Natural Health Products for Cardiovascular Risk Reduction: Panacea, Bust, or Work In Progress?
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Clinical Lecturer, School of Pharmacy, University of Waterloo

Relationships with commercial interests:
▶ Not Applicable

Potential for conflict(s) of interest:
▶ Not Applicable
Mitigating Potential Bias

- All the recommendations involving clinical medicine are based on evidence that is accepted within the profession.
- All scientific research referred to, reported, or used is in the support or justification of patient care.
- Recommendations conform to the generally accepted standards.
- Independent content validation.
- The presentation will mitigate potential bias by ensuring that data and recommendations are presented in a fair and balanced way.
- Potential bias will be mitigated by presenting a full range of products that can be used in this therapeutic area.
- Information of the history, development, funding, and the sponsoring organizations of the disclosure presented will be discussed.
Learning objectives

• List several natural health products that are commonly used by patients at risk for cardiovascular events.

• Describe the strength of evidence supporting the use of natural health products for cardiovascular disease.

• Identify safety concerns associated with natural health products that are used for cardiovascular disease.

• Explain pitfalls when recommending therapies based upon improvements in surrogate outcomes.
Outline

• Overview of Natural Health Products (NHPs)

• Case studies
  – Prevention of myocardial infarction and stroke
    • Dyslipidemia/hypertension
  – Heart failure
ARS Question #1

I am a:

A. Family physician or general practitioner
B. Medical specialist
C. Medical resident or intern
D. Nurse practitioner or advanced practice nurse
E. Registered nurse or registered practical nurse
F. Pharmacist
G. Dietitian
H. Other
ARS Question #2

Which of the following best describes your attitude towards NHPs for cardiovascular risk reduction?

A. Patients should generally use NHPs instead of drugs because they are safer.
B. If my patients prefer NHPs over drugs, I am willing to work with them to choose an NHP that is best for them.
C. I'm fine if my patients want to use NHPs, but I leave that to them to figure out on their own.
D. NHPs are a waste of money and I tell my patients not to use them.
E. I don’t like to ask my patients about NHPs because I am worried they will ask me something I can’t answer.
ARS Question #3

What NHP do you get asked about most often?

A. Fish oil
B. Other sources of omega-3 fatty acids (ex. krill oil, flaxseed)
C. Garlic
D. Phytosterols
E. Coenzyme Q10
F. Other
What are natural health products (NHPs)?

• NHPs include:
  – Vitamins and minerals
  – Herbal remedies
  – Homeopathic medicines
  – Traditional medicines such as traditional Chinese medicines
  – Probiotics
  – Other products like amino acids and essential fatty acids

• Must be safe for consideration as OTC products (no prescription)

• Must be available for self-care and self-selection
How are NHPs regulated?

• NHPs are regulated by Natural Health Product Regulations, which came into effect in 2004
• Regulated as a subset of drugs
• Pre-market review required for NHP to obtain a product license
• Approved products are given either a Natural Product Number (NPN) or DIN-HM (homeopathic medicines)
• Product license application must contain information on safety, efficacy, quality, and proposed label text

**Patient tip – only choose a product with an NPN**
ARS Question #4

In order for an NHP to have a product license (and NPN), there must be evidence from at least one RCT to support efficacy.

A. True
B. False
ARS Question #5

How strongly do you agree/disagree with the following:

"NHPs are produced using the same high quality standards as prescription products"

A. Strongly agree
B. Agree
C. Neutral
D. Disagree
E. Strongly disagree
Issues with herbal products

- Complex mixtures of compounds
- Active ingredient(s) may be unknown
- Reports of adulteration with drugs, other herbs, heavy metals, etc.
- Healthcare professionals often unaware of use
- Perceived vs. actual safety
- Herb-drug interactions
- Quantity of active ingredient different than label
- Quantity of active ingredient(s) may vary
  - Batch-to-batch variation
  - Variation between manufacturers

**Patient tip – do not switch brands if a product is working for you.**
Case #1: Mr. Bupinder Singh

• 56 year-old male, STEMI six-days ago
  –Primary PCI, bare-metal stent to his LAD

• Mr. Singh said that he’s a little tired, but otherwise doing well “all things considered”.

