand J Gastroenterol*. 1979;14(5):605-7.

# Best Support

- Optimal ranges of Vitamin C
- Optimal level multivitamin-mineral formula for folic acid and zinc plus their cofactors
- Check iron and add if blood loss
- Assure a healthy potassium diet
- Enteric coated
- DGL –chewable at least 350 mg **with each dose aspirin**

# Inotropic Agents- (Cardiac Glycosides)

- DIGOXIN (LANOXIN, LANOXICAPS, DIGITEK) known as digitalis
- **Mechanism of action**
  - **Increases strength of heart muscle contractions**
  - **Makes heart rhythm more regular**
  - **Increases left ventricular ejection fraction**
- INDICATION: mild to moderate heart failure and atrial fibrillation
- CONTRAINDICATION: Ventricular fibrillation, hypersensitivity to digitalis preparations
- WARNINGS/PRECAUTIONS: AV block (atrioventricular block), Sinus node disease/dysfunction, acute myocardial infarction (heart attack), thyroid disorders, electrolyte imbalances, malnutrition (elderly), moderate to severe vomiting and diarrhea, impaired renal function.
- SIDE EFFECTS: **Digitalis toxicity, heart rhythm disturbances**, visual disturbances, headache, mental disturbances, nausea, vomiting, diarrhea, gynecomastia, weakness, dizziness.

# Inotropic Agents- (Cardiac Glycosides)

- Nutrient Depletions

- Digoxin (Lanoxin)
  - Calcium, magnesium, phosphorus via increased urinary excretion
  - Magnesium deficiencies increase likelihood of cardiac dysrhythmias and atrial fibrillation


1. Crippa, et al. "Magnesium and cardiovascular drugs: interactions and therapeutic role," Ann Ital Med Int. 1999; 14: 40-45.
2. Kupfer S, et al. "Effects of cardiac glycosides on renal tubular transport of calcium, magnesium, inorganic phosphate and glucose in the dog," J Clin Investig. 1965; 44: 1143.

# Heart failure and electrolyte disturbances.

- Methods Find Exp Clin Pharmacol. 1992 May;14(4):315-25.
- Digoxin directly limits the renal tubular reabsorption of magnesium, therefore **increasing magnesium excretion.**
- **Low magnesium** and potassium concentrations **increase cardiac glycoside toxicity**.
- In contrast, **elevated levels of magnesium decrease the sensitivity** of human myocardium to antiarrhythmogenic actions of cardiac glycosides.
- PMID: 1507935

# Furosemide and digoxin inhibit thiamine uptake in cardiac cells.

- Eur J Pharmacol. 1998 Nov 13;361(1):151-5.

- Thiamine uptake by cardiac cells grown in a thiamine-free medium for 7 days **decreased significantly in the presence of furosemide or digoxin**.
- Our results demonstrate that furosemide and digoxin inhibit thiamine uptake by cardiac cells in culture and may therefore cause thiamine deficiency in patients undergoing chronic treatment with these drugs.

- PMID: 9851552

# Best Support

- Gender and Age specific Multivitamin mineral
  - thiamine works with other B vitamins in energy production; studies show 80-240 mg per day improved ejection fraction 13 to 22 percent in CHF
  - Magnesium is required in the conversion of thiamine to its active form
- Consider optimal magnesium range from 6-12 mg/kg
- Increase potassium in diet (no high dose in pill form)
  - Daily dietary requirements are 3600-5800 mg.
  - banana contains ~440 mg (that's a lot of bananas)
  - Can lose 3000 mg in one day of sweating
  - Multiple food choices provide better chance of patient compliance-provide patient with potassium food chart
- Address low gastric acid for mineral and b vitamin absorption
  - gastric acid is required for thiamine absorption and thiamine helps produce stomach acid
- Alcohol depletes thiamine

# Calcium Channel Blockers (Calcium Antagonist)

- Amlodipine (Norvasc)
- Felodipine (Plendil)
- Nicardipine (Cardene, Cardene SR)
- Nifedipine (Procardia, Adalat)
- Nisoldipine (Sular)
- Verapamil (Calan, Isoptin) also SR and ER
- Diltiazem ( Cardiazem) also SR, ER, LA

- MECHANISM OF ACTION: They disrupt the calcium conduction of calcium channels by inhibiting the movement of calcium ions across cell membranes of the heart and blood vessels.
- INDICATIONS: Hypertension, pulmonary hypertension, angina, arrhythmias, migraines Raynaud's, disease, brain aneurysm.
- CONTRAINDICATIONS: Hypersensitivity to drug, ventricular arrhythmias, acute MI, severe hypotension, cardiogenic block, atrial fibrillation or flutter, ventricular tachycardia, second or third degree AV block.
- WARNING/PRECAUTIONS: Hypotension, premature ventricular contraction, hypertropic cardiomyophathy, antiplatelet effects, withdrawal syndrome, impaired renal function, increased angina, children (safety and efficacy not established.
- SIDE EFFECTS: **Constipation, peripheral edema**, headache, tachycardia, rash, drowsiness, flushing, dry mouth, dyspepsia, nausea.

# Calcium Channel Blockers (Calcium Antagonist)

- NUTRIENTS DEPLETED
  - Copper: Based on human study, a lower concentration of copper was found in red blood cells after use of nifedipine.
  - Melatonin: Based on human study, verapamil may enhance excretion of melatonin.
  - Potassium


1. Misiewicz A, Jeleń B, Dziewit T, Radwan K, Srodoń-Sikora I. Levels of copper, zinc and vitamin C in erythrocytes of humans taking nifedipine. Pol Arch Med Wewn. 1998 May;99(5):398-402. PMID 9816889
2. Wikner J, Wetterberg L, Röjdmark S., Does hypercalcaemia or calcium antagonism affect human melatonin secretion or renal excretion? Eur J Clin Invest. 1997 May;27(5):374-9. PMID 9179543
3. Pelton R. LaValle JB. The Quick Reference Guide to Nutrient Losses. In: The Nutritional Cost of Prescription Drugs.2nd Edition Englewood, CO: Morton Publishing Company; 2004, 15.

# Levels of copper, zinc and vitamin C in erythrocytes of humans taking nifedipine

- Pol Arch Med Wewn. 1998 May;99(5):398-402.

- In red blood cells of men which take nifedipine in daily doses 30 mg was found: lower copper concentration, higher zinc concentration as compared to before administration of nifedipine.

- Changes in Cu and Zn blood concentrations were intensified during administration of the drug. The vitamin C concentration did not change substantially.

- PMID: 9816889

# Best Support

- Melatonin if quality of sleep affected
- Improve dietary potassium
- Assure healthy zinc to copper ratio (multi-vitamin-mineral)
  - High zinc or vitamin C decreases copper
- Copper deficiency can elevate LDL and reduce HDL while increasing risk of blood vessel damage/rupture by decreasing the enzyme (lysyl oxidase) required in cross linking of collagen.
- Wilsons disease should never take copper

# Vasodilators

- NITRATES
  - Amyl nitrate
  - Nitroglycerine (Lingual spray, sub-lingual tabs, extended-release tabs, ointment, transdermal patch)
  - Isosorbide dinitrate (immediate release)
  - Isosorbide monohydrate (extended-release)
  - Hydralazine

- MECHANISM OF ACTION:
  - Relaxation of vascular smooth muscle
  - Dilation of peripheral arties and veins

- INDICATION: Angina pectoris (acute and chronic)

- CONTRAINDICATION: Glaucoma, pregnancy, cerebral hemorrhage, hypersensitivity to nitrates

- WARNINGS/PRECAUTIONS: Postural or severe hypotension, hypertropic cardiomyophathy, withdrawal, tolerance.

- SIDE EFFECTS: **Headache, flushing**, dizziness, nausea, rash, hives, **itching**, paraesthesia, difficult breathing, chest tightness, swelling of mouth, face, lips, or tongue, visual changes, numbness of arm and legs, crushing chest pain, sudden leg pain, hypotension

# Vasodilators

- Nutrients Depleted
  - Coenzyme Q10
  - Magnesium
  - Vitamin B6 (Pyridoxine)


1. Raskin, NH.and Rishman, RA. Pyridoxine-deficiency neuropathy due to hydralazine. *New Eng. J. Med.* 273:1182-1185, 1965.
2. Roe, D.A. *Diet and Drug Interactions.* New York, Van Nostrand Reinhold, p. 150, 1989.

# Best Support

- Gender and Age specific Multivitamin mineral
- Optimal magnesium range from 6-12 mg/kg
- COQ10 (ubiquinone)
  - in those that are under 50, or with no diabetes or kidney health problems
  - assure the ubiquinone is 100% bio-identical and proof of cellular mitochondrial absorption
- Others will use ubiquinol (QH)
  - Aging, genetics and certain health concerns (glycemic control, kidney damage, liver, or aging) reduce the process where ubiquinone is converted to ubiquinol (reduced form)
- Low gastric acid will interfere with nutrient absorption (minerals and B vitamins)

# QH to Q10 to QH

- Optimal health is 97% ubiquinol (QH) and 3% ubiquinone (Q10)
  - Ubiquinone - oxidized form
  - Ubiquinol- reduced form
- QH (ubiquinol) gives electron up in presence of free radical
- Enzyme reaction converts COQ10 ubiquinone back to QH (ubiquinol)
  - enzyme reaction deficient in
    - aged
    - genetics (NQ01 gene)
    - health problems (i.e. diabetics, kidney or liver disease)

# Diuretics

- TYPES:
  - THIAZIDE DIURETICS (Hydrochlorothiazide, Chlorothiazide, Indapamide, Chlorthalidone, Metolazone.)
  - LOOP DIURETICS (Furosemide, Torsemide, Bumetanide, Ethacrynic Acid)
  - POTASSIUM SPARING DIURETICS (Spironolactone, Triamterene, Amiloride)
  - OSMOTIC DIURETICS (Mannitol, Glycerin)

- MECHANISM OF ACTION:
  - Thiazides: inhibits the reabsorption of sodium and chloride ions from the distal convoluted tubles in the kidney. Cause a **net decrease of calcium lost in the urine.**
  - Loops: inhibits the reabsorption of sodium at the ascending loop of henle in the kidney. Cause a significant **increase calcium excretion**.
  - Potassium Sparing: prevent the loss of potassium in the urine.
  - Osmotic: Increase the osmolarity of the filtrate and water is retained in the urine.

- INDICATIONS: **Edema, congestive heart failure**, liver cirrhosis, kidney disease (stones), female hirsutism (spironolactone), hypokalemia (spironolactone).

# Diuretics (cont.)

- TYPES:
  - THIAZIDE DIURETICS (Hydrochlorothiazide, Chlorothiazide, Indapamide, Chlorthalidone, Metolazone.)
  - LOOP DIURETICS (Furosemide, Torsemide, Bumetanide, Ethacrynic Acid)
  - POTASSIUM SPARING DIURETICS (Spironolactone, Triamterene, Amiloride)
  - OSMOTIC DIURETICS (Mannitol, Glycerin)

- CONTRAINDICATIONS: Anuria, renal impairment, hypersensitivity to any diuretic.

- WARNING/PRECAUTIONS: Renal function impairment, hypersensitivity reactions, dehydration, hepatic cirrhosis, **tinnitus**, **electrolyte imbalances**, hypokalemia, hypomagnesemia, hypocalcemia, hyperuricemia, irregular heartbeat.