• He said that his wife really wants him to start taking vitamins to prevent another heart attack. She said that Dr. Oz recommended vitamin E, folic acid, and a couple of other things that Mr. Singh now forgets.
ARS Question #6

Which of the following interventions has the strongest evidence for Cardiovascular Risk Reduction?

A. Vitamin E
B. Folic acid
C. Mediterranean diet
D. Vitamin B complex
E. A multivitamin
Vitamin E: A cautionary tale
(or how Jeff became a healthy skeptic...)

Beneficial effects (*in vitro*):

- Scavenges free radicals
  - May prevent oxidative damage to membranes and LDL
- Also inhibits smooth muscle proliferation and platelet aggregation
The evidence: Observational studies

Nurses Health Study
- 98,000 nurses free from CV disease
- Dietary questionnaires to assess vitamin E consumption
- 8 year follow-up
- Determined relative risk of CAD events based upon quintile of vitamin E consumption

Health Professionals Study
- 40,000 male HCPs free from CV disease
- Dietary questionnaires to assess vitamin consumption
- 5 year follow-up
- Determined relative risk of CAD events based upon quintile of vitamin consumption

The evidence: Observational studies

Nurses Health Study
Results:
RR of CAD (95% CI) by quintile of vitamin E intake (p<0.001):
• 4th quintile
  – 0.68 (0.57-0.98)
• 5th quintile
  – 0.59 (0.45-0.78)

Health Professionals Study
Results:
RR of CAD (95% CI) by quintile of vitamin E intake (p<0.001):
• 4th quintile
  – 0.74 (0.59-0.93)
• 5th quintile
  – 0.59 (0.47-0.75)

Vitamin E mania

• 1997 survey of cardiologists:
  – 44% reported self-use of vitamin E
  – 42% reported self-use of ASA for primary prevention

Mehta J. Am J Cardiol 1997; 79: 1558-60.
The evidence, cont’d: Randomized controlled trials
HOPE and HOPE-TOO trial design

9541 patients at 267 study centres
≥55 with vascular disease or DM + CV risk factor

4761 α-tocopherol 400 IU once daily
4780 matching placebo once daily

Study extension
3520 at 174 centres
(2025 continue txt)

Study extension
3510 at 174 centres
(1969 continue txt)

1139 at 93 centres do not continue 4.5 years
1147 at 93 centres do not continue 4.5 years

Primary endpoint:
Composite of CV death, MI, CVA
Results: Primary endpoint

HOPE main study

n = 9541

p > 0.2 for all comparisons

HOPE-TOO study

n = 7030

p > 0.2 for all comparisons

The HOPE and HOPE-TOO Trial Investigators*. JAMA. 2005;293:1338-1347
Results: Secondary endpoints

RR = 1.19 (1.05 to 1.35); p=0.007

RR = 1.4 (1.13 to 1.73); p=0.002

The HOPE and HOPE-TOO Trial Investigators*. JAMA. 2005;293:1338-1347
Stories with a similar plot:

- Folic acid
- B vitamins
- Vitamin C
- Beta-carotene
- Multivitamins

Mediterranean diet (PREDIMED study)

7447 Spanish patients with elevated CV risk (DM or three risk factors), but no prior CV disease

Mediterranean diet supplemented with either:
1) Olive oil (4 tbsp per day): n=2453
2) Mixed nuts (30 g per day): n=2454

Placebo (non-food gifts): n=2450

4.8 year median follow-up

Primary endpoint:
Time to myocardial infarction, stroke, death from cardiovascular causes

## Mediterranean diet (PREDIMED study)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mediterranean diet with EVOO</th>
<th>Mediterranean diet with nuts</th>
<th>Control diet</th>
<th>p-value EVOO vs. control</th>
<th>p-value nuts vs. control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of myocardial infarction (MI), stroke (CVA), death from cardiovascular (CV) causes (crude rate)</td>
<td>96 events 8.1 per 1000 person-year</td>
<td>83 events 8.0 per 1000 person-year</td>
<td>109 11.2 per 1000 person-year</td>
<td>0.009</td>
<td>0.02</td>
</tr>
<tr>
<td>Composite of time to MI, CVA, death from CV causes (unadjusted)</td>
<td>Hazard ratio, (95% CI) 0.70 (0.53-0.91)</td>
<td>Hazard ratio, (95% CI) 0.70 (0.53-0.94)</td>
<td>Hazard ratio, (95% CI) 1.00 (ref)</td>
<td>0.009</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Case #1: Mr. Bupinder Singh

• 56 year-old male, STEMI six-days ago
  –Primary PCI, bare-metal stent to his LAD

• Mr. Singh said that he’s a little tired, but otherwise doing well “all things considered”.

• He said that his wife really wants him to start taking vitamins to prevent another heart attack. She said that Dr. Oz recommended vitamin E, folic acid, and a couple of other things that Mr. Singh now forgets.
General thoughts....

• Observational studies versus RCTs
  – Unmeasured and/or unknown confounders

• Surrogate endpoints (homocysteine lowering, cholesterol lowering, etc.) versus patient-oriented endpoints (myocardial infarction, stroke, death, quality of life, etc.)

• Study designs with nutrients
  – Supplements versus dietary consumption
Case #2

Ms. Ima Leafan is a non-smoking 58 year-old female referred for assessment of her cardiovascular risk

PMH:
Dyslipidemia (2011)
?Hypertension (2016 – being worked up)

No significant family history of CVD

Medications:
• Garlicin 4 capsules once daily (x 4 months) – for blood pressure
• Salmon oil 1 g once daily (x 1 year) – for cholesterol
Case #2 (cont’d)

O/E: October 2016

- BP 148/88 mmHg; pulse = 73
- Height: 160 cm Weight: 73 kg

Labs:
- Total cholesterol: 6.7 mmo/L
- LDL-c: 4.8 mmol/L
- HDL-c: 0.8 mmol/L
- Triglycerides: 1.2 mmol/L

Ms. Leafan generally prefers natural products to medications, and asks what you think about krill oil, flaxseed, plant sterols, and soluble fiber – should she be taking them?
ARS Question #7

Which of the following has the best evidence for efficacy for Ms. Leafan?

A. Fish oil
B. Garlic
C. Krill oil
D. Flaxseed
E. Plant sterols
F. Soluble fiber
NHPs to consider

• NHPs with cardiovascular risk-lowering data from RCTs:
  – Omega-3 fatty acids (marine-source, a.k.a fish oil)

• NHPs without cardiovascular risk-lowering data:
  – Omega-3 fatty acids (flaxseed, krill oil)
  – Garlic
  – Soluble fiber
  – Plant sterols
NHPs to consider

• NHPs with cardiovascular risk-lowering data from RCTs:
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• NHPs without cardiovascular risk-lowering data:
  – Omega-3 fatty acids (flaxseed, krill oil)
  – Garlic
  – Soluble fiber
  – Plant sterols
Omega-3 polyunsaturated fatty acids

Most commonly used/best studied source:
• Marine-based (fish oil)

Proposed mechanisms for possible cardiovascular risk lowering:
– Modify the cholesterol profile
  • Reduce serum triglycerides
– Antithrombotic effects
– Mild anti-hypertensive effects
Does fish oil reduce the risk of cardiovascular events?

- Older meta-analyses: YES
- Newer meta-analyses: NO
Fish oil and CV risk

• Meta-analysis of 20 studies
  – 68,000 patients randomized to either omega-3 PUFA (median dose was 1 gram of EPA/DHA) or placebo
    • Mixture of primary and secondary prevention (mainly secondary prevention)
  – Median treatment duration 2 years
  – Outcomes of interest: mortality, sudden death, cardiac death, myocardial infarction, stroke

JAMA 2012;308(10):1024-1033
Fish oil and CV risk

Results:

- Fish oil had no statistically significant effect on the risk of overall mortality, cardiac death, sudden death, myocardial infarction or stroke
Fish oil and CV risk

Examples of “positive” fish oil studies:
• GISSI-Prevenzione¹
• JELIS²
• DART³

Examples of “negative” fish oil studies:
• ORIGIN⁴
• OMEGA⁵
• Alpha-Omega⁶

## Comparison of GISSI\(^1\) and ORIGIN\(^2\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GISSI (positive)</th>
<th>ORIGIN (negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of publication</td>
<td>1999</td>
<td>2012</td>
</tr>
<tr>
<td>Study location</td>
<td>Italy</td>
<td>40 countries</td>
</tr>
<tr>
<td>Dose of fish oil</td>
<td>850-882mg EPA/DHA</td>
<td>900 mg EPA/DHA</td>
</tr>
<tr>
<td>Primary prevention</td>
<td>0%</td>
<td>40%</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>90%</td>
<td>69%</td>
</tr>
<tr>
<td>ACE-i/ARB</td>
<td>46%</td>
<td>69%</td>
</tr>
<tr>
<td>Statins</td>
<td>4% (listed as “cholesterol-lowering medication”)</td>
<td>54%</td>
</tr>
</tbody>
</table>

Audience poll...