- SIDE EFFECTS: Hypovolemia (lassitude, thirst, muscle cramps, hypotension), **hypokalemia (muscle weakness**, paralysis, **arrhythmia**), hyperkalemia (arrhythmia, muscle cramps, paralysis), hyponatremia (CNS symptoms, coma), Metabolic alkalosis (arrhythmia, CNS symptoms), **metabolic acidosis** (**muscle weakness, lethargy**, coma, seizures, stupor), **hypercalcemia (gout, tissue calcification**, fatigue, depression, confusion, anorexia nausea, vomiting, constipation, pancreatitis, increased urination), **hyperuricemia (gout)**.

# Potassium-Sparing Diuretics- Drug Nutrient Interactions

- Magnesium- Magnesium tends to be preserved.
  - Amiloride, Aldactone®(spironolactone), Dytac®(triamterene)

1. Devane J, Ryan MP. The effects of amiloride and triameterene on urinary magnesium excretion in conscious saline-loaded rats. Br J Pharmacol 1981;72:285-89

# Potassium-Sparing Diuretics

- Nutrients Depleted
  - Calcium
  - Zinc
  - Folic Acid

1. Pelton R. LaValle JB. The Quick Reference Guide to Nutrient Losses. In: The Nutritional Cost of Prescription Drugs.2nd Edition Englewood, CO: Morton Publishing Company; 2004, 15.

# Loop Diuretics

- Nutrients Depleted[1]
  - Calcium
  - Magnesium
  - Potassium
  - Zinc
  - Thiamine
  - Vitamin B6
  - Vitamin C
- Loop diuretics **increase Mg excretion and inhibit passive Mg absorption**. [2]


1. Pelton R. LaValle JB. The Quick Reference Guide to Nutrient Losses. In: The Nutritional Cost of Prescription Drugs.2nd Edition Englewood, CO: Morton Publishing Company; 2004, 15.
2. Quamme GA, "Renal magnesium handling: new insights in understanding old problems." Kidney Int. 1997; 52(5): 1180-95.

# Thiazide Diuretics

- Nutrients Depleted
  - Magnesium
  - Potassium
  - Zinc
  - COQ10
  - Folic acid - increase homocysteine*


- Pelton R. LaValle JB. The Quick Reference Guide to Nutrient Losses. In: The Nutritional Cost of Prescription Drugs.2nd Edition Englewood, CO: Morton Publishing Company; 2004, 15.
- Pelton R. LaValle JB Drug Induced Nutrient Depletion Handbook 2nd Edition
- * South Med J. 1999 Sep;92(9):866-70. PMID: 10498160

**Long-term diuretic therapy in hypertensive patients: effects on serum homocysteine, vitamin B6, vitamin B12, and red blood cell folate concentrations.**

- South Med J. 1999 Sep;92(9):866-70.

- CONCLUSIONS: Chronic diuretic use is associated with a significant increase in serum **homocysteine** concentration, **a significant decrease in RBC folate concentration**, and no significant change in concentrations of vitamins B6 and B12.

- PMID: 10498160

# Diuretic-associated hypomagnesemia in the elderly.

- Arch Intern Med. 1987 Oct;147(10):1768-71.

- Serum magnesium concentration- 320 consecutive elderly patients (mean age, 81 years) receiving diuretic therapy at the time of hospital admission. When compared with serum concentrations of 250 elderly patients who were not taking diuretics at the time of hospital admission, **only the group taking thiazide diuretics had a significantly reduced mean serum level.**
- Patients taking therapy that included a potassium-sparing diuretic had no significant evidence of reduced magnesium-conserving ability.
- PMID: 3662705

## Thiazide treatment of systemic hypertension: effects on serum magnesium and ventricular ectopic activity.

- Am J Cardiol. 1989 Apr 18;63(14):22G-25G.
- **Potassium supplementation does not effectively restore electrolyte balance unless accompanied by magnesium**.
- Therefore, concomitant administration of potassium and magnesium supplementation appears to be an approach to reducing the risk of arrhythmias and death in thiazide-treated hypertensive patients.
- PMID: 2705372

# Miscellaneous Diuretics

- Indapamide, Metolazone, Chlorthialdone
- Nutrients Depleted
  - Magnesium
  - Potassium
  - Zinc


- Pelton R. LaValle JB. The Quick Reference Guide to Nutrient Losses. In: The Nutritional Cost of Prescription Drugs.2nd Edition Englewood, CO: Morton Publishing Company; 2004, 15.
- Pelton R. LaValle JB Drug Induced Nutrient Depletion Handbook 2nd Edition

# Drugs and folate metabolism.

- Drugs. 1985 Aug;30(2):145-55.
- Triamterene acts as a folate antagonists and produces folate deficiency by inhibiting the enzyme dihydrofolate reductase.
- PMID: 3896745

# Best Support

- Due to the multiple depletions of daily essential vitamins and minerals an Optimal multi vitamin mineral is recommended.
- Optimal magnesium range from 6-12 mg/kg
- Optimal Vitamin C
- Check homocysteine- (folic acid)
- COQ10 (ubiquinone)
  - in those that are under 50, or with no diabetes or kidney health problems.
  - assure the ubiquinone is 100% bio-identical and proof of cellular mitochondrial absorption
- Others will use ubiquinol (QH)
  - Aging, genetics and certain health concerns (glycemic control, kidney damage, liver, or aging) reduce the process where ubiquinone is converted to ubiquinol (reduced form)
- Low gastric acid will interfere with nutrient absorption (minerals and B vitamins)

# Antiadrenergics/Sympatholytic Agents- BETA-Adrenergic Blocking Agent

- ATENOLOL (TENORMIN)
- BISOPROLOL (ZEBATA)
- PINDOLOL (VISKEN)
- SOTOLOL(BETAPACE)
- ACEBUTOLOL (SECTRAL)
- NADOLOL (CORGARD)
- PROPRANOLOL (INDERAL & LA)
- LOBETALOL (TRANDATE)
- CARVEDILOL (COREG & CR)
- METOPROLOL (LOPRESSOR, TOPROL XL)