• Does the use of fish oil reduce the risk of cardiovascular events?
  – Older studies, perhaps
  – Newer studies, no
  • Could mean that it does not offer additional benefit to current standards of care (e.g. no effect when added to statin therapy)?
Fish oil

• **Cautions**
  – Gastrointestinal side effects (particularly dyspepsia) are common
  – Fishy aftertaste, fishy burp
  – Bleeding with doses greater than 3 g/day
  – Interaction with anticoagulants

• **Dose of EPA/DHA**
  – 3-4 g/d for hypertriglyceridemia
  – 1 g/d in heart failure patients and for secondary prevention
  – For primary prevention, just eat fish!
NHPs to consider

• NHPs with cardiovascular risk-lowering data from RCTs:
  – Omega-3 fatty acids (marine-source, a.k.a fish oil)

• NHPs without cardiovascular risk-lowering data:
  – Omega-3 fatty acids (flaxseed, krill oil)
  – Garlic
  – Soluble fiber
  – Plant sterols
Other sources of omega-3 fatty acids: Flaxseed

• Flaxseed contains:
  – Soluble fiber in seed
  – Lignans (phytoestrogens) in seed
  – Flaxseed oil – ALA (an omega-3 fatty acid) and other fatty acids
    • Note – does not contain EPA/DHA

• Generally reduce total and LDL-cholesterol levels
  – Most studies used dietary flaxseed (versus flaxseed oil)

• Main ADR: digestive symptoms due to soluble fiber

Other sources of omega-3 fatty acids: Krill oil

- Oil from krill, a shrimp-like crustacean
  - Contains EPA and DHA
  - Also contains omega-9 fatty acids, phospholipids, vitamin A, vitamin E, and other antioxidants
  - Not well-researched
  - One study:
    - Reduced triglycerides, LDL, total cholesterol and increased HDL

Garlic

• **Cholesterol-lowering**
  – Several conflicting meta-analyses (some show effect, some show no effect)
  – Perhaps at best, garlic may lower total cholesterol by about 8%, and LDL-c by about 9%

• **Blood-pressure lowering**
  – Conflicting meta-analyses (some show effect, some show no effect)
  – Perhaps at best, garlic may lower BP by 8/7 mmHg in patients with hypertension (“most” evidence with Kwai®)

• Data a bit more convincing for blood pressure than cholesterol

Garlic

• **Cautions**
  – Most common adverse effect – bad breath, body odour
  – GI effects - mouth and gastrointestinal burning or irritation, heartburn, flatulence, nausea, vomiting, and diarrhea
  – Antiplatelet activity (several case reports) – use caution with bleeding disorders, use of drugs that increase bleeding; may need to discontinue before surgery
  – May reduce warfarin concentrations

• **Dose**
  – 600-1200 milligrams per day of garlic powder in three divided doses, standardized to 1-3% allicin content
Soluble fiber
(e.g. beta-glucan in oatmeal)

- Observational studies – inverse association between dietary fiber and CHD risk
- Clinical trials – reduced LDL-C
  - Mechanism – reduced absorption of cholesterol and bile acids
- Meta-analysis of 67 trials (2290 subjects):
  - Soluble fiber (2-10g/d) lowered total cholesterol by about 5% and LDL-C by about 10%
  - Various soluble fibers (ex. psyllium, beta-glucan) reduced total cholesterol and LDL-C by similar amounts
- Authors’ conclusion:
  - “Increasing soluble fiber can make only a small contribution to dietary therapy to lower cholesterol”

Phytosterols

- Phytosterols include sterols (ex. beta-sitosterol) and stanols
- Reduce intestinal cholesterol absorption by displacing cholesterol from mixed micelles
- Present in small amounts in nuts, seeds, and vegetable oils
- Found in “functional foods” (ex. fat spreads with added phytosterols); also found in NHPs
- Cholesterol-lowering:
  - 2 g/d reduces LDL-C by 10%
- Additive effects with statins
- Well tolerated

Discussion

O/E: October 2016

- BP 148/88 mmHg; pulse = 73
- Height: 160 cm Weight: 73 kg

Labs:
- Total cholesterol: 6.7 mmo/L
- LDL-c: 4.8 mmol/L
- HDL-c: 0.8 mmol/L
- Triglycerides: 1.2 mmol/L

Ms. Leafan generally prefers natural products to medications, and asks what you think about krill oil, flaxseed, plant sterols, and soluble fiber – should she be taking them?
ARS Question #8

Which of the following has the best evidence for efficacy for Ms. Leafan?

A. Fish oil
B. Garlic
C. Krill oil
D. Flaxseed
E. Plant sterols
F. Soluble fiber
One clinician’s approach...
Guideline-driven versus patient-centred care

Shared decision making
Understanding patients’ experience
Building a relationship
Providing evidence (including uncertainty)
Presenting recommendations
Checking for understanding and agreement

Epstein RM et al. JAMA 2004;291:2359-2366
The Absolute CVD Risk/Benefit Calculator

**Framingham**
Heart attacks + angina/coronary insufficiency + heart failure + strokes + intermittent claudication

**QRISK®2-2014**
Heart attacks + strokes

**ACC/AHA ASCVD**
CHD death + nonfatal heart attacks + fatal/nonfatal strokes

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**Age**
- 58 years

**Gender**
- Male ✔ Female

**Race**
- Black ✔ Non-Black

**Smoker**
- Yes ✔ No
  - CVR risk is reversed after 5-10 years of no smoking

**Diabetes**
- Yes ✔ No

**Systolic Blood Pressure**
- 148 mmHg
  - 120 mmHg is used for baseline risk

**On treatment for BP**
- Yes ✔ No

**Total Cholesterol**
- 6.7 mmol/L
  - Cholesterol should be prior to drug treatment
  - 3.4 mmol/L is used for baseline risk.
  - [Click to change to mg/dL](#)

**HDL Cholesterol**
- 0.8 mmol/L
  - HDL should be prior to drug treatment
  - 1.3 mmol/L is used for baseline risk.

**Family History of Early CHD**
- 0%
  - The amount of additional risk conferred from a family member to a patient depends on: (1) how close a relative, (2) age of a relative, (3) number of affected family members.

**Relative Benefit: 0%**
- Benefit often has nothing to do with the effect on the surrogate marker. At present, you can only select one intervention at a time.
  - Physical Activity
  - Mediterranean Diet vs Low fat
  - Vitamin/Omega-3 supplements
  - BP mode (not atenolol/dxzazolol)
  - Low-med intensity statine
  - High intensity statins
  - Fibrates
  - Niacin
  - Ezetimbe
  - Metformin
  - Sulfonylureas
  - Insuline
  - Glitazones
  - GLPs
  - DPP-4s
  - Meglitinides
  - SGLT2
  - Smoking Cessation
  - ASA

**Risk Time Period**
- 10 years

**Outcome**
- 93.1% No event
- 6.9% Total with an event
- 0.0% Number who benefit from treatment
- NNT ∞ Number needed to treat
- 1.6% Baseline events using baseline factors alone
- 5.3% Additional events "caused" by risk factors

For more information, visit [http://chd.bestsciencemedicine.com/calc2.html#calculator](http://chd.bestsciencemedicine.com/calc2.html#calculator)
Medications that have been demonstrated to reduce the risk of a first cardiovascular event

- HMG CoA reductase inhibitors (statins)
- Certain blood pressure-lowering medications
- Acetylsalicylic acid
<table>
<thead>
<tr>
<th>Intervention and population</th>
<th>Absolute CV risk reduction over 10 years</th>
<th>Estimated absolute risk increase for adverse events over 10 years</th>
<th>Approximate relative risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (baseline 10 year risk of hard CVD = 20%)</td>
<td>2% (best-case scenario)</td>
<td>0.3-3% (major GI or serious extra-cranial bleeding)</td>
<td>10%</td>
</tr>
<tr>
<td>Statins (baseline 10 year risk of hard CVD = 20%)</td>
<td>4%</td>
<td>1-2% (diabetes) &lt;0.01% (rhabdomyolysis)</td>
<td>20%</td>
</tr>
<tr>
<td>Antihypertensive for BP 175/105 mmHg (baseline 10-year risk of hard CVD = 20%)</td>
<td>4-6%</td>
<td>Depends upon drug used</td>
<td>20-30%</td>
</tr>
</tbody>
</table>