- MECHANISM OF ACTION: Block the beta receptors in the heart which slows the heart rhythm down.
- INDICATIONS: Hypertension, angina, cardiac arrhythmias, MI, CHF, ventricular tachycardia, migraines.
- CONTRAINDICATIONS: Sinus bradycardia, sick sinus syndrome, shock, asthma, hypersensitivity to the drug.
- WARNINGS/PRECAUTIONS : Proarrhythmia, cardia failure, abrupt withdrawal, peripheral vascular disease, nonallergic bronchospasms, bradycardia, diabetes/hypoglycemia, electrolyte disturbances, hypotension, renal/hepatic impairment, category D, lactation (in breast milk), children.
- SIDE EFFECTS : **Bradycardia, ventricular arrhythmias,** dizziness, vertigo, tiredness, fatigue, nightmares, rash, sweating, alopecia, psoriasis, acne, eczema, gas, constipation, nausea, diarrhea, dry mouth, heartburn, impotence, decreased libido, joint pain, muscle cramps**, bronchospasms, cough, wheezing**, nasal stuffiness

# Antiadrenergics/Sympatholytic Agents- BETA-Adrenergic Blocking Agent

- Nutrients Depleted
  - COQ10
  - Melatonin


1. Folkers, K. Basic chemical research on coenzyme Q-10 and integrated clinical research on therapy of diseases, in *Coenzyme Q, G*. Lenaz, ed. John Wiley & Sons, 1985.
2. Pelton R. LaValle JB. The Quick Reference Guide to Nutrient Losses. In: The Nutritional Cost of Prescription Drugs.2nd Edition Englewood, CO: Morton Publishing Company; 2004, 15.

**Bioenergetics in clinical medicine XV. Inhibition of coenzyme Q10-enzymes by clinically used adrenergic blockers of beta-receptors.**

- Res Commun Chem Pathol Pharmacol. 1977 May;17(1):157-64.

- **Propranolol** is frequently used to treat hypertension; in some patients, it **depresses myocardial function** as an adverse reaction.

- This side effect may be related to the inhibition by propranolol of **CoQ10-enzymes** of the myocardium.

- PMID: 17892

# Best Support

- Melatonin - if sleep quality affected
- COQ10 (ubiquinone)
  - in those that are under 50, or with no diabetes or kidney health problems
  - assure the ubiquinone is 100% bio-identical and proof of cellular mitochondrial absorption
- Others will use ubiquinol (QH)
  - Aging, genetics and certain health concerns (glycemic control, kidney damage, liver, or aging) reduce the process where ubiquinone is converted to ubiquinol (reduced form)

# Renin Angiotensin System Antagonist-
## Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)

- BENZAPRIL (LOTENSIN)
- CAPTOPRIL (CAPOTEN)
- ENALAPRIL (VASOTEC)
- FOSINOPRIL (MONOPRIL)
- LISINOPRIL (PRINIVIL, ZESTRIL)
- MOEXIPRIL (UNIVASC)
- QUINAPRIL (ACCUPRIL)
- RAMIPRIL (ALTACE)

- MECHANISM OF ACTION: Blocks the angiotensin converting enzyme that converts angiotensin I to angiotensin II in the kidney.
- INDICATIONS: Hypertension, Congestive heart failure.
- CONTRAINDICATIONS: Hypersensitivity to the drug
- WARNINGS/PRECAUTIONS: Angioedema, anaphylactoid reactions, proteinuria, hypotension, renal and hepatic impairment, category D (2nd and 3rd trimester), children (safety and efficacy not established), hypokalemia, surgery/anesthesia, chronic cough, photosensitivity.
- SIDE EFFECTS: **Persistent dry cough**, orthostatic hypotension, hypotension, renal impairment, severe allergic reactions, hyperkalemia, dizziness, fatigue, headache, nausea.

# Renin Angiotensin System Antagonist-
## Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)

- NUTRIENTS DEPLETED
  - Na
  - Zinc

1. Pelton R. LaValle JB. The Quick Reference Guide to Nutrient Losses. In: The Nutritional Cost of Prescription Drugs.2nd Edition Englewood, CO: Morton Publishing Company; 2004,

# Zinc metabolism in patients treated with captopril versus enalapril.

- Metabolism. 1990 Jul;39(7):665-7.

- We conclude that (1) although **both** captopril and enalapril **produce renal zinc loss**, this loss is far greater in patients receiving captopril; and (2) captopril administration over 3 months or more generates RBC zinc depletion.

- PMID: 2195291

# Effects of captopril and enalapril on zinc metabolism in hypertensive patients.

- Am Coll Nutr. 1998 Feb;17(1):75-8.

- RESULTS: **Significant** enhancement of 24-hour **urinary zinc excretion** (micrograms/24 hour) after 6 months of treatment was observed only in the captopril-treated group ($p < 0.01$).

- CONCLUSION: Treatment of hypertensive patients with captopril or enalapril may result in zinc deficiency.

- PMID: 9477394

# Best Support

- Optimal multivitamin mineral for zinc
  - keep zinc and copper balanced
- If Na depletion is a problem then address
- Low gastric acid will interfere with nutrient absorption (zinc)

# Antiadrenergics/Sympatholytic Agents- Angiotensin II Receptor Antagonist (AT1-Receptor Antagonist)

- LOSARTAN (COZAAR)
- VALSARAN (DIOVAN)
- IRBESARTAN (AVAPRO)
- CANDESARTAN (ATACAND)
- TELMISARTAN (MICARDIS)
- OLMESARTAN (BENICAR)
- ALISKIREN (TEKTURNA)

- MECHANISM OF ACTION: Block the activation of angiotensin II AT1 receptor
- INDICATIONS: Hypertension, Nephropathy in type 2 diabetics
- CONTRAINDICATIONS: Hypersensitivity to the drug
- WARNINGS/PRECAUTIONS: Hypotension, salt depleted patients, renal and hepatic impairment, fertility impairment, category D ($2^{nd}$ and $3^{rd}$ trimester), children (safety and efficacy no established), potassium supplements, creatinine/blood urea nitrogen, serum potassium.
- SIDE EFFECTS: Dizziness, fatigue, diarrhea, heartburn, musculoskeletal pain, upper respiratory tract infection, cough.