Wright JM, Musini VM. Cochrane Database of Systematic Reviews 2009, Issue 3.  
Putting it together…

• Mrs. Leafan’s possible benefits/harms from:
  
  – A statin
  – A medication for blood pressure
  – ASA
  – Various natural health products
General thoughts

• Risk-lowering therapies
  – How do you monitor effectiveness?
Mr. Whyamia Leafan (Hapless’ brother) is a 72 year-old male with heart failure

• Generally doing well, but suffers from decreased exercise tolerance since his most recent hospitalization for an exacerbation of her heart failure (July 2016)
  – He gets a bit “winded” when he walks for about 10-15 minutes without a break.
  – He also said that his quadriceps muscles feel a little sore “almost all the time”.

His daughter-in-law recommended that he try Omega-3 fatty acids and Co-enzyme Q10.
Case #3, continued

Previous medical history:
• STEMI (2009)
• Heart failure (2009) (Last echo - LVEF = 29%)
• Dyslipidemia (2000)
• Hypertension (2002)

ASA 81mg once daily
Perindopril 8mg once daily
Rosuvastatin 20mg once daily
Carvedilol 25 mg BID
Furosemide 20 mg daily (dose adjusted according to weight)
Spironolactone 25 mg once daily

Allergies: Penicillin

Vital Signs: HR : 62 BP: 118/64 Temp: Afebrile 68 Kg 1.58 m tall
What would you recommend for Mr. Leafan?

A. Omega-3 fatty acids only
B. Coenzyme Q10 only
C. Both omega-3 fatty acids and coenzyme Q10
D. Neither omega-3 fatty acids or coenzyme Q10
GISSI-HF trial

7046 patients with NYHA class II (64%) and III (34%) heart failure in 357 centres in Italy

1 g n-3 PUFA per day (850-882 mg EPA plus DHA)

Placebo

3.9 year median follow-up

Co-primary endpoints:
1) Time to death
2) Time to death or admission for CV reasons

## GISSI-HF trial

<table>
<thead>
<tr>
<th>Outcomes at 3.9 years</th>
<th>n-3 PUFA</th>
<th>Placebo</th>
<th>Absolute risk reduction (95% CI), p</th>
<th>NNT (for 3.9yrs) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>27%</td>
<td>29%</td>
<td>1.8% (0.3-3.9), p = 0.041</td>
<td>56</td>
</tr>
<tr>
<td>Death or hospitalization for cardiovascular reason</td>
<td>57%</td>
<td>59%</td>
<td>2.3% (0.0-4.6), p = 0.009</td>
<td>44</td>
</tr>
</tbody>
</table>

- 93% of patients were taking ACE-I or ARB
- 65% of patients were taking beta-blockers
- 39% of patients were taking spironolactone

Coenzyme Q10

Actions in the body

• Antioxidant
• Co-factor in metabolic pathways (component of mitochondrial electron transport chain), important for synthesis of ATP

Rationale for use in cardiovascular conditions

• Evidence of coenzyme Q10 deficiency in hypertension and heart failure
  – And in patients using statins
• Causes vasodilation and lowers BP in hypertensive patients
Coenzyme Q10 in heart failure

- Meta-analysis of 13 RCTs
  - Total of 395 patients
    - Sample size of each trial ranged between 6 to 69 patients
    - Study durations ranged between 2 and 28 weeks
    - Most trials published prior to the year 2000 (less ACE-inhibitor/beta-blocker use)
  - Results:
    - Small improvement in ejection fraction (3.7%) in patients treated with Coenzyme Q10 (60 to 300 mg daily)

Coenzyme Q10: Q-Symbio trial

420 patients with NYHA class III/IV heart failure (88% class III, 90% on ACE-I or ARB, 75% beta-blocker)