# Antihyperlipidemic Agents- HMG-CoA Reductase Inhibitor ("Statins")

- LOVASTATIN (MEVACOR, MEVINOLIN)
- SIMVASTATIN (ZOCOR)
- PRAVASTATIN (PRAVACHOL)
- ROSUVASTATIN (CRESTOR)
- FLUVASTATIN (LESCOL AND XL)
- ATORVASTIN (LOPITOR)

- MECHANISM OF ACTION: NEXT SLIDE (STATIN PATHWAY)

- **INDICATIONS**:
  - Heterozygous familial hypercholesterolemia in adolescents
  - Homozygous familial hyperlipidemia
  - Hypertriglyceridemia
  - Mix dyslipidemia
  - Primary hypercholesterolemia

- CONTRAINDICATIONS: Hypersensitivity to the drug

- WARNINGS/PRECAUTIONS: Skeletal muscle effects (**myopathy, rhabdomyolysis**), endocrine effects, hypersensitivity reactions, hepatic impairment, alcholics, category X, lactation (in breast milk), **liver enzymes**.

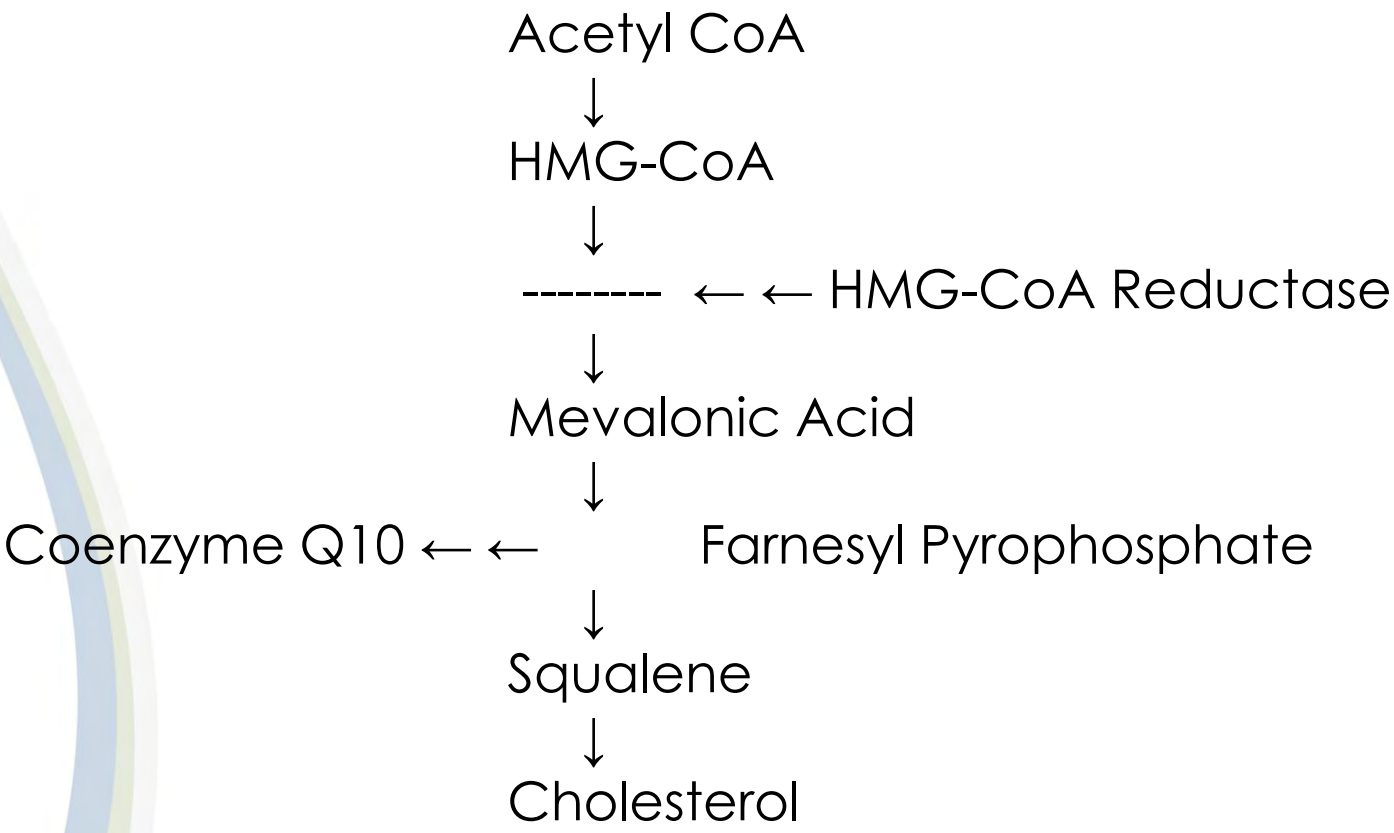
- SIDE EFFECTS: Asymptomatic serum transaminase increases, myalgia, back pain, headache, abdominal pain, diarrhea, gas, nausea, vomiting, sinusitis, fatigue.

# Antihyperlipidemic Agents- HMG-CoA Reductase Inhibitor ("Statins")

- Nutrient Depletions
  - COQ10
  - Selenium
  - Zinc
  - Copper
  - Lowers serum fatty acid concentrations and alters the relative % of PUFA's


1. Folkers K, et al. "Lovastatin Decreases Coenzyme Q Levels in Humans," Proc Natl Acad Sci USA. 1990 Nov; 87(22): 8931-34.
2. Mortensen SA, et al. "Dose-related Decrease of Serum Coenzyme Q10 during Treatment with HMG-CoA Reductase Inhibitors," Mol Aspects Med. 1997; 18 Suppl: S137-44.
3. Ghirlanda G, et al. "Evidence of Plasma CoQ10-lowering Effect by HMG-CoA Reductase Inhibitors: ADB PC Study," J Clin Pharmacol. 1993 Mar; 33(3): 226-29.
4. Bargossi AM, Grossi G, Fiorella PL, et al. Exogenous CoQ10 supplementation prevents plaxma ubiquinone reduction induced by HMG-CoA reductase inhibitors. Mol Aspects Med 1994;15(suppl):s187-93. Langsjoen PH,
5. Langsjoen, AM. The clinical use of HMG CoA-reductase inhibitors and the associated depletion of coenzyme Q10. A review of animal and human publications. Biofactors 2003;18 (1-4); 101-11.

# Biosynthetic Pathway of Cholesterol



# Atorvastatin decreases the coenzyme Q10 level in the blood of patients at risk for cardiovascular disease and stroke.

- *Arch Neurol.* 2004 Jun;61(6):889-92
- A **significant decrease** was already detectable **after 14 days of treatment** .
- CONCLUSIONS: Even brief exposure to atorvastatin causes a marked decrease in blood CoQ(10) concentration.
- Widespread inhibition of CoQ(10) synthesis could explain the most commonly reported adverse effects of statins, especially exercise intolerance, **myalgia,** and myoglobinuria.
- PMID: 15210526

# Evidence of plasma CoQ10-lowering effect by HMG-CoA reductase inhibitors: a double-blind, placebo-controlled study.

- *J Clin Pharmacol.* 1993 Mar;33(3):226-9
- We studied two groups
  - 5 healthy volunteers 20 mg/day of pravastatin or simvastatin for 1 month.
  - 30 hyper-cholesterolemic patients with pravastatin, simvastatin (20 mg/day), or placebo for 3 months.
- **40% reduction** (COQ10) after the treatment
- CoQ10 is essential for the production of energy and also has antioxidative properties. A diminution of CoQ10 availability may be the cause of membrane alteration with consequent cellular damage.
- PMID: 8463436

# Lipid-lowering drugs and essential omega-6 and omega-3 fatty acids in patients with coronary heart disease.

- *Nutr Metab Cardiovasc Dis.* 2005 Feb;15(1):36-41
- Male patients with CHD and high cholesterol levels (double-blind protocol) to receive either simvastatin 20mg (S) or fenofibrate 200mg daily (F) for 3 months.
- **LLD's significantly alter the metabolism of essential fatty acids** that are critically important for the pathogenesis and prevention of CHD.
- Further studies are urgently needed:
  - examine the effects of higher dosages
  - whether specific dietary intervention (combining low intake of n-6 fatty acids and high intake of n-3 fatty acids) may improve the effectiveness of these drugs
- PMID: 15871849

# Statin treatment alters serum n-3 and n-6 fatty acids in hypercholesterolemic patients.

*Prostaglandins Leukot Essent Fatty Acids.* 2004 Oct;71(4):263-9

- Subjects were 106 healthy adults with hypercholesterolemia randomly assigned to receive placebo or **40 mg simvastatin daily for 24 weeks**.
- Relative percentages of linoleic acid (LA, 18:2n-6) and alpha-linolenic acid (**LNA, 18:3n-3), decreased** while **AA** and DHA **increased**.
- Thus, simvastatin lowered serum fatty acid concentrations while also altering the relative percentages of important PUFAs.
- PMID: 15310527

# Statin-associated myopathy with normal creatine kinase levels.

- Ann Intern Med. 2002 Oct 1;137(7):581-5.
- Creatine kinase levels were normal in all four patients despite the presence of significant myopathy.
- CONCLUSION: Some patients who develop muscle symptoms while receiving statin therapy have demonstrable weakness and histopathologic findings of **myopathy despite normal serum creatine kinase levels**.
- PMID: 12353945

# Association between statin-associated myopathy and skeletal muscle damage.

- CMAJ. 2009 Jul 7;181(1-2):E11-8.
- Of the 44 patients with clinically diagnosed statin-associated myopathy, 29 were currently taking a statin, and 15 had discontinued statin therapy before the biopsy (minimal duration of discontinuation 3 weeks).
- RESULTS: Muscle injury was observed in 25 (of 44) patients with myopathy and in 1 patient without myopathy.
- Only 1 patient with structural injury had a circulating level of creatine phosphokinase that was elevated more than 1950 U/L (10x the upper limit of normal).
- **A lack of elevated levels of circulating creatine phosphokinase does not rule out structural muscle injury**. Upregulation of the expression of ryanodine receptor 3 is suggestive of an intracellular calcium leak.
- PMID: 19581603

# Best Support

- Due to the multiple depletions (zinc, selenium, copper) use of a daily essential vitamins and mineral formula is recommended.

- COQ10 (ubiquinone)
  - in those that are under 50, or with no diabetes or kidney health problems.
  - assure the ubiquinone is 100% bio-identical and proof of cellular mitochondrial absorption
- Others will use ubiquinol (QH)
  - Aging, genetics and certain health concerns (glycemic control, kidney damage, liver, or aging) reduce the process where ubiquinone is converted to ubiquinol (reduced form)

- Low gastric acid will interfere with nutrient absorption (minerals)

- Lower the omega 6 intake and increase omega 3's (natural stable ratio fish oil)

# Antihyperlipidemic Agents- Fibric Acid Derivatives

- Gemfibrozil (Lopid)
- Femofibrate (Tricor, Triglide)

- MECHANISM OF ACTION: Not definitely established.
  - Gemfibrozil inhibits peripheral lipolysis and decreases hepatic excretion of free fatty acids.
  - Gemfibrozil inhibits synthesis and increases clearance of VLDL (apolipoprotein B) leading to a decrease in VLDL.
- INDICATIONS: Hypertriglyceridemia, Prevention of cardiovascular disease.
- CONTRAINDICATIONS: Hypersensitivity to drug, hepatic or renal dysfunction,
- WARNING/PRECAUTIONS: Gallstones, concomitant anticoagulants, skeletal muscle effects, cataracts, renal and hepatic impairment, abnormal liver functions children (safety and efficacy not established.)
- SIDE EFFECTS: GI reactions (dyspepsia, abdominal pain, diarrhea, constipation, nausea, vomiting).