CoQ10 100 mg three times daily

Placebo

16 week follow-up

2 year follow-up

Composite endpoint: hospital stay with worsened HF, CV death, mechanical assist implantation, urgent transplantation

1. NYHA class
2. 6-minute walk test
3. NT-proBNP

## Q-Symbio: Functional status

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CoQ10 (n=202)</th>
<th>Placebo (n=218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term effect on NYHA, 6-min walk test, pro-NT BNP</td>
<td>No difference</td>
<td></td>
</tr>
</tbody>
</table>

### Outcomes at week 106

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CoQ10 (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved NYHA classification (p=0.028 for difference)</td>
<td>58%</td>
<td>45%</td>
</tr>
<tr>
<td>Echocardiographic measures</td>
<td>No difference</td>
<td></td>
</tr>
<tr>
<td>Serum pro-NT BNP</td>
<td>No difference</td>
<td></td>
</tr>
</tbody>
</table>

### Q-Symbio: Major cardiovascular events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CoQ10 (n=202)</th>
<th>Placebo (n=218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from MI</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Death from heart failure (HF)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Hospital stay for worsening HF</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Hospital stay for acute HF</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>LVAD</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total (p = 0.005 for difference)</strong></td>
<td><strong>30 (15%)</strong></td>
<td><strong>57 (26%)</strong></td>
</tr>
</tbody>
</table>

Limitations:
- Small study, did not reach original enrollment plan of 550 patients
  - Randomization is not as effective in small studies
- It took 10 years to complete a two year study (?!)
- Lower than expected death rate at 2 years
  - Very few deaths, imprecise estimates of benefit
    - E.g. GISSI-HF trial had 1969 deaths, Q-Symbio had 60
- Results not consistent with prior research
  - Plausibility important for hypothesis testing

Coenzyme Q10 and statin-induced myalgia

- Myalgia associated with statin use may be partly caused by coenzyme Q10 depletion
- Coenzyme Q10 supplementation has been recommended to reduce myalgia associated with statin use
- Small preliminary trial showed some benefit, not supported by more recent trials

Am J Cardiol 2012;110:526 –529
Coenzyme Q10 – Effect on blood pressure

- Meta-analysis of double-blind RCTs:
  - Three studies, 96 patients
  - All patients had SBP > 140 mmHg, or DBP > 90 mmHg
  - Coenzyme Q10 lowered blood pressure by about 11/7 mmHg
    - Data with ACE-I, thiazides suggest BP lowering of about 8/4 mmHg
- Reservations about study reliability
  - Authors suggest “it is uncertain whether or not coenzyme Q10 reduces blood pressure in the long-term management of primary hypertension”
Discussion - Case #3

Mr. Whyamia Leafan (Hapless’ brother) is a 72 year-old male with heart failure

• Generally doing well, but suffers from decreased exercise tolerance since his most recent hospitalization for an exacerbation of her heart failure (July 2016)
  – He gets a bit “winded” when he walks for about 10-15 minutes without a break.
  – He also said that his quadriceps muscles feel a little sore “almost all the time”.

His daughter-in-law recommended that he try Omega-3 fatty acids and Co-enzyme Q10.
Case #3, continued

Previous medical history:
- STEMI (2009)
- Heart failure (2009) (Last echo - LVEF = 29%)
- Dyslipidemia (2000)
- Hypertension (2002)

ASA 81mg once daily
Perindopril 8mg once daily
Rosuvastatin 20mg once daily
Carvedilol 25 mg BID
Furosemide 20 mg daily (dose adjusted according to weight)
Spironolactone 25 mg once daily

Allergies: Penicillin

Vital Signs: HR : 62 BP: 118/64 Temp: Afebrile 68 Kg 1.58 m tall
General thoughts….

- Is there a clear gold-standard therapy?
- Medication burden
- Symptom-based versus risk lowering therapies
ARS Question #10

What would you recommend for Mr. Leafan?

A. Omega-3 fatty acids only
B. Coenzyme Q10 only
C. Both omega-3 fatty acids and coenzyme Q10
D. Neither omega-3 fatty acids or coenzyme Q10
Closing thoughts

• The role for many natural health products in the prevention and treatment of Cardiovascular Disease remains somewhat ill-defined

• Incorporating principles of critical appraisal and shared decision making into your practice may help to manage the uncertainty