# Antihyperlipidemic Agents- Fibric Acid Derivatives

- Nutrient Depletions
  - COQ10
  - Vitamin E (alpha & gamma tocopherol)
  - B6, B12, Folic acid - Increases homocysteine

1. Aberg, et al. "Gemfibrozil-induced decrease in serum ubiquinone and alpha- and gamma-tocopherol levels in men with combined hyperlipidemia," Eur J Clin Invest. 1998; 28: 235-42.

## The effect of fibrates and other lipid-lowering drugs on plasma homocysteine levels.

- Expert Opin Drug Saf. 2004 Mar;3(2):101-11.
- fenofibrate and bezafibrate lead to a 20 - 40% elevation of plasma levels of the atherogenic amino acid homocysteine, thereby possibly counteracting the desired cardiovascular protection
- The increase of plasma homocysteine after fenofibrate can be lowered by the concurrent administration of folic acid and vitamins B(12) and B(6). Thus, patients with hypertriglyceridaemia can either be concurrently treated with **fenofibrate and vitamins (B6, folic acid, B12) or with gemfibrozil**.
- PMID: 15006716

# Serum homocysteine increases after therapy with fenofibrate or bezafibrate.

Lancet. 1999 Jul 17;354(9174):219-20.

- A 44% and 17.5% increase of homocysteine occurred in patients treated either with fenofibrate or bezafibrate.

- PMID: 10421307

# Best Support

- Mixed tocopherols  vitamin E
- Check homocysteine- Optimal b complex vitamins
- COQ10 (ubiquinone)
  - in those that are under 50, or with no diabetes or kidney health problems.
  - assure the ubiquinone is 100% bio-identical and proof of cellular mitochondrial absorption
- Others will use ubiquinol (QH)
  - Aging, genetics and certain health concerns (glycemic control, kidney damage, liver, or aging) reduce the process where ubiquinone is converted to ubiquinol (reduced form)
- Low gastric acid will interfere with nutrient absorption (minerals and B vitamins)

# Antihyperlipidemic Agents- Bile Acid Sequestrants

- COLESTIPOL (COLESTID)
- CHOLESTYRAMUNE (QUESTRAN)
- COLESEVELAM (WELCHOL)

- MECHANISM OF ACTION: Bind bile acids in the intestines to form an insoluble complex that is excreted in the feces. The increased fecal loss of bile acid leads to increased oxidation of cholesterol to bile acids and a decrease in LDL and serum cholesterol.

- INDICATIONS: Hyperlipoproteinemia, biliary obstruction, clostridium difficle, digitalis toxicity.

- CONTRAINDICATIONS: Hypersensitivity to any drug, complete biliary obstruction (Questran), bowel obstruction (Welchol).

- WARNING/PRECAUTIONS: Phenylketonurics, lactation, children (Questran only), thyroid function, **malabsorption** , reduced folate, GI disorders, constipation.

- SIDE EFFECTS: Abdominal discomfort, cramping, aggravating hemorrhoids, blood in stool, **constipation**, diarrhea, intestinal gas, nausea, vomiting, heartburn, indigestion.

# Antihyperlipidcermic Agents- Bile Acid Sequestrants

- Nutrients Depleted
  - Vitamins A, D, E, K, B12
  - Calcium
  - Magnesium
  - Phosphorous
  - Zinc
  - Iron
  - Folic Acid
  - Beta-carotene
  - Fat


1. Roe, DA. *Drug-Induced Nutritional Deficiencies.* Second Edition. Westport, CT, Avi Publishing, pp. 158-159, 1985.
2. Hoppner & Lampi, "Bioavailability of folate following ingestion of cholestyramine in the rat," Int J Vitamin Nutr Res. 1991; 61: 130-4.

# Best Support

- Due to the **multiple depletions** of daily essential vitamins and minerals an optimal multi vitamin mineral is recommended.

# NUTRIENT DEPLETIONS
# CARDIOVASCULAR REFERENCES

- **DIGOXIN**
- PMID: 1507935, "Heart failure and electrolyte disturbances".
- PMID: 9851552, "Furosemide and digoxin inhibit thiamine uptake in cardiac cells".
- **POTASSIUM**
- PMID: 4456986, "Drug-induced malabsorption of vitamin B12. VII. Malabsorption of B12 treatment with potassium citrate".
- PMID: 5032681, "Drug-induced malabsorption of vitamin B 12 . IV. Malabsorption and deficiency of B 12 during treatment with slow-release potassium chloride".

# NUTRIENT DEPLETIONS
# LIPID REDUCING DRUGS REFERENCES


- **FIBRATES**
- PMID: 15006716, "The effects of fibrates and other lipid-lowering drug on plasma homocysteine levels".
- PMID: 11500187, "Vitamin supplementation can markedly reduce the homocysteine elevation induced by fenofibrate".
- PMID: 12851616, "Effect of folic acid on fenofibrate-induced elevation of homocysteine and cysteine".
- PMID: 11527658, "Folate supplementation prevents plasma homocysteine increases after fenofibrate therapy".
- PMID: 12953339, "Comparative effects of atorvastatin, simvastatin, and fenofibrate on serum homocysteine levels in patients with primary hyperlipidemia".
- PMID: 9568470, "Gemfibrozil-induced decrease in serum ubiquinone and alpha and gamma tocopherol levels in men with combined hyperlipidaemia".
- PMID: 15019536, "Serum homocysteine concentrations, gemfibrozil treatment, and progression of coronary atherosclerosis".
- PMID: 12534325, "Fenofibrate-induced hyperhomocysteineaemia: Clinical implications and management".

# NUTRIENT DEPLETIONS
# LIPID REDUCING DRUGS REFERENCES (cont.)


- **BILE ACID SEQUESTRANTS**
- PMID: 8660081, "Low dose colestipol in adolescents with familial hypercholesterolaemia".
- PMID: 40578, "in vitro binding of various biological substances by two hypocholesterolaemic resins, cholestyramine and colestipol".
- PMID: 3881283, "Metabolic mechanism of drug-nutrient interactions".
- PMID: 1168607, "The effect of cholestyramine on intestinal absorption".
- PMID: 7627696, "Probucol treatment decreases serum concentrations of diet-derived antioxidants".
- PMID: 3547004, "Adverse effects of hypolipidaemic drugs".
- PMID: 3987479, "Alterations in calcium, magnesium, and zinc metabolism by dietary cholestyramine".
- PMID: 7046936, "Drug-nutrient interaction".

# NUTRIENT DEPLETIONS
# LIPID REDUCING DRUGS REFERENCES (cont.)


- **STATINS**
- PMID: 9266515, "Dose-related decrease of serum Coenzyme Q10 during treatment with HMG-CoA reductase inhibitors".
- PMID: 17681347, "Effects of CoQ10 supplementation on plasma lipoprotein lipid, CoQ10 and liver and muscle enzyme levels in hypercholesterolemic patients treated with atrovastatin: A randomized double-blind study".
- PMID: 15942122, "Reduction of serum ubiquinol-10 and ubiquinone-10 levels by atorvastatin in hypercholesterolemic patients".
- PMID: 16872244, "Effects of ezetimibe and/or simvastin on Coenzyme Q10 levels in plasma: A randomized trial".
- PMID: 8463436, "Evidence of plasma CoQ10-lowering effects by HMG-CoA reductase inhibitors: A double-blind, placebo-controlled study".
- PMID: 14695926, "Statins lower plasma and lymphocyte ubiquinol/ubiquinone without affecting other antioxidants and PUFA".
- PMID: "7752830, "Exogenous CoQ10 supplementation prevents plasma ubiquinone reduction induced by HMG-CoA reductase inhibitors".

# NUTRIENT DEPLETIONS
# LIPID REDUCING DRUGS REFERENCES (cont.)

- **STATINS (cont.)**
- PMID: 15210526, "Atorvastatin decreases the Coenzyme Q10 levels in the blood of patients at risk for cardiovascular disease and stroke".
- PMID: 17493470, "Effects of Coenzyme Q10 on myopathic symptoms in patients treated with statins".
- PMID: 17610923, "Reduced mitochondrial Coenzyme Q10 levels in HepG2 cells treated with high-dose simvastin: A possible role in statin induced hepatotoxicity".
- PMID: 15310527, "Statin treatment alters Serum N-3 and N-6 fatty acids in hypercholesertolemic patients".
- PMID: 15031036, "Selenoprotein synthesis and side-effects of statins".
- PMID: 19203713, "Fibrates but not statins increase plasma selenium in dyslipidemic aged patients – The EVA study".
- PMID: 16240674: "Effects of statin therapy on serum trace element status in dyslipidaemic subjects".

# NUTRIENT DEPLETIONS ANTIHYPERTENSIVES/DIURETICS REFERENCES


- PMID: 9350641, "Renal magnesium handling: new insights in understanding old problems".
- PMID: 3193027, "Is lymphocyte magnesium concentration a reflection of intracellular magnesium concentration?"
- PMID: 16272623, "Potassium and magnesium depletions in congestive heart failure--pathophysiology, consequences and replenishment".
- PMID: 8807629, "Effect of furosemide oral solution versus furosemide tablets on diuresis and electrolytes in patients with moderate congestive heart failure".
- PMID: 7722187, "Thiamin status, diuretic medications, and the management of congestive heart failure".
- PMID: 1867241, "Thiamine deficiency in patients with congestive heart failure receiving long-term furosemide therapy: a pilot study".
- PMID: 9851552, "Furosemide and digoxin inhibit thiamine uptake in cardiac cells".
- PMID: 14712323, "Thiamine deficiency in congestive heart failure patients receiving long term furosemide therapy".
- PMID: 7722187, "Thiamin status, diuretic medications, and the management of congestive heart failure".
- PMID: 9820088, "[The effect of furosemide on urinary excretion of oxalic acid, vitamin C and vitamin B6 in chronic kidney failure]".

# NUTRIENT DEPLETIONS ANTIHYPERTENSIVES/DIURETICS REFERENCES (cont.)


- PMID: 10681666, "Influence of water and sodium diuresis and furosemide on urinary excretion of vitamin B(6), oxalic acid and vitamin C in chronic renal failure".
- PMID: 9350682, "Metabolism of vitamin B6 and its requirement in chronic renal failure".
- PMID: 5588008, "Studies of the effect of the diuretics furosemide, ethacrynic acid and triamterene on renal magnesium and calcium excretion]".
- PMID: 3896745, "Drugs and folate metabolism".
- PMID: 3760669, "Competitive inhibition of folic acid absorption in rat jejunum by triamterene".
- PMID: 6635871, "Urinary magnesium output after a single dose of indapamide in healthy adults".
- PMID: 8750365, "Ramipril decreases chlorthalidone-induced loss of magnesium and potassium in hypertensive patients".
- PMID: 1778085, "Changes in blood pressure, serum potassium and electrolytes with a combination of triamterene and a low dose of chlorthalidone".
- PMID: 6376209, "Chlorthalidone-triamterene: a potassium-sparing diuretic combination for the treatment of oedema".
- PMID: 2915738, "Hypokalaemia in hypertensive patients treated with diuretics: no increase in cardiac arrhythmias".
- PMID: 17583180, "Effect of lipid-lowering and anti-hypertensive drugs on plasma homocysteine levels".